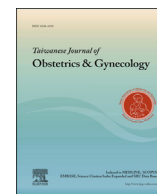


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Short Communication

Maternal and fetal outcomes in pregnant women with Takayasu aortoarteritis: Does optimally timed intervention in women with renal artery involvement improve pregnancy outcome?



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ABSTRACT

Objective: Takayasu aortoarteritis (TA) is common in the Southeast Asian and Indian subcontinent regions with a female-to-male ratio of 8:1. Age at diagnosis is < 30 years in 90% of the cases. Because the disease is common in women of child-bearing age, management of pregnancy in these patients becomes an important issue. The purpose of this study is to evaluate the maternal and fetal outcomes in pregnancies with TA and also to evaluate whether early intervention for renal artery involvement is associated with improved outcomes.

Materials and methods: We collected data of 12 patients with 18 pregnancies prospectively from 2006 to 2012. The patients were divided into three groups and their outcomes were noted: (1) without renal artery involvement; (2) with renal artery involvement without intervention; and (3) with renal artery involvement for which intervention has been done.

Results: Body mass index of patients was between 18.5 kg/m² and 23.2 kg/m². Renal artery involvement and hypertension were seen in four patients. One patient had percutaneous transluminal balloon angioplasty and another had renal artery stenting. In patients without renal artery involvement, gestational hypertension was seen in 50%, pre-eclampsia in 10%, abortion in 10%, and intrauterine growth restriction (IUGR) in 40% of pregnancies. In patients with renal artery involvement without intervention, gestational hypertension was seen in 90%, pre-eclampsia in 20%, abortion in 60%, preterm in 20%, IUGR in 20%, fetal demise in 20%, and neonatal death in 20% of pregnancies. In patients with renal artery involvement for which intervention has been carried out, gestational hypertension was seen in 66%, and abortion and IUGR were seen in 33% of pregnancies.

Conclusion: Patients with renovascular involvement without intervention are at high risk of having maternal and fetal complications. Early intervention prior to conception in these women is recommended to prevent pregnancy complications.

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Introduction

Takayasu aortoarteritis (TA) is panarteritis of the aorta, great vessels, and renal and pulmonary arteries. The arterial lesions can lead to secondary hypertension, retinopathy, cardiac involvement, cerebrovascular events, and premature death [1]. The prevalence of TA is reported to be in the range of 2.6–6/million in the general

population, and is common in the Southeast Asian and Indian subcontinent regions with a female-to-male ratio of 8:1. Age at diagnosis is < 30 years in 90% of the cases [2]. Because the disease is common in women of child-bearing age, management of pregnancy in these patients becomes an important issue. The disease is characterized by an early inflammatory phase, which is associated with nonspecific signs and symptoms such as fever, arthralgias, and weight loss, and a late occlusive or pulseless stage. Compared with the Western population with TA, where aortic arch involvement is common, the Asians have more common involvement of the abdominal aorta and renal arteries. There is paucity of data on pregnant women with Takayasu disease in Western literature. Only

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eight case series with 210 pregnancies have been reported to date [3–10]. The course of disease seems to be neither affected nor worsened by pregnancy unlike other autoimmune disorders. Many authors have reported adverse maternal and fetal outcomes during pregnancy but the outcome appears to be good with uncomplicated Takayasu arteritis. The outcome mainly depends on the maternal vascular involvement, severity of hypertension during pregnancy, presence of superimposed pre-eclampsia, and early institution of proper management. The optimal management for pregnant patients with TA is not yet defined due to the rarity of this condition. We herein present a series of pregnant patients with Takayasu arteritis who presented to us during the period between 2006 and 2012. We tried to correlate the disease severity and renal artery involvement with maternal and fetal complications.

Materials and methods

Study design and selection of patients

This was a prospective observational study. Being attached to a large cardiology referral center, TA is not an uncommon disease at our center. We started collecting data of this otherwise rare disease and performed analysis of prospectively collected data from 2007 to 2012 at a tertiary care hospital in Northern India. The patients were diagnosed on the basis of American College of Rheumatology Criteria, 1990, and supported by arterial Doppler findings. The criteria are as follows: age of disease onset <40 years, claudication of extremities, decreased brachial artery pulse, blood pressure difference of >10 mmHg, bruit over the subclavian arteries or aorta, and angiogram abnormality. Diagnosis of Takayasu arteritis requires that at least three of the six aforementioned criteria are met. We herein report the course and outcome of 18 pregnancies in 12 patients with Takayasu arteritis. Most patients (83%) were diagnosed with Takayasu arteritis prior to pregnancy. None of the patients was receiving any medical treatment for the disease remission. All the patients had spontaneous conception without any assisted reproductive technique. None of the patients underwent proper preconceptional counseling. The mode of presentation in these patients is shown in Figure 1.

The patients were classified according to Ishikawa's criteria into three groups (Groups I–III). Group I included patients without complications. Group II had one of the following complications: retinopathy, secondary hypertension, aortic regurgitation, and

arterial aneurysm; this group was subclassified into Class IIA and Class IIB according to the severity of each complication. Group III had two or more of the aforementioned complications. Two thirds of the patients in our series belonged to Ishikawa Group I, one fourth of patients belonged to Group II, and one twelfth belonged to Group III. The fetal and maternal complications in the three Ishikawa groups are mentioned in Table 1.

Doppler imaging of major vessels including renal vessels was performed in all the patients. Vascular involvement is shown in Figure 2. Renal artery involvement was seen in four patients. We observed that patients with renal artery involvement without any intervention had worst pregnancy outcomes. The pregnancy outcome in patients with and without renal artery involvement is discussed in the next section and summarized in Table 2.

Results

Patients without renal artery involvement

Eight patients with 10 pregnancies are reported in this group. The mean age of diagnosis of patients was 20 years. Body mass index of patients was in range of 18.5–23.2 kg/m². None of the patients had hypertension prior to pregnancy. The gestational age at presentation to us varied between 6 weeks and 24 weeks. Unilateral or bilateral radial pulse was not palpable in any of our patients except one. Erythrocyte sedimentation rate (ESR) was elevated in 40% of the patients. Lupus anticoagulant was negative in all the patients. Blood and urine investigations were normal. Electrocardiogram and echocardiography were normal in all the patients except for the patient with dilated cardiomyopathy. Her echocardiography revealed Type III diastolic dysfunction along with severe systolic dysfunction. There was evidence of mild aortic and mitral regurgitation and the left ventricular ejection fraction was 35%. She was started on oral furosemide (40 mg o.d.) and carvedilol (3.125 mg b.d.). Her Doppler imaging showed abdominal aorta involvement. The ejection fraction decreased from 35% at 12 weeks of gestation to 20% at 36 weeks of gestation. She was started on oral digoxin (0.25 mg o.d.) along with furosemide and carvedilol. She went into spontaneous labor at 39 weeks of gestation and had a ventouse-assisted delivery under epidural analgesia (birth weight 2590 g).

One patient had first-trimester missed abortion and was induced by vaginal misoprostol. Five of ten (50%) pregnancies had

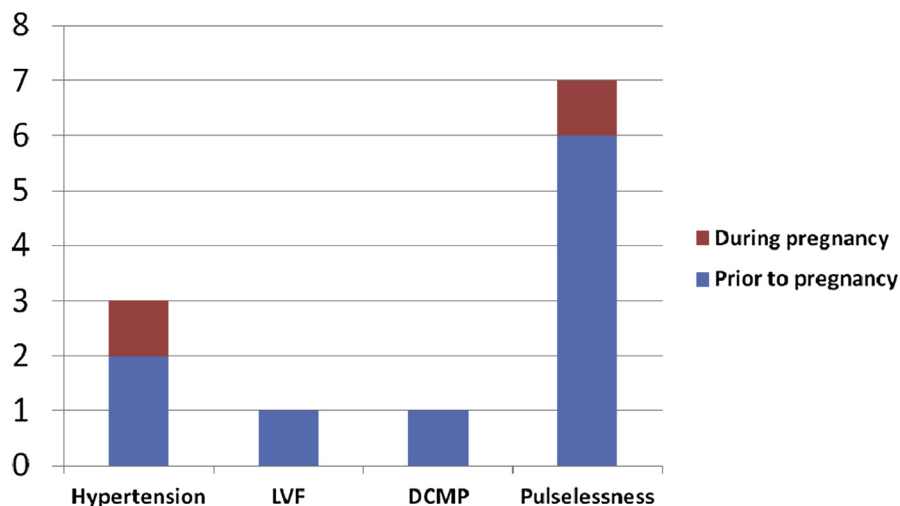


Figure 1. Mode of presentation in patients ($n = 12$). DCMP = dilated cardiomyopathy; LVF = left ventricular failure.

Table 1
Maternal and fetal complications in all the pregnancies (n = 18) divided according to Ishikawa groups.

Complications		Group I (n = 9)	Group IIa (n = 1)	Group IIb (n = 4)	Group III (n = 4)
Maternal	Gestational hypertension	4	—	1	3
	Pre-eclampsia	1	—	—	1
	Worsening of ejection fraction	—	—	1	—
Fetal	Abortion	1	—	1	3
	Intrauterine growth restriction	3	1	1	1
	Preterm	—	—	—	1
	Intrauterine device	—	1	—	—
	Neonatal intensive care unit admission	1	—	—	1
	Neonatal death	—	—	—	1

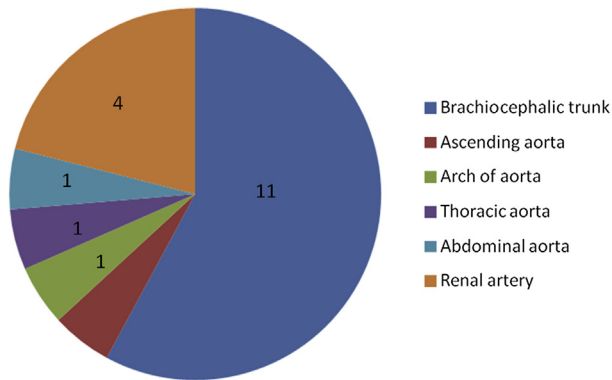


Figure 2. Arterial involvement in patients.

hypertension (4 had gestational hypertension and 1 had pre-eclampsia). Four patients required single drug (alpha-methyl-dopa) and one patient required two drugs (alpha-methyl-dopa and labetalol). The patient having pre-eclampsia had fetal growth restriction and was induced at 39 weeks (birth weight 2300 g). One patient with a history of second-trimester abortion in previous pregnancy was given prophylactic low-molecular-weight heparin (enoxaparin 40 mg subcutaneous o.d.) throughout pregnancy to improve placental perfusion. She was induced at 39 weeks because of gestational hypertension and delivered vaginally (birth weight 2700 g). Three patients were induced by cervical prostaglandin E₂ gel at 38–39 weeks of gestation due to hypertension. One patient delivered vaginally (birth weight 2900 g) and two had emergency cesarean section due to failed induction and fetal bradycardia (birth weight 2800 g and 2600 g, respectively). Three patients (33.3%) had intrauterine growth restriction (IUGR) diagnosed at 32–34 weeks of gestation and labor had to be induced at 37–39 weeks. Two patients delivered vaginally. Cesarean section was performed in one patient because of fetal bradycardia, and the baby had to be kept in neonatal intensive care unit for 3 days due to respiratory distress (birth weight 2320 g).

Table 2
Maternal and fetal complications in patients classified on the basis of renal artery involvement.

Complications		No renal artery involvement (n = 10)	Renal artery involvement	
			With intervention (n = 3)	Without intervention (n = 5)
Maternal	Hypertension	5	2	5
	Pre-eclampsia	1	0	1
Fetal	Abortion	1	1	3
	Intrauterine growth restriction	4	1	1
	Intrauterine device	—	—	1
	Neonatal intensive care unit admission	1	—	1
	Neonatal death	—	—	1

Patients with renal artery involvement with intervention

Two patients with renal artery involvement had intervention prior to conception. One had hypertensive crisis leading to left ventricular failure at the age of 21 years. She was diagnosed as TA thereafter, and had undergone stenting of the bilateral renal arteries. She required antihypertensives after the procedure. She had two pregnancies, the first being a missed abortion at 8 weeks. In the second pregnancy, she had hypertension and mild proteinuria. She was induced at 38 weeks' gestation because of hypertension and mild IUGR, and delivered vaginally (birth weight 2460 g).

Another patient had percutaneous transluminal balloon angioplasty of the left renal artery at the age of 16 years when she had developed severe uncontrolled hypertension. She remained normotensive after the intervention. She had a successful pregnancy outcome without any hypertension or growth restriction. She went into spontaneous labor and delivered vaginally at 37 weeks with birth weight of 2800 g.

Patients with renal artery involvement without intervention

Two patients had renal artery involvement and had no prior intervention for it. ESR was raised in both the patients. The first patient was diagnosed during pregnancy at the age of 21 years due to hypertension and pulselessness. She had deranged renal function tests at presentation with blood urea of 96 mg/dL and serum creatinine of 1.9 mg/dL. She also had gross proteinuria at presentation. Dilated fundus examination showed Grade II hypertensive retinopathy. Magnetic resonance imaging revealed shrunken bilateral kidneys (Figure 3). She was on atenolol (50 mg) for blood pressure control prior to pregnancy. She had four pregnancies registered with us. In three pregnancies, the patient presented to us with fetal demise at 9 weeks, 10 weeks, and 19 weeks and aborted spontaneously. In the fourth pregnancy, the patient presented to us at 6 weeks of gestation. We started her on low-molecular-weight heparin (enoxaparin 40 mg subcutaneous o.d.) along with antihypertensives. She required four drugs in maximum doses (alpha-methyl-dopa, labetalol, nifedipine, and prazosin) for blood pressure control. Despite all these measures, she had early onset IUGR at 24

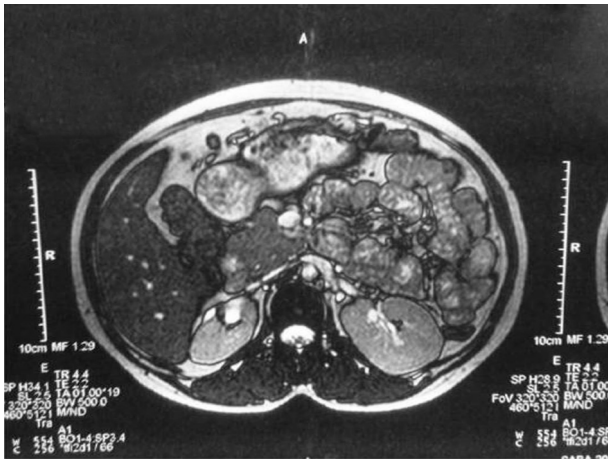


Figure 3. Magnetic resonance imaging reveals shrunken bilateral kidneys.

weeks of gestation. She was followed up by serial Doppler velocimetry. At 29 weeks of gestation, her fetal Dopplers were deranged with reversal of flow in ductus venosus. We performed an elective cesarean section at 29 weeks and delivered a baby weighing 900 g. The neonate was kept in the neonatal intensive care unit but died on the 25th day due to septicemia.

The second patient with renal artery involvement also had a poor obstetric outcome. She had renal asymmetry seen on ultrasonography; however, other investigations were normal. Magnetic resonance angiography showed renal arterial involvement (Figure 4). She also had hypertension and early onset IUGR at 26 weeks of gestation. She was on two drugs for blood pressure control. Unfortunately, she had intrauterine fetal demise at 29 weeks of gestation. The patient had spontaneous vaginal delivery at 30 weeks.

Postnatal follow-up

All of the patients were discharged with contraceptive advice and postpartum follow-up was done in all of the patients. The three

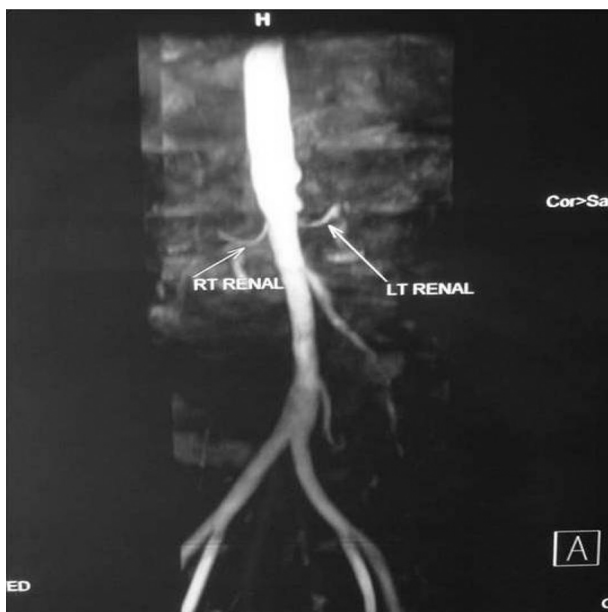


Figure 4. Magnetic resonance angiography shows renal arterial involvement.

patients with renovascular hypertension required antihypertensives after delivery too. Others did not require any antihypertensive. The patient with dilated cardiomyopathy continued diuretic and digoxin medications. Both of the patients with renal artery involvement without intervention were advised to receive renal artery stenting. The procedure could not be performed in the first patient because both her renal arteries were completely stenosed and there was a development of collaterals from the intercostal vessels to the kidneys. Hence, she was planned for angioplasty. They continue to be under follow-up in the cardiovascular department for performing interventions. They were also advised to plan their next conception after these interventions for a better outcome.

Discussion

There are several case series of pregnancies with TA (Table 3). Young women in the child-bearing age group are usually affected by this disease, and therefore, pregnancy management in these patients is critical. The age group of pregnant patients with TA, as reported in various studies, ranges between 15 years and 35 years [3–11]. In our series, the age of patients ranged from 22 years to 28 years. Most patients are diagnosed prior to conception and they may present with fatigue, myalgia, arthralgia, and low-grade fever in initial stages and intermittent claudication, visual defects, and fainting attacks in later stages. Many may be diagnosed after clinical examination, when one or more peripheral pulses are not palpable or blood pressures vary in two limbs. The classic sign of TA (i.e., pulselessness) was seen in 91.6% of the patients in our series, which is almost similar to other studies (range, 85–95%) [1,12]. Patients may also present with other dreaded complications such as myocardial ischemia, accelerated hypertension, pulmonary hypertension, cardiac failure, and dilated cardiomyopathy. One patient (8.3%) had dilated cardiomyopathy in our case series. It is reported to be seen in 5.58% of patients with TA in another series [13]. Pre-pregnancy hypertension was seen in 25% of our patients; other studies reported it to be varying from 20% to 60% in TA patients [14,15]. The mean age of onset of symptoms, as reported in a large case series on TA, is 24.0 ± 8.8 years [1]. Our patients have a mean age of diagnosis of 20 years. The earlier diagnosis among our patients may be due to increased health awareness among population and advances in health care facilities with time. Patients in this series did not have any element of infertility and all of them had spontaneous conception. Pregnancy should be planned in disease remission phase for better outcomes [16]. Preconception counseling is necessary regarding appropriate adjustment of dosage or cessation of cytotoxic drugs, folic acid supplementation in the periconceptional period, and optimal timing of pregnancy. The drugs used in TA are corticosteroids, cytotoxic agents such as cyclophosphamide and methotrexate, antihypertensive agents, antiplatelet drugs, anticoagulants, and immunosuppressants such as azathioprine. None of our patients were on corticosteroids or cytotoxic agents. ESR was elevated in 50% of our patients, compared with 45.5% in a large study involving 88 patients [1]. Renal function test was mildly deranged in one patient (8.3%) and none of the patients had renal failure, whereas in another study mild renal function derangement was seen in 1.25% of patients and renal failure was seen in 4.5% of patients [17]. Proteinuria was seen in 16.7% of patients in our series whereas a prior study reported it in 37.5% of patients [17]. There are also case reports of TA with positive lupus anticoagulant test results [18]. Aortic and mitral regurgitation were seen in one patient in our series, whereas they were found in 40.7% and 25% of patients, respectively, in another study [19]. Fundus examination showed hypertensive retinopathy in one patient in our series, whereas it was seen in 25% of the patients in

Table 3
Maternal and fetal outcomes in previously reported case series.

Study	No. of patients	Total pregnancies	Maternal complications	Obstetric outcome
Hidaka et al, Japan (2012) [10]	10	26	Aortic regurgitation, 6; pregnancy-induced hypertension, 2	Spontaneous abortion, 6; MTP, 3; IUGR, 2
Mandal et al, India (2012) [9]	16	29	Gestational hypertension, 100%; pre-eclampsia, 92.85%; PPH, 72.84%; CVA, 3.4%	IUGR, 51.72%; neonatal intensive care admission, 58.62%
Hernández-Pacheco et al, Mexico (2011) [8]	7	7	Pre-eclampsia, 3	IUGR, 2
Suri et al, India (2010) [7]	15	37	Gestational hypertension, 27%; pre-eclampsia, 62%; abruptio placentae, 2.7%; maternal death, 2.7%	IUGR, 16%; preterm delivery, 16%
Sharma et al, India (2000) [6]	12	24	Severe hypertension, 11; CHF, 2	Abortion, 2; IUD, 5; IUGR, 5; preterm, 4
Takeshi et al, Taiwan (1992) [5]	15	23	Hypertension, 13	MTP, 4 (active disease); IUGR, 6
Wong et al, China (1983) [4]	13	30	Hypertension, 14	IUGR, 9; abortion, 4
Ishikawa et al, Japan (1982) [3]	27	33	CVA, 1; severe hypertension, 6	Abortion, 1; IUGR, 5; preterm, 2
This study	12	18	Gestational hypertension, 5; pre-eclampsia, 2; aortic & mitral regurgitation, 1; worsening of EF in DCMP, 1	Abortion, 5; IUD, 1; IUGR, 5; preterm, 1

CHF = congestive heart failure; CVA = cerebral vascular accident; DCMP = dilated cardiomyopathy; EF = ejection fraction; IUD = intrauterine device; IUGR = intrauterine growth restriction; MTP = massive transfusion protocol; PPH = postpartum hemorrhage.

another study [1]. Renal ultrasound revealed asymmetry in 25% of patients in our series. One previous study reported renal asymmetry in 50% of patients with Takayasu disease [20]. Doppler examination of vessels in our patients showed aortic involvement in 16.7% of patients and renal artery involvement in 25% of patients, whereas in other study aortic and renal artery involvement was seen in 91% and 75%, respectively [6]. The most common maternal complication, as reported in prior studies, is severe pre-eclampsia [3–10]. Other maternal complications associated with TA are placental abruption, hypertensive retinopathy, intrapartum subarachnoid/intracranial hemorrhage, aortic regurgitation, and nephrotic syndrome. Gestational hypertension is the most common maternal complication, seen in 27.8% of our patients. Mandal et al [9] reported this condition in all patients they reported ($N = 29$). In other series, it ranges from 7% to 56.5% [4–11]. Pre-eclampsia also has a higher prevalence in patients with TA than normal pregnancies. Although some have not reported pre-eclampsia in their series, others have reported it to be seen in as high as 93% of patients [9]. It was seen in 5.6% of patients in our series. A prior study suggests that administration of antihypertensives (methyldopa or nifedipine) at early gestation improves maternal and fetal outcomes [4]. Drugs used to control blood pressures in our patients were alpha-methyldopa, labetalol, nifedipine, prazosin (administered in the order presented). One patient in our series had been diagnosed with dilated cardiomyopathy and she had worsening of ejection fraction during pregnancy. Aortic and mitral regurgitation has been reported earlier to complicate pregnancies with TA as seen in this patient [10]. This patient had an otherwise favorable outcome and the reason may be no renal involvement or renovascular hypertension. Previous studies also reported other complications such as cerebrovascular accidents, congestive heart failure, abruption placentae, postpartum hemorrhage, and even maternal death [7,9]. These complications were not seen in our patients. The fetal complications associated with TA are abortions, preterm deliveries, IUGR, and fetal demise. Spontaneous abortion was seen in 27.7% of pregnancies in our series, whereas it was reported to be 3–19% in various studies [3,6,10]. IUGR was seen in 27.7% of pregnancies in our series. It varied in the range of 7.7–51.7% in various studies [3–10]. Intrauterine fetal demise was seen in one patient (5.5%) in our series; others have reported it to be in 20.8% of cases [6]. Preterm delivery was reported in 5.5% of patients in our series. Others have reported it to range between 6% and 16% [3,6,7]. Because of the high incidence of maternal and fetal complications such as growth restriction and hypertension in pregnancies with TA, requirement for induction of labor is more in these patients (40% of our cases). The rate of cesarean section was

28.5% in our patients, whereas some have reported it to be as high as 57% [21]. In our series, the gestational age ranged between 29 weeks and 40 weeks and average birth weight was 2455 g. Another study reported a gestational period ranging from 34 weeks to 40 weeks and the birth weight from 1425 g to 3024 g [21]. Thromboprophylaxis is recommended by some for patients with TA as they might be associated with antiphospholipids antibodies, especially those of Oriental origin [18,22,23]. We also used thromboprophylaxis in two pregnancies. One had a favorable outcome. The other patient with renal artery involvement without intervention had severe fetal growth restriction despite thromboprophylaxis treatment and eventual neonatal death. The cause of poor obstetric outcome in this patient was severe renovascular hypertension due to bilateral renal arterial involvement. Use of low-molecular-weight heparin prolonged the duration of pregnancy as her previous demises were prior to 19 weeks of gestation. The routine use of low-molecular-weight heparin prophylaxis in these patients needs elucidation.

We observed that the patients in the higher Ishikawa group had higher maternal and fetal complications as expected. It was also observed that renal artery involvement led to poorer maternal and fetal outcomes. We also observed that patients with renal artery involvement, who had early interventions (angioplasty and stenting), had a favorable outcome as compared with those with and without any intervention for renal arterial involvement. The complications in the intervention group are comparable to patients without renal artery involvement. Delay in intervention can lead to increased surgical risks and difficulties. Therefore, we recommend that early intervention in TA patients with renal artery involvement, when damage is not irreversible, is beneficial.

In conclusion, young women diagnosed with TA need proper preconceptional counseling. Planning of pregnancy during the disease remission state is necessary to reduce maternal and fetal risks. Early intervention prior to conception in women with renal artery involvement is recommended to prevent complications in pregnancy. Patients with renovascular involvement and subsequent hypertension are at high risk of having maternal and fetal complications. Pregnancies with TA should be managed with a multidisciplinary approach. Adequate blood pressure control in pregnancy by judicious use of antihypertensives is the mainstay of management. Role of low-molecular-weight heparin in pregnancy with TA is controversial.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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