The Antiphopholipds Antibodies Syndrome Complicated With Intra-Uterine Growth Retardation And Fetal Death. Report Of 2 Cases And Literature Review

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Citation

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Abstract

We report two cases of anti-phospholipids syndrome in pregnancy complicated by intrauterine growth retardation and fetal death. The patients were 24 and 27 years old. The first patient had and uneventful past history and the second patient was followed up for Crohn's disease. The diagnosis of severe intrauterine growth retardation was made at 25 weeks and 22 weeks plus 6 days respectively with abnormalities in uterine and umbilical cord Doppler flow. The vasculorenal and the infectious workshops were negative. In both cases the assessment of thrombophilia found lupus anticoagulant. Treatment for the first patient was an expectation under ultrasound surveillance while in the second case, anticoagulant therapy had been introduced. The course was marked by the occurrence of intrauterine death at 27 weeks 6 days and 26 weeks 6 days respectively. Fetal weights were 600 g and 350 g. There were no apparent morphological malformations.

CASE 1

A 24 year old female on her 2nd pregnancy with a past history of voluntary abortion one year ago was regularly followed up by our service. An ultrasound to determine the course of the pregnancy was done at 12 weeks of gestation and showed no abnormality and the risk of trisomia (HT 21) was at 1/10,000. Her blood group was A rhesus positive and also tested negative for irregular antibodies, HIV/AIDS, BW and toxoplasmosis and she was vaccinated against rubella. An ultrasound done at 23 weeks of gestation showed normal growth with biparietal diameter at the 38th percentile, abdominal circumference at the 23th percentile, head circumference at the 61st percentile, and femoral length at the 10th percentile. Birth weight was estimated at 519 g. The Doppler ultrasound also showed a bilateral uterine pouch (grade 3). The Doppler ultrasound of the umbilical cord was normal. The placenta was corporo-fundic. Clinical evaluation showed a blood pressure of 110/80 mmHg and fundal height of 19 cm. The urine dipstick was also negative. Two weeks later, Doppler of the uterine artery still remained pathologic while the umbilical Doppler was at the 90th percentile and the cerebral Doppler was inferior to the 10thpercentile (resistance index). The biometric parameters where inferior to the 5th percentile for the abdominal circumference and femoral length and were to the 24th percentile and the 43th percentile for the biparietal diameter and cranial perimeter respectively. Fetal kicks where present with sufficient amniotic fluid. Parvovirus, cytomegalovirus and hepatitis B were negative. Urea, creatinine, SGOT, SGPT, serum electrolytes, full blood count, prothrombin time, cephalokaolin time, uric acid and 24 hours proteinuria were all normal. Thrombophilia test shows circulating antibodies of lupus type. The patient was informed of the fact that the pregnancy was compromised. Ultrasound realized at 27 weeks of gestation revealed harmonious growth restriction with all biometric parameters below the 5th percentile. Ultrasound Doppler of the umbilical vessels showed adiastolic and also severe oligoamnios. Six days later, intra uterine fetal death was noticed with a fetal weight at 600g. There were no morphologic abnormalities. Placental evaluation showed placental infarcts. The circulating anticoagulant was still present 12 weeks after dosing control.

CASE 2

A 27 year old female with a past history of spontaneous abortion and missed abortion at five weeks of gestation was

followed up by our service for her third pregnancy. She was also diagnosed with Crohn's disease two years and received an anti-inflammatory drug (PentasaTM). She reported persistent diarrhea and abdominal discomfort but her general condition was satisfactory. An ultrasound done at the 12th week of gestation was normal with a risk of trisomia at 1/2062. She had received rubella vaccine. Toxoplasmosis, syphilis and HIV serologies were all negative. She was of blood group O rhesus positive. The search of irregular agglutinins was negative. Ultrasound done at 22 weeks of gestation showed: fetal biometry inferior to the 3rd percentile for biparietal diameter, femoral length, cranial perimeter, and abdominal circumference. The estimated fetal weight was 375 g. Uterine Doppler was superior to the 90th percentile on each side. Umbilical Doppler showed adiastole, severe oligoamniose and episodes of bradycardia. Her blood pressure was 120/90 mmHg. Her vascular and renal exams were normal. Hepatitis B, cytomegalovirus, and parvovirus were all negative. Thrombophilia test was positive of circulating antibody of lupus type. An ultrasound done one week later confirmed the previous findings. The patient was placed on aspirine® (100 mg per day) and lovenox® (0.4 mg per day). Three weeks later, intra-uterine fetal death was noticed with fetal weight at 350g with no morphologic abnormalities. Placental enquiry showed placental infarct with thrombosis of different ages. No autopsy was done. Thrombophilia test confirms the presence of circulating antibodies of 13 weeks intervals.

DISCUSSION

The anti-phospholipids antibody syndrome (APS) also called by certain author Hughes syndrome has been identified 20 years ago [1] as recurrent thrombosis and / or fetal loss, and the presence of antibodies directed against membrane phospholipids (APL), circulating anticoagulant of lupus type (LA) and for anti cardiolipin antibody (aCL), or their associated plasma proteins [2] predominantly beta-2 glycoprotein 1 (2GP1). The presence of these antibodies has no value except in precise clinical context. So many situations can present with transitory APL. Thus to make the diagnosis of APL syndrome one should take into consideration the persistence of the APL antibodies over time, or two successive identification of these antibodies within an interval of 3 months [3]. In obstetric, the presence of anti-phospholipids alone is not sufficient enough to make a diagnosis of anti-phospholipid antibodies syndrome (APS). A precise definition of this syndrome was made by Branch and Sylver [4] including in their definition one or more intrauterine fetal death of more than 10 weeks of amenorrhea with ultrasound evidence of normal fetal morphology. Our two cases meet this definition because the gestational ages of our patient were 26 weeks 6 days and 27 weeks 6 days respectively in a context of severe intrauterine growth restriction without morphologic abnormalities and positive APL.

A classification criteria for APL [5] was made in 1998 and was modified in 2006. It includes the presence of moderate to high levels of greater than 40 IgG phospholipid units (GPL) per ml or IgM phospholipid unit (MPL) per ml or greater than the 99th percentile on two or more occasions at least 6-12 weeks apart. The detection of anti -2GP1 has been included in the classification. But unfortunately we did not carry out this test in our two patients. Even though recent literature suggests that laboratory findings of abnormal anti -2GP1 is more specific than aCL [6, 7] a multi-variant analysis showed that lupus anticoagulant confers the strongest risk of thrombosis and that the presence of anti -2GP1 did not add any extra information. Moreover, in a series of primitive APLS cases based on the clinical ad biological criteria, anti -2GP1 was negative in half of these cases [8].

The causes for APLS are multi-factorial [9]. Some patients with APLS have no evidence of any definable associated disease (Primary APLS) [1, 10] as in our first case or it could be associated with systemic lupus erythematosus (SLE) or any other auto-immune disease (secondary APLS). It could also be associated with Crohn's disease as described in literature [11, 12]. The risk of thrombosis is increased in patient with inflammatory bowel disease. The risk of APL is abnormally high despite the fact that the development of thrombosis is controversial. According to Lonjon [14], the prevalence of anti-phospholipid antibodies in Crohn's disease is 11%.

We decided to measure anti-phospholipid antibodies in our two patients based on the ultrasound findings on the 25th and 23rd week of gestation respectively showing intra-uterine growth restriction with abnormal Doppler from where a vascular origin was suspected. Fetal ultrasound with uterine and umbilical Doppler are the most important imaging studies carried out in the second trimester to detect materno-fetal abnormalities in case of anti-phospholipid antibody syndrome (bilateral uterine notch, umbilical adiastole, and stagnation of biometric parameters) [15]. Conventionally, according to CNGOF [3], the criteria for

detection of APL in case of any gestational vascular pathology include: the severity of the pathology and its consequences on the fetus (growth restriction), the mode of onset (before 34 week normally), and it re-occurrence characteristic in subsequent pregnancies. In our second case, with a past history of spontaneous abortion and Crohn's disease, the search for APL would have been evoked based on Jorge's et al [11] recommendation. But the existence of Crohn's disease does not meet with the criteria of Sapporo in the diagnosis of APL [16].

The pathophysiologic mechanism of the obstetrical complication of APL is linked to placenta thrombosis whose origin is uncertain. In our two reported cases, placental review revealed placental thrombosis which was responsible for ischemia with its possible consequences. These placental lesions altered the materno-fetal blood exchanges which subsequently led to growth restriction [17]. Dadhwal in 2011 [18] reports a prevalence of 21.4% of growth restriction in APL in patients on anti-coagulant prophylaxis started in the first trimester. According to Valensise [19], the prevalence varies from 30-60%.

The management of APL still remains a problem if the diagnosis is made late in the 2nd and 3rd trimesters. In reality, even if many authors agree to the benefits of heparin with or without aspirin in the prevention of complications when the diagnosis of APL is made [3, 20-22] there is still going to be divergence if the diagnosis is made late in the 3rd trimester. We opted for one but the results in our two cases were similar: same timing four weeks in the appearance of the first abnormality and the intra-uterine fetal death in both cases could mean that initiation of treatment when the diagnosis is late has no advantage. This shows that the appearance of vascular abnormalities is due to placentation which normally occurs around the 12 weeks of gestation. Once this abnormalities appears they are irreversible and quasi definitive. That is why it is important to initiate prophylaxis before ages of placentation. Valensise [19] recommends monthly immune-therapy as from the 15th week of gestation and every two months as from the 26th week to optimize fetal growth. As for Serrano et al [23], anticoagulant prophylaxis was initiated before the 12th week of gestation. The authors report the results: 85% of life birth with mean gestational age of 37 weeks and mean fetal weight of 2837 g. Our two patients where counseled on their subsequent pregnancies. They will benefit from anticoagulant prophylaxis in the 1sttrimester.

Despite advancement research, APL still remains a challenge to obstetricians because of it high risk state for both mother and fetus. Once the diagnosis is made by the 2nd or 3rd trimester, with a fetus presenting with growth restriction and vascular abnormalities, it is good to prepare the patient for possible negative outcomes. It is thus important to identify high risk patients and initiate anticoagulant therapy before the end of the first trimester.

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