Update on Takayasu's arteritis in pregnancy

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Abstract:

Takayasu's arteritis (TAK) is an inflammatory large-vessel vasculitis of unknownorigin, affecting primarily the aorta andits branches. It has been reported all over the world, with wide variation in its prevalence in different geographic areas. TAK is more characteristic inthe chronic phase, when it exhibits a patchy, transmural fibrous thickeningresulting in multiple vascular obstructions that lead to ischemic changes of the supplied tissues. Consequently, Clinical features are related to theaffected artery and thus diagnosis is based on signs and symptoms, inflammatory markers, and arteriography.It predominantly affects women of reproductive age. And it appearsthat the hemodynamic changes during pregnancy further exacerbate the pathologic cardiovascularmanifestations of the disease, thereby negativelyimpacting both mother and fetus. Pregnancy does not interfere on disease progression, although hypertensive complications such as preeclampsia and exacerbation of chronic hypertension, and fetal complications such a restriction of intrauterine growth, abortion, and fetal death have been reported. Prognosis is specially basedon severity of uncontrolled hypertension, timing of therapy, and extent ofarterial involvement. The mainstay of medical treatment is corticosteroids,which reach clinical remission in up to 60% of patients. The addition of cytotoxic agentsinduces remission in an additional 40%. Operative delivery (Cesarean section) is preferred for patients with stagesIIb or III.The maintenance of mean arterial

pressure (MAP) close to preoperative value is the main gaol of anesthetic managements.

The aim of our article is to present the epidemiological, genetic, clinical, therapeutic and anesthetic features of the management of TAK, especially during pregnancy. The data gathered is limited, and our work is proposed as a review of the literature gathering all that has been done in this case, and therefore insists on more research in this very interesting field.

Keywords: Takayasu's arteritis, pregnancy, preeclampsia, Anesthesia, Cesarean section.

Update on Takayasu's arteritis in pregnancy

Introduction:

In 1908, Mikito Takayasu, a Japanese ophthalmologist, reported the case of a 21-year-old woman with retinal arterio-venous anastomoses, syncope, and absent upper extremity pulses[1]. However, it is believed that the Italian pathologist Giovani Battista Morgani was the first reporting a case of Takayasu's arteritis (TAK) in 1761[2]. This disease is defined as an inflammatory large-vessel vasculitis of unknownorigin, affecting primarily the aorta andits branches[3]. It predominantly affects women of reproductive age. And it appearsthat the hemodynamic changes during pregnancyfurther exacerbate the pathologic cardiovascularmanifestations of the disease, thereby negativelyimpacting both mother and fetus[4].Optimal managementfor pregnant patients with this disease has not yet beenestablished. Due to the multiple cardiovascular complicationsthat can occur in the course of the disease, management of pregnancies in TAK patients is a challenge for the obstetrician,the anesthetist, the rheumatologist and the cardiologist[5].

The aim of our article is to present the epidemiological, genetic, clinical, therapeutic and anesthetic features of the management of Takayasu arteritis, especially during pregnancy. The data gathered is scattered and limited, and our work is proposed as a review of the literature gathering all that has been done in this case, and therefore insists on more research in this very interesting field.

Epidemiology:

TAK appears to be more common in persons of Asian ethnic origin although it has a worldwide occurrence[6]. In Japan an autopsy survey suggested a frequency of 1 in 3000 persons[7]. The incidence of TAKin North American studies was found to be 2.6 new cases/million/year[8- 9].In Europe, the prevalence rate is variable between 4.7cases/million population(in United Kingdom) [10]and 6.4 cases/million population (in Sweden) [11].

Females are more commonly affected, with women outnumbering men by 8-9:1[12]. The disease affects her in the reproductive years for almost 80% of the cases[13], with the peak incidence in the secondand third decades, although a substantial minority may present TAK in their teens[14] and up to 20% of patientsare diagnosed prior to age 19[12].

Pregnancy does not significantly affect the inflammatoryactivity of the disease. Wong et al studied 19 pregnancies in 11 patients and did not find any evidence of acute inflammatory exacerbation[15]. Although the majority of women with TAK do well in pregnancy and labor[16], those with secondary hypertensionand cardiac involvementmay be negatively impacted[5].

Pathogenesis:

TAK is a chronic inflammatory disease of unknown origin[5]. It represents agranulomatous vasculitis of medium and larger arteries, with a strongpredilection for the aortic arch, subclavian and extra-cranial arteries suchas carotids (60-90%)[17].Although it can affect other segmentsof the aorta as well as pulmonary and renal arteries[5].TAK is more characteristic inthe chronic phase, when it

exhibits a patchy, transmural fibrous thickeningresulting in multiple vascular obstructions[18] that lead to ischemic changes of the supplied tissues[19].The inflammation starts around the vasa vasorum and atmedio–adventitial junction, accompanied with a perivascular cuffing ofmononuclear infiltrate, mainly composed of CD4+/CD8+ lymphocytes,plasma cells and macrophages, then evolving to a panarteritis.Degeneration of elastic fibers is a striking feature and formation ofaneurysms can occur when both rapid and severe inflammation leads tothe loss of medial smooth muscle cells[20].

Consequently, Clinical features are related to theaffected artery. Subclavian and iliac arteries involvement present with limb claudication, carotid involvement may induce vertigo,and renal arterial lesions are associated with arterial hypertension, while some patients can progress toaortic insufficiency and congestive heart failure[16].

Genetics:

Genetic studies demonstrated HLA-B*52, and to a lesser extent B*67 in Japan, as the most important HLA alleles associated with TAK in different ethnicities[21]. Recently, the first two genome-wide association studies (GWAS) in patients from Turkey/USA and Japan confirmed another single nucleotide polymorphism association of TAK with IL-12B[22]and demonstrated a new one as FCGR2A/3A[23-24].The former study showed higher levels of IL-17 expression in aortic biopsies from patients with TAK[25].The latter study also showed higher levels of serum IL-23 in patients with TAK compared to healthy controls[26].

As novel biomarkers, Wang et al. found increased levels of apolipoprotein (Apo) B and lower ApoA1 and high-density lipoprotein-cholesterol (HDL-C) in patients with TAK[27]. That suggests a hitherto unknown role of lipids in driving pathogenesis of TAK. Other open-ended approaches may be appropriate to identify novel disease markers.

Classification:

Four types of TAK can be identified[28]:

- Type I: disease involving the aortic arch and its branches.
- Type II: lesionsrestricted to descending thoracic aorta and abdominal aorta.
- Type III: patients have characteristics of types I and II.
- Type IV: involvement of the pulmonary artery.

Ishikawa and Matsuura studied 27 Japanese women with TAK associated with 33 pregnancies and observed that the degree of severity of retinopathy, secondary hypertension, aortic regurgitation and arterial aneurysm wereparticularly significant indicators of maternal outcome. He classified patients into four stages[29].

- Stage I: no complications are observed.
- Stage IIa: patients have only one of these complications.
- Stage IIb: patients have onlyone of these complications, but the severe

form.

- Stage III: whenmore than one complication is present.

Diagnosis:

Diagnosis is based on signs and symptoms, inflammatorymarkers, and arteriography.

1. Common clinical features: the clinical picture can be divided into an early "prepulseless" systemicphase and a late occlusive phase.
    a. *Early "prepulseless" systemic phase*: it is dominated by generalized, nonspecificsymptoms, which include malaise, fever, night sweats, arthralgias,headaches, rashes (erythema nodosum or a lupuslike butterfly rash, whichcan be photosensitive), anorexia and weight loss[30].
    b. *Late occlusive phase*: Its manifestations include diminished orabsent pulses, mainly at the level of radial arteries; vascular bruits; renovascular hypertension; chronic mesenteric ischemia; retinopathy; aortic regurgitation (in case of ascending–aorta involvement); neurological symptoms, secondary to both hypertensionor ischemia (orthostatic hypotension and dizziness, seizures, fugal amaurosis, transient ischemic attacks, stroke, hemiplegia and paraplegia); myocardial injury and infarction; and limb claudication[31].
2. Pregnancy specificities: most cases of TAK during pregnancy have been reported in patients with known diagnosis prenatally, but each case is specific, depending on the location of the arterial lesions, the stage of the disease and the treatments in progress[32]. Few patients are asymptomatic and more than 60% have some kind of complication[33]. Pregnancy does not interfere on disease progression, although hypertensive complications such as preeclampsia and exacerbation of chronic hypertension, and fetal complications such a restriction of intrauterine growth, abortion, and fetal death have been reported in 60% to 90% of the cases[34].
    Cardiovascular manifestations due to TAK commonly (61.4%) have a negative effect on pregnancy, and these include congestive heart failure, aortic regurgitation, uncontrolled hypertension, stroke, hypertensive retinopathy, and asymmetric peripheral pulses[35].
3. Inflammatory markers: Erythrocyte sedimentation rate [ESR] and C-reactive protein are frequently advocated for disease assessment in TAK, despite being shown to be neither sensitive nor specific enough to

monitor disease activity. Serum autoantibodies such as anti-endothelial antibodies, circulating endothelial cells and serum biomarkers such as VEGF, IL-6, IL-8, IL-18, matrix metalloproteinase-9 and adipokines are also investigated[17].

Recently Pentraxin3 (PTX3), which is produced by immune and vascular cells in response to proinflammatory signals, is suggested as a biomarker for disease activity in patients with TAK[36].

4. Imaging of TAK: Arteriography, either traditional or magnetic resonance angiography, is the gold standard for delineating abnormal vessels in TAK. Typical findings include an irregular intimal surface, stenosis of the aorta or its branches, post-stenotic dilatations, saccular aneurysms, or the typical narrowed, "rattail" appearance.

   High-resolution duplex ultrasound technology maybe used to evaluate and monitor disease in the common carotid and subclavian arteries; however, this imaging modality is not useful for evaluation of the aorta[37]. But it has the advantages of avoiding the high radiation dosage of angiography, and is cheaper and more widely available, particularly relevant in countries with less resources where TAK is more common[17].

Differential diagnosis:

Its differential diagnosis is wide andit includes[38]:

- Other causes of large vessel vasculitis: syphilis,tuberculosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, seronegativespondyloarthropathies, Kawasaki disease, Behçet's disease, giant cell arteritis;
- Congenital abnormalities: Marfan syndrome, Ehlers Danlos syndrome;
- Traumaticinjuries;
- Genetic pathology: neurofibromatosis;
- Ergotis.

Prognosis:

Maternal death is rare (4.8%)[35]and intrauterine growth retardation is predictable basedon severity of uncontrolled hypertension, timing of therapy, and extent ofarterial involvement. Patients with abdominal aorticinvolvement and significant delay before seekingmedical attention have poor perinatal outcomes[39]. Also, when risk stratifying based on Ishikawa'scriteria, class IIB and class III have the poorest prognosisand pregnancy should be avoided, interrupted,or continued under conditions of hospitalization[15].

Treatment:

1. Medical treatments: The mainstay of medical treatment is corticosteroids, which reach clinical remission in up to 60% of patients[40]. The addition of cytotoxic agentsinduces remission in an additional 40%[41]. Unfortunately, relapse is common, and there is no

evidencethat clearly shows immunosuppressive therapyimproving long-term outcomes[35].

a. *Corticosteroids*: the first line in case of an outbreak of the disease during pregnancy, the recommended treatment usually combines the boluses of Methylprednisolone15 mg/kg/day (do not exceed 1 g) on three consecutive days with relay of Prednisone 1 mg/kg/day[32]for one month, which was then tapered after resolution ofsymptoms of active disease and normalization of acute-phase reactants.Prednisone dosage was reduced by 5 mg/week until reaching a dosage of20 mg/day[42].
b. *Immunosuppressive agents*: immunosuppressive agents are indicated forpatients with steroid resistance or in case of relapses. The safest immunosuppressant for women in pregnancy with TAK is Azathioprine (AZA)at 2 mg/kg/day. Other therapies, such as Methotrexate (MTX), are forbidden[32-43].
c. *Antihypertensive drugs*: hypertension should be treated with calcium channel blockers or alpha and beta-blockers. ACE inhibitors are contraindicated due to their fetal toxicity. In the case of subclavian arteries involvement, which is particularly common during TAK, taking blood pressure on the arm becomes unreliable because it underestimates the systemic pressure. The arterial pressure can be taking in the leg if absence of stenosis on the descending aorta[32].
d. *Anticoagulants*: patients with metallic valvular prosthesis should be maintained anticoagulated during pregnancy. The choice of medication should take into account the probable due date and reversibility of the method. Both vaginal delivery and cesarean section in an anticoagulated patient can lead to difficult bleeding control. Heparin should be discontinued 4 to 6 hours before anesthesia, and it can be reversed with protamine if the gravida goes into labor or in case of bleeding. Patients on prophylactic doses of enoxaparin should received their last dose 12 hours before anesthesia. In the case of therapeutic doses the drug should be discontinued 24 hours before anesthesia[33-44].

e. *Antibiotics*: prophylactic antibiotics should be used especially if aortic regurgitation is present to avoid infective endocarditis and puerperal sepsis[5].

2. Surgical intervention: patients with TAK requiring surgical intervention are a minority. Indications for surgery include uncontrolled hypertension, stenosis causing ischemic symptoms, and aneurysmalenlargement[35]. Endovascular surgery including percutaneous transluminal angioplasty and stent graft placement[45]. The surgical revascularization (open surgery), including surgical bypass grafting, patch angioplasty for short–segment lesions and endarterectomy[18]. In pregnancy, the patients with severe form of TAK needing surgical intervention may bebetter advised to avoid or even interrupt a pregnantstate.
3. Delivery managements: vaginal delivery, usually with epidural anaesthesia, isacceptable for patients in groups I, and IIa, although the durationof the second stage is often deliberately shortened byinstrumental delivery, particularly in hypertensive patients[15]. Operative delivery (Cesarean section) is preferred for patients with stagesIIb or III, but is reserved for specific obstetric indications in lessseverely affected individuals. Its aim is to avoid the increase inblood volume and arterial pressure found during uterine contractions.In association with the increased cardiac output normallyseen during pregnancy and labour, the likelihood ofcardiac decompensation is increased further and is bestavoided in these susceptible individuals[14].

Anesthetic management:

The main concern in conduction of anaesthesia in patientswith TAK is the maintenance of blood pressure during the perioperativeperiod. Indeed, we preloaded the patients with 20 ml/kg of Ringer's lactate, as these patients may not tolerate acute hypotension. The mean arterial pressure (MAP) should be maintained within 20% of the preoperative values[46].

Regional anesthesia is the technique of choice because itallows monitoring brain perfusion through the patient's level ofconsciousness. On continuous epidural fractionated doses oflocal anesthetic are administered and the level of the blockadecan be slowly titrated to maintain hemodynamic stability byreducing the need of vasopressors. Double block with low dosesof spinal local anesthetic to avoid sympathetic blockadeand hemodynamic instability is an alternative to continuousepidural anesthesia[47].

General anaesthesiainvolving endotracheal intubation, extubation and inadequatedepth may result in considerable fluctuations in blood pressureand may precipitate cerebral haemorrhage, rupture of aneurysmsand cardiac dysfunction in patients with TAK[48]. To avoid all this, induction of general anaesthesia should be very careful to avoid a hypertensive crisis during trachealintubation. In case when

general anesthesia is necessary brain monitoring is important. Options include electroencephalography[48]or transcranial Doppler[49], but there is noconsensus on which is the best method.

To avoid postoperative hypoperfusion of organs and hypertensivecomplications the patient should remain monitored inthe intensive or semi-intensive care unit for 24 hours[33].

Conclusion:

Takayasu's Arteritis (TAK) and pregnancy create a clinical and therapeutic challenging management. Despite his poorest outcomes, especially if the disease is active, pregnancydoes not significantly affect the inflammatoryactivity of the disease. And the maintenance of mean arterial pressure close to preoperative value should be a gaol to achieve favourable outcome. Indeed, management of pregnancies in TAKneeds careful patient evaluation, treatment of TAK complications, and anestheticsurgicalplanning.

Competing interest: The authors declare that they have no competing interests.

References:

1. Takayasu M. A case with peculiar changes of the retinal cerebral vessels [in Japanese]. Acta Ophthal Soc Jpn. 1908;12:554e555.
2. Lazzarin P, Pasero G, Marson P, et al. Takayasu's arteritis. A concise review and some observations on a putative case reported by Giovanni Battista Morgagni (1761). Reumatismo. 2005;57:305–13.
3. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis.N Engl J Med. 2003;349(2):160-169.
4. Kraemer B, Abele H, Hahn M, et al. A successful pregnancyin a patient with Takayasu's arteritis. Hypertens Pregnancy2008;27:247e52.
5. Dey M, et al., Takayasu arteritis in pregnancy, Medical Journal Armed Forces India (2015).04.013
6. Kerr GS, Hallahan CW, Giordono J, et al. Takayasu's arteritis. Ann Intern Med 1994;120:919–29.
7. Nasu T. Takayasu's truncoarteritis in Japan. A statisticalobservation of 76 autopsy cases. PatholMicrobiol (Basel)1975;43:140–6.
8. Hewill S, Barr W, Lie JT, et al. Takayasu arteritis study of 32North American patients. Medicine (Baltimore) 1985;64:89.
9. Jean Schmidt et al. Diagnostic Features, Treatment, and Outcomes of Takayasu Arteritis in a US Cohort of126 Patients. Mayo Clin Proc. 2013;88(8):822-830.
10. Waern AU, Andersson P, Hemmingsson A. Takayasu's arteritis: ahospital-regionbasedstudy on occurrence, treatment and prognosis.Angiology 1983;34:311–20.
11. Mathew AJ, Goel R, Kumar S, et al. Childhood-onset Takayasu arteritis: an update. Int J Rheum Dis. 2015. doi: 10.1111/1756-185X.12718.
12. Mitchell CS, Parisi MT. Magneticresonanceimaging of744 Takayasu's aortitis in an infant. J Am OsteopathAssoc 1997;97:607–9.
13. Ioscovich A, Gislason R, Fadeev A et al. – Peripartum anestheticmanagement of patients with Takayasu's arteritis: case series andreview. Int J ObstetAnesth, 2008;17:358-364.
14. Shashi Kiran, MamtaBhardwaj, Kiranpreet Kaur. Anaesthetic management in a parturientwith Takayasu arteritis. Egyptian Journal of Anaesthesia (2012) 28, 287–289.
15. Wong VC, Wang RY, Tse TF. Pregnancy and Takayasu'sarteritis. Am J Med. 1983;75:597e601.
16. Jesu´ s GR, Oliveira ICC, Santos FCD, et al. Pregnancy may aggravate arterial hypertension in women with Takayasuarteritis. IMAJ. 2012;14:725e728.
17. Alibaz-Oner F, Direskeneli H. Update on Takayasu's arteritis. Presse Med. (2015):01.015.
18. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review.J Clin Pathol. 2002;55(7):481-6.
19. Vaideeswar P, Deshpande JR. Pathology of Takayasu arteritis: Abriefreview.

Annals of PediatricCardiology 2013;6(1):52-8.

20. Hotchi M. Pathologicalstudies on Takayasu arteritis. HeartVessels 1992;7(1):11-7.
21. TeraoC,YoshifujiH,MimoriT.Recentadva ncesinTakayasuarteritis.IntJRheum Dis 2014;17:238–47.
22. Saruhan-Direskeneli G, et al. Interleukin (IL)-12, IL-2, and IL6 genepolymorphisms in Takayasu'sarteritis fromTurkey.HumImmunol 2006;67:735–40.
23. Saruhan-DireskeneliG,et al.Identification of multiple genetic susceptibilityLociin takayasu arteritis. AmJHumGenet 2013;93:298–305.
24. Terao C, et al.Twosusceptibilitylocito Takayasuarteritis reveal asynergisticrole of the IL12BandHLA-Bregionsina Japanese population. Am JHumGenet 2013;93:289–97.
25. Saadoun D, Garrido M, Comarmond C, et al. Th1 and th17 cytokines drive inflammation in takayasu arteritis. ArthritisRheumatol. 2015;67:1353–1360.
26. Misra DP, Chaurasia S, Misra R. Increasedcirculating Th17 cells, serum IL-17A, and IL-23 in Takayasu arteritis. Autoimmune Dis. 2016;2016:8.
27. Wang X, Chen B, Lv N, Liu Q, Dang A. Association of abnormallipidspectrum with the diseaseactivity of Takayasu arteritis. Clin Rheumatol. 2015;34:1243–1248.
28. Lupi-Herrera E, Sanchez-Torres G, Marcushamer J et al. – Takayasu'sarteritis. Clinicalstudy of 107 cases. Am Heart J, 1977;93:94-103.
29. Ishikawa K – Natural history and classification of occlusive thromboaortopathy(Takayasu's disease). Circulation, 1978;57:27-35.
30. Sano K. Takayasu diseasepulselessdisease. Brain Nerve2008;60:31– 35.
31. Gulati A, Bagga A. Large vessel vasculitis. PediatrNephrol.2010;25(6):1037-48
32. Belyamani L, et al. Takayashu et grossesse. Annales de Cardiologie et d'Angiologie 58 (2009) 187-188.
33. Leal P, et al. Takayasus's Arteritis in Pregnancy. Case Report andLiteratureReview. Rev Bras Anestesiol 2011;61(4): 479-485
34. Matsumura A, Moriwaki R, Numano F – Pregnancy in Takayasu arteritisfrom the view of internalmedicine. HeartVessels, 1992;7(Suppl):120-124.
35. Li L.T, et al. Takayasu Arteritis ComplicatingPregnancy in Adolescence. Ann VascSurg 2012; 26: 858.e7-858.e10.
36. Ishihara T,etal.Sensitive assessment of activity ofTakayasu'sarteritisbypentraxin3, a newbiomarker.JAmCollCardiol2011; 57:1712–3.
37. Kissin EY, Merkel PA. Diagnostic imaging in Takayasu arteritis.CurrOpinRheumatol. 2004 Jan;16:31e37.
38. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasuarteritis and

giantcell arteritis: a spectrumwithin the samedisease?Medicine (Baltimore) 2009;88(4):221-6.

39. Sharma BK, Jain S, Vasishta K. Outcome of pregnancy inTakayasu arteritis. Int J Cardiol 2000;75(Suppl. 1):S159e62.
40. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis.Ann Intern Med 1994;120:919e29.
41. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitationsof therapy and a guardedprognosis in an Americancohort of Takayasu arteritis patients. ArthritisRheum2007;56:1000e9.
42. Kötter I, Henes JC, Wagner AD, et al. Doesglucocorticosteroidresistant large-vessel vasculitis (giantcell arteritis and Takayasu arteritis)exist and how canremissionbeachieved? A criticalreview of theliterature. Clin ExpRheumatol 2012;30Suppl 70:S114-29.
43. Gasch O, Vidaller A, Pujol R. Takayasu arteritis and pregnancyfrom the point of view of the internist. J Rheumatol. 2009;36(7):1554-5.
44. Thornton P, Douglas J – Coagulation in pregnancy. Best PractResClin ObstetGynaecol, 2010;24:339-352.
45. Keser G, Direskeneli H, Aksu K. Management of Takayasu arteritis: a systematicreview. Rheumatology (Oxford) 2014;53(5):793-801.
46. Beilin Y, Bernstein H. Successfulepiduralanaesthesia for apatient with Takayasu's arteritis presenting for caesareansection. Can J Anaesth 1993;40:64–6.
47. Choi DH, Kim JA, Chung IS – Comparison of combined spinal epiduralanesthesia and epidural anesthesia for caesarean section. ActaAnaesthesiolScand, 2000;44:214-219.
48. Clark AG, Al-Qatari M. Anaesthesia for Caesarean section inTakayasu's disease. Can J Anaesth 1998;45:377–9.
49. Kawaguchi M, Ohsumi H, Nakajima T et al. – Intra-operative monitoringof cerebralhaemodynamics in a patient with Takayasu's arteritis.Anaesthesia, 1993;48:496-498.

