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Ph.D. Dissertation of Medicine

Incidence and Risk Factors for Pregnancy-Related de Quervain's Tenosynovitis in Korea: A Population-Based Epidemiologic Study

한국에서의 임신과 연관된 드퀘르벵 병의 발생률 및 위험 인자 분석: 인구 기반 역학 연구

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Incidence and Risk Factors for Pregnancy-Related de Quervain's Tenosynovitis in Korea: A Population-Based Epidemiologic Study

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Abstract

Background: Although pregnant or lactating women have been recognized to be predisposed to de Quervain's tenosynovitis (DQT), there is a lack of epidemiologic evidence. We purposed to estimate the nationwide incidence of pregnancy-related de Quervain's tenosynovitis (PRDQT) and to analyze risk factors using the Korean National Health Insurance (NHI) database.

Materials and Methods: A retrospective epidemiologic study of pregnant women in Korea from 2013 to 2017 was conducted using the NHI claim database. Using corresponding diagnostic codes, we identified pregnant women diagnosed with DQT during pregnancy or the postpartum period. We calculated the cumulative incidence and analyzed risk factors such as demographics, pregnancy type, delivery method, gestational complications, and comorbidities using multivariate logistic regression analysis.

Results: Between 2013 and 2017, 34,342 patients with PRDQT were identified among 1,601,501 pregnant women, representing a cumulative incidence of approximately 2.1%. Age ≥ 30, multiple gestation, cesarean delivery, hypertensive disorders in pregnancy, and underlying rheumatoid arthritis were all identified as significant risk factors for PRDQT occurrence, whereas diabetic disorders in

pregnancy and underlying diabetes mellitus were not.

Conclusion: In Korea, PRDQT was found to affect approximately 2.1 out of 100 pregnant women between 2013 and 2017. The incidence and risk factors identified in this study can be used for clinical consultation and prediction, as well as for development of national health policies.

Keyword: Wrist Joint; Tenosynovitis; De Quervain's Disease; Pregnancy complications; Epidemiology

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Introduction

De quervain's tenosynovitis (DQT) is a stenosing tenosynovitis of the first extensor compartment of the wrist. The first dorsal compartment is the fibro-osseous tunnel just proximal to the radial styloid, through which the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons glide. Attritional force secondary to repetitive friction of tendons causes swelling and thickening of the extensor retinaculum that covers the first dorsal compartment, resulting in the narrowing of the fibro-osseous tunnel. Resisted gliding of tendons though the narrowed tunnel provokes the pain and decreased motion.[1]

According to previous reports, DQT occurs up to six times more frequently in women than men and is associated with the dominant hand use during middle age.[1-3] The most common DQT patient is a woman in her fifties or sixties who overuses her wrist or thumb performing household tasks or occupations that require repetitive motions such as typing and lifting.[1] Another significantly younger cohort of patients who are diagnosed with DQT is consisted of pregnant or lactating women, who are classified as having pregnancy-related de Quervain's tenosynovitis (PRDQT).[3-7]

Although it has been recognized that PRDQT is usually self-limiting following delivery or cessation of breastfeeding, there is a paucity of epidemiologic evidence for PRDQT patients. As only a few case series involving a small number of patients have been reported, there is currently a lack of information to consult pregnant or lactating women complaining of their radial wrist pain or to predict the occurrence of PRDQT.[4-6] Since the occurrence of PRDQT is empirically considered to be much rarer than DQT, investigations involving a large number of pregnant or lactating women are anticipated to provide more relevant findings. Due to the fact that almost all Korean citizens are covered by the Korean National Health Insurance (NHI) system, analyzing the NHI database enables conducting epidemiological studies on a large population, providing an accurate estimate of this uncommon condition in Korea. Therefore, in this study, we used the NHI database to estimate the nationwide incidence of PRDQT in Korea and to analyze risk factors.

Materials and Methods

Data sources

A 5-year retrospective population-based epidemiologic study from 2013 to 2017 was conducted using the Korean NHI claim database. Almost all healthcare providers in Korea are required to submit claim data to the NHI, including each patient's diagnosis and medical costs, in order to be reimbursed by the government for medical expenses. As a result, except for procedures such as cosmetic surgery that are not covered by the NHI system, this centralized claim database covers over 50 million citizens, providing nearly all information about the nationwide volume and burden of any specific disease or condition. Several epidemiological studies on pregnant women in Korea have already been conducted using this centralized database. [8, 9]

Data collection

The NHI claim database contains de-identified information on all insurance claims, including demographics, diagnostic codes based on the 10th version of the International Classification of Diseases (ICD-10) system, medical services provided, and medical expenses incurred. We identified pregnant women aged 15 to 49 who gave

birth between 2013 and 2017 using the ICD-10 codes for delivery (O80, O81, O82, O83, and O84). We excluded those who gave birth at their ages of < 15 or ≥ 50, because they are extremely rare (less than 0.001% of total pregnancies) according to Korean National Statistics.10) The pregnancy period was defined as the 10 months prior to the delivery date and the postpartum period as the 1 year following. Although the delayed postpartum period is frequently defined in obstetrics as 6 months following delivery, we defined it as 1 year following childbirth, given that the average duration of lactation for Korean mothers is approximately 13 months according to Korean National Statistics.[10,11] The following criteria were used to identify patients with PRDQT: (1) gave a birth between 2013 and 2017, (2) had at least one claim under the ICD-10 code corresponding to DQT (M65.4) during the pregnant or postpartum period, and (3) did not have any claim for DQT prior to pregnancy (Figure 1). To exclude women who had been diagnosed with DQT prior to the study period, we excluded those who had any claim data related to DQT from 2011 to pregnancy. A woman who had two or more deliveries during the study period was counted as one mother.

We collected data on demographics, pregnancy type, delivery method, gestational complications, and comorbidities such as

rheumatoid arthritis (RA) and diabetes mellitus (DM) using the corresponding ICD-10 codes. According to pregnancy type, all subjects were classified as single gestation (O80, O81, O82, and O83) or multiple gestation (O84). They were classified according to their delivery method as vaginal (O80, O81, O83, O84.0, O84.1, O84.8, and O84.9) or cesarean section (O82 and O84.2) delivery. Data on the presence of two major gestational complications were collected: hypertensive disorders of pregnancy (O11, O13, O14, O15, and O16) and diabetic disorders of pregnancy (O24). Hypertensive disorders of pregnancy included disorders such as preeclampsia superimposed on chronic hypertension, pregnancy-induced hypertension, preeclampsia, and eclampsia. Regarding comorbidities, the presence of RA (M05.8, M05.9, M06.0, M06.8, and M06.9) and DM (E10, E11, E12, E13, and E14) were determined, respectively. Table 1 summarizes all ICD-10 codes that were used to collect data.

Data analysis

The cumulative incidence of PRDQT was calculated by dividing the number of patients with PRDQT by the total number of women who delivered during the study period. Additionally, the cumulative incidences for each 5-year age group were calculated and

compared with those of DQT in non-pregnant women and in total population. To determine the risk factors for PRDQT, all pregnant women were divided into two groups: those with PRDQT (PRDQT group) and those without PRDQT (non- PRDQT group). The chi-square test was used to compare categorical variables between the two groups. To analyze age as a categorical variable, subjects were divided into two groups: those aged < 30 and those aged ≥ 30. A multivariate logistic regression analysis was conducted on variables that had been determined to be significant in univariate analyses. SAS software version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used to analyze all data, with a P value < 0.05 considered statistically significant.

Figure 1. Criteria for identifying patients with pregnancy-related de Quervain's disease in the Korean National Health Insurance claim database

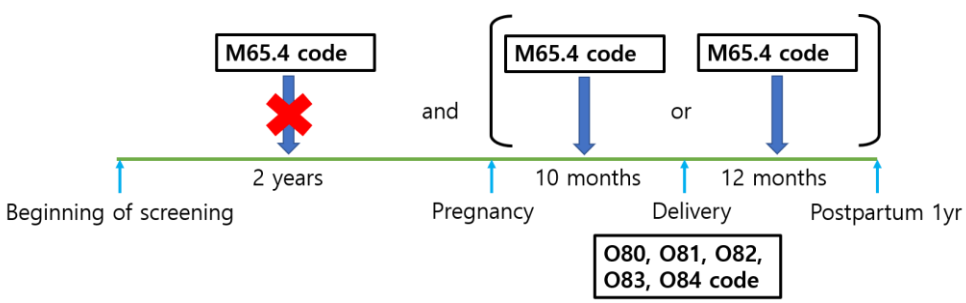

Table 1. Diagnostic codes used in this study and their related descriptions according to ICD-10

Conditions		ICD-10 code	Description
Delivery		O80	Single spontaneous delivery
		O81	Single delivery by forceps and vacuum extractor
		O82	Single delivery by caesarean section
		O83	Other assisted single delivery
		O84	Multiple delivery
de Quervain's tenosynovitis		M65.4	Radial styloid tenosynovitis (de Quervain)
Gestational complications	Hypertensive disorders of pregnancy	O11	Pre-eclampsia superimposed on chronic hypertension
		O13	Gestational (pregnancy-induced) hypertension
		O14	Pre-eclampsia
		O15	Eclampsia
		O16	Unspecified maternal hypertension
	Diabetic	O24	Diabetes mellitus in

	disorders of pregnancy		pregnancy
Comorbidity	Rheumatoid arthritis	M05.8	Other seropositive rheumatoid arthritis
		M05.9	Seropositive rheumatoid arthritis, unspecified
		M06.0	Seronegative rheumatoid arthritis
		M06.8	Other specified rheumatoid arthritis
		M06.9	Rheumatoid arthritis, unspecified
	Diabetes mellitus	E10	Type 1 diabetes mellitus
		E11	Type 2 diabetes mellitus
		E12	Malnutrition-related diabetes mellitus
		E13	Other specified diabetes mellitus
		E14	Unspecified diabetes mellitus

ICD-10, the 10th version of the International Classification of Diseases

Results

Between 2013 and 2017, the total number of women who gave birth was identified as 1,601,501. During this time period, the total numbers of women with PRDQT was identified as 34,342. As a result, the cumulative incidence of PRDQT can be estimated to be 2.1%. The cumulative incidence was 1.6% for those aged 15−19; 1.8% for those aged 20−24; 2.1% for those aged 25−29; 2.1% for those aged 30−34; 2.4% for those aged 35−39; 2.5% for those aged 40−44; 3.9% for those aged 45−49 (Table 2). The cumulative incidence of DQT in non−pregnant women and total population age 15−49 were 0.4% and 0.3%. Relative risk of pregnancy in occurring DQT was calculated as 5.4 (Table 3).

The univariate analysis revealed that the PRDQT group had significantly more patients aged ≥ 30 than the non− PRDQT group (70.2% vs 68.5%, $p < 0.001$). Both multiple gestation rate and cesarean section delivery rate were significantly higher in the PRDQT group (2.7% vs 1.8%, $p < 0.001$ and 42.3 % vs 37.1%, $p < 0.001$, respectively). Prevalence of hypertensive disorders of pregnancy was significantly greater in the PRDQT group (3.5% vs 2.7%, $p < 0.001$). However, diabetic disorders of pregnancy were significantly less prevalent in the PRDQT group than in the non−

PRDQT group (30.7% vs 33.4%). Both RA and DM were significantly more prevalent in the PRDQT group (1.9% vs 0.7%, $p < 0.001$, $p < 0.001$ and 3.3% vs 3.0%, $p = 0.005$, respectively) (Table 4).

The multivariate logistic regression analysis showed that age $\geq$ 30, multiple gestation, cesarean section delivery, hypertensive disorders of pregnancy, and underlying RA were significant factors, but underlying DM was not. The odds ratio for underlying RA was the highest of all significant factors, followed by multiple gestation, hypertensive disorders of pregnancy, cesarean section delivery, and age $\geq$ 30 (Table 5).

Table 2. Cumulative incidence of pregnancy-related de Quervain's tenosynovitis in Korea from 2013 to 2017

Age (years)	Total pregnant women	Patients with PRDQT	Cumulative incidence (%)
15-19	9,115	146	1.6%
20-24	90,434	1,628	1.8%
25-29	403,578	8,475	2.1%
30-34	772,798	16,229	2.1%
35-39	288,885	6,933	2.4%
40-44	35,710	893	2.5%
45-49	981	38	3.9%
Total	1,601,501	34,342	2.1%

PRDQT, pregnancy-related de Quervain's tenosynovitis

Table 3. Cumulative incidence of de Quervain's tenosynovitis in pregnant women, non-pregnant women, and total population

Age (years)	Pregnant women	Non-pregnant women	Total population	Relative Risk of pregnancy in women
15-19	1.60%	0.15%	0.11%	10.6
20-24	1.80%	0.27%	0.21%	6.7
25-29	2.09%	0.40%	0.32%	5.2
30-34	2.10%	0.66%	0.48%	3.2
35-39	2.39%	0.49%	0.37%	4.9
40-44	2.50%	0.38%	0.27%	6.6
45-49	3.87%	0.40%	0.27%	9.7

Total	2.14%	0.40%	0.30%	5.4

PRDQT, pregnancy-related de Quervain's tenosynovitis

Table 4. Univariate analysis of risk factors associated with pregnancy-related de Quervain's tenosynovitis

Risk factors		Patients with PRDQT (n = 34,342)		Patients without PRDQD (n = 1,567,159)		P-value
		n	%	n	%	
Age	< 30	10,249	29.8%	492,878	31.5%	<0.001
	≥ 30	24,093	70.2%	1,074,281	68.5%	
Pregnancy type	Single gestation	33,398	97.3%	1,538,238	98.2%	<0.001
	Multiple gestation	944	2.7%	28,921	1.8%	
Delivery method	Vaginal delivery	19,808	57.7%	986,231	62.9%	<0.001
	C-section delivery	14,534	42.3%	580,928	37.1%	
Gestational complications	Hypertensive disorders of pregnancy	1,207	3.5%	41,911	2.7%	<0.001
	Diabetic disorders of pregnancy	10,549	30.7%	523,153	33.4%	<0.001
Comorbidity	Rheumatoid arthritis	658	1.9%	10,395	0.7%	<0.001
	Diabetes mellitus	1,121	3.3%	46,284	3.0%	0.005

PRDQT, pregnancy-related de Quervain's tenosynovitis; C-section, cesarean section

Table 5. Multivariate logistic regression analysis for predicting pregnancy-related de Quervain's tenosynovitis

Risk factors		OR	95% CI	P-value
Age	< 30	1.000		<0.001
	≥ 30	1.130	1.106 - 1.154	
Pregnancy type	Single gestation	1.000		<0.001
	Multiple gestation	1.379	1.298-1.460	
Delivery method	Vaginal delivery	1.000		<0.001
	C-section delivery	1.150	1.121-1.179	
Gestational complications	Hypertensive disorders in pregnancy	1.233	1.160-1.306	<0.001
Comorbidity	Rheumatoid arthritis	2.461	2.267-2.655	<0.001
	Diabetes mellitus	0.935	0.878-0.992	0.03

OR, odds ratio; CI, confidence interval; C-section, cesarean section

Discussion

There have been only a few case series reports on the epidemiology of PRDQT. Schumacher et al. previously reported 6 patients with DQT associated with pregnancy.[6] All 6 patients' symptoms began prior to delivery. Another study by Schned reported that there were 6 pregnant women among 24 women diagnosed with DQT over a one-year period.[5] The onset was the second trimester for one patient and the third trimester for 5 patients. The author hypothesized that there might be a true relationship between pregnancy and DQT based on the fact that the mean age of the pregnant women (31.7 years old) was lower than that of the entire group (39.5 years old). Avci et al. described 18 patients with DQT who were either pregnant or breast-feeding.[4] The mean age of patients was 28 years (range, 20-36 years). Five patients developed symptoms during pregnancy, while 13 patients developed symptoms during lactation.

According to our review of the literature, this is the first population-based epidemiologic study focusing exclusively on PR DQT. The purpose of this study was to determine the nationwide incidence of PRDQT and the associated risk factors using the population-based NHI claim database. This study included over 1.7

million pregnant women across the country from 2013 to 2017 and determined that the nationwide incidence of PRDQT in Korea was approximately 2.1%. Among identifiable risk factors, age ≥ 30, multiple gestation, cesarean section delivery, hypertensive disorders of pregnancy, and underlying RA were all associated with the occurrence of PRDQT, but diabetic disorders of pregnancy and underlying DM were not.

Several hypotheses regarding the occurrence of PRDQT have been suggested. According to some authors, fluid retention during pregnancy and lactation contributed to the edematous state within the first dorsal compartment, increasing susceptibility to stenosing tenosynovitis of APL and EPB tendons.[12, 13] Another hypothesis is that hormonal changes, particularly increased prolactin secretion during pregnancy and lactation, may contribute to the occurrence of DQT.[5, 14] Changes in the secretion of estrogen and progesterone have also been proposed as possible hormonal contributors.[5] A recent molecular biologic study of intraoperative retinaculum samples from 16 patients with DQT discovered a correlation between estrogen receptor-β expression levels and histologic grades, indicating the presence of a hormonal background.[15] Another mechanical hypothesis is that postpartum infant care activities such as breastfeeding or milk feeding, lifting and

supporting infants in specific positions require continuous overexertion of the mothers' wrist, which may result in the development of DQT.[5, 12, 13]

This study discovered that pregnant women who aged ≥ 30 are more prone to DQT than those who aged < 30. Previous epidemiologic research on DQT in a young and active population using a large military personnel database indicated that age greater than 40 was a major risk factor for DQT, with an adjusted rate ratio of 3.65 when compared to the age <20 group.[16] Read et al. described the histologic characteristics of PRDQT in 6 tendon sheath specimens as myxoid degeneration in the absence of acute or chronic inflammation, which were comparable to pregnancy-unrelated DQT.[17] With these clinical and histologic features, one can surmise that PRDQT has a similar pathogenesis to other forms of degenerative tendinopathy. Further studies are necessary to ascertain which elements that contribute to the development of degenerative alterations in pregnant women who are relatively young.

In this study, we examined factors associated with pregnancy and delivery, such as pregnancy type, delivery method, and gestational complications. Multiple gestation, cesarean section delivery, and hypertensive disorders in pregnancy were identified

as gestational risk factors for PRDQT. Given the association between these factors and increased body fluid during pregnancy, it is quite probable that they did not exist in isolation, but rather interacted with each other throughout pregnancy.[18] Even though confounding effects between these factors cannot be ruled out, it can be extrapolated that edema caused by pregnancy-induced body fluid retention may be one of the elements responsible for PRDQT development. It is critical to explain the probability of PRDQT occurrence in women with certain gestational risk factors during prenatal evaluation.

Underlying RA was identified as a comorbid risk factor for PRDQT in this study. Previous epidemiologic study about DQT has shown that the RA is an independent risk factors with adjusted odds ratio as 1.53.[19] Interestingly, some prior studies have shown that women with RA had lower disease activity during their pregnancy or breastfeeding.[20-22] According to one observational cohort study, most women with RA improved significantly during pregnancy.[20] Another laboratory study on the cytokines in pregnant women with RA found that anti-inflammatory cytokines increased during pregnancy and decreased after delivery.[21] Another epidemiologic study based on a community-based registry found that women who breastfed for a longer period of time had a

significantly lower risk of developing RA.[22] These prior findings indicating improvement in RA during pregnancy and breastfeeding seem to be contradictory with the findings of this study, which indicate that pregnant women with underlying RA are more likely to develop PRDQT. Nevertheless, given that a paucity of inflammatory process was detected in previous histologic researches on DQT, it could be hypothesized that underlying RA-related inflammatory responses caused a narrowing of fibro-osseous tunnel, thereby increasing susceptibility to stenosing tenosynovitis of APL and EPB tendons regardless of the current inflammatory state.[15,23] Unlike RA, the multivariate analysis established that DM was not a risk factor for PRDQT in this study. However, prior epidemiologic research on DQT has demonstrated that DM is a risk factor.[19] These epidemiological distinctions regarding comorbidity between PRDQT and DQT may provide insight into the different pathogenesis of these two conditions.

There are several limitations to this study. To begin, the incidence of PRDQT was estimated by calculating the cumulative incidence, not the incidence rate in this study. Because the time period of observation is not considered when calculating the cumulative incidence, it cannot be interpreted as indicating the actual risk of a new disease occurrence at any given time, but

rather representing an approximate proportion of occurrence. Second, considering the ease accessibility of medical services in Korea, this study estimated the incidence based on the assumption that patients with PRDQT would seek medical services for their radial side wrist pain at least once during their pregnant or postpartum period. Nonetheless, given that pregnant or lactating women are generally reluctant to medications or injections, those who with milder symptoms might avoid seeking medical services, which could lead to underestimate the incidence of PRDQT. Third, because we included only pregnant women who delivered babies, those who terminated their pregnancy prior to delivery via abortion or stillbirth were excluded, which may have influenced the results. Fourth, DQT was clinically diagnosed by a variety of clinicians across the country. Although DQT could be easily diagnosed based on symptoms and simple physical examinations such as the Finkelstein test, less experienced clinicians might have difficulty differentiating DQT from other conditions such as thumb carpometacarpal or scaphotrapeziotrapezoidal joint osteoarthritis or intersection syndrome, all of which can cause radial wrist pain.1) Finally, claim data, which was originally intended to be used to obtain government reimbursement, has an inherent limitation. Data that are unnecessary for reimbursement, such as occupation, hand

dominance, and breastfeeding status, could not be identified in our data source.

Conclusion

Between 2013 and 2017, the cumulative incidence of PRDQT was approximately 2.1% in Korea. Age ≥ 30, multiple gestation, cesarean section delivery, hypertensive disorders in pregnancy, and underlying RA were identified as significant risk factors for PRDQT occurrence. The findings of this study could serve as a reference for clinicians seeking to consult patients with PRDQT or to predict its occurrence in pregnant women with certain risk factors, as well as for government health care administrators developing national public health strategies and distributing national health resources. Moreover, further research on identified risk factors in this study may provide clues to identify etiology and pathophysiology. Future study examining more risk factors in a larger study population recruited over a longer period of time is anticipated to enhance our understanding of not only PRDQT, but also DQT itself.

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국문 초록

연구 배경: 임신 중이거나 수유 중인 여성에서 드퀘르벵 병이 호발한다고 알려져 있지만, 이에 대한 역학적 연구 결과는 아직 없는 상태이다. 본 연구에서는 대한민국 국민건강보험 데이터베이스를 이용하여 임신과 관련된 드퀘르벵 병의 전국적인 발생률을 파악하고, 위험 요인을 분석하고자 하였다.

대상 및 방법: 2013년부터 2017년까지의 국민건강보험 청구 데이터 상에서 확인된 대한민국의 총 임산부를 대상으로 후향적인 분석을 시행하였다. 총 임산부 중에서 임신 기간 또는 산후 1년의 기간 동안 드퀘르벵 병의 진단 코드 하에 청구가 시행된 임산부를 확인하여 누적 발생률을 확인하였다. 다변량 로지스틱 회귀 분석을 사용하여 나이, 임신 유형, 분만 방법, 임신 합병증, 동반 질환에 관련된 위험 요인을 분석하였다.

결과: 2013년과 2017년 사이에 총 1,601,501명의 임산부 중 34,342명의 임신과 관련된 드퀘르벵 병으로 청구가 된 것으로 확인되었으며, 누적 발생률은 대략 2.1%로 계산할 수 있었다. 30세 이상의 나이, 다태아 임신, 제왕절개 분만, 고혈압성 임신 합병증, 기저 류마티스 관절염은 임신과 관련된 드퀘르벵 병 발병의 위험을 증가시키지만 당뇨병성 임신 합병증, 기저 당뇨병은 관계없는 것으로 드러났다.

결론: 대한민국에서 임신과 관련된 드퀘르벵 병은 100명의 임산부 당 약 2.1명의 비율로 발생하는 것으로 밝혀졌다. 본 연구에서 확인된 발생률과 위험 인자는 산모들에 대한 상담이나 발병 예측에 이용할 수 있으

며, 나아가서 국가 보건 정책 개발에도 활용할 수 있을 것이다.

색인 단어: 손목 관절; 건초염; 드퀘르벵 병; 임신 합병증; 역학

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