Maternal and Neonatal Outcomes in 89 Patients with Takayasu Arteritis (TA): Comparison Before and After the TA Diagnosis

Ana Paula Luppino Assad, Thiago Ferreira da Silva, Eloisa Bonfa, and Rosa Maria R. Pereira

ABSTRACT. ***Objective.*** To evaluate maternal and neonatal outcomes in patients before and after a diagnosis of Takayasu arteritis (TA).

Methods. Patients diagnosed with TA according to the American College of Rheumatology criteria were selected from the Vasculitis Outpatient Clinic of the Rheumatology Division. Healthy female staff members of this hospital of similar age and educational level were selected as the controls. The disease data were obtained from an ongoing electronic database protocol. A standardized questionnaire, emphasizing gestational history, was applied to both groups. The prevalence of fetomaternal complications and disease variables were evaluated between the groups and a statistical analysis was performed.

Results. A total of 89 patients with TA (156 pregnancies) and 89 healthy controls (181 pregnancies) were evaluated. There were 75.6% pregnancies that occurred before the TA diagnosis (pre-TA group) and 24.3% after (post-TA group). In the pre-TA group, higher rates of hypertension (HTN; 27.1% vs 3.9%, $p < 0.001$), low birth weight (16.8% vs 6.5%, $p = 0.012$), and perinatal mortality (7.9% vs 0.7%, $p = 0.003$) were observed compared with healthy controls. The frequency of abortions and the average number of children were similar in both groups ($p > 0.05$). Further comparison of the pre- and post-TA groups revealed similar rates of HTN, abortion, and low birth weight, and higher rates of Cesarean delivery ($p = 0.002$), prematurity ($p < 0.001$), and infection ($p = 0.045$) in the latter group.

Conclusion. Our study identified that patients with TA, even before the disease diagnosis, have a worse fetal outcome that is most likely associated with high rates of HTN. TA was identified as an additional differential diagnosis for HTN in pregnancy. (J Rheumatol First Release September 1 2015; doi:10.3899/jrheum.150030)

Key Indexing Terms:
TAKAYASU ARTERITIS PREGNANCY FETOMATERNAL OUTCOMES

Takayasu arteritis (TA) is a chronic inflammatory arteriopathy of the aorta and its major branches that leads to stenotic and occlusion changes[1,2,3,4,5]. The mean age of TA presentation is typically in the second and third decades of life[5,6,7,8]. Fertility and pregnancy outcomes associated with vasculitis have become a major topic of interest within the past decade[6]. Particularly with women with TA, at least 1 or more pregnancy events would be expected, considering the age associated with TA prevalence and the improvements in the survival and quality of life of these patients[5,6,7,8].

From the Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

A.L. Assad, MD, Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo; T.F. da Silva, MD, PhD, Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo; E. Bonfa, MD, PhD, Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo; R.M. Pereira, MD, PhD, Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo.

Address correspondence to Dr. A.P. Assad, Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo, Av. Dr. Arnaldo, 455, Cerqueira César, São Paulo, São Paulo, sp 01246-903, Brazil. E-mail: anastoamaro@yahoo.com.br, rosamariarp@yahoo.com

Accepted for publication June 22, 2015.

TA pregnancies were associated with maternal complications, such as sustained hypertension (HTN), superimposed preeclampsia, congestive heart failure, and progression of renal involvement, as well as an increased likelihood of low birth weight[5–15,16,17,18,19,20,21]. The reported unfavorable maternal and fetal outcomes were predominantly related to HTN complications[5–15,16,17,18,19]; however, most studies had a small sample size[8,9,10,11,12,13,14,17] and did not include a control population[8,10,11,12,13, 14,15,16,17,18].

The delay in the diagnosis of TA is very common[16,22,23,24], so women are subject to conceive without knowing the diagnosis of TA and without a regular specific treatment. The treatment of the disease can either positively or negatively influence pregnancy outcomes. More favorable outcomes are expected in patients with disease control, but adverse effects of the drugs used could influence the final outcome. So it is reasonable to think that the analysis of pregnancies that occurred before the TA diagnosis can help to identify the possible deleterious effects of the disease and of the therapy.

The purpose of our study was to evaluate the maternal and neonatal outcomes in patients with TA before and after the disease diagnosis in a single tertiary care center.

MATERIALS AND METHODS

Patients. A cohort study was conducted including all patients diagnosed with TA according to the American College of Rheumatology criteria[25], who were followed at the Vasculitis Outpatient Clinic of the Rheumatology Division of Hospital das Clínicas, University of São Paulo, from 2010 to 2012. Exclusion criteria were male sex, other concomitant vasculitis, and loss of followup. Eighty-nine patients were interviewed, and 156 pregnancies were identified. The date of TA diagnosis was defined and patients were divided into 2 groups: (1) the pre-TA group — pregnancies that occurred before TA diagnosis date, and (2) the post-TA group — pregnancies that occurred during or after the TA diagnosis date.

Controls. Eighty-nine healthy women with similar age and educational level were selected as the controls, providing 181 pregnancies for comparative analysis. These women were selected from the staff members of the Hospital das Clínicas.

Protocol. Retrospective data regarding the disease- and pregnancy-related events of these women were collected.

The disease data were obtained by a retrospective chart review from an ongoing electronic database protocol established in January 2000 that was applied to all the patients at 1-month to 6-month intervals and consisted of a clinical and laboratory evaluation. The diagnosis criteria, the angiographic data, and treatment were analyzed. All patients followed up at our service had at least 1 angiography performed, allowing the classification of the extension of the disease into the 5 subtypes devised by Hata, *et al*[26]: Type 1 affects the aortic arch branches; Type 2A, the ascending aorta, aortic arch, and its branches; Type 2B, similar to Type 2A, including the thoracic aorta; Type 3, thoracic aorta, abdominal aorta, and/or renal arteries; Type 4, abdominal aorta and/or renal arteries; and Type 5, a combination of Type 2B and Type 4.

In addition, at study entry, a standardized questionnaire was provided to all patients and controls to assess the general characteristics of the subjects (age, gestational age, and parity). The questionnaire was applied during the outpatient clinical visit or by phone. The maternal outcomes and the history of obstetric complications were based on the information provided by the patient, according to the questions applied. We asked about previous diagnosis of arterial HTN, eclampsia, infection, renal and cardiac failure, and other symptoms suggestive of TA (fever, syncope, claudication, carotidynia, erythema nodosum, and arthritis). Also, a part of the questionnaire was on the mode of delivery (vaginal or cesarean delivery), spontaneous abortion (defined as ones that occurred before the 12th week of gestation), and specific information about the fetal outcomes: birth weight (low birth weight being defined as 2500 g or less), prematurity (defined as birth before 37 weeks of gestation), and perinatal mortality (defined as deaths occurring from the 28th week of gestation to the seventh day after birth)[27].

Our study was approved by the local ethics committee (Comissão de Ética para Análise de Projetos de Pesquisa do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo), and all the subjects provided written informed consent.

Statistical analysis. The results are presented as the mean (SD) or as a percentage. The percentage of nulliparity was calculated among all the interviewed patients and controls. The complication, HTN, and abortion rates were calculated among the total number of pregnancies. The number of live births was calculated by subtracting the number of abortions from the total pregnancies in each group. The percentages of prematurity, low birth weight, and perinatal mortality were calculated among the number of live births. The data were analyzed by the Student t test, Mann-Whitney U test, or Fisher's exact test to determine the differences between the groups. P values < 0.05 were considered statistically significant.

RESULTS

Analysis of all patients with TA and healthy controls. The general data of the patients with TA and controls are presented in Table 1. The average time to TA diagnosis was 12.8 years (SD 8.8) after pregnancy, and 4 patients (3.4%) received the diagnosis during the gestation. The angiographic classification according to the Hata criteria[26] was Class V in 59 cases (66.3%), Class IV in 3 cases (3.4%), Class III in 3 cases (3.4%), Class II in 13 cases (14.6%), and Class I in 11 cases (12.3%). The renal and mesenteric arteries were involved in 40.4% and 26.9% of the patients with TA, respectively.

Table 1. General data of patients with TA and healthy controls. Values are mean (SD) unless otherwise specified.

Characteristics	Patients with TA, n = 89	Healthy Controls, n = 89	p
Age, yrs	41.7 (12.5)	41.2 (13.1)	0.815
Pregnancy age, yrs	25.1 (5.2)	25.3 (6.7)	0.787
Educational level, %			
> 11 yrs	8.9	16.9	0.179
9–11 yrs	30.3	33.7	0.748
4–9 yrs	13.4	4.5	0.064
< 4 yrs	11.2	11.2	1.000
Pregnancies, n	156	181	1.000
Pre-TA diagnosis	118	NA	
Post-TA diagnosis	38	NA	
Nulliparity, n	24	19	0.484

TA: Takayasu arteritis; NA: not applicable.

Analysis of pregnancies in the pre-TA group.

(1) Pregnancies in pre-TA group versus pregnancies in healthy controls (Table 2). Cesarean delivery was more frequent in the control group (p = 0.021). Complications were more frequent in the patients with pre-TA than in the controls (p < 0.001), with a higher frequency of HTN (p < 0.001), low birth weight infants (p = 0.012), and perinatal mortality (p = 0.003).

(2) Influence of HTN on outcomes (Table 3). In the pre-TA group, the cesarean rate (p = 0.003), prematurity (p = 0.016), and low birth weight (p = 0.019) were more frequent in the patients with HTN; however, abortion occurred more frequently in the group without arterial HTN (p = 0.006).

(3) Analysis of the pregnancies in the pre-TA versus in the

Table 2. Comparison between pregnancy outcomes in the pre-TA group and healthy controls. Values are n (%) unless otherwise specified.

Variables	Pre-TA Group, 118 Pregnancies	Healthy Controls, 181 Pregnancies	p
Live births	101 (85.6)	153 (84.5)	0.869
Cesarean rate	40 (39.6)	84 (54.9)	0.021
Complications	65 (55.1)	54 (29.8)	< 0.001
Hypertension	32 (27.1)	7 (3.9)	< 0.001
Eclampsia	3 (2.5)	1 (0.6)	0.334
Infections*	1 (0.8)	7 (3.9)	0.153
Abortion	17 (14.4)	28 (15.5)	0.869
Prematurity	12 (11.9)	17 (11.1)	0.843
Low birth weight	17 (16.8)	10 (6.5)	0.012
Perinatal mortality	8 (7.9)	1 (0.6)	0.003

* Urinary tract. TA: Takayasu arteritis.

Table 3. Comparison between the pregnancy outcomes in the pre-TA group with or without arterial HTN. Values are n (%) unless otherwise specified.

Variables	With Arterial HTN, 32 Pregnancies	Without Arterial HTN, 86 Pregnancies	p
Cesarean rate	18 (56.2)	24 (31.9)	0.003
Abortion	0	17 (19.8)	0.006
Prematurity	8 (25)	4 (5.7)	0.016
Low birth weight	10 (31.2)	7 (10.2)	0.019
Perinatal mortality	1 (3.1)	7 (10.1)	0.432

TA: Takayasu arteritis; HTN: hypertension.

post-TA group (Table 4). Comparable frequencies were found of HTN (p = 0.091), eclampsia (p = 1.000), abortion (p = 0.407), low birth weight infants (p = 0.053), perinatal mortality (p = 0.113), and symptoms suggestive of TA (p = 1.000). Higher rates of cesarean delivery (p = 0.002), infection (p = 0.045), and preterm labor (p < 0.001) were observed after diagnosis.

Analysis of pregnancies in the post-TA group. The fetomaternal outcomes of this group are shown in Table 4, and a subanalysis indicated that there was no relationship between the occurrence of complications and glucocorticoid used during the pregnancy (Table 5).

No differences were observed comparing the fetomaternal outcomes in patients with arterial abdominal involvement (Hata III, IV, V) and without abdominal arterial involvement (Hata I, II).

DISCUSSION

To our knowledge, our study from a single tertiary center identified for the first time that HTN represents the most common pregnancy complication among patients with TA before diagnosis. HTN appears to account for the unexpected worse fetal outcome in these pregnancies.

Table 4. Comparison between the pregnancy outcomes in the pre-TA and post-TA groups. Values are n (%) unless otherwise specified.

Variables	Pre-TA Group, 118 Pregnancies	Post-TA Group, 38 Pregnancies	p
Live births	101 (85.6)	35 (92.1)	0.407
Cesarean rate	40 (39.6)	24 (68.5)	0.002
Complications	65 (55.1)	27 (71.1)	0.091
Hypertension	32 (27.1)	12 (31.5)	0.091
Eclampsia	3 (2.5)	0	1.000
Infections	1 (0.8)*	3 (7.8)**	0.045
Abortion	17 (14.4)	3 (7.8)	0.407
TA symptoms	7 (6.8)[#]	2 (5.2)[##]	1.000
Prematurity	12 (11.9)	16 (45.7)	< 0.001
Low birth weight	17 (16.8)	12 (34.2)	0.053
Perinatal mortality	8 (7.9)	0	0.113

* Urinary tract. ** Varicella, ganglionar tuberculosis, pulmonary, urinary tract. [#] Fever, anemia, claudication, presyncope, carotidynia. [##] Carotidynia, fever. TA: Takayasu arteritis.

Table 5. Comparison between the pregnancy outcomes in the post-TA group with and without GC use. Values are n (%) unless otherwise specified.

Variables	GC Use, 9 Pregnancies	No GC Use, 29 Pregnancies	p
Live births	9 (100)	26 (89.7)	1.00
Cesarean rate	7 (77.8)	17 (58.6)	0.438
Complications	6 (66.7)	21 (72.5)	1.00
Hypertension	2 (22.3)	10 (34.5)	0.091
Eclampsia	0	0	1.00
Infections	1 (11.2)*	3 (10.3)**	1.00
Abortion	0	3 (10.3)	1.00
TA symptoms	2 (22.3)[#]	0	0.051
Prematurity	5 (55.6)	7 (24.1)	0.108
Low birth weight	5 (55.6)	7 (24.1)	0.108
Perinatal mortality	0	0	1.00

* Varicella. ** Ganglionar tuberculosis, pulmonary, urinary tract. [#] Carotidynia, fever. TA: Takayasu arteritis; GC: glucocorticoids.

The occurrence of HTN in the pre-TA group was similar to the rate in patients with established TA diagnosis (post-TA group) and was about 7 times higher than in our healthy control group. In fact, the arterial HTN frequency in our control group was similar to the general population, about 6–8%[28]. This finding suggests that these women were already pregnant, with TA still undiagnosed.

The worst fetomaternal outcomes might be associated with HTN. The analysis of the HTN influence over other complications revealed that the prevalence of prematurity and of low birth weight was higher in the group of patients with HTN. No abortions occurred in the group of women with HTN, most likely because the abortions occurred in the first trimester and the diagnosis of HTN was more likely in the late second or third trimester, attributable to blood pressure trends during pregnancy[28].

Perinatal mortality was more frequent in the pre-TA group compared with the controls, and all of the cases between patients with TA occurred in the pre-TA group, which emphasized the relevance of an earlier TA diagnosis to more appropriate prenatal care.

The average time between pregnancy and the diagnosis of TA was 12 years, even with the high frequency of HTN, suggesting that TA is not currently among the diagnostic hypotheses investigated in hypertensive pregnant women. Physical examination could be sufficient to alert to the presence of this disease. The blood pressure discrepancy, a pulselessness of unilateral or both radial arteries, and vascular bruit should be looked at in all cases of HTN.

Despite the similarity in the complication rates between the pre-TA and post-TA groups, there was a higher frequency of cesarean deliveries, infection, and prematurity rates in the post-TA group, suggesting that these complications could be influenced by TA disease activity or treatment. We found no relation between complications and the glucocorticoid use; however, it was with a restricted number of cases in this analysis.

Although the extent of arterial involvement has been associated with a higher incidence of maternal and fetal complications (preeclampsia, preterm delivery, and low birth weight)[7,18], it was not possible to determine this association in our study, most likely because the majority of our patients had an extensive involvement, with most of the cases being Hata Class V.

We found a low frequency of disease activity, and some patients reported improvement of symptoms, suggesting that pregnancy does not exacerbate the disease course, most likely because of Th2 cytokine polarization at the fetomaternal interface, as well as at the systemic level[2,6,10,11]. The manifestations of disease flare described during pregnancy, such as renal insufficiency, retinopathy, thrombocytopenia, and other complications of aortic valve disease[6,7,8,18,29,30] were not found in our patients.

The underdiagnosis of TA leads to worse pregnancy and fetal outcome, most likely associated with high rates of HTN. TA was identified as an additional differential diagnosis for HTN in pregnancy.

REFERENCES

1. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. Circulation 1994;90:1855-60.
2. Lupi-Herrera E, Sánchez-Torres G, Marcushamer J, Mispireta J, Horwitz S, Vela JE. Takayasu's arteritis. Clinical study of 107 cases. Am Heart J 1977;93:94-103.
3. Ishikawa K. Natural history and classification of occlusive thromboaortopathy (Takayasu's disease). Circulation 1978;57:27-35.
4. "Pulmonary pulseless disease:" pulmonary involvement in so-called Takayasu's disease. Clinical Conference in Cardiology from the third medical division, Kyoto University Hospital, Kyoto, Japan. Chest 1978;73:651-7.
5. Mandal D, Mandal S, Dattaray C, Banerjee D, Ghosh P, Ghosh A, et al. Takayasu arteritis in pregnancy: an analysis from eastern India. Arch Gynecol Obstet 2012;285:567-71.
6. Pagnoux C, Mahendira D, Laskin CA. Fertility and pregnancy in vasculitis. Best Pract Res Clin Rheumatol 2013;27:79-94.
7. Gatto M, Iaccarino L, Canova M, Zen M, Nalotto L, Ramonda R, et al. Pregnancy and vasculitis: a systematic review of the literature. Autoimmun Rev 2012;11:A447-59.
8. Sharma BK, Jain S, Vasishta K. Outcome of pregnancy in Takayasu arteritis. Int J Cardiol 2000;75 Suppl 1:S159-62.
9. Tanaka H, Tanaka K, Kamiya C, Iwanaga N, Yoshimatsu J. Analysis of pregnancies in women with Takayasu arteritis: complication of Takayasu arteritis involving obstetric or cardiovascular events. J Obstet Gynaecol Res 2014;40:2031-6.
10. Hidaka N, Yamanaka Y, Fujita Y, Fukushima K, Wake N. Clinical manifestations of pregnancy in patients with Takayasu arteritis: experience from a single tertiary center. Arch Gynecol Obstet 2012;285:377-85.
11. Matsumura A, Moriwaki R, Numano F. Pregnancy in Takayasu arteritis from the view of internal medicine. Heart Vessels Suppl 1992;7:120-4.
12. Burton RM. Pulseless disease. J Obstet Gynaecol Br Commonw 1966;73:113-8.
13. Wong VC, Wang RY, Tse TF. Pregnancy and Takayasu's arteritis. Am J Med 1983;75:597-601.
14. Aso T, Abe S, Yaguchi T. Clinical gynecologic features of pregnancy in Takayasu arteritis. Heart Vessels Suppl 1992;7:125-32.
15. Ishikawa K, Matsuura S. Occlusive thromboaortopathy (Takayasu's disease) and pregnancy. Clinical course and management of 33 pregnancies and deliveries. Am J Cardiol 1982;50:1293-300.
16. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med 1994;120:919-29.
17. Ioscovich A, Gislason R, Fadeev A, Grisaru-Granovsky S, Halpern S. Peripartum anesthetic management of patients with Takayasu's arteritis: case series and review. Int J Obstet Anesth 2008;17:358-64.
18. Suri V, Aggarwal N, Keepanasseril A, Chopra S, Vijayvergiya R, Jain S. Pregnancy and Takayasu arteritis: a single centre experience from North India. J Obstet Gynaecol Res 2010;36:519-24.
19. Doria A, Iaccarino L, Ghirardello A, Briani C, Zampieri S, Tarricone E, et al. Pregnancy in rare autoimmune rheumatic diseases: UCTD, MCTD, myositis, systemic vasculitis and Behçet disease. Lupus 2004;13:690-5.
20. Papantoniou N, Katsoulis I, Papageorgiou I, Antsaklis A. Takayasu arteritis in pregnancy: safe management options in antenatal care. Case report. Fetal Diagn Ther 2007;22:449-51.
21. Gasch O, Vidaller A, Pujol R. Takayasu arteritis and pregnancy from the point of view of the internist. J Rheumatol 2009;36:1554-5.
22. de Souza AW, de Carvalho JF. Diagnostic and classification criteria of Takayasu arteritis. J Autoimmun 2014;48-49:79-83.
23. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum 2007;56:1000-9.
24. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. J Clin Pathol 2002;55:481-6.
25. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129-34.
26. Hata A, Noda M, Moriwaki R, Numano F. Angiographic findings of Takayasu arteritis: new classification. Int J Cardiol 1996;54 Suppl:S155-63.
27. Howson CP, Kinney MV, McDougall L, Lawn JE; Born Too Soon Preterm Birth Action Group. Born too soon: preterm birth matters. Reprod Health 2013;10 Suppl 1:S1.
28. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183:S1-S22.
29. Vaysse C, Touboul C, Vaysse N, Delchier MC, Vayssiere C. [In utero fetal death in pregnancy complicated by Takayasu's arteritis: case report and review]. [Article in French] J Gynecol Obstet Biol Reprod 2009;38:595-8.
30. Jacquemyn Y, Vercauteren M. Pregnancy and Takayasu's arteritis of the pulmonary artery. J Obstet Gynaecol 2005;25:63-5.