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Poor obstetric outcomes in Indian women with Takayasu arteritis

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Abstract

Introduction: Takayasu's arteritis (TA) affects young women in the childbearing age group. We studied obstetric outcomes in these patients before and after disease onset.

Methods: Women aged more than 18 years with Takayasu's arteritis (ACR 1990 criteria) were included. Demographic data, clinical features, disease activity using Indian Takayasu Arteritis clinical score (ITAS), Disease Extent Index for TA (DEI.Tak) and damage assessment using TA Damage score (TA), history of conception and maternal and fetal outcomes were recorded from hospital records and telephonic interview. Results are in median and IQR.

Results: Of the 64 women interviewed, aged 29 (24–38) years and disease duration 5 (4–10) years, 74 and 38 pregnancies had occurred before and after disease diagnosis in 29 and 20 women respectively. In eight, the diagnosis was made during pregnancy. Age at disease onset was 22 (18–30) years. Type 5 disease was the most common ($n = 32$, 59.3%), and an equal number of patients had Ishikawa's class I and II disease ($n = 26$, 40.6%). Median ITAS ($n = 44$) was 13 (7–16), DEI.Tak 12.5 (9–16.75) and TADS 8 (6.5–10). Twenty-five patients wanted to get pregnant, of which 8 (32%) did not do so because of their disease. Fifteen were unmarried of whom 6 did not marry due to disease. Obstetric outcomes were poorer in pregnancies that occurred after the onset of disease as compared with those before it ($RR = 1.5$, $p = 0.01$). Pregnancies after the onset of TA carried a very high risk of maternal [$RR 3.9$ (1.8–8.5), $P < 0.001$] as well as fetal complications [$RR = 2.0$ (1.2–3.4), $p = 0.001$]. Hypertension was the most common maternal complication and occurred most often in the last trimester. The baby weight at birth was lower in pregnancies after disease (2.3 vs. 3.0, $p = 0.01$). Wong's score greater than or equal to 4 predicted lower birth weight ($p = 0.04$). ITAS, ITAS-A, DEI. Tak and TADS could not predict obstetric outcomes, and ITAS score exhibited moderate correlation with DEI. Tak ($r = 0.78$) and TADS ($r = 0.58$).

Conclusion: Women with TA suffer from extremely high risk of poor maternal and foetal outcomes. Wong's scoring can be useful to predict birth weight.

Keywords: Takayasu, Vasculitis, Pregnancy, Obstetric, Outcomes, Disease activity

Key messages

- Pregnancy in women with Takayasu's arteritis is associated with maternal and fetal morbidity
- Hypertension is the single most important complication
- Wong's score can predict outcomes in the neonate in TA

Introduction

Takayasu arteritis (TA) is a large vessel vasculitis predominantly found in Asian populations [1]. Recently various treatment options have come up, including multiple biologicals [2]. This, along with improved medical care, is bringing down mortality in this dreaded disease [3]. However, there is a lack of specific quality of life measures for Takayasu [4]. Thus, in the absence of specific measures, pregnancy outcomes could serve as an indirect measure of morbidity in this disease seen more often in females.

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Majorities of rheumatic diseases are more common in females, especially in the reproductive age group. Presence of rheumatic diseases often leads to lower fertility. This can be due to disease-related factors including drugs (impaired gonadal functioning, pregnancy loss, therapy-related avoidance of pregnancy) or due to psychosocial reasons (personal choice, depression leading to loss of libido, anxiety, altered self-image, etc) [5].

Takayasu is no different. It predominantly affects young women with a female to male ratio of 9:1. Most of the other vasculitis affect women beyond their reproductive years [6]. Still, overall fertility is reduced in vasculitis: pregnancy losses have been reported in around 10% of cases in granulomatosis with polyangiitis, up to 20% in eosinophilic granulomatosis with polyangiitis, 20–30% in Behçet's disease and up to 25–30% of TA in the developed world [7]. In a study in France, women with TA had a 13-fold higher risk of obstetric complications after diagnosis of pregnancy as compared to before [8]. Some studies have even shown no effect of TA on obstetric outcomes [9].

The scenario in India may be different [10]. In TA, it is well established that the pattern of vascular involvement differs by region with a plausible role of dynamic interactions of the genes with the environment. Vascular dynamics in pregnancy are likely to be differentially affected depending on vessel involvement. Type V with predominant abdominal aorta is most common in Indian patients [11].

The obstetric outcomes in Indian women are lesser known. The first series reported from India was from an institute in Northern India of 12 patients with 24 pregnancies (1979–1999, [12]. The authors followed this up with a second series (1999–2008) with 37 pregnancies in 15 women [13]. Another series is available from Eastern India which reported 16 patients with 29 pregnancies [14]. However, these were mostly Ishikawa Group IIa.

Also, the utility of outcome measures for disease activity such as ITAS [15] and DEI.TaK and for damage (TADS) [16] for prediction of pregnancy outcomes is unclear. A seminal paper by Wong et al. has suggested a score which can be used to predict fetal morbidity and gives room for pre-emptive escalated obstetric care [17].

Hence, we sought to explore the obstetric outcomes in patients with TA by comparing them in women who conceived before and after disease onset. In addition, the

predictive value of ITAS, DEI. Tak, TADS and Wong's score were tested for association with obstetric outcomes.

Methods

This was a retrospective study in a cohort of patients from a single tertiary care centre in Northern India. Ethics permissions were taken from the institute ethics committee. All women with Takayasu's arteritis by 1990 ACR criteria, above 18 years of age, were recruited. Data on demographic parameters, clinical profile and comorbidities were collected from hospital records and supplemented by a personal or telephonic interview in July 2017. Patients with age of disease onset more than 40 years were excluded. Where available, angiography records, ITAS, ITAS-A (ITAS with acute phase reactants), DEI.TaK and TADS scores were retrieved from the records. Data from all sources were used to calculate the Wong's prognostic score for newborns (Table 1).

Outcomes included fertility and pregnancy outcomes. Fertility outcomes were early menopause (defined as presence of sustained amenorrhea for more than 1 year after attaining menarche, before 40 years of age), deferring pregnancy due to disease process, inability to conceive, and abstinence due to drugs or disease activity. Data on contraception use was also collected.

Pregnancy outcomes were divided into maternal and fetal outcomes. Maternal outcomes were flare of disease, hypertensive diseases of pregnancy, diabetes, abortions (spontaneous or induced), stillbirths and live-births. Fetal outcomes were prematurity, low birth weight, congenital anomalies, or neonatal deaths.

Data analysis was carried out using GraphPad Prism® 7 and SPSS® 20 software. Since data was mostly non-parametric, it was represented as median (Intra-quartile range: IQR). Fisher's Exact test for comparing proportions and Man-Whitney U test for comparing means were used. To estimate the effect of disease on various outcomes, the pregnancies before disease onset were taken as controls. The relative risk of different outcomes was calculated. Two mixed generalised models with age, duration of disease, diagnostic category, education status, place of residence, and age at conception as covariates was used to determine the factors influencing maternal and foetal outcomes respectively.

Table 1 Wong's prognostic scoring for neonate born to mother with Takayasu's arteritis

Score	Involvement of abdominal aorta	Trimester when treatment started	Highest Mean arterial pressure in 3rd Trimester	Super-imposed pre-eclampsia
0	No	1st	< 100	None
1	Yes	2nd	101–130	3rd Trimester
2	Yes + Renal involvement	3rd	> 130	1st-2nd Trimester

Results

Clinical profile of patients with TA

Sixty-four women with median age and disease duration 29 (IQR 24–38) years and 5 (4–10) years respectively were interviewed. Median age at menarche was 13 (12.5–15) years. Menstrual patterns were unchanged after the onset of disease. Five (7.8%) were post-menopausal. Median age at menopause was 44 (40–47.5) years. Table 2 highlights the demographic profile of the patients.

Social impact and conception

Fifteen of the 64 interviewed (23.4%) were unmarried, and six (40%) of them attributed it to the disease. Of those who were married, 25 wished to conceive, but 8 (32%) decided against due to the disease. One had infertility with no other cause found and the infertility was attributed to Takayasu by the treating physician.

Of the forty-nine married women, 32 had discussed contraceptive issues with their physicians. The others had declined due to personal preferences or lack of need. Barrier method was the most common ($n = 21$) mode of contraception.

Table 2 Demographic profile of interviewed patients

Characteristics	Women with TA ($n = 64$)
Age ^a	29 (24–38)
Disease duration ^a	5 (4–10)
Age of disease onset ^a	22 (18–30)
Clinical Profile	N
Type of TA (Angiographic)	
I	15 (23.4)
IIb	4 (6.2)
III	2 (3.1)
IV	1 (1.6)
V	32 (50)
Unknown	10 (15.6)
Ishikawa type	
1	11 (17.1)
2	26 (40.6)
3	12 (18.8)
Unknown	15 (23.4)
Outcome Measures ($n = 44$)	
ITAS	13 (7–16)
ITAS A	15 (7.25–18)
DEI.Tak	12.5 (9–16.75)
TADS	8 (6.5–10)

^ain years [Median (IQR)]. For abbreviations (see text)

Obstetric outcomes in TA

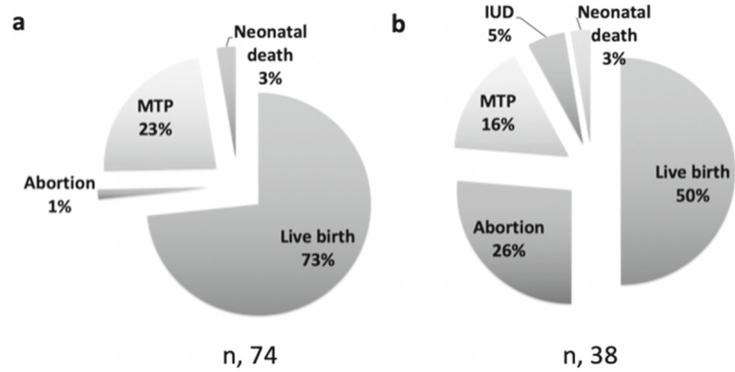
Seventy-four conception events occurred before the diagnosis of TA in 30 women while 38 were after the diagnosis in 26 women (Table 3).

Out of 38, there were 10 spontaneous abortions, 6 medical termination of pregnancy (MTP) and 19 live births (Fig. 1). Of the live births, 10 had foetal morbidity (Table 4). Six had low birth weight and one each had neonatal sepsis and meconium-stained liquor. Four of the six MTPs were advised due to inadvertent iatrogenic exposures (2 Methotrexate, 1 Azathioprine, and Computed tomogram (CT) scan done with foetus in utero) at another hospital and one due to uncontrolled hypertension while for the sixth one reason was unclear. Of maternal complications, hypertension was the most common, seen in 15 pregnancies of the 38, most often in the last trimester (Table 4). Of the 11 children whose birth weight was available, 6 had weighed normal at birth while 4 were of low birth weight and one was macrosomic.

Table 3 Women with TA who conceived before or after the diagnosis

Characteristic	Patients with conception before the diagnosis of TA ($n = 30$)	Patients with conception concurrent or after the diagnosis of TA ($n = 26$)
Age ^a	40 (32–44.5)	30 (27–33.5)
Disease duration ^a	7 (4–14)	6.5 (3–11.8)
Age of disease onset ^a	30 (25–35)	23.5 (20.5–27.1)
Clinical Profile	N	
Type of TA (Angiographic)		
I	9 (30)	4 (15.4)
IIb	4 (13.3)	2 (7.7)
III	0	0
IV	0	0
V	15 (50)	16 (61.5)
Unknown	2 (6.7)	4 (16.7)
Ishikawa type		
1	5 (16.7)	4 (16.7)
2	14 (46.7)	10 (38.5)
3	6 (20)	4 (16.7)
Unknown	6 (20)	8 (30.8)
Outcome Measures ($n = 44$)		
ITAS	14 (7–17)	14.5 (9.3–17.8)
ITAS A	15.5 (7.3–20)	11 (2–20.5)
DEI.Tak	13 (9–17)	17 (12.5–19)
TADS	8 (6.5–11)	8 (7–10)

^ain years [Median (IQR)]. For abbreviations (see text)



IUD, Intra-uterine death; MTP, Medical Termination of pregnancy; n, number of patients

Fig. 1 Obstetric outcomes of conception before and after diagnosis of TA. **a** and **b** Obstetric outcome before and after the diagnosis of TA respectively. IUD, Intra-uterine death; MTP, Medical Termination of pregnancy; n, number of patients

Peripartum diagnosis of disease

Eight women had a diagnosis of TA during pregnancy, of which only 2 had prior (undiagnosed) symptoms.

Comparisons between obstetric outcomes before and after onset of TA

Obstetric complications were more common in pregnancies after the onset of TA as compared with those before (RR = 1.5, $p = 0.01$. Figure 1). Pregnancies after TA onset had higher maternal complications (RR = 3.9 (1.8–8.5),

Table 4 Maternal and fetal complications in conceptions before and after diagnosis of Takayasu arteritis

Obstetric outcomes	Before TA (n = 74, %)	After TA (n = 38, %)
Maternal complications		
Hypertension	1 (1.3)	15 (39.4)
Post-dated	0	2 (5.2)
Gestational Diabetes	0	2 (5.2)
Premature rupture of membranes	1 (1.3)	1 (2.6)
Prolonged labour	1 (1.3)	1 (2.6)
Jaundice	0	1 (2.6)
Polyhydramnios	0	1 (2.6)
Post-Partum Haemorrhage	2 (1.6)	0
Anti-Partum Haemorrhage	1 (1.3)	0
Fetal complications		
Low Birth Weight	2 (1.6)	6 (15.8)
Preterm	4 (5.4)	2 (5.2)
Congenital malformation	1 (1.3)	0
Meconium stained Liquor	1 (1.3)	1 (2.6)
Neonatal sepsis	0	1 (2.6)
Neonatal jaundice	1 (1.3)	0

$P < 0.001$) as well as fetal complications (RR = 2.0 (1.2–3.4), $p = 0.001$). Conception after the diagnosis of TA was more likely to result in abortions as compared to conception before TA diagnosis (RR 3.6, $p < 0.0001$).

Baby weight at birth was lower in pregnancies after disease diagnosis (2.3 kg vs 3.0 kg, $p = 0.01$). Wong’s score ≥ 4 was associated with lower birth weight ($p = 0.04$). ITAS, ITAS A and TADS ($n = 15$) at baseline could not predict outcomes (Area under Curve - 0.5 & 0.7) and did not correlate with Wong’s score.

In the multivariate analyses, age at disease onset, disease duration, type of TA, ITAS, or TADS were not associated with obstetric outcomes, including maternal or fetal complications individually or combined.

Discussion

Women with TA had poor obstetric outcomes, with increased risk of maternal as well as fetal complications. Hypertension was the most common maternal complication. Peripartum diagnosis was established in 12.5% of all cases. Angiographic type, disease activity measures like ITAS, DEI.Tak and damage score TADS could not predict pregnancy outcome. However, Wong’s score envisaged neonatal outcomes.

Similar to our data, poor obstetric outcomes are seen in most series, though most lack a valid control group for comparison (Table 5) [8, 9, 12–14, 18–22]. Although hypertension is the most reported complication through most series, the percentages vary remarkably. While all prospective series describe hypertension in almost three fourths or more, all retrospective data sets (e.g. from Osaka and another multicentre from France), including the current one, describe HTN in 15–40% of women.

While most other studies describe live birth rates of around 80% (65–100%), our study had a lower percentage of live births (50%) [8, 9, 12, 13]. Implications from

Table 5 Comparison of obstetric outcomes in Takayasu arteritis across the world

Centre (year of publication)	No of Pregnancies	Hypertension	Fetal complications	Live birth-n (%)	Maternal mortality	Wong's scoring	Disease active	Controls	Conclusion
Wong et al., Hong Kong (1983) [17]	19	16 (84.2%)	9 (60%)	15 (78.9%)	1 (5.2%)-MI	Yes	0	Yes-TA before diagnosis	IUGR can be predicted by scoring system
PGI Chandigarh, India(2000) [12]	24	22 (91.7%)	9 (52.9%)	17 (70.8%)	0	No	NA	No	Abdominal vessel disease & delay in care predict poor outcomes
University de Estado, Brazil (2012) [18]	11	7 (63.6%)	7 (63.6%)	11 (100%)	0	No	0	No	Close monitoring with combined care is useful; No disease activity seen during pregnancy
IPGMER, Kolkata, India (2012) [14]	29	29 (100%)	20 (86.9%)	23 (89.7%)	1 (5.8%)-CVA	Yes	NA	Yes-Healthy	Conception usually spontaneous, Disease not active
Osaka, Japan (2014) [19]	27	5 (18.5%)	4 (14.8%)	27 (100%)	0	No	3	No	Ishikawa stage II fares worse
Istanbul University, Turkey (2015) [20]	19	3 (16%)	1 (5.2%)	19 (100%)	0	No	2 (10.5%)	Yes-TA before diagnosis	TA pregnancies have favorable outcome
Multicentre Paris, France (2015) [21]	98	26 (27%)	13 (16.7%)	78 (79.6%)	0	No	6 (6.1%)	Yes-TA before diagnosis	Smoking and NIH score > 1 predict poor outcomes
CMC, Vellore, India [22]	16	7 (43.8%)	7 (43.8%)	16 (100%)	0	NA	4 (25%)	No	Good outcomes are seen in type V disease when in remission
Multicentric, Oslo, Norway (2017) [9]	37	17 (29.3)	12(32%)	25 (68)	0 (1 had stroke)	No	10(60%)	Yes-TA before diagnosis	Maternal and foetal outcomes were favourable.
Tel Aviv, Israel (2018) [23]	20	8/13 (61.5%)	9(45%)	13 (65%)	0	No	NA	No	Targeted treatment of high blood pressure emphasised
Ankara, Turkey (2019) [24]	22	8 (36.4)	18 (81.8%)	16 (72.7%)	0	No	5 relapsed during pregnancy	No	Almost half had disease relapse during pregnancy
Current study, Lucknow, India	38	15 (39.5%)	12 (63.2%)	19 (50%)	0	Yes	15 (7.25–18) ^a	Yes-TA before diagnosis	Wong's score useful, ITAS needs evaluation in larger cohort

MI myocardial infarction, NA Not available, NIH National Institute of Health indices index

^aMedian (IQR) CVA, cerebrovascular accident

the type of TA could be one factor although absence of uniform angiographic study in patients limits our ability to comment on that. In most other series angiographic type I and II predominate while our patients mostly had type V disease [8, 9]. This involvement of the abdominal aorta with or without renal artery involvement may be leading to pregnancy losses. Also noteworthy is that one-third (6 cases) had medical termination of pregnancy due to various reasons like unwanted pregnancy, conceived while on methotrexate, radiation exposure but only in one case reason was directly attributed to the disease (uncontrolled hypertension).

Poor obstetric care in a developing nation could be another reason. It has been previously shown from our hospital that women with inflammatory myositis, suffer from much poorer maternal outcomes than reported

from other countries [10]. However, since the type of TA and consequently patterns of vascular involvement also differ geographically, it might be difficult to allocate attributability to poor outcomes from disease phenotype viz. a viz. socio-economic impact.

While Wong's score for prediction of outcomes in neonates of mothers with TA has been described way back in 1983, it not being used in routine practice [8, 9, 12, 13]. In our scenario, this may, in fact, be the best predictor for poor neonatal outcome. The study from eastern India also had found similar significance of the Wong score [14]. The other study from Chandigarh, India also found that abdominal aorta involvement (one of the components of Wong's score) portends poorer obstetric outcomes [13]. The fact that Wong's score > 4 predicted low birth weight suggest that this simple tool

should find application in the clinic and rheumatologists and obstetrician should get together in this initiative to improve obstetric care in this morbid disease.

Another multicentre study from France found that (National Institute of Health) NIH score > 1 predicts poor prognosis [21]. Our data was limited, and we could not calculate the NIH score. However, the ITAS score or DEI.TaK or TADS score could not predict obstetric outcomes. This may be a type 2 error due to small numbers. But it is more likely that ITAS did not show a correlation because mostly the patients in remission had gotten pregnant. The fact that there was no correlation with the TADS score (as compared to the Wong score) seems to imply that abdominal aorta involvement and hypertension were better predictors than overall damage score. However, these need evaluation in a larger cohort. A recent study from India failed to establish utility of ITAS in 16 women although this could be as most women were in remission [22].

Peripartum onset of disease is seen in many autoimmune diseases [10, 24]. In TA which tends to be latent in a subset of individuals, the altered hemodynamics of pregnancy can lead to decompensation and consequent diagnosis. Our observations were comparable to those of others; although notably, only 25% of those diagnosed in the peripartum period had prior symptoms.

This study has the advantage of being one of the largest data set relating to obstetric outcomes from a single centre so far. The utility of TADS and DEI.TaK is being explored for the first time. However, the study has its limitations since data was collected retrospectively and used disease but not healthy controls for comparisons. The interviews can have a recall bias.

The results suggest that improved patient counselling and close watch for foetal well-being at a tertiary care centre should be provided to women of childbearing potential. Incorporation of Wong's score in the clinic can be useful to predict outcomes and institute higher priority care.

Conclusion

Women with Takayasu's arteritis suffer from 1.5-fold higher complications and poor maternal (RR 3.9) as well as fetal (RR 2.0) outcomes. Wong's scoring is useful to predict fetal outcomes.

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Authors' contributions

LG, DPM, SA, AJ and AZ co-wrote the manuscript and all authors have reviewed and approved it. LG, SA, and AZ compiled and analysed the data.

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Consent for publication

Yes

Competing interests

The authors declare that they have no competing interests.

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