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Pregnancy issues in Takayasu arteritis

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Abstract

Takayasu arteritis (TAK) is a chronic inflammatory vasculitis of unknown origin affecting large vessels, predominantly the aorta and its main branches. TAK usually affects young women and the management of pregnancy during this vasculitis may be a challenging situation. After a review of the literature, we analysed the data of 505 pregnancies in 373 TAK patients. We discuss main results to clarify if the pregnancy outcome is affected by TAK, especially during disease clinical onset or disease activity. We also discuss the potential impact of pregnancy on TAK prognosis. Disease activity of TAK appears independently associated with a poor pregnancy outcome. More than 5% of pregnant women with TAK develop a life-threatening maternal cardiovascular complication. A good control of TAK disease activity and arterial hypertension before conception and during pregnancy is critical to improve both maternal and foetal outcomes. Pregnancies in the setting of TAK should be considered high-risk, requiring a close collaboration between specialists involved in the care of TAK and obstetricians.

Keywords: Takayasu arteritis; pregnancy

Takayasu arteritis (TAK) typically occurs in young women during childbearing age (1). Therefore, it is more common to observe pregnancy in TAK patients than in patients with other systemic vasculitis (2). Pregnancy may affect the diagnosis, management, and outcome of TAK. Interestingly, profound modifications of the hormonal and cytokine microenvironment occur during pregnancy. Some physiologic adaptive changes of the cardiovascular system, such as increased circulating blood volume and increased cardiac load, superimposed on an acute ongoing inflammatory process in the vasculature may contribute to the deterioration of vascular lesions in a pregnant woman with TAK. Moreover, variations in maternal cytokines during pregnancy, such as elevated IL-6 and TNF frequently observed during infection or inflammatory disease, could be associated with increased risk of preterm birth (3). This review aimed at discussing the maternal management and obstetrical outcome, based on the data obtained after a literature review.

Methods

We used the terms "pregnancy", "obstetrical complication", "Takayasu arteritis", and "Takayasu" in the PubMed Database, and we searched main articles published in the literature from 1980 to 2019. We analysed pregnancies in TAK patients from cohort studies including at least 5 pregnancies. Cases reports and small cases series with less than 5 pregnancies were excluded.

Results

We found 183 citations in the PubMed Database until March 2020. All articles with sufficient data in English language were included in the literature review. We analysed the data of 505 pregnancies in 373 TAK patients. **Table 1** summarizes main results obtained in studies reporting obstetrical outcome for at least 5 patients. A live birth was reported in 84% of pregnancies, eclampsia or preeclampsia in 24%, preterm live birth in 15% and miscarriage in 12%.

1. Pregnancy outcome before established TAK disease

Takayasu arteritis can have a preclinical period and a long prodromal phase. Few studies described foetal and maternal outcomes in women before TAK diagnosis (4–9). However, none of these studies analysing pregnancies before established TAK disease described inflammation markers or vascular imaging. So, pregnancies during prodromal phase or truly before diagnosis remain difficult to distinguish. Gudbranson et al described 73 pregnancies in 33 patients before TAK diagnosis (6). The frequencies of miscarriages, induced abortions, and maternal complications did not differ between pregnancies occurring before and after TAK onset (6). Among 25 pregnancies occurring before the diagnosis of TAK was done, 15 live births, 6 early miscarriages, and 4 voluntary terminations of pregnancy were observed (8). Wong et al described 11 pregnancies before TAK diagnosis which were all uneventful (4). On the contrary, Assad et al identified that patients with TAK, even before the disease diagnosis, have a worse foetal outcome that were most likely associated with high rates of hypertension, suggesting that pre-disease diagnosis may be eventful in terms of reproductive history (9). Women with unknown diagnosis of TAK and delay in TAK diagnosis are very frequent. As in other rheumatologic diseases (rheumatoid arthritis, lupus erythematosus, scleroderma, antiphospholipid syndrome), TAK may remain quiet or asymptomatic until pregnancy, period during which TAK disease may become more aggressive, putting both mother and foetus high-risk. The risk of gestational hypertension, preeclampsia, or eclampsia in pregnant women before TAK diagnosis seems to be lower than during pregnancies at same time or after TAK diagnosis. Among 142 pregnancies occurring in 52 patients before TAK diagnosis, obstetrical complications before 37 weeks of gestation occurred in 6% of pregnancies before TAK diagnosis compared to 40% of pregnancies at the same time or after TAK diagnosis (5). A Brazilian study found that pregnancies before TAK diagnosis had high rates of hypertension (27%), more frequent low birth weight (17%), and perinatal mortality around

8% (9). Pregnant patients before TAK diagnosis with arterial hypertension presented more frequently caesarean rate, prematurity and low birth weight than the group without hypertension (9). In this study, hypertension represented the most common pregnancy complication among patients who had a TAK diagnosis before the pregnancy. The occurrence of hypertension during pregnancy before TAK was similar to the rate described in patients with established TAK diagnosis while it was about 7 times higher than in healthy control group. This finding suggests that these women were already pregnant, with TAK still undiagnosed (9).

2. Pregnancy outcome in patients with established Takayasu arteritis

Obstetric complications, such as gestational hypertension, preeclampsia, spontaneous abortion, intrauterine growth retardation (IUGR), preterm birth, and caesarean section seem to be more frequent in pregnancies of patients with TAK. Among 379 pregnancies in 294 Takayasu arteritis patients from studies of different countries, high rate of maternal complication and poor pregnancy outcomes were reported. In patients with TAK, hypertension disorders are observed in 35%, caesarean section in 30%, prematurity in 16%, IUGR in 15%, foetal loss in 12%, and therapeutic abortions in 7% (**Table 1**). In general population, pregnancy hypertension occurs in 3 to 9%, pre-eclampsia in 1 to 4%, caesarean section in 6 to 20%, preterm birth in 5 to 7%, and IUGR in 3 to 7%.

The most common complication in pregnant patients with TAK was hypertension with an overall incidence reaching 35%. The timing of therapy, the severity of hypertension, and the extent of arterial involvement were predictive of IUGR (4). Sharma et al reported that patients with poor perinatal outcome had abdominal aortic involvement and a significant delay in seeking medical attention (10). Pregnancies in women with TAK diagnosis had higher rate of obstetric complications compared to pregnancies before TAK diagnosis (4,5,11). Obstetric complications were observed in 40% of pregnancies at the same time or

after TAK diagnosis, including hypertension/preeclampsia (21%), miscarriage (9%), prematurity (8%), IUGR or foetal death (5%), and eclampsia (3%). Three neonatal deaths were observed in 2 patients: 2 stillbirths after eclampsia and 1 neonatal death that occurred 48 hours following a delivery at 27 weeks due to severe intrauterine growth restriction and placental ischemia (5). Kirshenbaum et al reported 8 out of 13 (61.5%) pregnant women suffering from hypertension during their pregnancy (12). Chronic hypertension was observed in 2 patients prior to conception. Elevation in blood pressure began at the third trimester in other cases. Blood pressure was controlled with labetolol and nifedipine. Two out of 13 cases required hospitalization during pregnancy for evaluation and management of hypertension (12). Four patients had premature delivery due to active TAK disease (n=2), preeclampsia (n=1) and IUGR with abnormal fetal arterial flow (n=1) (12). Different factors associated with maternal and foetal complications and adverse outcomes have been reported. Suri et al described that abdominal aorta involvement is associated poor obstetric outcome (13). We reported that factors associated with risks of obstetric and maternal complications were smoking and active TAK disease with an NIH score >1 (5). Abisror et al also reported a high rate of obstetrical complications (47%) in women with Takayasu arteritis (8). Obstetrical complications included 35% of arterial hypertension (n = 15), 9% of pre-eclampsia (n = 4), 2% of HELLP syndrome (n = 1) and 14% of IUGR (n = 6), leading in one case to a medically indicated termination of pregnancy. Obstetrical complications were more frequent in TAK patients with arterial hypertension, renal artery stenosis and infra-diaphragmatic artery involvement (8). Despite frequent obstetrical complications, no significant impact was observed on live birth rates with 98% of live births.

A small number of studies reported excellent maternal outcomes and favourable foetal outcomes (6,14,15). However, these series included only TAK patients who became pregnant during remission of the vasculitis. Only 2 cases (2/18, 11%) of superimposed pregnancy-

induced hypertension were included (14). No case with aortic aneurysm, cardiac failure, coronary involvement or pulmonary arteries involvement were described (14). In addition, post-partum period in TAK patient is usually uncomplicated.

3. Impact of pregnancy on Takayasu arteritis

The impact of pregnancy on Takayasu's disease remains unclear. The most frequently observed maternal complication during pregnancy of TAK patients is hypertensive disorder. Nevertheless, gestational hypertension is present in about 1:15 pregnancies and can occur independently of TAK disease. Rare fatal maternal complications have been reported such as aortic aneurysm and cerebral haemorrhage (4,13). Manifestations of TAK disease described during pregnancy are various, such as renal insufficiency, retinopathy, aortic dissection, cerebrovascular accidents and cardiac insufficiency (10,16–18). Symptoms of TAK may respond variably during pregnancy. Some patients had worsening of their symptoms during pregnancy while others had milder symptoms than they had had prior to pregnancy (12,19). Among 98 pregnancies in TAK patients, maternal complications were observed in 39%, including specific TAK complications (5). The most frequent maternal complications were new-onset arterial hypertension (15%), worsening arterial hypertension (11%), and arterial stenosis/occlusion (8%). More than 5% of pregnant women with TAK develop a life-threatening maternal cardiovascular complication such as aortic aneurysm, stroke, end-stage renal disease (5,16). During pregnancy, TAK may arise de novo, and pre-existing vascular symptoms and/or arterial lesions of TAK may be significantly worsened and may potentially become life-threatening (16,18,20). Severe maternal vasculitis related complications can be observed during pregnancy, including cardiac failure, cerebral ischemia, transient ischemic attack, instances of end-stage renal disease, aortic aneurysms, aortic dissection, haemoptysis) (4,5,16,20). In the literature, three cases of maternal mortality are reported, following myocardial infarction, cerebrovascular accident and stroke (4,6,21).

High blood pressure in the late gestational period, abdominal and renal involvement, disease activity during the early pregnancy, and delay in medical attention are described as predictive factors of poor outcome (22). Disease activity of TAK could be associated with a poor pregnancy outcome (5,13,15). Disease activity is assessed using the NIH definitions, which include 4 components: systemic features (no other cause identified); elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level; features of vascular ischemia or inflammation (such as extremity claudication, diminished or absent pulse, bruits, pain over large vessels, or asymmetric blood pressure); and new vascular lesion(s) on imaging studies, i.e., new stenosis or new dilatation (1). Active disease is defined as the new onset of 2 or more of these features. However, ESR elevation is a part of normal pregnancies and complicates determining disease activity by NIH criteria. In our experience, active disease (NIH score ≥ 2) was observed in 39 pregnancies (40%) whereas inactive disease (NIH score ≤ 1) was observed in 59 pregnancies (60%). Obstetric complications were more frequent in women with active versus inactive TAK disease (64% versus 24%; $P < 0.0001$). Preeclampsia was more frequent in pregnant women with active than in pregnant women with inactive disease (46% versus 5%; $P < 0.0001$). Overall, complications during pregnancy were 3 times more likely to occur in women with active than in those with inactive TAK disease (5). Tanaka et al observed relapse of TAK in five pregnancies (5/22, 23%) (15). Two relapses occurred in the first trimester, and both resulted in a miscarriage. The remaining three relapses occurred in the last trimester, including 2 with IUGR. Suri et al found that the incidence of maternal and foetal complications was higher among TAK patients with more severe disease (according to the Ishikawa criteria) and/or with a greater number of damaged vessels (13).

Pregnancy has also been reported to neither interfere with TAK disease progression nor negatively affect fertility (9,10,14,21,23). Rare cases of TAK improvement during pregnancies have been reported (19,23). No adverse influence of pregnancy and delivery on

Takayasu arteritis was observed in the puerperium of any patients. Inflammatory activity of the disease was not enhanced by the pregnancy (24). Matsumura et al reported that CRP levels improved significantly during pregnancy and 1 year after delivery. Hemodynamic state (pulse amplitude and wave) also improved with pregnancy (23). In a recent study, no correlation was reported between TAK activity and any of the obstetrical complications (8).

4. Management of pregnancy and labour in patients with TAK

The under diagnosis of TAK can lead to worse pregnancy and foetal outcome, most likely associated with hypertension. TAK should be identified as an important differential diagnosis for hypertension in pregnancy. Physical examination could be sufficient to alert to the presence of this disease. Headaches, a blood pressure discrepancy, a pulselessness of unilateral or both radial arteries, vascular bruit or limb weakness should be looked at in all cases of hypertension (5,13).

Discussion of contraception and pregnancy intentions with patients since multiple teratogenic medications are used to treat TAK and contraception allows for appropriate timing of pregnancy. Preconceptional conselling to assess disease activity, to optimize control of blood pressure and to eventually change medication compatible with pregnancy prior to conception are recommended. Ideally, pregnancy should be planned when TAK disease is in sustained remission. The patient can be off treatment or on a stable therapeutic maintenance regimen that allows conception and must be continued during pregnancy. Medications prior to pregnancy, such as methotrexate, mycophenolate mofetil, cyclophosphamide and angiotensin converting enzyme inhibitor should be avoided during pregnancy. This highlights the importance of pre-pregnancy consultations with obstetricians and specialists of TAK disease (internists/rheumatologists) to review medications, switch potentially teratogenic medications with those considered safe during pregnancy, and ensure disease stability prior to conception to ensure favourable outcomes. To ensure better compliance, physician need to reassure

patient concerning many medications used for TAK disease and considered as low risk such as prednisone, azathioprine, and tumour necrosis factor inhibitors (anti-TNFα). Ideally, pregnancy should be planned when the TAK disease is in remission. Antenatal counselling need shape medical treatment for maintaining disease remission prior to conception. For patients flaring during pregnancy, we recommend to intensify medical treatment according to the severity of flare. Suppression of inflammatory syndrome due to TAK disease with glucocorticoids associated to immunosuppressants if necessary, is a cornerstone to improve outcome during pregnancy (14,25). Monitoring and ensuring satisfactory blood pressure control with calcium-channel blockers and/or methyldopa, are also essential. When TAK disease is severe, glucocorticoids associated to azathioprine or anti-TNFα are indicated. Life threatening condition can lead to consider therapeutic abortion or premature delivery.

Control of TAK disease activity and of arterial hypertension before conception and during pregnancy is critical to optimize both maternal and foetal outcomes (5,22). Most of obstetric and maternal complications occurred during the second and third trimesters of pregnancy and are indeed due to TAK vasculitis damage, mainly hypertension. When TAK disease is known before the pregnancy and is inactive state with controlled hypertension, outcomes for the mother and new-born are usually good. When the disease is still active at pregnancy initiation and/or hypertension is uncontrolled, outcomes are more uncertain. Decisions about treatment and/or pregnancy continuation can be difficult. Inclusion of pregnant patients in cohort studies and protocol may be helpful to better identify patients with high risk of complications during pregnancy. Pregnancies in the setting of TAK should be considered high-risk, requiring close collaboration between obstetricians and rheumatologists/internists with experience in TAK disease and high-risk pregnancies.

Labour and delivery can be managed with epidural analgesia for the majority of patients (26–29). Regional anaesthesia can induce variations of blood pressure and should be used with

caution during delivery. Increases in blood pressure can cause rupture of the aneurysms, aortic dissection and decreases in blood pressure can lead to cerebral ischemia (16,18,30). However, the control of blood pressure is not always easily achieved because of difficult brachial blood pressure measurements in TAK patients with pulseless upper extremities. The rate of caesarean deliveries in TAK patients is around 30%. Caesarean sections and operative vaginal deliveries are performed for obstetric indications. Low-dose spinal anaesthesia seems also safe for emergency caesarean section (27,31). TAK disease itself, regardless of maternal complication, evolution during pregnancy and severity, should not be an indication for caesarean delivery.

Conclusion

Disease activity of TAK is frequently associated with a poor pregnancy outcome. More than 5% of pregnant women with TAK develop a life-threatening maternal cardiovascular complication. A good control of TAK disease activity and arterial hypertension before conception and during pregnancy is critical to improve both maternal and foetal outcomes. Pregnancies in the setting of TAK should be considered high-risk, requiring a close collaboration between specialists involved in the care of TAK and obstetricians.

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Table 1 Pregnancies in Takayasu arteritis patients in studies reporting obstetrical outcome for at least 5 patients

Authors, year	Patients, *n*	Pregnancies, *n*	Age at conception, *mean*	Miscarriage, *n* (%)	Prematurity <37wks, *n* (%)	Induced abortions, *n* (%)	IUGR, *n* (%)	Live births, *n* (%)	Relapse or disease activity, *n* (%)	Hypertension, *n* (%)	Eclampsia or preeclampsia, *n* (%)	Caesarean, *n* (%)
Ishikawa, 1982 **(24)**	27	33	28.4	2 (6)	2 (6)		4 (12)	33 (100)		15 (45)		10 (30)
Wong, 1983 **(4)**	11	15		0	1 (7)	4 (27)	4 (27)	15 (100)		11 (73)		4 (27)
Matsumura, 1992 **(23)**	18	22		2 (9)	6 (55)					4 (18)		7 (28)
Aso, 1992 **(22)**	15	23		4 (17)	4 (17)		2 (9)		4 (17)	13 (56,5)		13 (56,5)
Sharma, 2000 **(10)**	12	24	23.6+/-3.6	0	4 (17)		5 (21)	17 (71)	2 (8)	11 (46)	4 (17)	
Suri, 2010 **(13)**	15	30	27.6		6 (55)		6 (20)	25 (83)		22 (73)	1 (3)	7 (28)
Hidaka, 2012 **(14)**	10	26	29.3 ± 5.2	5 (19)		3 (11.5)	2 (8)	18 (69)		8 (30)		2 (8)
Mandal, 2012 **(21)**	17	29		1 (3)	5 (17)		15 (52)	26 (90)	1 (6)	29 (100)	24 (83)	
Tanaka, 2014 **(15)**	20	27	30 [22–35]	0		1 (4)	1 (4)		3 (11)	5 (18)	4 (15)	9 (33)
Assad, 2015 **(9)**	89	38	25.1 (5.2)	0	16 (45.7)	3 (8)	12 (32)	35 (92)	2 (5)	12 (31.5)		24 (68.5)
Comarmond, 2015 **(5)**	52	98	27 [24–31]	9 (9)	8 (8)	3 (3)	5 (5)	95 (97)	21 (21)	24 (24)	24 (24)	16 (16)
Gudbrandsson, 2017 **(6)**	23	37	29.4 ± 4.9	6 (16)	6 (16.7)	6 (16)	5 (12.5)	25 (68)		3 (8)	2 (4.5)	8 (35)
Tanacan, 2019 **(32)**	11	22	30.30 ± 4.80	5 (23)	4 (18)	1 (4.6)	3 (14)	16 (73)	5 (23)	8 (36)		8 (50)
Gupta, 2020 **(7)**	20	38	30 [27–33.5]	10 (26)	2 (5)	6 (16)	6 (16)	19 (50)	15 (39)	15 (39)		
Abisror, 2020 **(8)**	33	43	30.3	excluded	9 (21)	1 (2)	6 (14)	43 (100)		12 (28)	4 (9)	20 (47)
Total	**373**	**505**		**12%**	**15%**	**8%**	**15%**	**84%**	**18%**	**45%**	**24%**	**29%**

IUGR = intrauterine growth retardation