Favourable pregnancy outcome in Takayasu arteritis: a single-centre experience

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ABSTRACT

Introduction. *Takayasu arteritis is a chronic large-vessel vasculitis in young women of reproductive age. We aimed to obtain information on pregnancy in TA retrospectively.*

Methods. *Takayasu arteritis patients with history of pregnancy were included in this study. The evaluations included physical findings, serum C-reactive protein, erythrocyte sedimentation rate as well as history and symptoms. Information about pregnancies, abortus, deliveries and newborns was obtained from medical records. Disease activity score, disease damage index appraised Kerr's criteria and vasculitis damage index (VDI) and medication were recorded.*

Results. *Thirty-six Takayasu arteritis patients who had a total of 84 pregnancies were evaluated. The mean age of patients ranged 24.5±6.6 years. Subclavian arteries (86%) were the most frequently involved vessels. We were able to complete the follow-up of ten patients who had a pregnancy after diagnosis during the period of pregnancy. Two patients who had renal artery involvement and active disease in third trimester suffered from preeclampsia and a worsening of hypertension. In one of them, disease flared up in the third trimester. There was no active disease in the postpartum sixth month. Maternal heart failure, cerebrovascular accident, death or cerebral hypoperfusion at the time of delivery, asphyxia and newborn anomalies were not seen in any of these patients.*

Conclusion. *TA pregnancies may have a favourable outcome with regular follow-up schedule and close monitorisation of blood pressure.*

Introduction

Takayasu arteritis (TA), is a chronic vasculitis of young and middle-aged women that mainly affects the aorta and its major branches. The etiology of granulomatous panarteritis in TA, which may lead to stenosis, occlusion and/or aneurisms in involved vessels, is yet unknown. Acute or chronic ischaemic changes leading to tissue hypoxia define the severity of the signs and symptoms. Limb claudication and hypertension are the major clinical findings of TA. Cardiac and/or cerebral involvement can occur as a primary involvement of TA or in association with hypertension (1, 2). Several studies have reported different pregnancy outcomes in TA. Pregnancy may change the symptoms of TA due to the alterations in circulating volume and cardiac function. Impact of disease activity on pregnancy has not been clearly understood yet and the treatment strategy has not been standardised for pregnant TA patients either. In this study, we aimed to investigate the pregnancy outcome retrospectively in a prospectively followed-up TA cohort.

Material and methods

TA patients with a history of pregnancy and fulfilled ACR classification criteria and regularly followed-up between 1995–2012 were included in the study (3). Pregnancy and newborn outcomes consisting of history of abortus (fetal loss in first trimester), delivery mode, hypertension (blood pressure obtained from upper or lower extremites higher than 140/90), worsening hypertension (needs to be controlled by dose increment or adding a new anti-hypertensive drug.), preeclampsia (hypertension and proteinuria), eclampsia (hypertension and seizure), prematurity (birth before 37th weeks) and intrauterine growth retardation were obtained from personal contacts (at the follow-up visit and by phone calls) and medical records. The history of prematurity was obtained by personal contact with all patients who had pre-disease pregnancies. They were

asked for the delivery time whether they gave birth at estimated delivery time based on their last menstrual period calculated by their health professionals or gynaecologists. TA patients were grouped according to the occurrence of pregnancies during the pre-disease (pre-d) or post-disease (post-d) period. In a subgroup of patients who became pregnant after 2010, disease activity and damage evaluated by Kerr criteria and VDI, serum C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) and concomittant immunosuppressives were noted within the 3rd trimester and 6 months of pre and postpartum period, prospectively. All retrospective and prospective data were noted into a predefined protocol. Maternal and foetal outcomes were compared between pre-d and post-d pregnancies. Statistical analysis was performed with Mann-Whitney U-test by using the software package SPSS 17 running on Windows NT.A two-tailed *p*-value of <0.05 was considered statistically significant.

Table I. Patients characteristic at the time of diagnosis of Takayasu arteritis.

Clinical features	n=36 (%)		
Hypertension	17 (47)		
Limb claudicatio	16 (44)		
Pulselessness	13 (34)		
Cardiac valve disease	9 (25)		
Conjestive heart failure	0		
Pulmonary hypertension	6 (16)		
Cerebrovascular accedant	1 (3)		
	Affected vessels		
Subclavian artery	31 (86)	Abdominal aorta	8 (22)
Carotis artery	16 (44)	Coeliac artery	4 (11)
Renal artery	10 (27)	Thorasic aorta	3 (8)
Axillar artery	9 (25)	Arcus aorta	2 (6)
Vertebral artery	8 (22)	Pulmonary artery	2 (6)

Table II. The frequency of fetomaternal complications in Takayasu arteritis patients with pregnancy before and after diagnosis.

	All pregnancies n=84(%)	Pre-d pregnancies n=63(%)	Post-d pregnancies n=21(%)	*p*-values
Worsened HT	5 (6)	2 (3)	3 (14)	0.038
Cesarean section	15 (18)	6 (10)	9 (42)	0.032
Abortion*	5 (6)	4 (6)	1 (5)	0.125
Preeclampsia	2 (2)	0	2 (10)	0.024
IUGR	4 (5)	3 (5)	1 (5)	0.254
Prematurity	3 (4)	1 (2)	2 (10)	0.042
Asphyxia	0	0	0	NA
Newborn anomalies	0	0	0	NA

Pre-d: Before diagnosis; Post-d: After diagnosis; HT: Hypertension; IUGR: Intrauterin growth retardation; NA: Not available; *All abortions were miscarriages.

Results

Infertility caused by tubal obstruction and azoospermia had been diagnosed in three patients (3%) of TA cohort. Data of 36 TA patients with pregnancy history were assessed in TA cohort of 103 patients. Demographic data were as follows: Mean (median) age at pregnancy period was 24.5±6.6 (22) years, mean time of total disease duration was 46±24 months. Subclavian (86%), carotid (44%) and renal arteries (27%) were the most frequently involved vessels. Hypertension (HT) (47%), limb claudication (44%) and pulselessness (34%) were the prominent clinical features of TA cohort (Table I). Organ insufficiency was not observed in any patient. Eighty-four pregnancies for 36 TA patients (63 in 24 pre-d and 21 in 17 post-d patients) were evaluated. Twenty-two (61%) patients were multiparous (17 in pre-d, 5 both in pred-d and post-d period). Comparison of fetomaternal prognosis between the pre-d and post-d pregnancies demonstrated that worsened hypertension (3% *vs*. 14%, *p*=0.038), preeclampsia (0% *vs*. 10%, *p*:0.024), prematurity (2% *vs*. 10%, *p*=0.042) and Cesarean section (CS) (9% *vs*. 42%, *p*=0.032) were significantly high in post-d pregnancies (Table II). The post-d TA patients with worsened HT have been treated with 7.5 mg (5–15) mean daily dose of prednisolone. No life-threatening fetomaternal complication was observed in TA cohort. Two patients with pre-eclampsia were succesfully treated with alpha-methyldopa. Intrauterine growth retardation with unknown etiology was observed only in one of two pregnancies resulting in pre-term delivery. Five (1 in pre-d, 4 in post-d) of 84 pregnancies (6%) were complicated with miscarriage abortion. All but one patients who underwent to CS were given general anesthesia. One patient had epidural anesthesia without any complication. Ten out of 36 pregnant TA patients were followed-up, prospectively. The extension of vessel involvement, Kerr's activity and VDI scores, the dose of immunosuppressives for each prepartum, 3rd trimester and postpartum periods, and fetomaternal complications of those patients were demonstrated in Table III. Prepartum data was not available for 4 of the 10 patients who were diagnosed as TA during pregnancy. All four patients who were diagnosed during the pregnancy were referred to our clinic because of the pulselessness or the difference between the blood pressures in upper extremities during the routine pregnancy follow-up. They were suffering from ischaemic symptoms for sometime before the pregnancy period when they were further questioned in our clinic.

Disease activity during the time of conception could only be evaluated in 6 post-d TA patients followed-up prospectively. There were no clinical data on conception time of four patients who were diagnosed during pregnancy. Six out of 10 pregnancies had inactive TA at the time of conception maintained with low dose corticosteroid treatment. Methotrexate was stopped six months prior to conception. Two patients had continued to take azathioprine (AZA)

Table III. Disease activity, disease damage index and the outcomes of pregnancies that occurred during our follow-up.

Age	Involved vessels	Before pregnancy			Last trimester			Postpartum sixth month			Maternal complication	Pregnancy outcomes and delivery root
		KAS/VaDI	CRP	Treatment	KAS/VDI	CRP	Treatment	KAS/VDI	CRP	Treatment		
24*	Abdominal aorta, carotis, subclavian, renal arteries	-/-	-	No	Active/5	26	No	Inactive /3	16	MPRD 4 MTX 15	Worsening HT	TD, NSD
32*	Abdominal aorta, carotis, subclavian arteries	-/-	-	No	Inactive /2	4	PRD 7,5	Inactive /3	2,3	PRD 7.5 MTX 15	No	TD, CS
44*	Abdominal aorta, renal, coeliac arteries	-/-	-	No	Active /3	15	PRD 10	Inactive /3	1,7	PRD 7.5 MTX 15	Pre-eclampsia	Prematurity CS
22*	Carotis, subclavian, axillary, vertebral arteries	-	-	No	Active /3	42	No	Inactive /3	14	MPRD 8 MTX 15	No	TD, CS
32	Arcus aorta, subclavyan, axillary, coeliac arteries	Inactive /3	28	AZA 150 MPRD 6	Inactive /3	14	AZA 100 MPRD 6	Inactive /3	15	AZA 150 MPRD 6	No	TD, NSD
24	Carotis, subclavian, renal, coeliac arteries	Inactive /2	0.5	MPRD 4 AZA 100 INF 300	Inactive /2	1.2	MPRD 4 AZA 100	Inactive /3	12	MPRD 4 AZA 100	No	TD, CS
33	Carotis, subclavian, axillary, vertebral arteries	Inactive /3	15	MPRD 6	Active /3	52	MPRD 10	Inactive /3	24	MPRD 4 MTX 12.5 INF 300	No	TD, CS
30	Subclavian arteries	Inactive /3	20	PRD 5	Inactive /3	5	PRD 5	Inactive /3	35	PRD 5 MTX 12.5	No	TD, CS
33	Carotis, subclavian, renal arteries	Inactive /2	5	PRD 5	Inactive /3	7	PRD 5	Inactive /2	0,7	PRD 5	No	TD, CS
28	Abdominal aorta, subclavian, axillary arteries	Inactive /2	3.9	MPRD 4	Inactive /2	8.2	MPRD 4	Inactive /2	4	MPRD 4	No	TD, CS

VDI: vasculitis damage index; KAS: Kerr's activity scores; CRP: C-reactive protein (mg/l, normal range: 0–5); HT: Hypertension; NSD: normal spontaneous delivery; PRD: prednisolone (mg/gun); MPRD: methylprednisolone (mg/gün); AZA: mzatioprine (mg/day); INF: infliximab (mg/six months); TD: term delivery; CS: Cesarean section; *diagnosed at the time of pregnancy.

during their pregnancies. One patient had been treated with infliximab (INF) just before the time of conception. Probable risks were discussed with the patient and a signed written informed consent was obtained. INF was not continued after the patient became pregnant. Fetomaternal complication was not observed in any of those patients exposed to AZA and INF. Flare was observed in only one TA patient with planned pregnancy who discontinued INF after conception. TA was diagnosed in the second trimester of 4 patients. Disease activity could not be suppressed in 1 of 2 patients who were treated only with prednisolone (7.5–10 mg/d). Two patients denied to take treatment were still active in the last trimester.

There was no increase in VDI scores of 10 patients at the 6th month postpartum evaluation. Only two of 4 patients with renal artery involvement were complicated with accelerated hypertension and pre-eclampsia in the third trimester. Eight patients underwent CS with the expert opinions reservations of cerebral hypoperfusion risk related to carotid involvement, hypertension and severe anxiety.

Discussion

In this study, we evaluated fetomaternal prognosis in a regularly followed-up TA cohort characterised with a younger age of pregnancy and the absence of end-organ damage. Clinical and radiological features of our cohort were similar with the literature. Multiparity was observed in two thirds of our cohort. Mean pregnancy number of TA patients (2.3) was compatible with our healthy population data (2.08) (Turkey Statistical Institue 2012). There is no clear data on fertilisation potential in TA in the literature.

Newly-diagnosed TA during pregnancy was observed in 4 patients. TA as a Th1 type autoimmune disease (4) is not expected to occur in pregnancy. Asymptomatic or mild TA may firstly be diagnosed in pregnancy period during the routine monitorisation of blood pressure. This might be the reason for some TA patients diagnosed during pregnancy. There are some published data reporting severe morbidity and mortality in TA during pregnancy, based on case series. We did not observe any serious maternal complications such as congestive heart failure, stroke and sudden death in our cohort. The only maternal complication was elevated HT in a relatively small number (18%) of hypertensive pregnant patients. One of these patients developed preeclampsia and premature delivery. Antihypertensive treatment was able to control hypertension in the majority of those patients. The frequency of HT in TA pregnancies varies (11%–100%) in different studies (5, 6) and they were treated with alpha-methyldopa, amlodipine and metoprolol. TA patients who already had a child, uncontrolled inflammation, severe hypertension or renal artery stenosis were discouraged to further pregnancies that might reflect the overall favourable maternal outcome in our cohort. A recent study comparing pre and post-d pregnancy outcome in 46 TA patients

demonstrated a high prematurity and fetal loss rates in post-d pregnancies, as similar to our study (7).

Neonatal abnormality was not seen in any of our patients. Abortion rate was found lower (6%) when compared to previous reports (8%–30%) (5, 8). Prematurity (4%) and intrauterine growth retardation (5%) were the fetal complications in our cohort and did not result in fetal death. Prematurity rate was reported as low especially in our pre-d pregnancy cohort. Multiparity has been accepted as a risk factor of prematurity in the literature. This subgroup of cohort was consisting of 40% nullipar women. We considered that this might be the reason of our low rate of prematurity in this subgroup. In addition to this, we found a relatively wide range of prematurity rate (5–18%) reported by WHO while searching the literature. Fetal deaths related to maternal cardiac insufficiency were reported in two different studies (5, 8). There are only few reports on intrauterine growth retardation in TA (9, 10).

The main root of delivery was NSD (63%) in our cohort. It has been observed that the clinicians might be reluctant to refer their patients for normal delivery with the concern of strain induced cerebral hypoperfusion although there is sufficient favourable data on vaginal delivery (8). There were no reported anesthesia complications in patients underwent CS. Epidural anesthesia was also succesfully applied in one of our TA patients.

Pregnancy can be a challenging period to differentiate physiological changes from active symptoms of TA. Mechanical stress related symptoms such as back pain or extremity pain in a pregnant patient may mimic ischaemic symptoms of TA. Hypertension as the most important cause of morbidity in all pregnancies, should be carefuly evaluated in TA patients before assuming an activity sign. A number of physiological vascular changes, such as increase in cardiac output, reduction in peripheral resistance and blood pressure can be seen in pregnancy (11, 12) TA patients complicated with preeclampsia related to endothelial dysfunction can interfere the physiological decrease in peripheral vascular resistance and instigate hypertension during pregnancy. It is well known that increased ESR due to the higher fibrinogen levels and CRP with unknown mechanisms might be observed during pregnancies. Therefore, acute phase response is not mostly helpful to exclude inflammatory ischaemic symptoms from physiological changes (13, 14). This study is the first to report prospectively evaluated a group of TA patients according to their disease activity and damage before, during and after the pregnancy. There is only one study consisting of 18 TA cases which evaluated the effect of pregnancy on disease activity in TA and reported a favourable outcome with only CRP scores (15). In our study, only one patient had a flare during the prospective follow-up. The absence of severe disease activity did not necessitate an increase of prednisolone >10 mg/d in any patient. Damage was not increased in any active pregnant patient evaluated at the 6th month of post-partum period. We were aware that it might be difficult to differentiate the activity and damage with the clinical or imaging findings in some TA cases. Activity and damage can also overlap in an important number of TA patients. In this study, no serious damage was observed in any TA patient in a relatively short time period. On the other hand, postpartum 6th month may be early to detect damage accrual in such a chronic, indolent vasculitis like TA.

In conclusion, the majority of pregnancies were successful in a well established TA cohort although TA seemed to be a risk for pregnancy outcome when compared to prediagnosis pregnancies. Disease activity and GC treatment which has a well-known side effects on fetomaternal prognosis were likely to happen on high rates of prematurity and preeclampsia in post-d subgroup although no comparison could be made with pre-d subgroup. Flare has to be differentiated from the physiological changes and acute phase increase of pregnancy in TA patients. Accelerated damage may not occur in pregnant TA patients having mild ischaemic symptoms, mild-moderate acute phase response and no requirement of higher doses of GC. TA pregnancies may have a favourable outcome with regular follow-up schedule and close monitorisation of blood pressure.

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