

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

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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 decade⁶. 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}.

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.

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MATERIALS AND METHODS

Patients. A cohort study was conducted including all patients diagnosed with TA according to the American College of Rheumatology criteria²⁵, 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

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.

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 criteria²⁶ 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.

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, ganglionic 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. ** Ganglionic 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 pregnancy²⁸.

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.

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