Pregnancy Outcomes of Patients with Takayasu's Arteritis – A Retrospective Clinical Analysis

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Research article

Keywords: Takayasu's arteritis, pregnancy outcomes, premature delivery and medical complications

Posted Date: July 21st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-37247/v1>

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Abstract

Background: Takayasu's arteritis (TA) often occurs in women of reproductive age and affect gestational outcomes. However, TA is a rare disease, and the number of reports addressing the effect of TA on pregnancy in Chinese women is small. We aimed to analyse the influence of TA on gestational outcomes and explore related factors.

Methods: We studied the medical records of 28 pregnancies among 27 women with TA. Patient characteristics, TA activity and classification, treatment, laboratory test results, delivery mode, obstetrical complications, medical complications during pregnancy and pregnancy outcomes were evaluated and compared.

Results: The mean age of all patients at delivery was 30.28 ± 4.54 years. The live birth rate was 96.4%, and the gestational age at delivery was 36.5 ± 2.78 weeks. Gestational complications included preeclampsia (22.2%), foetal distress (14.8%), intrauterine growth restriction (22.2%) and premature delivery (37.0%). Medical complications during pregnancy included heart failure (11.1%), pulmonary hypertension (3.7%), and Sjogren syndrome (3.7%). The TA status in ten pregnancies was active, and compared with those of pregnancies with inactive TA, the rates of obstetrical complications and medical complications were higher ($P=0.014$ and $P=0.047$, respectively). The rate of seeking standard treatment and follow-up was lower among patients with active disease ($P=0.021$). Among all patients, the Kerr scores and severity scores during pregnancy were similar to those before pregnancy ($P=0.664$ and $P=0.134$, respectively).

Conclusions: Active TA may increase the risk of pregnancy complications and medical complications. When treated in a timely and appropriate manner, the gestational outcome is good.

Background

Takayasu first reported a case of Takayasu's arteritis (TA) in 1908 [1]. TA is a kind of chronic inflammatory disease involving the aorta and its main branches. It occurs in people of all ethnicities worldwide but has the highest incidence among Asian populations, affecting 40 out of 10^6 people in the Far East [2]. The cause of the disease remains unclear. The diagnosis of TA is mainly based on clinical manifestations and imaging results. The most widely used diagnostic criteria are those developed by the American Rheumatology Association in 1990 [3]: 1) Age at disease onset < 40 years; 2) Claudication of extremities; 3) Decreased brachial artery pulse; 4) Blood pressure difference > 10 mm Hg; 5) Bruit over subclavian arteries or aorta; and 6) Arteriogram abnormality. TA can be diagnosed if 3 or more of the above 6 criteria are met. Arteritis is also classified according to the site of involvement. TA is classified according to the standard proposed by Moriwaki et al in 1997 [4]: type I, branches of the aortic arch; type IIa, ascending aorta, aortic arch, and its branches; type IIb, ascending aorta, aortic arch and its branches, and thoracic descending aorta; type III, thoracic descending aorta, abdominal aorta, and/or renal arteries; type IV, abdominal aorta and/or renal arteries; and type V, combined features of types IIb and IV. According to this classification system, involvement of the coronary or pulmonary arteries should be designated as C (+) or P (+), respectively.

The severity of TA is classified into three groups: group I, uncomplicated disease, with or without pulmonary artery involvement; group IIa, mild/moderate single complication together with uncomplicated disease; group IIb, severe single complication together with uncomplicated disease; and group III, two or more complications together with uncomplicated disease [5]. According to the current literature, the course of pregnancy does not affect the progression of TA. When TA is properly managed, good pregnancy outcomes can be obtained [6, 7]. However, TA may be associated with the development of certain gestational diseases, such as preeclampsia, abruption and foetal growth restriction [8, 9]. Disease activity may also affect pregnancy outcomes [10]. However, there are few research reports on the relationship between TA and the pregnancy outcomes of Chinese women. We aimed to evaluate factors that may be associated with the pregnancy outcomes of women with TA by retrospectively analysing the clinical data of patients with TA-complicated pregnancies.

Methods

The medical records of all pregnant patients with TA admitted to Peking Union Medical College Hospital (PUMCH) from January 2002 to March 2019 were retrospectively analysed [7]. The study protocol was approved by the ethical review board of PUMCH. Patient characteristics, TA activity and classification, medical and obstetrical treatment, laboratory test results, delivery mode, obstetrical complications, medical complications during pregnancy and pregnancy outcomes were evaluated for all patients. The diagnostic

criteria for TA are as described above. There is no unified standard for evaluating TA activity, but the most commonly used standard is the Kerr scoring system [11]: 1) systemic clinical features (i.e., fever, weight loss, or myalgia); 2) increased erythrocyte sedimentation rate (ESR); 3) characteristics of ischaemia or inflammation, claudication, weakened pulse, absence of pulse, vascular murmurs, and asymmetrical blood pressure; and 4) new abnormal angiography. Each item contributes 1 point to the score. Disease was considered active if the score was ≥ 2 and was considered inactive otherwise. Necessary laboratory tests, such as complete blood counts, clinical urine tests, liver function tests, ESR/C-reactive protein levels and ultrasound exams, were performed during pregnancy. Other prenatal tests, such as glucose tolerance tests, were performed routinely.

Obstetric complications were defined as the occurrence of at least one of the following events: preeclampsia and/or eclampsia, premature delivery (< 37 weeks of gestation), foetal distress, intrauterine foetal growth restriction, or intrauterine foetal death.

Statistical analysis

Continuous variables are presented as the average, and the standard deviation and non-normally distributed data are presented as the median and range. Categorical variables are presented as the number and percent and were compared between groups using Fisher's exact test. Odds ratios (ORs) are provided with 95% confidence intervals (95% CIs). A logistic regression model was used in the univariate analyses. Variables that were significant at $P < 0.05$ were included in the multivariate analysis. All tests were 2-sided; P values < 0.05 were considered significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS® version 17.0; IBM, Armonk, NY, USA).

Results

From January 2002 to March 2019, 27 patients diagnosed with TA were admitted to PUMCH, and there were 28 pregnancies among them. The general characteristics of the 28 pregnancies with TA are presented in Table 1. TA was diagnosed during pregnancy in only 4 cases and before pregnancy in all others.

Table 1
Characteristics of the 28 pregnancies complicated by TA

Mean age at delivery, years	30.28 ± 4.54
Interval between TA diagnosis and delivery, median (range), years	6.5 (1, 18)
Gravida, median (range), times	1.5 (1, 5)
Parity, median (range), times	1 (1, 2)
Classification	
I	10 (35.7)
IIa	1 (3.6)
IIb	2 (7.1)
III	0
IV	4 (14.3)
V	10 (35.7)
Unknown	1 (3.6)
Except where indicated otherwise, values are the number (%) of patients. The classification was not clear in one patient because vascular imaging examination had not been performed in that patient while in the hospital. TA = Takayasu's arteritis	

All the patients were pregnant spontaneously, and only three of the pregnancies were in the multiparous patients. In one pregnancy, the patient underwent artificial termination of pregnancy at 14.7 weeks of gestational age; the pregnancy was unintended, and the patient requested termination of pregnancy. The remaining 27 (96.4%) pregnancies resulted in live births, and among them, the gestational age at delivery was 36.5 ± 2.78 weeks. The caesarean delivery rate was 88.9% (24/27). Ten patients (37%) delivered preterm. The patients' mean age at delivery was 30.28 ± 4.54 years. The average birth weight of the 27 new-borns was $2666.73 \pm$

801.03 g. One patient underwent caesarean section at 30.1 weeks for preeclampsia. The blood flow of the foetal umbilical artery in late diastole had disappeared and the 1-minute Apgar score was 6 points. Another woman underwent caesarean section at 30.7 weeks because of acute heart failure, with a 1-minute Apgar score of 8 points. The 1-minute and 5-minute Apgar scores of the remaining new-borns were all 10. Seven new-borns were transferred to paediatric wards due to preterm delivery, foetal distress or small for gestational age, and the outcomes were good.

We retrospectively analysed the 27 pregnancies that achieved live birth. We found that the obstetrical complications included preeclampsia (22.2%), foetal distress (14.8%), intrauterine growth restriction (22.2%) and premature delivery (37.0%). In addition, there were 4 cases of gestational diabetes (14.8%), and blood sugar was controlled through diet and exercise. Medical complications included heart failure (11.1%), pulmonary hypertension (3.7%), and Sjogren syndrome (3.7%). In 15 pregnancies, hypertension had occurred in the patients during and/or before pregnancy. Although without statistical significance ($P = 0.173$), preeclampsia occurred more frequently among patients with hypertension before pregnancy than in patients without hypertension (5/15 versus 1/13). In ten pregnancies, TA was active, and the features of these cases are shown in Table 2. Compared with that of patients with inactive TA during pregnancy, the gestational age at delivery of patients with active disease was lower (34.01 ± 2.78 weeks versus 37.96 ± 1.43 weeks, respectively, 95% CI: -6.01, -1.89). Fisher's exact tests revealed that the rates of obstetrical complications ($P = 0.014$) and medical complications ($P = 0.047$) were higher among active TA cases. In 24 pregnancies, TA was diagnosed before pregnancy, and the patients with inactive TA during pregnancy were more likely to seek follow-up visits at the medical department regularly before and during pregnancy than patients with active TA (14/16 versus 3/8, $P = 0.021$). The comparison between pregnancies with active TA and inactive TA is shown in Table 3.

Table 2
Information on patients with active TA

No.	Age at admission (years)	Gravida (times)	Parity (times)	Classification	Kerr score	Gestational age of delivery (weeks)	Method of termination	Obstetric complications	Medical complications
1	27.50	3	1	I	2	35.00	C-section	Premature delivery	N/A
2	27.38	1	1	I	2	34.29	C-section	Intrauterine foetal growth restriction, premature delivery	N/A
3	24.78	2	1	V	2	30.14	C-section	Preeclampsia, premature delivery, intrauterine foetal growth restriction, foetal distress	N/A
4	31.07	1	1	IV	2	31.29	C-section	Preeclampsia, premature delivery, intrauterine foetal growth restriction	N/A
5	38.80	1	1	V	2	35.57	C-section	Premature delivery	Heart failure
6	27.39	2	1	Ila	2	32.29	C-section	Premature delivery	Heart failure
7	33.41	3	2	I,c(+)	2	35.57	C-section	Premature delivery	Pulmonary hypertension
8	31.06	1	1	V	3	37.00	C-section	N/A	Heart failure
9	26.00	2	1	V	2	30.71	C-section	Premature delivery, intrauterine foetal growth restriction, foetal distress	Heart failure
10	30.34	5	1	I	2	38.29	C-section	Preeclampsia	N/A
TA = Takayasu's arteritis									

Table 3
Pregnancy outcome and complications among the 27 pregnancies that achieved live birth by disease activity group

	Pregnancies in patients with active TA (n = 10)	Pregnancies in patients with inactive TA (n = 17)	P value
Mean age at admission (years)	29.77 ± 4.14	30.96 ± 4.67	0.512
Gravida, median (range) times	2 (1–3)	1 (1–5)	0.57
Parity, median (range) times	1 (1–2)	1 (1–2)	0.941
Mean gestational age at delivery (weeks)	34.01 ± 2.78	37.96 ± 1.43	0.001
Obstetric complications (percentage)	9 (90.0)	6 (35.3)	0.014
Medical complications (percentage)	4 (44.4)	1 (6.25)	0.047
Except where indicated otherwise, values are the number (%) of patients. TA = Takayasu's arteritis			

Among all the pregnancies, the Kerr scores and severity scores during pregnancy were similar to those before pregnancy ($P = 0.664$ and $P = 0.134$, respectively).

In our series, the classification of TA was not associated with the rate of gestational complications ($P = 0.94$), medical complications ($P = 0.921$), or hypertension ($P = 0.436$).

In this study, drugs used during pregnancy included glucocorticoids, aspirin, immunosuppressants and antihypertensive agents. In our series, glucocorticoids were used in 14 pregnancies during pregnancy alone or in combination with other drugs, and in four pregnancies, immunosuppressants were used during pregnancy.

Discussion

TA is a rare kind of chronic vascular inflammatory disease, and its aetiology is unclear. It is more common in young women and mainly affects the aorta and its major branches. TA has been reported to be associated with different human leucocyte antigen (HLA) alleles in different populations, and Asian countries have the highest incidence [3]. In the acute phase of TA, vessels showed inflammatory changes: inflammatory cell infiltration and neovascularization were observed in the media, and the intima of the vessels were thickened. In the healed phase, the vessels showed fibrosis. Scholars have reported that T cells and natural killer cells play an important role in the process of TA vascular injury. A 65-kDa heat shock protein is strongly expressed in the aortic tissue of TA patients, to which CD4 T cells respond [12]. Inflammatory and immune responses also play an important role in the pathogenesis of many pregnancy complications. During pregnancy, immune function, hormones and the microenvironment are all modified, and the cardiovascular system has to bear a heavier burden. At this period, the acute inflammatory reaction of blood vessels (especially the increasing level of interleukin-6 and tumour necrosis factor) may have adverse effects on pregnancy [13].

According to Comarmond c. et al [10], the activity of TA during pregnancy is associated with the occurrence of gestational complications. Our analysis is consistent with the fact that pregnant women with TA in the active phase are at increased risk of gestational complications, including preeclampsia, foetal growth restriction, foetal distress, premature delivery, and medical complications, mainly cardiovascular events. Therefore, more attention should be paid to patients with active TA during pregnancy, and prevention and treatment of complications should be given in a timely manner. In our series, most patients were diagnosed with TA before pregnancy. We retrospectively collected the medical follow-up information of TA for all patients before and during pregnancy and found that patients with active TA during pregnancy had a higher rate of irregular treatment than those with inactive TA during pregnancy. Therefore, patients with TA who plan to deliver a baby should be regularly followed up by physicians, and advice on the optimal timing of pregnancy should be given to avoid the negative effects of active TA on the mother and foetus. However, the current activity score is based on the general population, and there are no special criteria for pregnant women; thus, this score may not be accurate enough for the assessment of TA activity in pregnant women.

Although without statistical significance, we observed a trend that patients who had hypertension before pregnancy were more likely to be diagnosed with preeclampsia during pregnancy. As a result, TA patients with hypertension should be monitored closely during pregnancy.

Based on our results, the course of pregnancy may not affect the activity and severity of TA, which is consistent with previous literature. According to Matsumura A et al., in TA patients, the CRP scores and digital plethysmography results improve during the course of pregnancy, and these improvements continue for one year after delivery [14]. The secretion of corticosteroids from the adrenal glands and placenta increases during pregnancy, which may be the reason for such alleviation.

According to Suri V et al [15], TA patients with abdominal aorta and renal artery involvement have a higher rate of pregnancy complications, such as preeclampsia and intrauterine growth restriction. However, our study did not observe an association between the classification of TA and obstetrical complications. We speculated that although the involved vessels of different classifications were distinct, the systemic inflammatory response and cytokine changes were similar. Based on our data, the activity of the inflammatory state appeared to be more closely associated with gestational complications. In addition, TA is a rare disease, the number of pregnant patients with TA is small, and this study is a retrospective study; thus, these factors may be limitations of our analysis.

Conclusions

In general, active TA may increase the risk of pregnancy and medical complications, so TA patients, especially those who have not received standard treatment before pregnancy, should be closely followed by obstetrics and internal medicine specialists during pregnancy. When treated in a timely and appropriate manner, the gestational outcome is good.

Abbreviations

Takayasu's arteritis

TA

Peking Union Medical College Hospital

PUMCH

erythrocyte sedimentation rate

ESR

Odds ratios

ORs

95% confidence intervals

95% Cis

human leucocyte antigen

HLA

Declarations

Conflict of Interest: None.

Declarations:

Ethics approval and consent to participate: The study protocol was approved by the ethical review board of Peking Union Medical College Hospital and the project No. was S-K 1111. Written informed consent was obtained from from all participants.

Consent for publication: Not applicable.

Availability of data and materials: All data are fully available without restriction.

Competing interests: the authors declare they have no conflicts of interest.

Funding: Our research was supported by the National Natural Science Foundation of China (Project No. 81871191). Yingna Song was the head of the project. The fund was used in the statistical analysis and language modification.

Authors' Contributions: SL was responsible for article writing and material gathering; JL and JG were in charge of article editing and YS was in charge of research designation and article editing.

Acknowledgements: The study was funded by National Natural Science Foundation of China, project number 81871191.

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