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Pregnancy Outcome of Women with Antiphospholipid Syndrome, a Retrospective Descriptive Case Study

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Abstract

There is now a consensus on the need to provide healthcare, before and during pregnancy, to women at high risks of APS related obstetric complications diagnosed based on their medical (thrombosis) or obstetric (repeated embryo-fetal losses) history. However, the best therapeutic options are yet to be agreed upon. This study presents the experience of the Departement C of the Maternity and neonatology Center of Tunis (CMNT), a tertiary hospital in managing this pathology.

Patients and methodologies: This is a five-year descriptive retrospective study of cases reported to CMNT maternity department.

Outcome: 34 patients records were analyzed. The average age of the patients was 32 years with extremes of 21 and 44 years. The therapeutic option was a combination of acetyl salicylic acid and low molecular weight heparin. The success rate of the treatment was 97% full-term pregnancies against 12% without treatment.

Keywords: Pregnancy; Outcome; Antiphospholipid syndrome

Introduction

The anti-phospholipid syndrome (APS), identified as such in the 80s, is an autoimmune pathology.

Its diagnosis is based on the 1999 SAPPORO diagnostic criteria which were updated in 2006 in Sydney. According to these criteria, the diagnosis could be made using the combination of at least one of the clinical criteria and the biological presence of an anti-phospholipid antibody using a reference method.

At clinical level

- **Thrombosis:** One or more symptomatic episodes of arterial or venous thrombosis or thrombosis in the vessel of any tissue/organ.
- **Obstetric manifestations:** One or more unexplained morphologically normal fetal deaths after at least week 10 of gestation; one or many premature births of a morphologically normal newborn before week 34 of gestation following an eclampsia or known signs of placental deficiency or at least three consecutive spontaneous miscarriages before week 10 of gestation without any anatomical or maternal hormonal causes and without maternal or paternal chromosomal causes.

At biological level

- The presence of a circulating anticoagulant (lupus anticoagulant LA) identified twice at least 12 weeks apart, using the recommended methods of the International Society on Thrombosis and Homeostasis (ISTH).
- Isotype IgG and/or IgManticardiolipid antibodies (aCL) in medium or high quantity in serum or plasma (>40 GPL or MPL or >99th percentile) identified twice at least 12 weeks apart, using standardized ELISA.
- Anti β_2 glycoprotein–I antibodiesin medium or high quantity in serum or plasma (>40 GPL or MPL or >99th percentile) twice at least 12 weeks apart, using standardized ELISA.

Antiphospholipid antibodies include circulating lupus anticoagulant and a heterogeneous antibody group identified using immunological techniques (ELISA).

They are found usually in low quantities in 5 to 10% of the general population and up to 50% among the elderly. At such low rates these antibodies are rarely associated with clinical manifestations. They are found in 2.2 to 4% of normal pregnancies [1].

Several studies showed that the presence of antiphospholipid antibodies is associated with an increase risk of miscarriage or fetal death [2-4].

Indeed, the impact of the presence of anti-phospholipid antibodies varies from 10 to 20% in women with a history of at least two spontaneous miscarriages with no apparent causes. A woman living

with an APS has one in two chances of carrying a pregnancy to term without treatment. Pregnant women who have anti-phospholipid antibodies and a history of fetal loss or repeated miscarriage are at very high risks of recurrence. Without treatment, the risk could be higher than 90%.

In mothers, the combination of pregnancy and anti phospholipid syndrome (APS) can lead to various complications such as pulmonary embolism, preeclampsia, eclampsia, abruptio placentae, Hemolysis Elevated Liver Enzymes Low Platelet count (HELLP) syndrome or even maternal death.

APS treatment remains highly controversial. There are two theoretical therapeutic approaches: elimination of the anti-phospholipid antibodies and/or impediment of their thrombogenicactivity [5].

Although there is now a consensus on the need to provide healthcare to women at high risk (with a history of thrombosis or recurrent antiphospholipid antibodies related miscarriages) during pregnancy, the appropriate protocols to be used are yet to be agreed upon [6,7]. Thus, combinations of low doses of acetyl salycilic acid (100 mg/day), low molecular weight heparin, corticosteroids (0.5 mg/kg/day), and intravenous immunoglobulins are the available therapeutic options.

This study, aiming at evaluating the treatment provided to patients with a combination of APS and pregnancy, focuses on cases reported at Department C of Tunis Maternity and Neonatology Center (CMNT).

Patients and Study Method

This is a five-year retrospective descriptive study. It focuses on the records of pregnant women admitted to the CMNT for recurrent miscarriages during the study period.

The study includes allthe medical files of patients with a confirmed APS diagnosis. The diagnosis was made using the clinical and/or biological criteria set by the Sydney conference. So the patients with a past obstetric history of embryo-fetal losses have undergone biological lab tests. In orderto recruite the records of women with confirmed diagnosis of APS we used the register of the hospitalisation where the diagnosis were mentionned. Then were corded the patient's identity and file number to find out their files. Data were collected using a tested, corrected and validated fact sheet. These data were generated through the review of consultation, laboratory and medical records of the patients.

Patients with other causes of miscarriage or premature birth such as infections, malformation, and cervical insufficiency were not taken into consideration.

The variables studied include the patients' socio-demographic data, medical and gynecological and obstetric history, clinical and biological data of pregnant women, the treatment, the pregnancy course and outcome, and postpartum complications.

All immunoassays were performed in the same immunology laboratory of the CMNT.

The standard treatment used in our center for this case study includes 40 mg low molecular weight heparin (LMWH); 100 mg acetyl salicylic acid and a preventive dose of 20 mg prednisone corticosteroids before or from the beginning of pregnancy.

Thus:

For 33 patients the protocol used was 100 mg prophylactic dose of acetyl salicylic acid per day from the beginning of pregnancy to week 34 of amenorrhea. A 40 mg per day prophylactic dose of LMWHwas also given until the eve of delivery. The treatment is given from the beginning of the pregnancy in order to have the best effect. The beginning of pregnancy is considered as a positive pregnancy test.

The patient suffering of erythematosus lupus syndromwith a medical follow-up history received in addition prednisone at the dose of 4 tablets/day.

There were bi-monthly clinical, biological and ultrasound surveillances up to week 32 and weekly surveillances till delivery.

Word and Excel were used to enter process and analyze the data.

Results

A total of 34 records were selected.

APS frequency

A total of 19,982 high-risk pregnancies representing a daily average of 11 cases were recorded during the period under study. APS diagnosis was confirmed with 34 patients representing a frequency of 1%.

Age of patients

The average age of the patients was 32 years with extremes of 21 and 44 years; half of them were between 31 and 35 years.

Medical, gynecological and obstetric history

Gravidity-parity: The average gravidity was 4.5 against a low parity of 1.7. Prior to treatment, out of a total of 119 pregnancies, 107 miscarriages with live fetuses were recorded among the 34 women.

Pathological history: A patient had a history of Systemic Lupus Erythematosus (SLE).

Two patients had a history of recurrent deep venous thrombosis.

Pathological obstetric history revealed pre-eclampsia, IUGR, premature birth and HELLP síndrome.

Term of embryo-fetal losses: We noticed 119 pregnacies in the past obstetric history of the patients with 107 losses ranged like this:

- 71% in fisrt trimester
- 15% in second trimester
- 13% in third trimester

The 14 remaining pregnanciesresultedin full term live birth.

Immunological data of patients

All the patients were immunologically tested for antiphospholipid antibodies.

14 cases representing 41% were positive while 20 cases representing 59% were negative. Below is the distribution of the various types of anti-phospholipid antibodies identified (Figure 1).

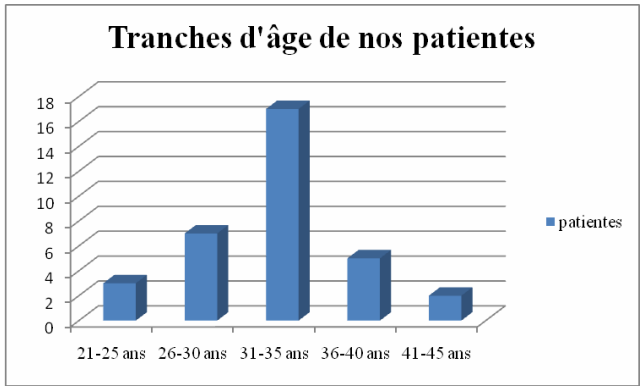

Figure 1: Patients distribution per age group.

However, negative immunological lab test does not exclude the diagnosis of APS if the clinical criteria are fulfilled. Then it doesn't influence the treatment and the prognosis.

Complications during pregnancies

Thepregnancies were characterized by complications.

Gestational diabetes and pregnancy toxemia were the main complications recorded.

Outcome of pregnancies of women under treatment

Out of 34 pregnant women put under prophylactic treatment and followed up in the Department, 33 live births (97%) and a single case of week 30 IUFD were recorded among patients with a positive immunoassay.

The average term of delivery is 36 weeks with extremes of 30 and 39 weeks; the average fetal weight at birth is 2511.5 g with extremes of 1.100 g and 3.870 g.

No spontaneous miscarriages were recorded.

Mode of delivery

Caesarean sessions were performedon 24 women, representing 71%.The main reasons for cesarean was fetal asphyxia and IUGR.

Evolution of pregnancies without treatment and with treatment

Without treatement, out of 119 pregnancies, only 14 (11,7%) went to term.

Discussion

This study has some limitations due to the factthatitis a retrospective study. So, some data were missing in the medical files without possibility to get them.

The clinico-biological characteristics of the anti-phospholipid syndrome (APS) include arterial or venous thromboses, recurrent fetal losses, presence of anticardiolipins IgG or IgM and/or circulating anticoagulant and thrombocytopenia.

5 to 10% of the general population and up to 50% of the elderly have these antibodies usually in a low quantity such that they are rarely associated with clinical manifestations. However, in average 15% and 8% of women with recurrent first-quarter miscarriages have respectively the anti-cardiolipid antibodies and anti-lupus antibodies [1].

In this study, APS prevalence rate represents 1‰ of high risk pregnancycases received at CMNT during the period under study and 41% of women with recurrent miscarriages with 14% for β_2 glycoprotein –I and 8% for anti-cardiolipin antibodies.

According to other publications, the anticardiolipine antibody frequency varies between 8 and 50% and this large variation might be caused, on the one hand, by the criteria used in selecting the women (women with 2 or 3 miscarriages, different terms, premature birth or IUFD), and on the other hand, by the differences existing between the dosing techniques used. It points to the need for standard definitions and techniques to make studies comparable.

Obstetric complications are characterized by recurrent miscarriages without any chromosomal cause or a malformation identified through ultrasound or direct or hormonal screening.

In this study, out of 119 pregnancies with no treatment, 105 embryo-fetal losses, representing 88.2% of pregnancies, were recorded.

These results are in line withthose of F. Ben HadjSlama et al., who recorded, in a series of 146 patients, a total of 615 pregnancies and 537 (87%) losses.

In addition, the history of the pregnant women revealed 14 cases of IUFD representing 38.2% and 2 cases of IUGR representing 5.8%.

An utero-placental insufficiency combined with a thrombosis-led placental ischemia within the placental circulation might cause intra-uterine growth restriction, chronic fetal distress and IUFD. APls would activate the endothelial cells through membrane phospholipids adhering β_2-GP1, and by inducing a pro-coagulant phenotype, they would inhibit activated protein C and annexin V, this mechanism might play a major role in obstetric complications.

The management of pregnant patients with APS aims to prevent the risks of thrombosis on the one hand and obstetric complications related to this syndrome on the other hand.

With treatment, 63 to 100% of women with live birth were recorded [8,9]. The rate of full term pregnancies without treatment is modestly around 10%.

However, although there is currently a consensus on the need to treat pregnant women considered at high risk based on their medical (thrombosis) or obstetrical (recurrent pregnancy losses) history of anti-phospholipid antibodies presence, the best therapeutics to be used [10,11] are yet to be agreed upon. To date, only few randomized controlled series have been published on this issue. The first treatment was based on corticosteroids and led to full term pregnancies and live births. However, there were significant adverse effects associated with corticosteroids. A random comparative study between corticosteroids therapy and heparin therapy with both groups receiving acetyl salicylic acid showed that some obstetric complications supposedly related to the antiphospholipid syndrome (pre-eclampsia, premature birth) were in fact caused by corticosteroids [12]. Acetyl salicylic acid monotherapy has been successfully used but a prospective double-blind study proved that the acetyl salicylic acid/heparin combination is more efficient than using acetyl salicyclic acid alone [13]. Heparin

monotherapy is associated with positive obstetric results but no study has been conducted to compare its combination with acetyl salicylic acid. Low-molecular-weight heparins are increasingly used in treating APS [14]. They present a few advantages as compared to fractionated heparin. Because of their longer half-life and higher bioavailability, only a single daily injection is required to provide a better comfort for patients. Moreover, they are as efficient as unfractionated heparin but with less adverse effects (hemorrhage, thrombocytopenia, osteoporosis). The issue of efficiency was discussed during the sixth North American consensus on anti-thrombotic therapy (10). Intravenous gamma globulins are to be considered when other treatments (acetyl salicylic acid heparin) have proved ineffective.

In this study, the combination of acetyl salicic acid and LMWH was positive with a success rate of 97%.

Therefore, it is important, in view of the encouraging therapeutic options, that APS cases among women with recurrent miscarriages history are identified and put under treatment.

Conclusion

The combination of APS and pregnancy is a reality among CMNT patients. The combined acetyl salicylic acid and low molecular weight heparin therapeutic protocol produced positive results in preventing embryo fetal losses and maternal complications.

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