Pregnancy may Aggravate Arterial Hypertension in Women with Takayasu arteritis

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ABSTRACT: Background: Takayasu arteritis (TA) is a rare chronic granulomatous inflammatory disease of the aorta and/or its major branches and more frequently affects female patients before menopause. Since persistent inflammation may lead to arterial ischemia, hypertension is an important complication of TA.

Objectives: To evaluate gestational results and complications in patients with TA.

Methods: We conducted a retrospective analysis of the medical records of patients with TA admitted to the high risk pregnancy clinic for women with systemic autoimmune diseases at Hospital Universitário Pedro Ernesto.

Results: From 1998 to 2011 we followed 11 pregnancies in 9 patients with TA; the patients’ age ranged from 17 to 42 years and disease duration from 2 to 28 years. In 7 of the 11 pregnancies, uncontrolled blood pressure occurred before labor and preeclampsia was diagnosed in one. Two deliveries were preterm, one newborn was treated for sepsis, and four (36%) had intrauterine growth restriction (IUGR).

Conclusions: Close monitoring improves the perinatal outcomes in patients with TA who are more prone to develop hypertension, preeclampsia and IUGR. Disease activity was not observed in our group of patients during pregnancy. Coordinated care between the obstetric, rheumatologic and cardiologic teams is the ideal setting to follow pregnant women with TA.

KEY WORDS: Takayasu arteritis (TA), pregnancy, hypertension, intrauterine growth restriction (IUGR), vasculitis

PATIENTS AND METHODS

We retrospectively analyzed the medical records of nine patients with TA admitted to our high risk pregnancy clinic for women with systemic autoimmune diseases at Hospital Universitário Pedro Ernesto-Universidade do Estado do Rio de Janeiro during the period 1998 to 2011. The diagnosis of TA was established according to the American College of Rheumatology criteria [11]. All affected vessels were documented as were all medications used during pregnancy (including antihypertensive and immunosuppressive agents). Admissions to the gynecology obstetric ward not related to the birth were recorded.

Patients were classified according to Ishikawa’s criteria: group I – no complications; group Ia – mild retinopathy,
mild or moderate secondary hypertension, aortic or arterial aneurism, aortic regurgitation; group IIb – severe retinopathy or secondary hypertension; group III – two or more complications of group II [12].

Obstetric complications during pregnancy were explored including the gestational age at which the diagnosis was reached. Oligohydramnios, intrauterine growth restriction, preeclampsia, HELLP syndrome, abruptio placentae, premature rupture of membranes and gestational diabetes were diagnosed according to the usual criteria [13]. All patients were submitted to monthly ultrasonography and Doppler velocimetry study of umbilical artery starting at 26 weeks to check for signs of fetal distress.

The type of delivery, indication in cases of cesarean section, gestational age at birth, birth weight and Apgar score were noted, as were all complications observed during the puerperal period. Medical records of all newborns were also reviewed for complications in the neonatal period.

**RESULTS**

We studied 11 pregnancies in 9 patients previously diagnosed with TA, including a dichorionic diamniotic twin pregnancy. Patients’ ages when pregnancy was diagnosed ranged from 17 to 42 years and disease duration from 2 to 28 years. This group of patients had a median of nine outpatient clinic visits (range 5–12). The affected vessels, disease duration, other comorbidities and Ishikawa’s criteria for each patient are described in Table 1.

One patient had, in addition to the diagnosis of TA, rheumatic heart disease. All but one patient presented systemic arterial hypertension prior to conception and were on regular treatment with antihypertensive agents that were maintained during pregnancy [Table 2]. Low dose aspirin was prescribed during pregnancy for all patients to prevent preeclampsia. Two patients did not comply due to allergy. We had no case of disease activity according to National Institutes of Health criteria [14], and image studies were avoided. All pregnancies resulted in live-born fetuses.

**ISHIKAWA’S CLASSIFICATION CRITERIA**

Five patients were classified as Ishikawa’s IIa. One patient who had two pregnancies was classified as Ishikawa IIa in the first gestation, but she had severe hypertension in the second pregnancy and her criteria changed to IIb. The other three patients were classified as Ishikawa’s III, one due to moderate hypertension and retinopathy and two had severe hypertension with aortic regurgitation. One of these patients with aortic regurgitation had rheumatic heart disease but we could not accurately determine the cause of the valve defect.

**HYPERTENSION/PREECLAMPSIA**

In 7 of the 11 pregnancies, patients had uncontrolled blood pressure above 160 x 110 mmHg before labor. We had only one case of preeclampsia among our patients, but this diagnosis was impaired in a few instances because proteinuria at the beginning of prenatal care was already greater than 300 mg/24 hours. Even in the cases of uncontrolled blood pressure, there was only a small change in 24 hour urine protein excretion during the prenatal period.

**HOSPITALIZATIONS**

Five patients had to be hospitalized during pregnancy for indications not related to childbirth. In one it was due to high BP in the second trimester, in another because of threatened preterm labor, and a third patient was hospitalized due to diarrhea caused by *Giardia lamblia*. One patient was hospitalized twice during the same pregnancy, the first time due to abdominal pain with an inconclusive diagnosis and the second

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**Table 1.** Disease duration, age of conception, arteries involved, comorbidities and Ishikawa’s classification in 9 patients who became pregnant after the diagnosis of Takayasu arteritis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease duration (yrs)</th>
<th>Age at conception (yrs)</th>
<th>Arteries involved</th>
<th>Comorbidities</th>
<th>Ishikawa’s classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>17</td>
<td>Abdominal aorta, renals, celiac trunk, left subclavian</td>
<td>Hypertension, retinopathy</td>
<td>III</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>30</td>
<td>Carotids, left vertebral, left renal, thoracic aorta</td>
<td>Hypertension, aortic regurgitation, rheumatic heart disease</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>5 and 14</td>
<td>23 and 32</td>
<td>Carotids, left subclavian, brachioccephalic trunk</td>
<td>Hypertension</td>
<td>Ila / Iib</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>36</td>
<td>Carotids, vertebrales, left subclavian, left axillary</td>
<td>Hypertension</td>
<td>Ila</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>29</td>
<td>Abdominal aorta, renals, left iliac</td>
<td>Hypertension</td>
<td>Ila</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>42</td>
<td>Abdominal aorta, iliacs, renals, right subclavian</td>
<td>Hypertension, aortic regurgitation</td>
<td>III</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>18</td>
<td>Carotids, abdominal aorta, renals</td>
<td>Hypertension</td>
<td>Ila</td>
</tr>
<tr>
<td>8</td>
<td>3 and 6</td>
<td>28 and 31</td>
<td>Left subclavian, left common carotid</td>
<td>Hypertension</td>
<td>Ila</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>28</td>
<td>Ascending aorta, left subclavian, renals</td>
<td>Hypertension</td>
<td>Ila</td>
</tr>
</tbody>
</table>
time for cardiac evaluation. The only patient who presented with preeclampsia was admitted at 31 weeks of pregnancy and cesarean section was indicated one week later after a definitive diagnosis and the inability to control BP.

IUGR

Four (36%) of our pregnancies had intrauterine growth restriction. Interestingly, the two newborns from the twin pregnancy had adequate weight for gestational age. The cases of IUGR were diagnosed between 33 and 38 weeks. Only one of those cases had normal flow in umbilical artery as assessed by Doppler velocimetry, while three cases showed an increase in umbilical artery resistance. One case also showed oligohydramnios.

Table 2. Gestational results and medications in 11 pregnancies in patients with Takayasu arteritis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ishikawa classification [12]</th>
<th>Medications used during pregnancy</th>
<th>Delivery and gestational age</th>
<th>Birth weight (g)</th>
<th>Apgar score 1/5 min</th>
<th>NICU</th>
<th>Obstetric complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>III</td>
<td>Md, Hdz, Anl, LDA</td>
<td>Cesarean 37 wks</td>
<td>1850</td>
<td>8/9</td>
<td>Yes</td>
<td>IUGR, increased resistance in umbilical artery, uncontrolled BP</td>
</tr>
<tr>
<td>2</td>
<td>III</td>
<td>Md, Hdz, Nif, Pdn 5mg, Aza LDA</td>
<td>Vaginal 34 wks</td>
<td>2065</td>
<td>9/9</td>
<td>No</td>
<td>Intestinal infection, spontaneous premature labor, uncontrolled BP</td>
</tr>
<tr>
<td>3</td>
<td>IIa</td>
<td>Md, Nif, Pdn 20mg, Aza</td>
<td>Cesarean 38 wks</td>
<td>2900</td>
<td>9/10</td>
<td>No</td>
<td>Uncontrolled BP</td>
</tr>
<tr>
<td>(2nd pregnancy, twins)</td>
<td>IIb</td>
<td>Md, Nif, Aza</td>
<td>Cesarean 38 wks</td>
<td>2545 and 2835</td>
<td>8/9 and 9/9</td>
<td>No</td>
<td>Uncontrolled BP, worsening in puerperium</td>
</tr>
<tr>
<td>4</td>
<td>IIa</td>
<td>Md, LDA</td>
<td>Cesarean 38 wks</td>
<td>2020</td>
<td>8/9</td>
<td>IUGR</td>
<td>IUGR, oligohydramnios, increased resistance in umbilical artery</td>
</tr>
<tr>
<td>5</td>
<td>IIa</td>
<td>Clon, Anl, LDA</td>
<td>Cesarean 39 wks</td>
<td>2915</td>
<td>9/9</td>
<td>Yes</td>
<td>Uncontrolled BP</td>
</tr>
<tr>
<td>6</td>
<td>III</td>
<td>Md, Hdz, Prop, Aza, LDA</td>
<td>Cesarean 38 wks</td>
<td>2375</td>
<td>8/9</td>
<td>No</td>
<td>IUGR, increased resistance in umbilical artery, intrapartum fetal distress, uncontrolled BP</td>
</tr>
<tr>
<td>7</td>
<td>IIa</td>
<td>Nif, LDA</td>
<td>Vaginal 38 wks</td>
<td>2390</td>
<td>9/9</td>
<td>No</td>
<td>IUGR</td>
</tr>
<tr>
<td>8</td>
<td>IIa</td>
<td>Md, Pdn 15 mg, Aza</td>
<td>Cesarean 32 wks</td>
<td>1670</td>
<td>9/9</td>
<td>Yes</td>
<td>Preeclampsia, infection of surgical site</td>
</tr>
<tr>
<td>(2nd pregnancy)</td>
<td>IIa</td>
<td>Pdn 7.5 mg (alternate days)</td>
<td>Cesarean 37 wks</td>
<td>3305</td>
<td>9/10</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>IIa</td>
<td>Md, pdn 5 mg, LDA</td>
<td>Cesarean 38 wks</td>
<td>2680</td>
<td>9/10</td>
<td>No</td>
<td>Small rise in BP during immediate puerperium</td>
</tr>
</tbody>
</table>

Md = methyldopa, Hdz = hydralazine, Pdn = prednisone, LDA = low dose aspirin, Anl = anlodipine, Aza = azathioprine, Clon = clonidine, Nif = nifedipine, Prop = propranolol, IUGR = intrauterine growth restriction, BP = blood pressure, uncontrolled blood pressure defined as > 160 x 110 mmHg during prenatal care, labor or puerperium not associated to preeclampsia.

IUGR = intrauterine growth restriction

OTHER OBSTETRIC COMPLICATIONS

In this group of patients, there were no cases of HELLP syndrome, abruptio placentae, premature rupture of membranes, gestational diabetes or abortion.

BIRTH

Seven pregnancies ended with elective cesarean delivery. One patient underwent cesarean section due to IUGR and increased resistance in the umbilical artery, and another patient underwent cesarean section because she had already had two previous cesarean operations, both before the diagnosis of TA. The two patients who had had two pregnancies underwent a cesarean section in the first pregnancy for uncontrolled BP and in the second due to previous uterine incision. The last elective cesarean operation was due to aortic ectasia. Two deliveries were preterm: one was elective due to preeclampsia and the other was spontaneous at 34 weeks and 5 days. Another patient began spontaneous labor at 38 weeks. In two patients labor was induced with misoprostol between 38 and 39 weeks, but both underwent cesarean section because of failed induction in one and fetal distress during labor in the other. The birth weight ranged from 1670 to 3305 g. All newborns had an Apgar score of 9 or 10 at 5 minutes.

PUERPERIUM

Four patients had prolonged hospital stay in the immediate postpartum period due to severe uncontrolled blood pressure, including the patient who had the twin pregnancy and another with infection at the surgical site. One of the patients had sudden chest pain postpartum and underwent empiric full anticoagulation after all examinations for myocardial infarction were normal, with amelioration of the symptoms. The other six pregnancies had an uneventful puerperium.

NEWBORNS

One newborn had sepsis due to coagulase-negative Staphylococcus and was hospitalized for 20 days in the neonatal intensive care unit. Two infants with IUGR were hospitalized in the NICU for weight gain for 14 and 40 days because their birth weights were 1850 g and 1670 g, respectively. The first one...
had to be readmitted 27 days after birth due to bronchiolitis caused by syncytial respiratory virus. Another infant had to be hospitalized for 10 days in the pediatric ward due to jaundice and polycythemia. After being discharged, he returned 5 days later with a diagnosis of cellulitis in his left foot that required intravenous antibiotic therapy. The twins had no complications and remained hospitalized while the mother was treated for uncontrolled blood pressure. The other six newborns had no complications in the neonatal period.

**DISCUSSION**

Our group of patients with TA had an overall satisfactory gestational outcome. Their pregnancies did not seem to induce disease activity and the main concern was hypertension and IUGR, which may have been associated with the previous diagnosis of TA.

Other authors reported that uncontrolled hypertension during pregnancy was associated with abortion, stillbirths, aortic dissection, cardiac and renal insufficiency, stroke and maternal death [5,6,10]. Almost all our patients needed antihypertensive medications, and five of them were on two or more medications. Controlling blood pressure during pregnancy may be difficult considering the physiological changes in this period, so patients with TA should plan to conceive when BP and the disease are stable. Adjusting the antihypertensive medication to avoid angiotensin-converting enzyme inhibitors and angiotensin inhibitors must be considered. In their series of 18 pregnancies (in 10 patients) among whom only 2 patients needed antihypertensive medications, Hidaka and collaborators [15] found a low incidence of IUGR (11.1%), one premature labor and two hypertensive disorders, without other maternal or obstetric complications. This finding suggests that normal BP at the beginning of the prenatal care is associated with better outcomes.

Most of our patients had difficulty controlling their hypertension despite the correct use of medications, a condition that has also been described by others in pregnant patients with TA [10,15,16], and hospitalization was necessary in two patients. One of our patients was admitted due to preeclampsia, which should always be considered since it is more frequent in patients with rheumatic diseases such as TA [17]. We observed in this small series of patients a lower frequency of preeclampsia in comparison to the 61% and 75% noted by other authors [6,10], and it may have been underestimated due to the presence of proteinuria > 300 mg/24 hours at the beginning of prenatal care, which may have made the diagnosis more difficult and less accurate. The proper use of angiogenic and anti-angiogenic factors might be helpful for the diagnosis of preeclampsia in these patients [18], but studies in TA are lacking. Meanwhile, it is advisable to evaluate the urinary protein excretion (by spot test or 24 hour urine collection) at the first visit, before 20 weeks pregnancy, to enable a more precise distinction between preeclampsia and previous renal involvement.

Another reason for the low incidence of preeclampsia in this group may have been the use of low dose aspirin by all but two patients, and it is noteworthy that the only patient who developed preeclampsia was not using this prophylactic medication. Several studies and a recent meta-analysis showed that patients at high risk of preeclampsia who took low dose aspirin during pregnancy had a lower incidence of this disease, especially severe preeclampsia, as well as IUGR. These benefits were more pronounced when the prophylactic medication was started before 16 weeks [19]. None of the reviewed articles described similar treatment and we believe that it might be indicated for all TA patients due to its low cost, few side effects and good results with other high risk pregnancies, such as those with primary hypertension [20].

Considering pregnancy in patients with TA as high risk, good prenatal care is essential to prevent pregnancy complications. Our patients had a median of nine outpatient clinic visits during pregnancy and were advised to measure their BP at home between the visits. One author suggests that apart from the severity of the disease most major complications were associated with delayed antenatal reporting leading to late treatment [10]. Eclampsia, a terrible complication of pregnancy that is directly associated with the quality of medical care, is more prevalent in developing countries [20].

IUGR was present in most studies in pregnant women with TA. Mandal et al. [6] reported fetal growth restriction in 51.7% of fetuses in a study in India. This rate is extremely high when compared to low risk populations and is similar to our study – 36% of our cases. On the other hand, Suri and co-researchers [10] found IUGR in only 16.7% of 37 pregnancies, but they noted that obstetric complications including IUGR were more commonly seen in patients with Ishikawa IIb and III criteria, especially those with more than two vessels involved.

Some studies have associated involvement of the abdominal aorta and renal artery with a higher incidence of hypertension, preeclampsia and IUGR, suggesting that fetal growth restriction was the result of impaired placental blood flow. Another mechanism could be the occlusion of renal artery leading to an increase in renin production with consequent increase in blood pressure [10,21,22]. Among the four patients with IUGR in our study, three had involvement of the abdominal aorta and/or bilateral renal artery, while in the patients without IUGR two had bilateral involvement of the renal arteries. The other three patients without IUGR, besides not having such an impairment of the renal arteries, had involvement of the ascending aorta and its branches only. This finding is consistent with the conclusion of other authors. We can assume that another reason for the high rate of IUGR in our study may be that most patients had uncontrolled blood pressure in early pregnancy.
The patients included in this series underwent monthly obstetric ultrasound and Doppler velocimetry studies beginning at 26 weeks, as indicated in all high risk pregnancies where the main objective is to allow early diagnosis of IUGR and impaired umbilical artery blood flow as it can be silent and present without maternal signs. Obstetric ultrasound is the best and most accessible method to evaluate fetal growth, while elevated resistance of umbilical artery measured by Doppler velocimetry is directly associated with prenatal outcomes in fetuses with IUGR [23].

The type of delivery is of great concern since BP may rise during the second stage of labor [10]. Vaginal birth is possible, but only in patients with stable hemodynamic status and frequent evaluation of BP, sometimes with invasive methods. The second period should be shortened with oxytocin, and relief of pain with conduction analgesia may be helpful. Since there is an increased rate of IUGR in pregnant women with TA, acute fetal distress can be more frequent and intensive monitoring of these fetuses is advised. Elective cesarean delivery should be considered in patients with severe retinopathy, impaired umbilical artery flow, associated preeclampsia or inability of maternal and fetal monitoring.

All newborns had high 5 minute Apgar score (9 or more), similar to the findings of Mandal et al. [6]. Our birth weight ranged from 1670 to 3305 g and only two babies stayed in the NICU for weight gain, indicating that the increased incidence of IUGR does not necessarily require immediate intensive care after birth. Suri et al. [10] described an elevated incidence of preterm birth (19.4%) that was not reported by us or other authors; we believe that this was not directly related to TA as preterm labor is multifactorial. Hauenstein et al. [4] reviewed 137 pregnancies in patients with TA and found 83.9% healthy preterm labor is multifactorial. Hauenstein et al. [4] reviewed preterm birth (19.4%) that was not reported by us or other after birth. Suri et al. [10] described an elevated incidence of IUGR does not necessarily require immediate intensive care.

In conclusion, perinatal outcomes in pregnant patients with TA are satisfactory but require close monitoring of mother and fetus. Hypertension, preeclampsia and IUGR are the most frequent problems in this group of patients; pregnancy does not seem to induce disease activity. Maternal and fetal death can be avoided if prompt and appropriate treatment is administered and if the management is coordinated between the obstetrics, rheumatology and cardiology teams.

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