Reasons for the High Cesarean Delivery Rate among Women with Ankylosing Spondylitis: Using the Korean National Health Insurance Database

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ABSTRACT. ***Objective.*** Women with ankylosing spondylitis (AS) have reported a higher rate of cesarean births than healthy controls. This study aimed to identify factors associated with cesarean births in women with AS.

Methods. Based on the Korean Health Insurance Review and Assessment Service claims database, the subjects comprised female patients aged 20–49 years old with AS. In total, 1293 deliveries after AS diagnosis were included. A logistic regression analysis was performed to identify factors associated with cesarean births.

Results. Among the 1293 deliveries in women with AS, 657 were cesarean and 636 were vaginal deliveries. Compared to vaginal delivery, the women who had cesarean deliveries were older, had a longer disease duration, and had a higher portion of primipara and dispensation of drugs. These factors were associated with a higher risk of cesarean delivery: maternal age (OR 1.08, 95% CI 1.04–1.12), disease duration (OR 1.09, 95% CI 1.03–1.14), and preeclampsia (OR 3.94, 95% CI 1.17–13.32). Further, compared to no drug dispensation, these drugs showed higher risks of cesarean delivery: nonsteroidal antiinflammatory drugs (NSAID; OR 1.64, 95% CI 1.31–2.37), tumor necrosis factor inhibitor (TNFi), disease-modifying antirheumatic drugs (DMARD), or corticosteroids (OR 2.01, 95% CI 1.57–2.58). In the subgroup analysis in primiparas, maternal age, or dispensation of NSAID alone, or TNFi, DMARD, or corticosteroids was associated with a higher risk of cesarean delivery.

Conclusion. Women with AS showed a higher cesarean delivery rate, influenced by both maternal age and disease-related factors. (J Rheumatol First Release February 15 2020; doi:10.3899/jrheum.190754)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS PREGNANCY DELIVERY CESAREAN BIRTH

The cesarean delivery rate has increased in many countries during recent decades[1]. Increasing maternal age, a higher proportion of previous cesarean deliveries, maternal preference for cesarean delivery, and increasing numbers of women with obesity or preexisting diseases are known risk factors for cesarean birth[2,3,4]. In South Korea, the cesarean delivery rate was 38% in 2015, which is the fourth highest among Organisation for Economic Cooperation and Development countries[5]. This high rate is associated with older maternal age, improvement of socioeconomic status, and maternal obesity[6].

Previous studies have shown that women with rheumatic diseases have a higher cesarean delivery rate[7,8]. Women with rheumatoid arthritis (RA) have a higher risk of cesarean delivery, and it is more common in patients with moderate to high disease activity[9]. Interestingly, the risk of primary cesarean delivery is higher in women with RA, but the risk factors for primary cesarean delivery do not differ compared to women without RA[10]. Further, elective cesarean delivery is twice as frequent among patients with chronic inflammatory arthritis, which could reflect maternal or obstetrician preference[8].

Ankylosing spondylitis (AS) affects the sacroiliac joints and commonly develops during reproductive age. Although the sacroiliac joint does not cause a mechanical hindrance during the delivery process, the rate of cesarean delivery was higher in women with AS than in healthy populations in

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Supported by a grant from the Asan Institute for Life Sciences, Asan Medical Centre, Korea [2019-772].

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Accepted for publication September 27, 2019.

previous studies[11,12]. The reason for the high rate of cesarean delivery in women with AS is unclear; however, women with AS are more likely to be exposed to drugs, to be older, and to have a higher prevalence of comorbidities or pregnancy complications including preterm birth than the general population[11]. Therefore, our present study aimed to identify factors related to AS that might have contributed to the choice of that delivery method in women with AS, using the Korean Health Insurance Review and Assessment Service (HIRA) claims database.

MATERIALS AND METHODS

Data sources. We conducted our study using patient records extracted from the HIRA claims database. The HIRA includes all health-related information on about 50 million individuals in the entire South Korean population covered by the National Health Insurance (NHI) program. It contains information on patient demographics, diagnosis [using the International Classification of Diseases, 10th revision (ICD-10)], medical procedures, prescriptions, and rare intractable disease (RID) registration information[13]. The prescription data include the generic name of the drug according to the HIRA drug formulary code, prescription date, days of supply, and route of administration. Since 2006, the NHI has operated a registration system for 133 RID, including AS. In the Korean RID system, a diagnosis is based on uniform diagnostic criteria distributed by the NHI and carefully reviewed by the corresponding healthcare institution and the NHI before registration.

Study design and study subjects. The study cohort included female patients with AS aged 20–49 years who gave birth between July 1, 2007, and June 30, 2017. Patients who had been diagnosed with AS (ICD-10, M45) and had the RID code (V140) were included. All deliveries in the HIRA after the first date of AS diagnosis were included. The following data were collected from the HIRA database: demographic information, including age at delivery and diagnosis of AS, and whether the mother had experienced preterm birth, preeclampsia, twin pregnancy, or was a primipara; and comorbid medical conditions, including hypertension (HTN), diabetes mellitus, uveitis, inflammatory bowel disease (IBD), and psoriasis. Each delivery was categorized by the method of delivery: vaginal delivery or cesarean. To compare the cesarean delivery rate with women with RA or the general population, delivery records in women 20–49 years old who had been diagnosed with RA (ICD-10, M05) and women 20–49 years old without AS or RA during the study period were also evaluated.

Medications for AS. AS medications 12 months prior to delivery included oral nonsteroidal antiinflammatory drugs (NSAID; aceclofenac, celecoxib, diclofenac, etodolac, ibuprofen, indomethacin, ketorolac, mefenamate, meloxicam, morniflumate, nabumetone, naproxen, nimesulide, piroxicam, and sulindac); oral corticosteroids (defrazacort, methylprednisolone, prednisolone, and triamcinolone), disease-modifying antirheumatic drugs (DMARD; methotrexate and sulfasalazine), and tumor necrosis factor inhibitors (TNFi; adalimumab, etanercept, infliximab, and golimumab). Based on the AS medication, the treatment pattern was divided into 3 categories: (1) no dispensation of drugs, (2) NSAID alone, and (3) TNFi, DMARD, or corticosteroids.

Statistical analyses. All statistical analyses were performed using SAS Enterprise Guide software (version 6.1, SAS Institute Inc.). The baseline characteristics are presented as numbers with percentages for the categorical variables and as means with SD for the continuous variables. Characteristics of the AS patients were analyzed, including age, comorbidities, and medications. The comorbidities were identified by the ICD-10 codes (Supplementary Table 1, available with the online version of this article) for each patient and included HTN, diabetes mellitus, renal insufficiency, uveitis, IBD, and psoriasis. A logistic regression analysis was performed to identify the factors associated with cesarean delivery. Variables that had a p value of < 0.1 in the univariate analysis were selected for the multivariable analysis, but a p value of < 0.05 was otherwise considered statistically significant in all analyses. To exclude the possibility of confounding by parity, which might affect the delivery methods, we also performed a logistic regression analysis in the primiparas (subgroup analysis).

Ethical approval. This study fulfilled the ethical guidelines of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Asan Medical Center (number 2017-0431). The requirement for informed consent was waived because it used an existing database.

RESULTS

Baseline characteristics according to delivery methods. In the Korean HIRA claims database, there were 1293 delivery records for women with AS, 8297 for women with RA, and 4.2 million for the general population between July 1, 2007, and June 30, 2017. The rate of cesarean delivery was the highest in women with AS (50.8%), followed by women with RA (44.1%), and the general population (38.0%).

Table 1 shows the baseline characteristics according to delivery methods in women with AS. Among the 1293 delivery records from 996 women with AS, there were 657 cesarean deliveries and 636 vaginal deliveries. The mean maternal age was higher in the women with cesarean deliveries than in women with vaginal deliveries (32.54 ± 3.34 vs 31.85 ± 3.33 yrs, $p < 0.001$). Further, the disease duration was longer in the women with cesarean deliveries than in the women with vaginal deliveries (4.42 ± 2.48 vs 3.93 ± 2.24 yrs, $p < 0.001$). The frequency of primipara was higher in the women with cesarean deliveries than in the women with vaginal deliveries [404 (61.5%) vs 345 (54.2%), $p = 0.01$]. However, the incidences of twin pregnancy and comorbidities including uveitis, IBD, and psoriasis did not differ between the 2 groups. When the patients were divided into 3 groups according to the treatment pattern 12 months prior to delivery, the frequency of no dispensation of medication was higher in women with vaginal deliveries than in women with cesarean deliveries [382 (60.1%) vs 300 (45.7%), $p < 0.001$]. However, the proportions of NSAID alone and TNFi, DMARD, or corticosteroids were higher in women with cesarean deliveries than in women with vaginal deliveries. Further, 41.6%, 24.7%, 19.8%, and 12.6% of women with cesarean deliveries were exposed to NSAID, corticosteroids, DMARD, or TNFi within 12 months prior to delivery, respectively. For vaginal deliveries, the corresponding frequencies were 30.8%, 17%, 14.6%, and 8.3%, respectively.

Clinical factors associated with cesarean delivery in women with AS. A logistic regression analysis was performed to evaluate the factors associated with cesarean delivery (Table 2). In the univariate analysis, maternal age, disease duration, being primiparous, preterm birth, preeclampsia, and the pattern of treatment were associated with cesarean delivery. In the multivariable analysis, maternal age was associated with a higher risk of cesarean delivery (OR 1.08, 95% CI 1.04–1.12, $p < 0.001$). In addition, a longer disease duration (OR 1.09, 95% CI 1.03–1.14, $p < 0.001$), being primiparous (OR 1.49, 95% CI 1.16–1.89, $p < 0.001$), and the presence

Table 1. Baseline characteristics according to delivery methods in women with ankylosing spondylitis.

Characteristics	Vaginal Delivery, n = 636	Cesarean Delivery, n = 657	p*
Maternal age, yrs	31.85 ± 3.33	32.54 ± 3.34	< 0.001
20 ≤ 25	7 (1.1)	5 (0.8)	0.01
> 25 ≤ 30	144 (22.6)	116 (17.7)	
> 30 ≤ 35	347 (54.6)	361 (54.9)	
> 35 ≤ 40	133 (20.9)	154 (23.4)	
> 40 ≤ 45	5 (0.8)	20 (3.0)	
> 45 ≤ 50	0 (0)	1 (0.2)	
Disease duration, yrs	3.93 ± 2.24	4.42 ± 2.48	< 0.001
Primipara	345 (54.2)	404 (61.5)	0.01
Twin pregnancy	6 (0.9)	12 (1.8)	0.18
Comorbidity			
Hypertension	8 (1.3)	17 (2.6)	0.08
Diabetes mellitus	14 (2.2)	19 (2.9)	0.43
Uveitis	88 (13.8)	116 (17.7)	0.06
IBD	62 (9.7)	76 (11.6)	0.29
Psoriasis	11 (1.7)	8 (1.2)	0.44
Preterm birth	14 (2.2)	4 (0.6)	0.01
Preeclampsia	4 (0.6)	12 (2.0)	0.03
Pattern of treatment			< 0.001
No dispensation of medication	382 (60.1)	300 (45.7)	
NSAID alone	66 (10.4)	80 (12.2)	
TNFi, DMARD, or corticosteroids	188 (29.6)	277 (42.2)	
Drug exposure†			
NSAID	196 (30.8)	273 (41.6)	0.01
Corticosteroids	108 (17)	162 (24.7)	< 0.001
DMARD	93 (14.6)	130 (19.8)	0.01
TNFi	53 (8.3)	83 (12.6)	0.01

Results expressed as the mean ± SD or n (%). * P value was estimated by the t test for continuous data and the chi-square test or Fisher's exact test for categorical data. †12 months prior to delivery. NSAID: nonsteroidal anti-inflammatory drugs; DMARD: disease-modifying antirheumatic drugs; TNFi: tumor necrosis factor inhibitor; IBD: inflammatory bowel disease.

Table 2. Factors associated with cesarean delivery in women with ankylosing spondylitis.

Variables	Univariate			Multivariable†		
	OR	CI	p	OR	CI	p
Maternal age	1.06	1.03–1.10	< 0.001	1.08	1.04–1.12	< 0.001
Disease duration	1.09	1.04–1.14	< 0.001	1.09	1.03–1.14	< 0.001
Primiparous	1.35	1.08–1.67	0.01	1.49	1.16–1.89	< 0.001
Twin pregnancy	1.95	0.73–5.24	0.18			
Hypertension	2.09	0.89–4.87	0.09			
Diabetes mellitus	1.32	0.66–2.66	0.43			
Uveitis	1.34	0.99–1.81	0.06			
IBD	1.21	0.85–1.73	0.29			
Psoriasis	0.70	0.28–1.75	0.45			
Preterm birth	0.27	0.09–0.83	0.02	0.25	0.08–0.80	0.02
Preeclampsia	3.19	1.03–9.83	0.04	3.94	1.17–13.32	0.03
Pattern of treatment‡			< 0.001			< 0.001
No dispensation of medication	1.00			1.00		
NSAID alone	1.54	1.08–2.21	0.02	1.64	1.31–2.37	0.01
TNFi, DMARD, or corticosteroids	1.88	1.48–2.38	< 0.001	2.01	1.57–2.58	< 0.001

† Data were the final results of a backward logistic regression analysis after selecting factors that were significantly associated in the univariate analysis ($p < 0.1$). ‡ 12 months prior to delivery. NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; TNFi: tumor necrosis factor inhibitor; IBD: inflammatory bowel disease.

of preeclampsia (OR 3.94, 95% CI 1.17–13.32, p = 0.03) were associated with a higher risk of cesarean delivery. However, preterm birth (OR 0.25, 95% CI 0.08–0.80, p = 0.02) was associated with a lower probability of cesarean delivery. Compared to no dispensation of medications, NSAID alone and TNFi, DMARD, or corticosteroids were associated with a higher risk of cesarean delivery. Regarding drug exposure, NSAID (OR 1.57, 95% CI 1.22–2.01, p < 0.001) or corticosteroids (OR 1.38, 95% CI 1.02–1.85, p = 0.03) were associated with a higher risk of cesarean delivery (Supplementary Table 2, available with the online version of this article).

Subgroup analysis on primiparas. The results of the subgroup analysis are shown in Table 3. Among the 749 deliveries in primiparas, 404 cases (53.9%) were cesarean deliveries. In the univariate analysis, maternal age, disease duration, and pattern of treatment were associated with cesarean delivery. In the multivariable analysis, maternal age (OR 1.14, 95% CI 1.08–1.19, p < 0.001) was associated with a higher risk of cesarean delivery. Compared to no dispensation of medications, NSAID alone (OR 1.89, 95% CI 1.17–3.04, p = 0.01) and TNFi, DMARD, or corticosteroids (OR 1.99, 95% CI 1.44–2.74, p < 0.001) were associated with a higher risk of cesarean delivery. In addition, regarding drug exposure, corticosteroids (OR 1.70, 95% CI 1.25–2.32, p < 0.001) were associated with a higher risk of cesarean delivery (Supplementary Table 3, available with the online version of this article).

DISCUSSION

In this Korean population-based study, more than 50% of the pregnant women with AS underwent cesarean delivery; this rate was higher than in the general population and in women with RA. Older maternal age, longer disease duration, and the presence of preeclampsia were associated with a higher risk of cesarean delivery in women with AS. Further, compared to no dispensation of medications, extensive treatment of AS was associated with a higher risk of cesarean delivery in women with AS.

Previous studies have shown that women with AS showed a higher rate of cesarean delivery than the general population[11,12]. In our present study, the cesarean delivery rate was higher in women with AS than in both women with RA and the general population. Several studies have reported that the risk factors of cesarean delivery in the general population are older maternal age, higher education level, breech presentation, previous cesarean delivery, and maternal request[3,4,14]. Clearly, in our present study, older maternal age was a risk factor for cesarean delivery in women with AS. Further, factors related to AS also contributed to those women choosing cesarean delivery. A longer disease duration of AS was associated with an increased risk of cesarean delivery in the total deliveries but not in the subgroup analysis with primipara. According to our results, the effect of disease duration on the risk of cesarean delivery may be modulated by inherent factors, including prior cesarean delivery. In addition, compared to no dispensation of medications, a higher risk of cesarean delivery was associated with TNFi, DMARD, or corticosteroid, and NSAID alone. In a previous Swedish study, the dispensation of TNFi, DMARD, or corticosteroids was associated with a higher risk of cesarean delivery in women with AS compared to the general population[11]. Interestingly, the analysis of drug exposure revealed that corticosteroids associated with a higher risk of cesarean delivery in women with AS (Supplementary Tables 2 and 3, available with the online version of this article).

Table 3. Factors associated with cesarean delivery in primiparas among women with ankylosing spondylitis (subgroup analysis).

Variables	Univariate			Multivariable†		
	OR	CI	p	OR	CI	p
Maternal age	1.13	1.07–1.18	< 0.001	1.14	1.08–1.19	< 0.001
Disease duration	1.10	1.04–1.17	< 0.001			
Twin pregnancy	0.34	0.07–1.76	0.20			
Hypertension	1.20	0.38–3.81	0.76			
Diabetes mellitus	1.73	0.58–5.10	0.32			
Uveitis	1.50	1.00–2.24	0.05			
IBD	1.06	0.66–1.71	0.81			
Psoriasis	0.51	0.12–2.14	0.36			
Preterm birth	0.12	0.02–0.98	0.05	0.12	0.01–0.97	0.05
Preeclampsia	1.94	0.59–6.36	0.27			
Pattern of treatment‡			< 0.001			
No dispensation of medication	1.00			1.00		
NSAID alone	1.69	1.07–2.68	0.03	1.89	1.17–3.04	0.01
TNFi, DMARD, or corticosteroids	1.82	1.33–2.49	< 0.001	1.99	1.44–2.74	< 0.001

† Data were the final results of a backward logistic regression analysis after selecting factors that were significantly associated with the univariate analysis (p < 0.1). ‡ 12 months prior to delivery. NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; TNFi: tumor necrosis factor inhibitor; IBD: inflammatory bowel disease.

Several previous studies have reported that corticosteroids are associated with a higher risk of preterm birth or preeclampsia[15,16]. However, this association is not merely the effect of corticosteroids; rather, the severity of the disease leads to a need for corticosteroid therapy[17]. Corticosteroids are not typically used to treat AS, with the exception of during pregnancy; thus, the use of corticosteroids might reflect an increasing disease activity. Taken together, our results suggest that disease severity or the presence of symptoms requiring more extensive treatment and a longer disease duration before pregnancy affect the choice of delivery method.

Pregnancy-related lower back and/or pelvic girdle pain is common in pregnant women[18], and patients with AS report higher back pain scores during pregnancy than the general population[19]. Unlike patients with RA, previous studies have reported that most patients with AS experience unchanged or slightly worse disease activity during pregnancy[20,21,22]. Further, aggravation of disease activity is observed in 45–87% of patients with AS at the 6-month period following delivery[23,24]. In a recent prospective study, pregnant women with AS exhibited a gradual increase of disease activity in the second trimester[25]. Therefore, the presence of symptoms during pregnancy, particularly in the pelvic region, and concerns about pain during delivery or aggravation of disease activity (which might play a role in the preference for cesarean delivery), could be factors behind the higher rate of cesarean delivery in women with AS.

Our present study has some limitations. First, cesarean delivery included both emergent and elective types, and we could not distinguish between them based on the HIRA database. The risk factors for elective and emergent cesarean delivery differ[3]. Thus it is difficult to conclude whether the reason for the high cesarean delivery rate in pregnant women with AS is due to elective cesarean delivery based on maternal request or emergent cesarean delivery based on pregnancy complications. Moreover, although data on disease activity during pregnancy and grade of sacroiliitis were not available, these variables might have contributed to the choice of delivery method. Second, other confounding factors that affect the choice of the delivery method such as socioeconomic status, education level, obesity, smoking history, or baby weight were not identified in the HIRA claims database.

The rate of cesarean delivery was 50.8% in Korean women with AS, and older maternal age, longer disease duration, and extensive treatment for AS were risk factors for cesarean delivery. The higher cesarean delivery rate observed in women with AS may result from the effects of both maternal age and disease-related factors.

ACKNOWLEDGMENT

We thank the Korean Health Insurance Review and Assessment Service and the National Health Insurance Service for providing the insurance claims data.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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