



# Pregnancy Morbidities in Korean Patients with Takayasu Arteritis: A Monocentric Pilot Study

Jung Yoon Pyo<sup>1</sup>, Jason Jungsik Song<sup>1,2</sup>, Yong-Beom Park<sup>1,2</sup>, and Sang-Won Lee<sup>1,2</sup>

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul;

<sup>2</sup>Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Korea.

We investigated pregnancy morbidities in Korean patients with Takayasu arteritis (TA) in a single tertiary hospital as a pilot study. We retrospectively reviewed the medical records of 12 pregnancies in seven patients with TA. All patients were diagnosed with TA based on the 1990 American College of Rheumatology classification criteria. The medical records of patients were well-documented, allowing review of clinical data including pregnancy morbidities. The angiographic and Ishikawa classifications at diagnosis and TA activity at delivery were assessed. Of the 12 pregnancies, two pregnancies ended in spontaneous abortion (16.7%), and one pregnancy (8.3%) had therapeutic abortion at 9 weeks due to maternal morbidity. Among the remaining nine pregnancies, only one child was delivered via normal spontaneous vaginal delivery, and the remaining eight were delivered by Caesarean section. Two out of nine (22.2%) neonates were born with low birth weight, and one of them was born at 30 weeks of gestation. The most common maternal complication was hypertension affecting 7/12 (58.3%) pregnancies. Preeclampsia occurred in one pregnancy, and gestational diabetes mellitus (GDM) occurred in two pregnancies. At delivery, disease activity of TA was stable in all pregnancies, and glucocorticoids were administered in nine pregnancies. Live birth rate of pregnant Korean patients with TA was 75%. Future studies are needed to reduce pregnancy-related complications.

**Key Words:** Arteritis, morbidity, pregnancy, vasculitis

Takayasu arteritis (TA) is a rare chronic vasculitis that affects the large-sized vessels, such as the aorta and its major branches, coronary arteries, and pulmonary arteries. In 1908, the first case of TA was reported in a 21-year-old woman with retinal arteriovenous anastomoses and absence of pulse on the upper extremity.<sup>1</sup> TA is currently classified based on the American College of Rheumatology (ACR) 1990 criteria (1990 ACR criteria), which include the following six items: 1) age  $\leq$ 40 years at disease onset, 2) claudication of the extremities, 3) decreased pulsation of one or both brachial arteries, 4) difference of at least

10 mm Hg in systolic blood pressure between the arms, 5) bruit over one or both subclavian arteries or the abdominal aorta, and 6) arteriographic narrowing or occlusion of the entire aorta, its primary branches or large arteries in the proximal upper or lower extremities, excluding arteriosclerosis, fibromuscular dysplasia, or other causes. If more than three of these six items are met, a patient can be classified as TA.<sup>2</sup>

TA often occurs in young women, and most patients are classified before the age of 40 years.<sup>3,4</sup> Hence, concerns over pregnancy morbidities, which may be induced by either TA itself or medications for its treatment, or both in patients with TA of the childbearing age, have been raised. In clinical practice, pregnancy morbidities, such as spontaneous abortion, intrauterine growth restriction (IUGR), preeclampsia or eclampsia, gestational diabetes mellitus (GDM), and preterm birth, have been reported in patients with TA.<sup>5</sup> However, it remains unclear whether the rate and severity of pregnancy morbidities in patients with TA are higher than that of the general population.<sup>6-8</sup> Korea is one of the countries with the highest prevalence of TA worldwide.<sup>9</sup> However, to date, no study has evaluated pregnancy morbidities of TA in Korea. Therefore, we investigated pregnancy mor-

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**Corresponding author:** Sang-Won Lee, MD, PhD, Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.

Tel: 82-2-2228-1984, Fax: 82-2-393-6884, E-mail: sangwonlee@yuhs.ac

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bidities in the Korean patients with TA in a single tertiary hospital as a pilot study.

We retrospectively reviewed the medical records of 58 pregnancies in 37 patients with TA. We excluded 46 pregnancies due to lack of delivery data, such as gestational age. Finally, 12 pregnancies in seven patients with TA were included in this study. All patients fulfilled the 1990 ACR criteria<sup>2</sup> and were classified as TA at the Rheumatology Division of Yonsei University College of Medicine, Severance Hospital between January 1995 and December 2017. The medical records of all patients were well-documented, allowing to collect and review clinical and laboratory data and medical histories, particularly pregnancy morbidities. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2019-0699), and the need for written informed consent was waived by the approving IRB due to the retrospective nature of this study.

The angiographic classification of TA was defined based on the new classification proposed by Hata, et al.<sup>10</sup> in 1996: Type I involves branches from aortic arch; Type IIa involves ascending aorta, aortic arch, and its branches; Type IIb involves ascending aorta, aortic arch, and thoracic descending aorta; Type III affects thoracic aorta, abdominal aorta, and/or renal arteries; Type IV affects only the abdominal aorta and/or renal arteries; and Type V involves combined features. The Ishikawa's<sup>11</sup> classification of TA was also applied to patients with TA based on Ishikawa's severity criteria, which include the following three groups: Group 1 (patients with no complications), Group 2 (patients with one of following complications: Takayasu retinopathy, secondary hypertension, aortic regurgitation, or aortic or arterial aneurysm); Group 2 was subdivided into class 2a and 2b by severity, and Group 3 (patients with two or more complications listed above).

Active disease was defined as a state with the new onset of two or more of the following features: 1) systemic features, such as fever or myalgia; 2) elevation of erythrocyte sedimentation rate or C-reactive protein level; 3) features of vascular ischemia or inflammation, such as claudication of extremities, diminished pulse, bruits, vascular pain, or asymmetric blood pressure; and 4) new vascular lesion(s) on imaging studies.<sup>12</sup> Stable disease was defined as a state without the abovementioned features.

In this study, spontaneous abortion, therapeutic abortion, and fetal and maternal complications, such as preterm birth, IUGR, congenital anomaly, neonatal intensive care unit admission, preeclampsia or eclampsia, gestational hypertension, GDM, were considered as pregnancy morbidities.<sup>6</sup>

Continuous variables are presented as medians with interquartile ranges, and categorical variables are presented as numbers with percentages. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 25 for Windows (IBM Corp., Armonk, NY, USA).

The median age at diagnosis of seven patients with TA was 27.0 years, and that at the time of delivery of 12 pregnancies was 32.0 years. Initial presentation, arterial involvement, angi-

ographic and Ishikawa classification are shown in Table 1. The most frequently affected vessel was the common carotid artery (71.4%), followed by descending aorta (57.1%). All but one patients were diagnosed with TA before conception. All except one patient, who was diagnosed with TA after delivery, had stable disease activity at delivery. Glucocorticoids were maintained throughout the pregnancies in nine out of 12 cases with the daily dose within 10 mg per day (prednisolone equivalent). Immunosuppressive agents, such as azathioprine and methotrexate, were used in eight out of 12 cases before conception,

**Table 1.** Disease Characteristics of 7 Patients at the Diagnosis of TA and 12 Cases of Pregnancies

Variables	Values
Seven patients with TA	
Ages at diagnosis (yr)	27.0 (13.0)
Clinical features at diagnosis	
Bruit (subclavian or aorta)	5 (71.4)
Blood pressure difference >10 mm Hg	4 (57.1)
Decreased brachial pulse	1 (14.3)
Claudication	0 (0)
Involved vessels at diagnosis	
Common carotid artery	5 (71.4)
Descending aorta	4 (57.1)
Subclavian artery	2 (28.6)
Ascending aorta	2 (28.6)
Aortic arch	2 (28.6)
Abdominal aorta	2 (28.6)
Renal artery	2 (28.6)
Iliac artery	0 (0)
Pulmonary artery	1 (14.3)
Angiographic classification at diagnosis	
I	2 (28.6)
IIa	0 (0)
IIb	2 (28.6)
III	1 (14.3)
IV	0 (0)
V	2 (28.6)
Ishikawa classification at diagnosis	
1	1 (14.3)
2a	5 (71.4)
2b	0 (0)
3	1 (14.3)
Twelve pregnancies	
Age of delivery	32.0 (12.0)
Maternal age >35 years at delivery	5 (41.7)
Assisted by reproductive technology	0 (0)
Previous abortion history	
Spontaneous abortion	2 (16.7)
Induced abortion	2 (16.7)

TA, Takayasu arteritis.

Values are expressed as a median (interquartile range) or n (%).

but withheld while planning pregnancy.

Of the 12 pregnancies, nine neonates were delivered alive; two pregnancies ended in spontaneous abortion (16.7%) at 4 and 9 weeks of gestation, and one pregnancy (8.3%) underwent therapeutic abortion at 9 weeks of gestation due to maternal morbidity (Table 2 and 3). No antiphospholipid-related antibodies were detected in the patients experiencing spontaneous abortion.

Of the nine live neonates, the median gestational age at delivery was 38 weeks, and the median birth weight was 3060 g. Among them, preterm birth before 37 weeks of gestation occurred in one (11.1%). Three pregnancy morbidities occurred. One pregnancy developed GDM and preeclampsia, and the baby was born at 38 weeks of gestation with birth weight of 2200 g due to IUGR. Another pregnancy developed GMD, but delivered normal weight baby. The other pregnancy resulted in premature labor, and underwent emergency caesarean section at 30 weeks of gestation. That baby was born with birth weight of 1240 g. Only one child (11.1%) was delivered via normal spontaneous vaginal delivery, and the remaining eight (88.9%) were delivered by Caesarean section.

Six out of 12 cases of pregnancy (50%) had underlying hypertension before pregnancy, which was assumed to be related to TA. Among them, maternal blood pressure in one pregnancy was poorly controlled at delivery, but there were no maternal/fetal complications.

**Table 2.** Pregnancy Outcome of TA

Pregnancy outcome	Values
Total pregnancies	12
Live births	9 (75.0)
Gestational age at delivery (weeks)	38.0 (13.0)
C/sec	8 (88.9)
NSVD	1 (11.1)
Spontaneous abortion	2 (16.7)
Termination of pregnancy	1 (8.3)
Fetal outcome	
Birth weight (g)	3060 (260)
Preterm birth <37 weeks gestation	1/9 (11.1)
Intrauterine fetal demise	0
Small for gestational age	1/9 (11.1)
Congenital anomaly	0 (0)
Fetal NICU admission	2 (16.7)
Neonatal death	0 (0)
Maternal complications	
Preeclampsia	1 (8.3)
Gestational hypertension	0 (0)
Gestational diabetes	2 (16.7)
Pregestational diabetes	1 (8.3)
Thyroid diseases	0

TA, Takayasu arteritis; C/sec, Caesarean section; NSVD, normal spontaneous vaginal delivery; NICU, neonatal intensive care unit. Values are expressed as a median (interquartile range) or n (%).

**Table 3.** Detailed Pregnancy Outcomes of 12 Pregnancies in 7 Patients with TA

Patient	Age at delivery	Gestational age at delivery (or abortion)	Mode of delivery	Live birth	Birth weight (kg)	Pregnancy-morbidities	Angiographic classification	Ishikawa classification	Disease activity of TA	Daily dose of glucocorticoid during pregnancy*	Underlying comorbidities
1-A	35	40 weeks	C/sec	Yes	3.24	No	III	2a	Stable	10 mg	Hypertension
1-B	38	39 weeks	C/sec	Yes	3.41	No	III	2a	Stable	10 mg	Hypertension
2-A	26	38 weeks	C/sec	Yes	2.20	GR, GDM, Pre-eclampsia	I	2a	Diagnosis after delivery	0 mg	
2-B	28	(9 weeks)	N/A	No	N/A	Therapeutic abortion	I	2a	Stable	0 mg	Hypertension, diabetes
3-A	31	40 weeks	C/sec	Yes	2.90	No	IIb	2a	Stable	2.5 mg	Hypertension
4-A	35	38 weeks	C/sec	Yes	3.16	GDM	V	3	Stable	5 mg	Aortic aneurysm
5-A	25	30 weeks	C/sec	Yes	1.24	Preterm birth	IIb	1	Stable	2.5 mg	
5-B	27	38 weeks	C/sec	Yes	2.93	No	IIb	1	Stable	2.5 mg	
6-A	35	(9 weeks)	N/A	No	N/A	Abortion	I	2a	Stable	5 mg	Retinopathy
6-B	36	37 weeks	NSVD	Yes	3.09	No	I	2a	Stable	5 mg	Retinopathy
7-A	26	(4 weeks)	N/A	No	N/A	Abortion	V	2a	Stable	1 mg	Hypertension
7-B	33	38 weeks	C/sec	Yes	3.06	No	V	2a	Stable	0 mg	Hypertension

TA, Takayasu arteritis; C/sec, Caesarean section; NSVD, normal spontaneous vaginal delivery; GR, growth restriction; GDM, gestational diabetes mellitus; N/A, not applicable. \*Prednisolone equivalent dose.

Among the eight cases of Caesarean section, only one case was planned for the surgery due to disease of the circulatory system associated with TA. Other indications for Caesarean section included advanced maternal age (2/8), arrest of descent (1/8), minimal variability of fetal heart rate (1/8), prior cesarean section (1/8), and unknown (2/8). Table 3 shows pregnancy outcomes for each of the 12 pregnancies in seven patients with TA, and Table 4 summarizes previous published reports and compares data with the current data.

To our knowledge, this is the first study to assess pregnancy morbidities in Korean patients with TA. In this study, successful delivery was observed in nine of 12 pregnancies (75.0%) in a total of seven patients with TA. Three pregnancies had pregnancy morbidity: one pregnancy had preeclampsia, GDM, and IUGR; the other had GDM; and the last one was born prematurely.

Disease activity of TA remained stable at the time of delivery in all patients in our study. This observation was supported by a study demonstrating the influence of pregnancy on TA, which showed improving inflammatory markers during pregnancy in TA patients.<sup>13</sup> Nonetheless, pregnancy morbidities were higher compared to the general population in Korea. We looked at the factors that caused this observation. First, we reviewed the angiographic classification. There were four pregnancies in angiographic classification Type I, three pregnancies in Type IIb, two pregnancies in Type III, and three pregnancies in Type V. Among pregnancies with Type I, two cases resulted in abortion (either therapeutic or spontaneous); one pregnancy was complicated with GDM, preeclampsia, and IUGR; and the other pregnancy resulted in normal delivery without complication. Among pregnancies with Type IIb, one pregnancy resulted in preterm birth, and the other two pregnancies resulted in normal delivery. Two pregnancies with Type III ended without complication; and among two Type V pregnancies, one pregnancy ended in spontaneous abortion, but the other pregnancy

resulted in normal delivery. However, we could not conclude that Types I and V TA might be associated with pregnancy morbidities due to the small number of pregnancies in this study. Furthermore, we had assumed that the risk of gestational hypertension or preeclampsia may be theoretically increased in Types III, IV, and V TA, as renal arterial involvement in TA could increase the risk of renovascular hypertension; however, in our patients, preeclampsia was observed in only one patient with Type I TA. The absence of patients with Type IV TA made the interpretation of this association difficult. Second, the possibility of association between the Ishikawa classification of TA with pregnancy morbidities was assessed. There were two pregnancies with Ishikawa Type 1; one pregnancy ended in preterm birth, but the other resulted in normal delivery. There were nine pregnancies with Ishikawa classification Type 2a; and among them, three pregnancies ended in abortion (either therapeutic or spontaneous), and one pregnancy had pregnancy morbidity (GDM, preeclampsia, and IUGR). Remaining five pregnancies with Type 2a resulted in normal delivery. One pregnancy with Type 3 was complicated with GDM, but delivered normal weight neonate. Therefore, although the clinical significance is not strong, we suggest that attention should be paid to patients with Types I and V and Ishikawa Groups 2 and 3 TA. Lastly, the disease activity of TA remained stable at the time of delivery in all patients. This suggests two things. First, maintaining stable TA through proper steroid administration would not have resulted in serious complications, such as maternal death or TA aggravation. Second, the disease courses of TA, including established arterial stenosis or aneurysm, did not seem to directly affect pregnancy morbidities. Therefore, we suggest that physicians should not be negative for steroid use and should make efforts to maintain low TA activity during pregnancy.

We searched for previous studies investigating the pregnan-

**Table 4.** Comparison of Pregnancy-Related Morbidities among the Previous and Present Studies

Reference number (year)	Countries	Time of pregnancy based on diagnosis	Number of patients	Number of pregnancy	Age at pregnancy	Live birth [n, (%)]	Pregnancy morbidities (%)
14 (2010)	India	After diagnosis	15	37	27.6 (4.7)*	25 (67.6)	GR (16.2), preterm birth (16.2), preeclampsia (59.5)
7 (2012)	Japan	After diagnosis	10	26	30.0 (6.0)	18 (69.2)	GR (7.7), preterm birth (7.7)
15 (2015)	Brazil	Before diagnosis After diagnosis	89	118 38	25.1 (5.2)*	101 (85.6) 35 (92.1)	GR (16.8), preterm birth (11.9), eclampsia (2.5) GR (34.2), preterm birth (45.7)
6 (2015)	France	After diagnosis	52	98	27.0 (7.0)	86 (87.8)	GR (5.1), preterm birth (8.2)
16 (2017)	China	After diagnosis	13	13	29.0 (5.0)	11 (84.6)	GR (15.4 preterm birth (15.4), preeclampsia (15.4)
17 (2017)	Norway	Before diagnosis After diagnosis	33 23	73 37	25.7 (4.6)* 29.4 (4.0)*	51 (69.9) 25 (67.6)	Preeclampsia (9.1) Preeclampsia (4.3), eclampsia (4.3)
18 (2019)	Turkey	After diagnosis	11	22	31.0 (7.0)	16 (72.7)	GR (13.6), preterm birth (18.2)
Present study (N/A)	Korea	After diagnosis except for one	7	12	32.0 (12.0)	9 (75.0)	GR (8.3), preterm birth (8.3), preeclampsia (8.3), GDM (16.6)

GR, growth restriction; GDM, gestational diabetes mellitus.

Age at pregnancy are expressed as median (interquartile range) or \*mean (standard deviation).

cy outcomes in patients with TA, and summarized their findings in Table 4.<sup>6,7,14-18</sup> The median maternal age in this study was 32.0 years, which was higher than the median or mean maternal ages in the previous studies (range: 25.1 to 31.0 years). Although our results are limited by the small sample size of this study, it could be explained by the socioeconomic aspect considering that the mean age of conception was the highest in Korea among the Organization for Economic Cooperation and Development (OECD) nations.<sup>19</sup> In this study, the live birth rate of all pregnancies was 75%, which was not significantly higher than that in previous studies. The highest age at conception of Korean patients may partially explain this result. However, it may be impossible to directly compare pregnancy morbidities between this study and the previous ones, due to varying study methods and medical services of different countries.

Our study had several limitations. The number of pregnancies in this study was too small to represent pregnancy morbidities in all Korean patients with TA. In particular, the retrospective design of this study resulted in a small number of available pregnancies due to missing data on the pregnancy and delivery outcomes in a considerable number of patients with TA. However, this is this first study to investigate pregnancy morbidities in Korean patients with TA. Since Korea is one of the countries with the highest prevalence of TA worldwide, it may be meaningful to describe and provide ethnic information on pregnancy morbidities in patients with TA in Korea as a pilot study. Therefore, a future study with a larger number of patients with TA may provide reliable information. In conclusion, the live birth rate of Korean patients with TA was 75%. Pregnancy morbidities might be associated with the angiographic and Ishikawa classifications of TA, but further studies are needed for confirmation. Maintaining stable disease during pregnancy might be important to prevent serious maternal complications or TA progression.

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## AUTHOR CONTRIBUTIONS

**Conceptualization:** all authors. **Data curation:** Jung Yoon Pyo. **Formal analysis:** Jung Yoon Pyo and Sang-Won Lee. **Funding acquisition:** Sang-Won Lee. **Investigation:** Jung Yoon Pyo and Sang-Won Lee. **Methodology:** Jason Jungsik Song and Yong-Beom Park. **Project administration:** Sang-Won Lee. **Resources:** Jung Yoon Pyo and Sang-Won Lee. **Software:** Jung Yoon Pyo. **Supervision:** Jason Jungsik Song and Yong-Beom Park. **Validation:** Jason Jungsik Song and Yong-Beom

**Park. Visualization:** Jung Yoon Pyo and Sang-Won Lee. **Writing—original draft:** Jung Yoon Pyo. **Writing—review & editing:** Sang-Won Lee. **Approval of final manuscript:** all authors.

## ORCID iDs

Jung Yoon Pyo <https://orcid.org/0000-0002-1866-6885>  
 Jason Jungsik Song <https://orcid.org/0000-0003-0662-7704>  
 Yong-Beom Park <https://orcid.org/0000-0003-4695-8620>  
 Sang-Won Lee <https://orcid.org/0000-0002-8038-3341>

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