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ORIGINAL ARTICLE

Hepatic infarctions during pregnancy are associated with the antiphospholipid syndrome and in addition with complete or incomplete HELLP syndrome

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Summary. Antiphospholipid antibody syndrome (APS) is associated with adverse pregnancy outcomes and maternal complications including thrombotic events and early pre-eclampsia. HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) represents a unique form in the spectrum of pre-eclampsia. This report describes four patients with pregnancy-associated hepatic infarctions. All four had APS and HELLP syndrome, which was complete in one patient and incomplete in three patients, with elevated liver enzymes in all, and either thrombocytopenia or hemolysis in two. In the literature, we found descriptions of an additional 24 patients who had 26 pregnancies with concomitant hepatic infarction. Of the total 28 patients, anticardiolipin antibodies (aCL) and/or lupus anticoagulant (LAC) were assessed in 16 patients, out of whom 15 were found to be positive. Hepatic infartction during pregnancy was associated almost always with APS, with HELLP (2/3 complete, 1/3 incomplete), and only in one-third of the pregnancies with pre-eclampsia (PE).

Keywords: antiphospholipid antibody syndrome, HELLP, hepatic infarction, pregnancy, thrombophillia.

Antiphospholipid syndrome (APS) is associated with several adverse pregnancy outcomes, including recurrent pregnancy loss at all gestational ages, intrauterine growth restriction and pre-eclampsia (PE) – especially of early onset [1]. Although the incidence of PE is 5% of all pregnancies, in APS pregnancies the incidence is as high as 40% [2].

A subgroup of pre-eclamptic patients with increased maternal and perinatal mortality has been found to have: Hemolysis, Elevated Liver enzymes, and Low Platelets. This combination was named the 'HELLP syndrome' by Weinstein in 1982 [3]. In most cases, diffuse hepatocellular damage is responsible for the elevated liver enzymes. However, hepatic hematomas, hepatic rupture and rarely hepatic infarctions may occur.

This report describes four patients with primary APS, whose pregnancy was complicated by hepatic infarctions. A review of the English language literature has revealed another 26 cases of pregnancy-associated hepatic infarctions in 24 women. Anticardiolipin (aCL) antibodies/lupus anticoagulant (LAC) were present either prior to, or found after hepatic infarction, in 15 of the 16 patients assessed for APS. Not all the patients fulfilled all the criteria for the diagnosis of PE or HELLP.

Just as Dieckmann used the collective term, *The Toxemias of Pregnancy* in his classic textbook of 1952 [4], we suggest the term 'HELLP syndromes'. These may also include hepatic infarction that is usually associated with APS.

Patients and methods

Four patients with primary APS whose pregnancy was complicated by hepatic infarctions presented to our service between 1993 and 2001.

The first part of this report discusses these cases, their relationship to PE, HELLP and their association with APS.

PE is defined as: elevated blood pressure, systolic $\geq$140 mmHg, diastolic $\geq$90 mmHg, accompanied by proteinuria of $\geq$300 mg day^{-1} occurring after the 20th week of gestation [5]. HELLP is defined according to Sibai as: lactic dehydrogenase (LDH) $>600\,\mathrm{IU\,L^{-1}}$, platelets $<100\times10^{3}\,\mathrm{mL^{-1}}$, and aspartate aminotransferase (AST) $>70\,\mathrm{IU\,L^{-1}}$ [6].

We define incomplete HELLP as including abnormal liver enzymes with or without hemolysis or thrombocytopenia, and specify whether or not it was associated with PE.

The second part of this report consists of a comprehensive literature search of MEDLINE for hepatic infarctions during pregnancy. The diagnosis of hepatic infarction was based on at least one of the following examinations: ultrasound (US), computed tomography (CT), magnetic resonance imaging

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(MRI), angiography, or liver biopsy. Cases in the literature were also analyzed for their association with PE, HELLP, and APS.

Results

Part I: case reports

Case 1. A 33-year-old mother of one, in whom primary APS has been diagnosed in 1985 at the age of 25, had had 13 previous pregnancy losses, three of which were after the 20th week of gestation and two thrombotic events associated with pregnancies: popliteal artery thrombosis, and femoral vein thrombosis. High levels of aCL antibodies, and LAC were present. Hereditary thrombophilia, heterozygosity for the prothrombin gene polymorphism (G20210A) was also diagnosed (Table 1). Her only successful pregnancy was achieved following therapy with a combination of aspirin, dypiridamole, anticoagulants and prednisone. In the 15th (index) pregnancy, at 25 weeks of gestation, while being treated with aspirin 100 mg day^{-1} and subcutaneous enoxaparin 20 mg day^{-1}, she presented with an acute right epigastric pain radiating to the right shoulder. On admission, the patient appeared well, BP 180/115 mm Hg^{-1}, temperature normal. The liver was enlarged and tender, and pitting ankle edema was observed. The laboratory results are shown in Table 2.

Doppler US examination of the abdomen showed multiple small vessel thromboses in the enlarged liver, portal hypertension, hypoechogenic areas in the spleen and kidneys and a small amount of ascites. Dynamic and static liver scans with Tc-Na-phytate showed multiple defects, the largest being a 4-cm triangular shaped area at the dome of the liver. Therapy included full anticoagulation, with heparin followed by warfarin, and high-dose intravenous immunoglobulin (IVIG) for 4 days. The pregnancy was terminated at 26 weeks of gestation due to severe fetal distress. The severely growth retarded fetus died at delivery. The laboratory results normalized within 10 days.

The patient continues to be treated with warfarin. No complications developed during 9 years of follow-up.

Table 1 Serological and thrombophilic data of our patients

Cases	Case 1	Case 2	Case 3	Case 4
ACL-IgG (0–18 IU mL^{-1})	153	300	276	190
ACL-IgM (0–10 IU mL^{-1})	2.9	3.4	80	7.7
LAC index (<15%)	36%	51.5%	NA	NA
LAC-PTTLA (0.9–1.4)	NA	2.8	2.6	4.5
LAC-DRVVT (0.9–1.3)	NA	2.5	1.6	1.9
ANF titer	1 : 40	1 : 640	Negative	1 : 40
Anti-DNA	Negative	Negative	Negative	Negative
C3	Normal	Normal	Normal	Normal
C4	Normal	Normal	Normal	Normal
Genetic thrombophillia	FII G20210A heterozygote	None	None	None

In parenthesis: normal values. IgG, immunoglobulin G; IgM, immunoglobulin M; PTTLA, partial thromboplastin time reagent sensitive for the detection of lupus anticoagulant; DRVVT, dilute Russell Viper Venom time; ANF, anti-nuclear factor.

Table 2 Clinical and laboratory data during hepatic infarct episodes in our patients

Cases	Case 1	Case 2	Case 3	Case 4
Age/preg/w*	33/15/25	37/2/17	31/4/17	28/4/7
Rx in current pregnancy	LMWH, aspirin Steroids	High-dose IVIG LMWH, aspirin Steroids	LMWH, aspirin	LMWH, aspirin
Steroids				
BP (mmHg)	**180/115**	140/90	**150/100**	**180/110**
Proteinuria (mg day^{-1})	**800**	Negative	240	**9350**
Hemoglobin (g L^{-1})	**9.1**	11.2	**9.1**	9.3
Platelets (10^3 μL^{-1})	**66**	**59**	125	308
AST/ALT (7–40 IU L^{-1})	**290/611**	**97/208**	**579/816**	**292/279**
LDH (100–260 IU L^{-1})	**829**	225	**541**	197
Treatment	Subcutaneous enoxaparin 1 mg kg^{-1} BID^{-1}, aspirin 100 mg day^{-1} prednisone high-dose IVIG TOP** 26th week	High-dose IVIG full heparinization aspirin 100 mg day^{-1} prednisone	TOP Subcutaneous enoxaparin 1 mg kg^{-1} BID^{-1}, aspirin 100 mg day^{-1} prednisone	Subcutaneous enoxaparin 1 mg kg^{-1} BID^{-1} prednisone aspirin 100 mg day^{-1} TOP
Outcomes				
Obstetric	TOP	IUFD: 4 weeks later	TOP	TOP
Maternal	Recovery	Recovery	Recovery	Recovery

*Age of the mother/number of pregnancy/gestational week. **Termination of pregnancy. ***Bold numbers refer to the criteria for PE and HELLP. LMWH, low molecular weight heparin. AST, asparate aminotransferase; ALT, alanine aminotransferase.

Case 2. A 37-year-old childless woman who, 6 years prior to the current admission, had had an intrauterine fetal death (IUFD) at 26 weeks of gestation, complicated by hepatic infarctions diagnosed by angiography, that led to the diagnosis of primary APS [7]. She had been treated with low-dose prednisone for several years, and was maintained on warfarin. Prior to the current pregnancy high levels of aCL and strongly positive LAC were found (Table 1). High-dose IVIG given preconception and during the first month of the current pregnancy failed to reduce the levels of the aCL antibodies. Enoxaparin 60 mg day^{-1} and aspirin 100 mg day^{-1} were administered in the current pregnancy. The patient was hospitalized at 17 weeks of gestation because of mild right epigastric pain and elevated liver enzymes. The laboratory results are tabulated in Table 2. A single Doppler-US examination of the abdomen was normal. As the clinical features of this episode were similar to the previous episode, it is highly probable that there was a recurrent hepatic infarction. Despite full heparinizaton and steroids, fetal death occurred at 23 weeks of gestation. The liver enzymes normalized two days after delivery. The platelet count however, continued to decrease to a nadir of 59×10^3 mL^{-1}, but normalized within a few days. During follow-up of 8 years, despite continuous therapy with aspirin and warfarin, the patient had three episodes of TIA.

Case 3. A 31-year-old childless woman in whom primary APS was diagnosed following the history of three fetal losses at 15 and 17 weeks of gestation, with high levels of aCL antibodies and strongly positive LAC (Table 1). The third pregnancy was complicated by epigastric pain, fever and abnormal liver function tests. From the 7th week of the current 4th pregnancy, she was treated with aspirin 100 mg day^{-1} and subcutaneous enoxaparin 40 mg twice daily. The patient presented at 17 weeks of gestation with acute onset of epigastric pain radiating to the right shoulder, BP was 150/100 mmHg; temperature was 37.4 °C. The normal-sized liver was tender. The clinical and laboratory findings (Table 2) were suggestive of early HELLP syndrome, and the pregnancy was terminated. The initial Doppler-US examination of the liver was normal. However, a repeated examination, 3 days later, showed multiple hypoechogenic areas, mainly in the right lobe, compatible with multiple infarctions. CT-angiography of the abdomen showed similar findings. The dose of subcutaneous enoxaparin was increased to 1 mg kg^{-1} twice daily followed by warfarin, aspirin 100 mg day^{-1} was continued and prednisone 60 mg day^{-1} was added for a short period of time. The blood tests normalized within 2 weeks, and a repeated US examination of the liver 3 weeks later was normal. Warfarin was administered for 10 weeks. Two years later the patient is well and is maintained only on low-dose aspirin.

Case 4. A 28-year-old childless woman in whom APS was diagnosed following the history of three previous fetal losses at 20, 15 and 11 weeks of gestation, with high levels of aCL antibodies and strongly positive LAC (Table 1). In the first pregnancy, IUFD occurred at 20 weeks of gestation with severe PE: elevated blood pressure, proteinuria up to 3 g day^{-1} and abnormal liver function tests. Two years prior to admission, she had popliteal vein thrombosis unrelated to pregnancy or contraceptive pills. Since then the patient had been maintained on warfarin and aspirin. Chronic mild hypertension (140/90 mmHg), and chronic proteinuria (up to 1 g day^{-1}) without any evidence of systemic lupus erythematosus, were observed. Conception followed ovulation-induction therapy with clomiphene citrate and chorionic gonadotrophin. As soon as the αHCG turned positive, warfarin was replaced by subcutaneous enoxaparin 60 mg day^{-1} (1 mg kg^{-1} day^{-1}). She was hospitalized on the 8th week of gestation, 10 days after acute onset of right upper abdominal pain and vomiting. The patient looked ill, BP was 180/110 mm Hg^{-1}, temperature was 38 °C. There was tenderness in the right upper abdominal quadrant. Vasculitic lesions were observed at the tips of the fingers and in one toe. The laboratory results are summarized in Table 2. Doppler-US examination of the abdomen revealed hepatosplenomegaly with normal blood flow. Over 3 days the patient's condition deteriorated, the fever persisted, abdominal pain increased, new vasculitic lesions appeared, and shortness of breath with hypoxemia developed. No hepatic lesions were found on a repeated US examination. Ascites and bilateral pleural effusions developed. Treatment included enoxaparin, 1 mg kg^{-1} twice daily, aspirin 100 mg day^{-1}, prednisone 80 mg day^{-1}, antibiotics, and nifedipine 60 mg day^{-1}. Despite the negative Doppler-US, thrombosis of small vessels in the liver was strongly suspected. Prior to termination of pregnancy CT-angiography of the chest and abdomen was performed and showed bilateral pleural effusions with interstitial infiltrates, but with no filling defects in the pulmonary vessels. In the left lobe of the liver a few hypodense but poorly defined areas compatible with hepatic infarctions were demonstrated. Dynamic and static liver and spleen plenary and SPECT scans with Tc-^{99m}-Na phytate were performed 4 days after the pregnancy was terminated, and demonstrated triangular filling defects in the left lobe and a smaller filling defect in the right lobe compatible with hepatic infarctions. Following termination of the pregnancy, the recovery was dramatic. The laboratory tests normalized within 2 weeks, however, hypertension persisted, while proteinuria returned to the baseline gradually. The patient continues to be treated with warfarin. No complications developed during 18 months of follow-up.

Summary

Only patient 1 fulfilled the criteria for both PE and HELLP. The hepatic infarctions in the other three patients occurred early in pregnancy, during the 17th (two cases) and 7th weeks of gestation. Thus they fail to satisfy the onset time required for the definition of PE.

Table 2 shows that these three patients do not fulfill the other criteria for PE or HELLP and, hence, these three patients had incomplete HELLP.

The diagnosis of hepatic infarctions was established by Doppler-US in two patients: patients 1 and 3 (in patient 3,

only the second examination was positive). In patient 4, repeated Doppler-US was negative, and the diagnosis was established only by CT-angiography and liver scan. Patient 2 had only a single Doppler-US examination, which was negative. As the clinical picture resembled her previous episode of liver infarction, it is highly probable that her clinical course was due to a recurrent episode of hepatic infarction.

Analysis

A review of the English language literature revealed additional 26 cases of hepatic infarction during pregnancies in 24 women [7–26]. The description herein includes both these 24 women and our four patients, a total of 30 pregnancies in 28 women. The mean age was 28 years (range 17–40). Obstetric history was available for 24 women. They had a mean of 1.75 (range 0–14) pregnancies prior to the hepatic infarction, and a mean of 1.45 (range 0–13) pregnancy losses. In eight women, hepatic infarction occurred during the first pregnancy. It occurred at all stages of pregnancy, from 8 to 41 weeks of gestation (mean 26.5 ± 8.1 weeks). The symptoms of hepatic infarctions started prior to delivery in nine pregnancies, postpartum in seven, and in 13 pregnancies, symptoms appeared prior to delivery and continued into the puerperium (no data for one pregnancy).

Complete information regarding PE is available for 29 pregnancies, 12 of them had PE. Information regarding HELLP is available for 22 pregnancies: 16 pregnancies were complicated by HELLP, while six had incomplete HELLP.

Complete information regarding both HELLP and PE is available for 21 pregnancies complicated by hepatic infarction (Table 3). Six pregnancies had complete HELLP and PE ([15,19,22,23] and our case 1). One had incomplete HELLP and PE [18], nine had complete HELLP and no PE [7,14,16,17,19,21–23,26] and five pregnancies had incomplete HELLP and no PE ([10,11] and our cases 2, 3 and 4). Only 33% of patients had PE, and complete HELLP occurred in 71% of the pregnancies.

Anticardiolipin (aCL) antibodies were found in 15 of the 16 women examined [7,17–24,26]. APS was diagnosed prior to infarction in nine pregnancies, four of them were under our care, and in seven pregnancies it was diagnosed after the infarction. Most patients with no data regarding aCL/LAC were diagnosed as having hepatic infarction either prior to, or during the first few years after APS was described. The aCL titer was high, both in our four patients, and in five additional cases reviewed.

Other possible contributing factors for thrombosis were investigated in only few cases. One patient was homozygous for the factor (F) V Leiden mutation [24] and one was heterozygous for FII polymorphism G20210A (our case 1). Two patients had sickle cell trait [9,13].

Table 3 Classification of reviewed pregnancies with hepatic infarction according to presence of pre-eclampsia, HELLP and APS

	HELLP complete	HELLP incomplete	Total
Pre-eclampsia	6 (15*, 15, **19****, **22**, **23**, **our case 1**)	1 (18)	7
No pre-eclampsia	9 (7,14,16, **17**, **19**, **21**, **22**, **23**, **26**)	5 (10,11 **our cases 2**, **3**, **4**)	14
Total	15	6	21

*Numbers in parenthesis refer to references. ** Bold numbers in parenthesis: pregnancies with APS.

Maternal and fetal outcome

There were two maternal deaths due to the complications of the hepatic infarction. The pregnancies failed in 13 of 23 pregnancies with adequate information.

Discussion

Our case series summarizes the features of four pregnant patients with primary APS that developed hepatic infarctions despite anticoagulant and antiaggregant therapy in all four, as well as steroids and high-dose IVIG in two patients. The diagnosis of hepatic infarction was confirmed in three patients, and infarction was most probably the diagnosis in the fourth patient. All four fetuses were lost.

Review of the literature revealed 26 episodes of hepatic infarction during pregnancy in additional 24 women. Clinically all the patients presented with right abdominal pain, abnormal liver function tests, usually accompanied by fever, and hypertension. It occurred at all stages of pregnancy, from as early as the 7th week up to the postpartum period. Even though many of these patients having hepatic infarction suffer from a disease that resembles HELLP syndrome, they do not fulfill the classical criteria for HELLP. These may be considered as a unique group within the spectrum of HELLP syndromes.

The pathogenesis of both PE and HELLP is unknown. Thrombophilia and especially APS is an important contributing factor to the development of PE [27] and HELLP [28]. It is also unclear why the liver is the major target organ of HELLP. In this syndrome, the hepatic histology shows periportal hemorrhage and necrosis, with fibrin microthrombi and fibrinogen deposits in the sinusoids of areas of normal parenchyma as well as in areas of necrosis [29]. Hepatic hemorrhage and infarction are rare in HELLP [30–32]. In a retrospective analysis of 777 patients with HELLP syndrome, Sibai *et al*. found only three cases of liver hemorrhage and none of hepatic infarction [30]. Hemorrhagic complications, such as subcapsular hematoma, or less frequently, intraparenchymal hemorrhage have been documented in 19 of a series of 34 patients (47%) with HELLP syndrome, evaluated by CT and/or MRI, or abdominal US. However, infarction was seen only in one patient [32].

Because of the liver's dual blood supply, hepatic infarction is rare. Causes of hepatic infarction include unintentional ligation of the hepatic artery during surgery, sepsis, decreased portal venous flow, emboli and thrombosis [8]. In a retrospective radiological analysis of 10 patients with hepatic infarction,

one patient had APS secondary to systemic lupus erythematosus, and the liver infarction was one of other arterial abdominal thrombotic events [33]. Both hepatic and portal veins may be involved in APS. Arterial thrombosis of both the large and small hepatic arteries are also seen [34–36]. The pathological findings in the patients reviewed, showed areas of necrosis, small vessels occlusive disease and inflammatory changes [8–12,14,17,26].

Mor *et al*. were the first to look for aCL/LAC in a patient with hepatic infarction during pregnancy [7]. In the present review, 15 of the 16 examined patients had APS, in most of them, the aCL titer was very high. The only patient without APS was homozygous for the FV Leiden mutation. Combined thrombophilia was found in one of our patients. Another contributing factor for thrombosis – sickle cell trait – was found in two of the reviewed patients.

It seems that most cases of hepatic infarction during pregnancy are associated with aCL/LAC, and in few cases with other thrombophilic defects. The risk of pregnant women with APS to develop this catastrophic event cannot be estimated.

We suggest that the diagnosis of hepatic infarction should be considered in any pregnant woman presenting with right abdominal pain, febrile or not, with PE, HELLP or incomplete HELLP. The search for aCL/LAC becomes axiomatic. Doppler-US, in the forefront of investigation, may confirm the diagnosis in most cases. When negative, repeat examinations, MRI, CT or isotope scans are indicated. Although in seven pregnancies described in the literature, infarction occurred after delivery, and in 13 the process continued into the postpartum period, there is no doubt that termination of pregnancy is obligatory in order to try to curb this catastrophe. In the four patients that were under our care, there was a dramatic improvement following termination of pregnancy and institution of medical treatment with full heparinization and aspirin. The value of steroids in the management of these cases is not clear. The use of heparin is a double-edged sword as hepatic infarction may lead to major hemorrhage, or to rupture of the liver. The use of heparin therefore requires expertise and close monitoring.

Our experience with hepatic infarction during pregnancy in patients with APS is very frustrating, and since we do not know how to prevent this life-threatening event, we recommend to our patients not to conceive again.

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