Takayasu's disease and pregnancy

Three case studies and a review of the literature

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Takayasu's disease is commonest in women of childbearing age. Obstetricians are therefore faced with the dilemma of optimal management in pregnancy. This report of 3 cases suggests that Takayasu's disease is associated with a good maternal and fetal outcome. The basic disease appears to be unaffected by pregnancy.


Takayasu's disease is an idiopathic chronic granulomatous large-vessel arteriopathy, affecting predominantly the aorta and its main branches. The condition, although rare, is more common in women in whom it presents at childbearing age. Obstetricians are thus faced with the dilemma of optimal management in pregnancy. We report 3 cases of Takayasu's disease managed recently at King Edward VIII Hospital and review the literature on this rare condition.

Case reports

Case 1

A 21-year-old primigravida was referred from a community clinic with a diagnosis of 'aproteinuric hypertension' in the 30th week of pregnancy. She was asymptomatic. On examination, all pulses in both upper limbs were absent. The carotid pulses were weakly palpable and all pulses in both lower limbs were present. The popliteal blood pressure was 190/100 mmHg and precordial examination revealed no evidence of established hypertension. There were no abdominal bruits. Fundoscopy was normal and urine examination did not reveal proteinuria. A clinical diagnosis of group II Takayasu's disease was made.

Investigations revealed a positive Rhesus factor and an erythrocyte sedimentation rate (ESR) of 18 mm/h. The chest radiograph, electrocardiogram and echocardiogram and an ultrasonograph of the kidneys were normal. Doppler studies of the upper limb and carotid vessels revealed good collateral circulation. Serological tests for syphilis and rheumatoid factor were negative. The Mantoux test was accepted 28 July 1993.
non-reactive. The haemoglobin concentration was 10 g/dl; the serum creatinine value 80 µmol/min and 24-hour creatinine clearance 75 ml/min.

In view of the patient's consistently elevated popliteal blood pressure, methyldopa was prescribed. Over the next 3 weeks her popliteal blood pressure remained at 150/100 mmHg but clinical intra-uterine fetal growth retardation was detected and confirmed on ultrasonography. An elective induction of labour was therefore planned but the patient went into spontaneous labour and underwent a caesarean section for fetal distress at a regional hospital.

**Case 3**

A 33-year-old woman, para 1 gravida 2, was diagnosed as having Takayasu's disease 6 months after her most recent pregnancy in 1990. She had had an uncomplicated vaginal pregnancy in 1990. She had had an uncomplicated antihypertensive therapy.

Investigations, which included syphilis serology, antinuclear factor and rheumatoid factor, were negative. The Mantoux test was non-reactive. The antinuclear factor, rheumatoid factor and rapid plasma reagin test, full blood count, serum creatinine and immunoglobulin values; chest radiograph and ECG were all normal. The ESR was 88 mm/h. Ultrasound examination confirmed stenotic and ectatic lesions of both common carotid vessels. A pan aortogram revealed type I disease.

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**Epidemiology**

Takayasu’s arteritis was initially characterised as a disease of Orientals; however, it has been found to have a worldwide distribution and is much more frequent in lower socio-economic groups. The age of onset is between 10 and 20 years.

She presented to the vascular surgeons at this hospital 6 months thereafter with a 2-month history of intermittent claudication of both upper limbs. Examination revealed bilateral carotid and subclavian bruits. The right brachial and radial pulses were absent, while the left brachial and left radial pulses were weakly palpable. The carotid pulses were palpable; the blood pressure in the left upper limb was 92/50 mmHg and the popliteal blood pressure was 144/62 mmHg. Precordial examination and funduscropy were normal.

The Mantoux test was non-reactive. The antinuclear factor, rheumatoid factor and rapid plasma reagin test, full blood count, serum creatinine and immunoglobulin values; chest radiograph and ECG were all normal. The ESR was 88 mm/h. Ultrasound examination confirmed stenotic and ectatic lesions of both common carotid vessels. A pan aortogram revealed type I disease.

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**Review**

Takayasu’s disease was first described in 1908 by two Japanese ophthalmologists, Takayasu and Onishi, who observed retinopathy and absent limb pulses. The disease is also known by several other names, viz. aortic arch syndrome, pulseless disease, occlusive thrombo-arthropathy, aortitis syndrome, Takayasu’s arteriopathy and brachial neuritis. The condition can be summarised as a chronic idiopathic occlusive panarteritis of the aorta and its major branches. Women are more commonly affected, the female/male ratio being 8.5:1.

**Case 2**

A 33-year-old multigravida was diagnosed as having Takayasu’s disease during her 7th pregnancy in 1988. Her first 6 pregnancies had concluded with uncomplicated vaginal deliveries at a community clinic. In 1988 she had presented with hypertension and signs and symptoms of upper limb ischaemia. An aortogram performed post-delivery confirmed bilateral subclavian artery occlusion, narrowing of the origin of the right common carotid, and narrowing of the abdominal aorta at the level of the renal arteries. She had an uncomplicated vaginal delivery of a live male infant weighing 3 750 g. The patient refused tubal ligation despite counselling.

In February 1991 she presented at 36 weeks’ gestation without having had antenatal care. Examination revealed absent left upper limb pulses and weakly palpable right upper limb pulses. Both carotid pulses and all lower limb pulses were present. Radiofemoral delay was not detected and blood pressure in the right arm was 150/100 mmHg. Precordial examination and funduscropy were normal and there were no abdominal bruits. Urine examination did not reveal any abnormalities. She did not require antihypertensive therapy.

Investigations, which included syphilis serology, antinuclear factor and rheumatoid factor, were negative. The Mantoux test was non-reactive and the full blood count, ESR (20 mm/h), serum creatinine, urate and immunoglobulin values were normal. The echocardiogram, ECG, chest radiographs and ultrasonography of the kidneys did not reveal any abnormalities. The patient went into spontaneous labour 2 days after admission. Labour was allowed to progress but she required an emergency caesarean section for cephalopelvic disproportion. A live male infant weighing 3 750 g was delivered. There were no intra-operative or postoperative complications, and the patient was discharged a week later.

**Case 3**

A 33-year-old woman, para 1 gravida 2, was diagnosed as having Takayasu’s disease 6 months after her most recent pregnancy in 1990. She had had an uncomplicated caesarean section for fetal distress at a regional hospital.

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In view of the patient's consistently elevated popliteal blood pressure remained at 150/100 mmHg but clinical intra-uterine fetal growth retardation was detected and confirmed on ultrasonography. An elective induction of labour was therefore planned but the patient went into spontaneous labour and underwent a caesarean section for fetal distress at a regional hospital.
Aetiology
The cause of the disease remains unknown. Suggestion of an auto-immune aetiology has been made because of similarities between systemic lupus erythematosus and the early phases of Takayasu’s disease. Furthermore, auto-immune diseases are more common in women and in some cases anti-aortic antibodies and circulating immune complexes have been detected. The response to corticosteroid therapy and cyclophosphamide in the active stage of the disease also supports an auto-immune pathogenesis.

In India, tuberculosis has been implicated in the aetiology. A registry for the disease in Bombay showed that 70% of patients had tuberculosis. In an autopsy study of 15 patients with Takayasu’s arteritis, coexisting tuberculosis distant from the arterial lesion was present in 37%. This association, however, may be coincidental, given the high prevalence of tuberculosis in Asia. In 3 case reports, all 3 Mantoux tests were negative. This may be a consequence of the small number of patients in our reports which studied pregnant women only. Various associations with Cronh’s disease, ulcerative colitis, immune complex glomerulonephritis and renal amyloid disease have been described in the literature. Hormone imbalances, ethnic susceptibility and genetic factors have also been suggested in the pathogenesis.

Pathological features
The lesions in Takayasu’s disease show a panarteritis of the aorta and its main branches. The pulmonary artery may also be affected. The arterial wall lesions begin with a chronic granulomatous vascular inflammation with subsequent fibrosis. The initial mesoperiarteritis is followed by fibrotic thickening of the adventitia and the vasa-vasorum. These lesions lead to an intimal fibrosis, which progresses to marked thickening, often with thrombus formation and a decrease in luminal size. The fibroed adventitia shows a heavy focal infiltration of plasma cells and lymphocytes. The walls of the media thicken and lose their elasticity as a result of degeneration of muscle cells and their replacement by fibrosis, collagen and inflammatory cells. The vasa vaso form a constriction or occlusion and occasionally a saccular anerysm. These affected portions are clearly demarcated from the adjacent normal sites, and segmental ‘skip lesions’ are visible.

Classification
The disease is classified according to three criteria: (i) presence of complications, (ii) anatomical site of the lesion; and (iii) activity of the disease. This is based on the ESR. An ESR of > 20 mm/h in non-pregnant women denotes activity. In pregnancy, because of the normally elevated ESR, higher levels (> 40 mm/h) are used to denote activity.

Anatomical site. The disease is typed according to the anatomical site of the lesions. Type I (Shimizu-Sanu) is confined to the aortic arch and its branches; type II (Kimoto) involves the descending thoracic aorta and abdominal aorta and its branches; type III (a combination of types I and II) is the extensive type; and type IV involves the pulmonary artery in addition to any one of the above types.

The presence of complications. Prognostically, the disease is further classified into four groups, I, IIa, IIb and III, depending on the presence and severity of four complications attributed to the disease: (i) group I — uncomplicated Takayasu’s disease with or without pulmonary involvement; (ii) group II — mono-complicated Takayasu’s disease with any one of the following four complications: retinopathy, secondary hypertension, aortic incompetence, aneurysm formation; (iii) group IIa — mild single complication; (iv) group IIb — severe single complication; and (v) group III — multilcomplicated disease with two or more of the above complications.

The classification according to the presence or absence of complications is used in clinical practice because it has more prognostic value than the other two.

Clinical features and diagnosis
Symptoms. The disease shows protean clinical features and there is a long interval between the onset of symptoms (usually in the early teens) and established diagnosis (age 20 - 40 years). Symptoms and signs depend on the phase of disease (early or late), anatomical site of lesion and the presence of the complications mentioned before.

The acute phase is usually one of inflammatory activity. Most patients have systemic symptoms. Syncopal attacks are also not uncommon. The disease usually remains undiagnosed at this stage, the symptoms being attributed to a viral illness. Minimal signs are present.

The diagnosis is most often made in the late phase of the disease. The majority of patients are asymptomatic. Hypertension and pulselessness may, however, be detected incidentally during routine antenatal care, as was the case with our first patient. The disease in this late phase may be active or inactive, and symptoms depend on the site of involvement and presence of complications. Patients with primary aortitis very often present with hypertension; Lupi Herrera et al. reported an incidence of hypertension of 72% in a study on 107 patients, and Teoh et al. found an incidence of 69% in non-pregnant patients.

Physical signs
Arterial pulses may be unequal, diminished or absent either unilaterally or bilaterally. The left radial artery pulsation is more commonly diminished than the right. Unequal blood pressure recordings may be found in the limbs. A murmur of aortic incompetence may be heard, and auscultation over the neck, chest, abdomen and down the entire spine often reveals a harsh ejection systolic murmur. Retinopathy, changes in increased arteriovenous anastomosis, and pre-retinal haemorrhages may be seen.

Laboratory investigations
Other than a raised ESR (> 40 mm/h in the active phase during pregnancy), there is no consistent abnormality indicative of Takayasu’s disease. Mild anaemia, leucocytosis and elevated globulin levels may be present. Occasionally the C-reactive protein, serum IgG, IgM and IgA levels, and antistreptolysin O titre are elevated; the haemagglutination test is positive and anti-aorta antibodies are present.
Tuberculin tests are invariably positive. The presence of lupus erythematosus cells has occasionally been reported.

**Radiology**

Aortography is indispensable for confirmation and exclusion of congenital aortic coarctation, giant cell arteritis and atherosclerosis. Angiography usually demonstrates more extensive disease than is suspected at clinical examination. Aneurysms — diffuse, saccular or fusiform — are often present. The ascending aorta may be dilated, with the thoracic aorta gradually decreasing in diameter towards the diaphragm (the 'comma-shaped' aorta). The narrowing may involve the aorta down to its bifurcation, and it may cause occlusion at, or distal to, the origin of the renal arteries. Localised or diffuse dilatation, partial or complete occlusion may affect the branches at their origins, or extend peripherally. 'Skip' lesions may be seen. Aortography is not indicated in the asymptomatic patient who presents during pregnancy.

Echocardiography is helpful in determining accurately the degree of left ventricular hypertrophy, left ventricular function and aortic valve pathology, and assessing aortic root abnormalities. Doppler studies may assist in assessing the adequacy of collateral flow.

**Management**

Management requires a multidisciplinary approach, i.e. the obstetrician, cardiologist and anaesthetist need to liaise in the total care of the patient.

**Medical**

Corticosteroid therapy is beneficial in the early active stage of the disease, lowering the ESR, causing fever to subside and retarding or preventing progression of arterial involvement. In some cases, arterial pulsations may be restored with steroid therapy. Kulkarni et al. noted reduction of hypertension and improvement of stenotic lesions in a patient on steroids. The recommended daily dose of corticosteroids is usually 30 - 50 mg of prednisone. This initial dose is gradually reduced to a maintenance dose. In some cases, arterial pulsations may be introduced later in pregnancy. Most patients in groups I and IIa benefit from medical treatment. Routine antituberculosis treatment is not recommended, and should be given only if features of active tuberculosis are present. Surgery is usually reserved for group IIb and group III patients who have severe symptoms.

**Antenatal management**

Management of the patient who desires pregnancy usually begins with pre-conceptual counselling. A careful evaluation of the disease before pregnancy needs to be made jointly by the obstetrician, cardiologist and anaesthetist. Patients need to be made aware of potential problems, such as exacerbation of hypertension, cardiac failure and low-birthweight babies, that may occur during pregnancy, and hence the need to limit the number of pregnancies.

Vigorous medical treatment of hypertension from early pregnancy is associated with a favourable pregnancy outcome. The mode of delivery needs to be planned, and both obstetric and non-obstetric factors taken into account. Antenatal care should entail regular blood pressure and pulse recordings in all limbs and the detection of any change in symptoms and signs. Inflammatory activity does not usually worsen in pregnancy; in fact, conversion to inactive disease may be noted in some patients.

**Labour management**

Previously, all patients with Takayasu's disease were delivered by caesarean section, but this policy is no longer advocated. One should aim for normal vaginal delivery. In labour, continuous non-invasive or invasive monitoring of blood pressure is required. Blood pressure may be recorded in the supine or lateral positions, with a mid-thigh cuff and placement of the stethoscope on the popliteal artery (if these are the only pulses present). Narcotic analgesics are safe for use in labour. Epidural analgesia is considered ideal because it prevents the wide fluctuation in blood pressure levels which occurs in the second stage of labour. Epidural analgesia is also suitable for caesarean section if indicated. If general anaesthesia is employed, then hyperextension of the neck during intubation must be avoided, as this may severely compromise cerebral bloodflow. Doppler flow measurements, use of mid-thigh cuffs for popliteal blood pressure recordings, and pulmonary wedge pressure monitors may be required during anaesthesia. Vasoconstrictor drugs should also be avoided and ergot preparations should not be used in the second stage of labour.

Incremental rises in blood pressure values during the first and second stages of labour are much higher than in normal controls, and careful attention should be given to this. Prophylactic antibiotics should be used to prevent puerperal sepsis and infective endocarditis, especially if aortic regurgitation is present. The second stage of labour should be assisted and expedited, either with outlet forceps or a ventouse.

**Puerperium**

Care should be taken to guard against cardiac failure and infection. Breast-feeding is advocated, but if suppression of lactation is necessary, ergot alkaloids should be avoided because of their vasoconstrictive effects.

**Contraception**

Oral contraceptives containing oestrogens should be avoided. Progestrone-only contraceptives, both oral and injectable, are preferable. Tubal ligation is advised on completion of family. The intra-uterine contraceptive device should not be used because of the possibility of infection. Further pregnancies are not advised in patients with group IIb and group III disease.

**Differential diagnosis**

Secondary to Takayasu's disease, blood pressure in the lower limbs may be significantly lower than the central blood pressure. Atherosclerosis, syphilitic aortitis, giant cell arteritis, ankyllosing spondylitis, Reiter's syndrome, rheumatoid arthritis and systemic lupus erythematosus should be considered in the differential diagnosis.
Prognosis

The anatomical extent of disease on angiography is not reliable in predicting outcome, and Ishikawa's classification, based on the presence of four major complications, is much more helpful. The overall 10-year survival rate is 89.7% (i.e. after established diagnosis). Patients with untreated primary arteritis may survive for up to 20 years. These survival rates should be carefully considered when patients are selected for surgery. The 10-year survival rate is 100% in patients in groups I and IIa, compared with 74.2% in patients in groups IIb and III. Severe single or multiple complications (i.e. groups IIb and III) are therefore associated with a poorer prognosis.

The course of the disease is slowly progressive and thus allows the development of extensive collateral circulation. The major causes of death are congestive cardiac failure, cerebrovascular accidents, rupture of aneurysms, myocardial infarction, hypertension, renal failure and severe aortic incompetence.

Pregnancy-related effects

The largest two series of pregnant patients were reported by Ishikawa et al. (27 patients - 33 pregnancies) and Wong et al. (13 patients - 30 pregnancies). Pregnancy, labour and delivery have not been shown to alter the course of prognosis significantly in patients with Takayasu's disease. Both studies revealed no maternal deaths directly attributable to pregnancy. Nevertheless, unfavourable events such as rising levels of high blood pressure, heart failure, and increased disease activity may occur during the third trimester, labour and the puerperium.

Some patients show a transient improvement during pregnancy. Occasionally a transient improvement may be noted in the blood pressure of patients who were hypertensive before pregnancy. Occasionally aortic regurgitation murmurs may disappear in pregnancy and re-appear in the puerperium. Very rarely does an unfavourable effect persist after the puerperium.

Effects of disease on pregnancy and fertility

Labour and delivery

There is no increase in caesarean section rates, preterm labour or induction of labour in patients with Takayasu's disease. Caesarean section is usually performed for obstetric indications. Caesarean section for non-obstetric indications may be recommended in patients who show marked symptomatic elevation of systolic blood pressure with uterine contractions in the first stage of labour, and in those patients in whom medical treatment fails to lower very high blood pressure levels. The increments in systolic blood pressure in the second stage of labour are significantly higher than in controls.

Fetal and maternal outcome

An increase in neonatal deaths has not been documented, nor has there been any report of an increase in congenital abnormalities. The stillbirth and spontaneous abortion rates are the same as in the general population. Increased severity of disease (i.e. groups IIb and III) may be associated with an increased likelihood of low-birth-weight babies because of the greater prevalence of renovascular hypertension and the resultant diminished bloodflow via the uterine arteries to the fetus. Involvement of the lower abdominal aorta may also lead to uteroplacental insufficiency. Ishikawa et al. showed a significant difference in birth weights of babies in groups I and IIa (3 000 g ± 400 g), compared with groups IIb and III (2 500 g ± 400 g). Superimposed pre-eclampsia may also affect fetal outcome adversely. The overall maternal mortality rate is 4.8%. The increased risk of death is mainly in the peripartum period, and this is due to cardiac failure and/or cerebrovascular accident. The major causes of death, however, in both pregnant and non-pregnant patients are similar.

Fertility

Fertility is generally not affected by the disease. There was a 7.9% infertility rate in Wong et al.'s series, which was comparable to that of the control population. Some authors have suggested that the disease is associated with abnormal menstruation caused by hormone imbalance.

Conclusions

Takayasu's disease in pregnancy may be associated with a good maternal and/or fetal outcome. The basic disease is usually unaffected by pregnancy. The cardiovascular complications attributed to this disease, however, may be transiently modified or significantly enhanced in some patients. Our 3 patients all had a satisfactory course during pregnancy and delivery, and satisfactory fetal outcome.

To ensure good maternal-fetal outcome, the following are essential: (i) detailed pre-pregnancy evaluation of the disease; (ii) assessment of safety of pregnancy; (iii) careful management in the period in which unfavourable events may occur; (iv) planning of mode of delivery, assessing both obstetric and non-obstetric factors; and (v) intrapartum and anaesthetic considerations with special reference to appropriate control and management of blood pressure. Close co-operation between the cardiologist, obstetrician and anaesthetist is essential for successful pregnancy, labour, delivery and puerperium in women with Takayasu's disease.

REFERENCES

It is impossible to contemplate the present or the future state of the country, and to reflect upon the possible changes in administration relative to ourselves, without coming to the conclusion that brighter days are yet in store for us. We have waited long and patiently in the hope that the Government would legislate for us and put medical men in this country on a better and more privileged footing. At present the apparent studied indifference to the claims of the qualified practitioner is felt acutely and sometimes bitterly...

I hold it to be the duty of the State to see that the public is provided with skilled help in cases of sickness, both in the way of medical men and nurses, as much as I hold that those who have been trained and are ready to devote their skilled energies to the curing and stamping out of disease should be upheld in their status and privileges by the public and the State.


50 years ago...

Probably the most valuable single article of food which we have is milk. It is unfortunately, too, the most frequent vehicle for the spread of communicable diseases...


...two Johannesburg milk-pasteurising depots have maintained an efficiency level of over 99.9 per cent. in regard to heat-treatment of the milk. Out of 17 other firms operating throughout eight South African towns, none showed an efficiency of 99.0 per cent. When uncontrolled, efficiency was as low as 50 per cent., but when subjected to strict control it was possible to bring most depots to an efficiency level between 90.0 and 99.0 per cent. Improvement beyond the level of 99.0 per cent. is dependent upon the use of good plant, coupled with whole-hearted and unrelaxing co-operation on the part of the depot management and staff. This is a state of affairs which can only be obtained with certain commercial firms. ...

...pasteurisation by an unlimited number of commercial firms will never prove satisfactory.