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Evaluation of obstetric outcomes in Brazilian pregnant women with Takayasu arteritis

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Abstract

Objective Takayasu arteritis (TAK) is a rare chronic granulomatous vasculitis that affects large vessels and usually begins in women of childbearing age, so it is not uncommon for pregnancies to occur in these patients. However, there is limited information about these pregnancies, with reports of adverse maternal and obstetric outcomes. The objective of this study is to evaluate adverse maternal, fetal and neonatal events in pregnant patients with TA.

Methods This is a cross-sectional study with retrospective data collection. We reviewed 22 pregnancies in 18 patients with TAK, according to the American College of Rheumatology criteria, that were followed up in a high-risk prenatal clinic specialized in systemic autoimmune diseases and thrombophilia (PrAT) at Hospital Universitário Pedro Ernesto, from 1998 to 2021.

Results In twenty-two pregnancies, the mean age of patients was 28.09 years and the mean duration disease was 10.9 years. Of the 18 patients with TAK studied, only one had the diagnosis during pregnancy and had active disease. All other patients had a previous diagnosis of TAK and only 3 had disease activity during pregnancy. Twelve patients (66.6%) had previous systemic arterial hypertension and eleven (61.1%) had renal involvement. Among maternal complications, eight patients (36.3%) developed preeclampsia and six (27.2%) had uncontrolled blood pressure without proteinuria, while 10 (45%) had puerperal complications. Four (18.1%) births were premature, all due to severe preeclampsia and eight newborns (34.7%) were small for gestational age. When all maternal and fetal/neonatal outcomes included in this study were considered, only 6 (27.2%) pregnancies were uneventful.

Conclusion Although there were no maternal deaths or pregnancy losses in this study, the number of adverse events was considerably high. Hypertensive disorders and small for gestational age newborns were more common than general population, while the number of patients with active disease was low. These findings suggest that pregnancies in patients with TAK still have several complications and a high-risk prenatal care and delivery are necessary for these patients.

Keywords Takayasu arteritis, Pregnancy outcome, High risk pregnancy, Vasculitis, Hypertension

Background

Takayasu arteritis (TAK) is a rare granulomatous chronic vasculitis that affects large arteries including the aorta and its main branches, such as carotid, subclavian, vertebral, iliac and renal arteries. The associated inflammatory process is related to the thickening of the vascular wall,

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generating stenosis, occlusion, dilatation and aneurysms with the progression of the disease.

The pathogenesis remains uncertain. Some studies have shown the existence of multiple factors involved, including immunological, genetic, infectious and hormonal [1].

Clinical manifestations depend on the affected vessel and may progress to lipothymia and vertigo if the carotid arteries are involved, limb claudication when damage occurs to subclavian and iliac arteries and arterial hypertension if the renal arteries are affected. Aortic insufficiency and congestive heart failure can also occur with the progression of the disease, leading to more severe symptoms [2]. Suggestive findings on physical examination include difference in systolic blood pressure between limbs higher than 10 mmHg, asymmetric pulses in upper extremities and vascular murmurs. Laboratory tests such as PCR and ESR, although nonspecific, reflects the inflammatory process related to the disease. Imaging studies reveal arterial thickening with lumen narrowing and occlusion [3].

It is estimated that the annual incidence is around 1.2 to 2.6/million inhabitants (10^6) and Asia holds the highest prevalence. Japan has 40 cases/10^6, while a recent study calculated the prevalence in the city of Rio de Janeiro of 16.9 cases/10^6 [4]. Most patients with TAK are female (ratio of 4 women: 1 man) in the second or third decade of life. Therefore, it predominantly affects women of childbearing age [3, 4] and reproductive health is an important issue to be considered. Most pregnancies in these patients are successful, however women diagnosed with the disease are prone to complications particularly during the peripartum period, including aggravated or recent-onset high blood pressure, preeclampsia/eclampsia, fetal growth restriction, intrauterine fetal death, prematurity, and low birth weight [5, 6]. Maternal complications such as the development of aortic aneurysm, stroke, congestive heart failure, aortic failure, acute myocardial infarction, and aortic dissection are rare but devastating events.

The objective of this study is to identify the main gestational outcomes in pregnant patients with TAK in a Brazilian cohort, describing adverse maternal, fetal and neonatal events in this population.

Methods

A cross-sectional observational study was carried out retrospectively, by reviewing medical records and collecting data of patients followed at high-risk maternal prenatal care of autoimmune diseases and thrombophilia (PrAT) at Hospital Universitário Pedro Ernesto, from 1998 to 2021. Data collection occurred from April to September of 2022 and a descriptive analysis was performed considering retrieved results.

The diagnosis of TAK was established according to the 1990 American College of Rheumatology (ACR) criteria [7] or the 1995 Ishikawa criteria modified by Sharma [8]. Ishikawa's criteria [8–11] was used for disease-related complications and disease activity was accessed according to National Institute of Health (NIH) criteria [12].

Maternal age at the beginning of prenatal care, disease duration, associated comorbidities and medications used during pregnancy were reviewed. Disease extension according to angiographic classification of Hata-Numano were also reported for each patient: subtypes- type 1, which affects branches of the aortic arch; type 2 (2a, ascending aorta, aortic arch and its branches; type 2b, the same as the previous one, including the thoracic aorta); type 3, thoracic aorta, abdominal aorta and/or renal arteries; type 4, abdominal aorta and/or renal arteries; type 5, junction of types 2b and 4 [13–15].

The analysis of obstetric and perinatal outcomes included route of delivery, gestational age and weight at birth and APGAR index. For this study, the following variables were considered as adverse maternal outcomes: worsening of pre-existing hypertension, pre-eclampsia/eclampsia, disease activity, complications during the puerperium, and additional obstetric complications (fetal death, placental abruption, HELLP syndrome).

Data from the twenty-three newborns in 22 pregnancies were also reviewed, in order to identify complications during neonatal period. Adverse fetal/neonatal outcomes were defined as: intrauterine growth restriction (IUGR—estimated fetal weight < 10th in obstetric ultrasound), premature birth (delivery before 37 weeks of gestation), small for gestational age newborn (SGA—newborn weight < 10th percentile for gestational age), neonatal intensive care unit (NICU) admission and neonatal death.

Results

During the study period, there was 22 pregnancies in 18 patients diagnosed with TAK. Two patients had two pregnancies and another patient had three pregnancies. At beginning of prenatal care, included patients had the following vascular involvement according to angiographic classification of Hata-Numano: six patients were classified as type 2 (33.3%), two being type 2a and four type 2b; three (16.6%) as type 3; two (11.1%) as type 4 and seven (38.8%) presented as type 5.

Characteristics of included patients are described in Table 1. The age of the patients ranged between 17 and 42 years (mean 28.09 years) and the duration of the disease ranged from 0 to 28 years (mean 10.9 years). Twelve patients (66.6%) had diagnosis of chronic systemic arterial hypertension at the beginning of prenatal care. All of them were using antihypertensive medications, being

Table 1 Distribution of maternal variables

Variable	**n = 22**	
Age at childbirth (years) mean ± *SD*	28.09 ± 7.81	
Duration of disease (years) mean ± *SD*	10.90 ± 7.65	
Medications in use	**n = 18***	**%**
Cardiovascular (n, %)		
Anlodipine	3	16.6
Clonidine	3	16.6
Hydralazine	3	16.6
Methyldopa	9	50
Nifedipine	4	22.2
Propranolol	1	5.5
Immunosuppressors (n, %)		
Azathioprine	9	50
Aspirin/anticoagulant (n, %)		
Low dose aspirin	17	94.4
Unfractioned heparin	1	5.5
Steroids (n, %)		
Prednisone	10	55.5
Dose (min–max.) (5–60 mg)		
< 10 mg	4	16.7
10–20	4	22.2
> 20	2	11.1
Ishikawa criteria	**n = 18**	**%**
I	4	22.2
II		
IIa	9	50
IIb	1	5.5
III	4	22.2

Categorical data were expressed as frequency and percentage, and numerical data as mean

± standard deviation

* 1 patient was not using any medication

methyldopa the most frequently prescribed drug (50%). Ten (55,5%) were using prednisone, of these 60% using moderate (10–20 mg/day) to high dose (> 20 mg/day), 9 (50%) used azathioprine and all but one patient received low-dose aspirin, prescribed to prevent pre-eclampsia [11].

Other associated comorbidities in this population were diabetes mellitus (1), previous history of pulmonary and tuberculous lymphadenitis (2), generalized anxiety and depressive disorder (1), panic syndrome (1), obesity (1), gangrenous pyoderma (1) and benign neoplasm of the lumbar spine (1).

Nine patients (50%) were classified as Ishikawa IIa due to mild to moderate arterial hypertension or aortic aneurysm. One patient (5.5%) was reclassified from IIa to IIb during her second pregnancy because of worsening arterial hypertension, developing a severe form. Four patients (22.2%) were classified as Ishikawa III, one (5.5%) due to moderate hypertension and retinopathy, two (11.1%) due to severe hypertension and aortic regurgitation, and the last one (5.5%) due to hypertension and aortic aneurysm. Considering all patients, 10 (55.5%) had previous renal involvement.

Of the 18 studied patients, only one was diagnosed with TAK during pregnancy. Considering disease activity, four of the 22 pregnancies (18.18%) had active disease during pregnancy, including the patient that had diagnosis while pregnant. Of the four active patients during pregnancy, three had adverse pregnancy outcomes.

Among maternal complications (Table 2), 14 (63.6%) of 22 pregnancies had hypertensive disorders: eight patients (36.3%) developed preeclampsia, including six cases with signs of severity, and six (27.2%) had uncontrolled blood pressure without proteinuria. Six fetuses (23%) had diagnosis of IUGR during routine obstetric ultrasound and there were no cases of HELLP syndrome, placental abruption or intrauterine fetal death in this study.

Regarding delivery, 15 (68%) occurred by cesarean section and almost half of them in an emergency setting, mainly due to hypertensive disorders or fetal distress. Four (18.1%) were premature births justified by severe preeclampsia. The mean gestational age at delivery was 37.27 (± 2.46) and the mean weight of newborns was 2609.78 (± 602.63).

Eight newborns (34.7%) were small for gestational age and of these six (26%) were admitted to the neonatal intensive care unit, mainly due to low birth weight (Table 3). One newborn developed early neonatal sepsis due to coagulase-negative Staphylococcus and remained in intensive care for 20 days. There were no neonatal deaths.

Ten patients (45%) developed complications in the puerperium. Seven women had prolonged hospitalization in the postpartum period due to lack of appropriate blood pressure control. One puerperal woman developed surgical site infection, another had post-spinal anesthesia headache, and another patient had sudden chest pain and underwent full anticoagulation with symptom improvement after ruling out acute myocardial infarction. When all maternal and fetal/neonatal outcomes included in this study were considered, only 6 (27.2%) pregnancies were uneventful.

There were no cases of venous thromboembolism or worsening of heart or renal disease in this study. Similarly, there were no reports of miscarriage, probably due to the characteristic of the center as a referral hospital.

Table 2 Maternal complications

Variable (n, %)	Takayasu	
	n = 22	%
Preeclampsia	8	36.3
Uncontrolled blood pressure	6	27.2
HELLP syndrome	0	0
Active disease during pregnancy	4	18.1
Placental abruption	0	0
Puerperal complications	10	45

Table 3 Characteristics of births and newborns

Variable	Takayasu	
	n = 22	%
Route of delivery (n, %)		
Vaginal	7	31.82
Spontaneous	5	22.72
Induced	2	9.09
Cesarean	15	68.18
Elective	7	31.81
Emergency	8	36.36
Delivery, gestational age (weeks)		
Mean ± SD	37.27 ± 2.46	
Newborn Weight* (g)		
Mean ± SD	2609.78 ± 602.63	
Weight rating* (n, %)		
SGA	8	36.36
AGA	15	63.64
LGA	0	0
Prematurity*	4	18.18
IUGR*	6	23
Apgar 1st min*		
Mean ± SD	8.65 ± 0.47	
Apgar 5th min*		
Mean ± SD	9.2 ± 0.4	
Neonatal ICU admission*	6	26%

*Variables considering 23 newborns (one twin pregnancy)

SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; IUGR, intrauterine growth restriction

Discussion

Our gestational results, in general, were favorable since we had no maternal, fetal or neonatal deaths. However, 72.7% (16/22) of our pregnancies had adverse obstetrical outcomes. In a recent review about pregnancies in patients with TAK, the number of live births (84%) and of general adverse outcomes (51%) were lower than those reported in this study [16]. Other publications have demonstrated fewer adverse pregnancy outcomes, ranging from 40 to 47% [17, 18].

The main complications described in this study were worsening blood pressure, preeclampsia, premature birth, emergency cesarean section, small-for-gestational-age newborns and admission to neonatal intensive care unit. Such complications seem to be related to the diagnosis of TAK associated with previous arterial hypertension and renal involvement, according to previous reports [1, 2, 19–21]. The large number of patients with these events in this study may justify the higher number of adverse obstetric outcomes compared to previous studies [19, 20].

About a third of pregnancies developed preeclampsia, which is compatible with previous studies that observed a prevalence between 11 to 73% and considerably higher than general population (4 to 7%) [1, 16–18, 20–23]. One meta-analysis demonstrated that low dose aspirin reduced the incidence of preeclampsia in patients at high risk for developing the disease, especially in its severe form, and also reduced the incidence of intrauterine growth restriction [24]. Although there are no specific studies considering patients with vasculitis and the incidence of preeclampsia is still high despite the use of aspirin, it seems reasonable to use this medication in pregnant women with these morbidities.

Studies have observed a direct relationship between maternal complications and uncontrolled blood pressure, with worse maternal–fetal outcomes in hypertensive patients. Complications such as preeclampsia, fetal growth restriction, miscarriage, prematurity, heart failure, aortic dissection, stroke, progression of renal failure, maternal and fetal death have been described [4, 9].

A recent report described a very low incidence of preeclampsia/eclampsia (5.3%) in 38 pregnancies, but the majority of the 20 patients were diagnosed with TA after gestational period [19]. Hidaka et al. analyzed 18 pregnancies in 10 patients with TAK, among which only two required antihypertensive medication during pregnancy. Fetal growth restriction occurred in only 11.1% and just two patients had uncontrolled hypertension, without other maternal or fetal significant complications [20]. In the same way, Abisnor et al. analyzed 43 pregnancies in 33 patients, 15 (35%) had previous systemic arterial hypertension, 5 (9%) had preeclampsia and 6 (14%) had fetal growth restriction [18]. Considering the six included pregnancies in which patients were normotensive, two developed preeclampsia and one presented late fetal growth restriction. The other three had no complications. These results suggest that absence of chronic hypertension is associated with a better prognosis during pregnancy.

The occurrence of secondary hypertension seems to be related to aortic narrowing, renovascular origin, reduced vascular wall elasticity and aortic regurgitation [9]. Patients with renovascular involvement and subsequent arterial hypertension are at higher risk of developing maternal–fetal complications [25]. Some studies have associated the involvement of the abdominal aorta and renal arteries with a higher incidence of hypertension, preeclampsia and fetal growth restriction [21, 25]. Among twelve pregnancies of patients with renal involvement in this study, only two remained normotensives during follow-up. All others evolved with uncontrolled blood pressure, including five cases with diagnosis of preeclampsia, and three were premature deliveries.

Premature delivery occurred in 18.1% of patients, a frequency that is higher than that found in the general population. In Brazil, the incidence of preterm birth is estimated at 11% [26]. Pedreira et al. also reported a lower incidence of preterm delivery, occurring only in 7.9% of pregnancies [19].

Intrauterine growth restriction was observed in almost a quarter of patients in this study, being compatible with the frequency reported in the literature considering pregnant women diagnosed with TAK (11 to 29%) [20]. The incidence of IUGR in general population is difficult to interpret as some studies use the term small for gestational age, which may include both newborns with growth restriction as well as small constitutional ones. It is estimated that the incidence of small for gestational age newborns in low-risk pregnancies is approximately 7 to 15% [24]. In our center, we perform monthly obstetric ultrasound after 24 weeks for early diagnosis and appropriate follow-up of growth restricted fetuses.

When comparing the Ishikawa criteria with obstetric and perinatal complications, there is an association between the presence of clinical complications and adverse outcomes in this study, similar to data previously published in the literature [27]. The Ishikawa classification represents the natural history of the disease and its clinical manifestations that directly influence the prognosis. According to Ishikawa, approximately one third of patients classified as IIb and III at the time of diagnosis died within five years, despite treatment [9]. Of the five patients classified as Ishikawa IIb and III in this study, all had uncontrolled blood pressure, and two were diagnosed with severe preeclampsia. Two patients had spontaneous premature deliveries and two of the newborns required admission to NICU, including the newborn who had very low birth weight.

Pregnancy apparently did not induce disease activity. Previous studies concluded that pregnancy could attenuate the inflammatory response to TAK during and even after pregnancy [20, 28]. However, physiological changes in pregnancy such as increased circulatory volume and cardiac output are associated with possible clinical repercussions, such as exacerbation of aortic regurgitation, arterial hypertension, and congestive heart failure [20].

The cesarean rate observed in the present study was 68.1%, which is compatible with the rate found in the literature (mean of 39.6 to 68%) [5, 21–23]. Ishikawa and Matsuura recommend C-section in groups IIb and III, mainly in patients with severe hypertension and/or retinopathy, while in groups I and IIa there is a significant increase in blood pressure in the first stage of childbirth despite the use of medications [21].

The mean APGAR score of all newborns was 8.65/9.2, similar to the findings found by Mandal et al. [21]. A study by Hauenstein et al. observed that 83.9% of newborns were born healthy and only 2.8% were stillborn [29].

The main limitations of the current study are the retrospective design, which can lead to information biases, and relatively small sample size, although TA is a rare disease with few of reports during pregnancy. Furthermore, the incidence of miscarriage is underestimated because patients could have miscarried before starting prenatal care or reaching the tertiary hospital where the study was conducted.

Conclusion

Although there were no maternal deaths or pregnancy losses in this study, the number of adverse events was considerably high. The presence of prior arterial hypertension seems to be an important factor related to these events, as well renal involvement, while the number of patients with active disease was low.

Hypertensive disorders, including severe forms of preeclampsia, occurred in a high frequency, while small for gestational age newborns were also more common than general population. These findings suggest that pregnancies in patients with TAK still have several complications, despite the use of prophylaxis with low dose aspirin. High risk prenatal care and delivery are necessary for these patients, preferably including a multidisciplinary team with obstetricians, rheumatologists, cardiologists and anesthesiologists.

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Author contributions
MILA, MGM, MEAMR, FCS: data acquisition, statistical analysis, manuscript writing. MILA, GRRJ: study concept and design. MLGO, NRJ, GRRJ, CSOE: manuscript review, interpretation of data. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethical Committee of Hospital Universitário Pedro Ernesto, approval number 25681619.4.0000.5259.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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