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PREGNANCY AND ANTIPHOSPHOLIPID SYNDROME

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ABSTRACT

Antiphospholipid syndrome (APS) is responsible in its obstetric form for both maternal and fetal complications. It is then defined by the occurrence of at least three false sofas consecutive spontaneous before ten weeks of amenorrhea (WA), fetal death or birth premature before 34 WA related to preeclampsia, eclampsia, or severe placental insufficiency (intrauterine growth retardation, oligohydramnios). During pregnancy, APS can also appear complicate retroplacental hematoma, hemolysis syndrome, elevated liver enzymes, low platelet count (HELLP) and thrombosis which can sometimes form part of catastrophic antiphospholipid syndrome. A history of thrombosis or the presence of a circulating anticoagulant are predictors of complications during pregnancy. The management of these high-risk pregnancies is multidisciplinary (internist, anesthesiologist, obstetrician) and requires a consultation preconception in order to find the rare contraindications and to optimize the treatment. This one rest on aspirin combined with heparin, the dosage of which varies according to the patient's history. The duration of the therapeutic window around childbirth depends on the type of history but must be short in order to limit maternal risks in the postpartum period (thrombosis, HELLP, catastrophic syndrome). Clinical and biological monitoring is monthly, closer if necessary, at the end of pregnancy. Obstetric ultrasound with Doppler, performed regularly, looks in particular for the presence of notches on the uterine arteries which are predictive of an increased risk of complications placental vascular.

The combination of appropriate treatment and close multidisciplinary monitoring clearly improves the prognosis and most often makes it possible to obtain a question favorable to the pregnancy.

The link between fetal loss and the presence of an anticoagulant circulating was established in the 1970s, and a support therapy was proposed in the 1980s. The criteria standards used to define antiphospholipid syndrome (APS) established in 1999 and revised in 2006 leave a broad place for obstetric manifestations.[1,2] These criteria are:

- At least three consecutive spontaneous miscarriages unexplained before the tenth week of amenorrhea (SA);
- Or fetal death (from ten WG);
- Or a premature birth (at or before the 34th WG) due to of severe pre-eclampsia, eclampsia, or severe placental insufficiency, of a newborn morphologically normal.[2,3]

Placental insufficiency is defined by the presence of a intrauterine growth retardation (IUGR), oligohydramnios, umbilical Doppler abnormalities or fetal heart rhythm abnormalities.

In this review, we will successively address these different manifestations and discuss the treatments, which remain still often controversial. The part concerning the pathophysiology is dealt with in the article by Pasquali et al. of this number thematic of the Review and will therefore not be discussed here.

Under the APS, the concept of miscarriage stops at ten WG, which corresponds to the passage from the embryo to the fetus. After ten WG, we talk about fetal death, which implies stopping the cardiac activity in utero without ultrasound fetal malformation or anatomo-pathological. These definitions are very different from what is used in gynecology-obstetrics where we group all causes of fetal loss (mechanical miscarriages cervical open bite for example and deaths in utero) in miscarriages (or abortions) that are usually divided early (first trimester) or late (or up to 20, or even 24 WG). These differences make it difficult to cross-reference the data. from the literature and their analysis must therefore take into account these subtleties.

Epidemiology

In the European APS cohort (1000 patients included including 820 women), the inaugural event was fetal loss

in 10% of patients, and 15% of women had only obstetric manifestations during follow-up.[4]

At inclusion in the registry, 71.9% of women (n = 590) had had one or more pregnancies (range: 1–23) that had 74.1% of them resulted in the birth of one or more children alive (mean 1.7; range: 1–8). Preeclampsia (9.5% of pregnant women), eclampsia (4.4%) and hematoma retroplacental (2.0%) were the most common maternal complications more frequent. The most common fetal complications had been an FCS before ten WG (35.4% of pregnancies), a late fetal loss after this date (16.9% of pregnancies) and premature birth (10.6% of live births).[4] He was not specified whether these complications had occurred during treatment or not. During the five years of follow-up of this cohort (1999 to 2004), 9.4% of women (n = 77) had one or more pregnancies (range: 1–4) and 81.8% of these women had at least one birth of a live child (range: 1–3). The most common obstetric complications were early miscarriage (17.1% of pregnancies), fetal death (6.7% of pregnancies), premature delivery (35% of live births) or IUGR (13.7% live births).[5] If the rates of early miscarriage and IUGR are comparable to those observed in the general population (the the rate of IUGR being by definition 10%), the rate of prematurity is, on the other hand, significantly higher. Patients with APS with obstetric manifestations have an increased risk of subsequent thrombotic complications. However, the annual risk varies greatly depending on the studies, from less than 1%,[6] to 7.4% without treatment by aspirin at an anti-aggregating dose.[7]

2. When should we search a biological APS during pregnancy?

There is no justification for testing for antiphospholipid biology (APL) in all pregnant women. Indeed, the APL are present in approximately 3 to 5% of the general female population with often low rates, and without demonstration of an association with a worse obstetric prognosis.[8] The studies carried out in this area are few. Some have showed a lower rate of live births among women having APL (62 to 84% versus 90 to 98% in those who do not have APL).[8,9] The justification for abstaining from therapy in this context is based on a randomized trial carried out in 19 patients which showed a live birth rate greater than 90% with or without aspirin.[10]

On the other hand, the search for an APL biology is necessary at patients with known lupus or an abnormality suggesting APS (history of fetal loss or venous thrombosis or arterial, notion of spontaneously prolonged TCA, livedo pathological, cardiac valve disease of obscure cause, thrombocytopenia peripheral, dissociated positive VDRL in particular). Indeed, in this context, APL biology is generally 'pathological' and may justify a preventive treatment, at least with aspirin, associated to appropriate monitoring.

Clinical manifestations suggestive of obstetric APS can be observed in the absence of antiphospholipid biology. The possibility of seronegative APS should then be considered and a proposed treatment.[11]

3. Obstetric manifestations of the syndrome antiphospholipids

Maternal complications attributable to APL are high blood pressure, preeclampsia, eclampsia, hematoma retroplacental, Hemolysis syndrome, elevated liver enzymes, low platelet count (HELLP), and the occurrence of a thromboembolic event, sometimes in the context of catastrophic syndrome of antiphospholipids (catastrophic antiphospholipid syndrome [CAPS], see the article on CAPS in this thematic issue of the Journal). The drug toxicity is also part of the complications and when LPS is associated with lupus, the patient may present complications related to lupus flare-ups. Fetal risks are dominated by FCS, fetal death, IUGR and prematurity. These risks are reduced by taking adapted therapeutic load.

The perception of the risks associated with APS varies between internists and obstetrician-gynecologists. Indeed, depending on the mode of entry into the disease whether by three FCS, by a death second or third trimester fetal or event thrombotic, the course is not comparable and neither are the obstetric risks. The study by Bramham et al. who studied the prognosis obstetrics of patients with APS according to their clinical phenotype shows it: 83 pregnancies in 67 women were analyzed. Group 1 included 21 pregnancies in women with a history of repeated miscarriage, group 2, 21 pregnancies with a history of fetal death or prematurity due to placental insufficiency and group 3, 41 pregnancies in women having APS with a history of thrombosis. The patients had more often associated lupus in group 3 (41.5%) than in group 1 (4.7%; p = 0.003) or 2 (4.8%; p = 0.002).[12] The prognosis was also significantly worse in group 3 (history of thrombosis) and this despite appropriate treatment, as we will see in the next chapter.

3.1. Repeated early spontaneous miscarriages (<10 WG) and fetal deaths Sporadic miscarriage are common in the general population but their recurrent nature (at least three episodes) is rarer. In this situation, 10 to 20% of women have an APL biology.[13] Late miscarriage (after ten WG) which are called fetal deaths within the framework of the APS are much rarer in the general population.

3.2. Preeclampsia

Pre-eclampsia is defined by a systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg, associated with proteinuria greater than or equal to 0.3 g / 24 h. Eclampsia is defined by the occurrence of seizures.

This complication occurs outside of any APS in 2 to 8% pregnant or postpartum women and mainly concerns first-time mothers. It most often occurs in the third trimester of pregnancy but sometimes in the second trimester. In a population analysis of 141,286 births in Florida, the positivity of APL biology significantly increased the risk of preeclampsia (OR 2.93; 95% CI: 1.51–5.61) and placental insufficiency (OR 4.58; 95% CI: 2.00–10.51).[14] In another study, a history of preeclampsia and the existence of APS. are the two most important risk factors for developing preeclampsia.[15] The early (from 15 to 16 weeks old) or severe nature of preeclampsia is suggestive of APS.[16] In the different series of pregnancies carried out in patients with APS and a history of thrombosis or associated APS lupus, gestational hypertension (without proteinuria), or even pre-eclampsia is observed in 32 to 50% of cases.[13,17,18] This risk appears to be much lower in patients with APS manifested by repeated miscarriage.[13] It is sometimes difficult to tell the difference between preeclampsia and lupus flare, as much as the two pathologies can coexist. Extra-renal lupus manifestations, the presence of hematuria and a decrease in the C3 and C4 fractions of the supplement (especially since the fractions of the complement increase physiologically during pregnancy) are all elements in favor of lupus glomerulonephritis.

3.4. Intrauterine growth retardation (IUGR), prematurity Placental insufficiencies with IUGR justifying induction of delivery are frequently reported. This largely explains the importance of prematurity which is thus induced during the APS with a frequency varying from 32-65%.[13,17,18] Even with current treatments, the rate of IUGR still reaches 30% in some series.

3.5. Maternal thrombosis, catastrophic syndrome of antiphospholipids (CAPS)

The frequency of thrombotic events during pregnancy with APS has not been well assessed, but seems rare in our experience when the treatment is adapted, except during CAPS. A study from the international register of CAPS reported 15 CAPS occurring during pregnancy (n = 7) or postpartum or postabortion (n = 7) (no information was available in one case).[20] This represented 6% of the whole CAPS of the register. Pregnant had a high prevalence history of fetal loss (miscarriage or fetal death). A HELLP syndrome was associated in 53% of cases and a placental infarction in 27%. Maternal mortality was 46% and fetal mortality by 54%.[20] In our experience in nine cases, only four pregnancies resulted in the birth of a live child but none Maternal death has not been observed.[22] An obstetric complication is the cause of the occurrence of CAPS in 7% of cases.[23] Others factors can precipitate its occurrence such as infection, lupus flare or interruption of anticoagulation during labor.[24]

3.6. Complications of treatments

Potential complications of heparin treatment during pregnancy are hemorrhages, osteoporosis and heparin-induced thrombocytopenia. Bleeding is rarely reported or observed in practice. Associated osteoporosis treatment with heparin is also rare, but this risk can or even must be taken into account, especially when these patients are being treated with corticosteroid therapy for an autoimmune disease associated. An intake of calcium and vitamin D is then necessary. Heparin-induced thrombocytopenia is a complication rare, but serious. Its incidence during pregnancy is however so low that it's not recommend the monitoring of platelet count when using low weight heparin molecular weight (LMWH).[25]

3.7. Infertility

There are arguments in vitro and in mice that allow to think that APL plays a role in infertility. Many work has shown that primary infertility is associated with higher prevalence of APL. It varies according to the studies from 24 to 42%.[17] However, prospective studies have not shown significant influence of APLs on the implantation rate and the rate of pregnancies in patients treated by in vitro fertilization.[26] The link between APL and infertility therefore remains controversial.

4. Obstetric prognostic factors

4.1. Clinical factors

In the retrospective study by Bramham et al.[12] who studied the obstetrical prognosis of patients with APS based on of their clinical phenotype (see above), dams in group 3 (history of thrombosis) were receiving treatment with aspirin associated with two daily injections of LMWH (or even just one injection). Group 1 patients (history of repeated miscarriage) were on aspirin alone (sometimes in combination with an injection of LMWH) and those in group 2 (history of fetal death or prematurity due to placental insufficiency) were under aspirin and an injection of LMWH. Patients in group 3 had significantly more premature infants (26.8% versus 4.7%, $p = 0.05$) than those in group 1 and they had more children with IURR than mothers in group 2 (39.5% versus 4.8%, $p = 0.003$).[12]

As we have also shown.[27] the existence of an APS with thrombosis is therefore a factor of poor obstetric prognosis, even if the treatment seems appropriate. Patients with APS manifested by miscarriage recurrent patients usually have a good prognosis by the time the first trimester of pregnancy has passed, with few accidents of the second or third trimester and a prematurity rate much lower than patients with a history of thrombotics (5 to 40% versus 43 to 92% depending on the study).[12]

4.2. Biological factors

The main data come from the prospective study American PROMISE on pregnancies during lupus or APS and whose results have so far only been reported under the form of abstracts. A circulating anticoagulant was present in 44 of 91 pregnancies with APL biology (48%). The presence of a circulating anticoagulant was an element of poor prognosis with 41% obstetric

complications versus none in female patients without circulating anticoagulant (47 pregnancies, p <0.0001). There was not no link between obstetric prognosis and existence of high rates ACL or anti-2GP1.[28] These results are in line with our clinical experience where the existence of a circulating anticoagulant is a pejorative element. Ruffatti et al. retrospectively analyzed the factors of poor prognosis in 410 pregnancies with APS.[29] Complication occurred in 57 pregnancies (14%). The risk factors found were the association with a systemic lupus or another autoimmune disease, a history of thrombosis and complications during pregnancy anterior, and the presence of triple APL positivity.[29]

It should nevertheless be remembered that no predictive factor clinical or immunological morbidity or mortality obstetrics was not detected in the study of the European 1000 APS.[5]

4.3. Ultrasound factors

We studied obstetric prognostic factors (clinical, biological or ultrasound) in a series of 100 pregnancies in women with systemic lupus or an APS.[27] During the Doppler performed on the second trimester, the presence of a uteroplacental resistance index abnormally high, the persistence of a protodiastolic notch and a decrease in diastolic flow are considered as pathological. A Doppler abnormality of the umbilical artery on the second trimester Doppler ultrasound (OR: 7.44; 95% CI: 1.02–54, p = 0.047) and a history of phlebitis (OR: 13.78; 95% CI: 1.56–121.38, p = 0.018) are predictors fetal or neonatal death. An artery Doppler abnormality umbilical on the second trimester Doppler ultrasound was predictive of a pejorative evolution of pregnancy (p = 0.001). Thus, in 18 patients with uterine Doppler abnormalities at the during the second trimester of pregnancy, 13 (72%) developed preeclampsia, HELLP syndrome, severe prematurity, or IUGR, whereas such a complication was only observed in eight of 72 patients (11%) without uterine Doppler abnormalities.[27]

The prognostic value of obstetrical Doppler ultrasound in women with various systemic diseases has been confirmed by other teams.[30,31]

5. Treatment

Pregnant with APS, when therapeutic management is appropriate, more than 70% of pregnancies result in upon the birth of a living child.[32,33] Ideally, pregnancy must be preceded by a preconception consultation in order to do not ignore the rare contraindications to pregnancy, to organize the management of a possible associated lupus as well as anti-SSA antibody if present, to adapt the treatments and organize multidisciplinary follow-up. This preconception consultation allows the woman or the couple to be informed about the risks and treatment options for pregnancy ahead and on its prognosis. This information promotes a decision early and adapted by professionals accustomed to management of pregnant women in this context. Note that we are currently developing this type of preconception consultation in order to offer management of the future pregnancy to the doctors who will continue to follow the patient. The main contraindications to pregnancy are the existence of severe pulmonary arterial hypertension (PAH) which would endanger the maternal prognosis, hypertension severe arterial disease, poorly tolerated valve disease and a history of major and recent thrombotic. Kidney failure increases clearly the risks of complications both maternal and fetal and in this case the possibility of pregnancy should be discussed on a case-by-case basis with the nephrologists. Quitting smoking is also essential. The goal of treatment during pregnancy in a woman having a defined APS is to prevent complications both fetal and maternal. The treatments are based on aspirin and LMWHs. Even though there are theoretical contraindications, the data available on the complications of these treatments during pregnancy are very reassuring and should be provided to the patient. It is indeed not uncommon for patients to worry read, for example, on the leaflet of aspirin, that its use is contraindicated during pregnancy.

5.1. Treatment if a history of spontaneous miscarriages repeatedly

Various protocols have been proposed, using to varying degrees variable anti-aggregating dose aspirin, heparin, corticosteroid therapy, intravenous immunoglobulins (IVIG) and exchanges plasma. Empson et al.[34] analyzed in their review of the literature published by the Cochrane in 2005, treatments for women with APS with repeated fetal losses (miscarriages but also fetal deaths according to studies). As the authors point out, the analysis of the literature is greatly complicated by the fact that the studies are very heterogeneous. Indeed, some include patients with "only" two miscarriages or fetal deaths or having used very variable biological criteria (APL versus circulating anticoagulant; persistent or not). Birth rates living in the aspirin group which vary from 17 to 100% are the reflection of this great heterogeneity. The authors finally selected 13 studies on 849 women. Treatment with unfractionated aspirin and heparin (2 studies, n = 140) significantly reduced the risk of recurrence of miscarriages compared to aspirin alone (RR: 0.46; 95% CI: 0.29–0.71).

Treatment with aspirin and LMWH (1 study; n = 98) did not reduce not this risk in a significant way compared to aspirin alone (RR: 0.78; 95% CI: 0.39–1.57). There was no difference between high and low doses of unfractionated heparin (1 study; n = 50). Three studies with aspirin alone (n = 135) did not show a significant reduction in the number of fetal losses (RR: 1.05; 95% CI: 0.66–1.68). Prednisone in combination with aspirin (3 studies; n = 286) was as effective as treatment with heparin and aspirin but at the cost of a significant increase in risk of prematurity, high blood pressure and gestational diabetes. Intravenous immunoglobulins (IVIG) with (1 study; n = 16[35]) or without (1 study; n = 42.[36]) unfractionated heparin and aspirin did not reduce

the risk of loss fetal versus unfractionated heparin therapy and aspirin. Compared with prednisone and aspirin, IVIG (1 study; n = 82) did not significantly modify the prognosis.[37]

The authors concluded that the combination of aspirin and of unfractionated heparin reduces fetal loss by 54% while corticosteroids and IVIG have not shown any benefit in the prevention of recurrent fetal loss occurring as part of an APS.[34] Superiority of heparin no fractionation on LMWHs is possible and the authors emphasized the need for randomized studies to better compare these two types of heparin. Since then, three studies have compared unfractionated heparin and LMWH in combination with aspirin. They did not show any differences between the two treated groups.[38–40] In practice, LMWHs are mostly prescribed, because they offer the advantage over unfractionated heparins of better bioavailability, longer half-life, with a lower risk of thrombocytopenia and osteoporosis.[25.41] Mak et al. published a meta-analysis in 2010 which shows that the combination of heparin and aspirin allows the birth of children alive in 74% of cases versus 56% on aspirin alone in patients with repeated fetal loss with biology APL without associated lupus.[42] The number of patients to be treated by aspirin and heparin to achieve a live birth was 5.6 patients.[42] A study published in 2010 showed that patients with APS with repeated fetal loss particularly benefit from the treatment with aspirin and heparin in subsequent pregnancies.

The rate of live births then reached 79% versus 62% under aspirin alone (OR: 2.7; 95% CI: 1.3–5.8).[33] He is interesting to note that women with a history of unexplained miscarriages (therefore without APS) had no more live births when receiving LMWH in addition to aspirin.[33] It is therefore likely that this scheme is only beneficial in female patients really at risk, that is to say those with lupus or a validated firm biology (confirmed at 12 weeks, at average rates or high for ACL, or with a circulating anticoagulant). Note that this subject remains controversial enough for some experts consider that the option of monotherapy with aspirin also remains possible.[32] In situations of failure despite treatment with aspirin and heparin, Bramham et al. reported, in an uncontrolled study published in 2011, the benefit of adding small doses of corticosteroids (10 mg per day) during the first trimester and this even in the case of primary APS.[43] It has recently been shown that hydroxychloroquine (Plaquenil®) played a protective role on the shield annexinA5 forms on the target phospholipid layer of APLs. This potentially gives him a role preventive in the occurrence of FCS.[44] Some experts suggest therefore to add hydroxychloroquine in patients with Primary APS with recurrent thrombosis despite treatment anticoagulant.[32,45] even with persistent obstetric accidents despite the more traditional treatments. Finally, the role of IVIG in these failure situations have never been evaluated.

5.2. Treatment if a history of fetal death, pre-eclampsia, or retroplacental hematoma

There are very few studies and no controlled trials of treatment indicated in this group of patients. The only data come from studies of fetal loss in which these patients are sometimes included. Most experts recommend combining heparin and aspirin.[32] We offer start aspirin before conception (especially when there is had early and severe accidents), and to introduce heparin upon confirmation of an intrauterine pregnancy even if one does not have any explicit recommendation on this subject in the literature.

The optimal dose of heparin (preventive or curative) has not been that very partially studied in the various studies on fetal loss. In practice, in a patient with a defined APS, with previous obstetric events that occurred in the absence of treatment, we offer the combination of low-dose aspirin with low preventive dose LMWH (enoxaparin Lovénox® 0.4 ml / day). In a patient who has had fetal loss or another obstetric complication with this association, a heparin therapy with LMWH in two injections daily can be offered (at a high preventive dose, i.e. enoxaparin 0.4 ml × 2 / day or at a curative dose). These practices remain of course at adapt on a case-by-case basis.

5.3. Treatment if a history of thrombosis

Usually, outside of pregnancy, patients with an APS with venous or arterial thrombosis are anticoagulated long-term by anti-vitaminK (AVK). When pregnancy occurs, VKA should be stopped as soon as possible, due to the risk of embryopathy. The risky period is essentially between six and nine WA, 4 to 7% of exposed pregnancies with embryonic damage.[46] During exhibitions after nine WG, the AVK cause central nervous system abnormalities in 1 to 2% of cases.[46] VKA are replaced by LMWH at an associated curative dose to aspirin at an anti-aggregating dose. Ideally, the patient should have a prescription given to him during the preconception consultation. This attitude is justified to prevent maternal thromboembolic recurrence but also due to the obstetric risk, which is high in these patients.[12,27]

Enoxaparin is the molecule most often used in France, with a subcutaneous injection every 12 hours. The goal is the achievement of effective anti-Xa activity (between 0.5 and 1 IU / mL plasma). Due to changes in the volume of distribution of heparin during pregnancy, it seems justified to monitor the effectiveness of this anticoagulation by dosing regularly anti-Xa activity and adapting heparin therapy if necessary.[47] To simplify treatment, some replace enoxaparin at curative dose with tinzaparin (Innohep®) or nadroparin (Fraxodi®), these two molecules having no authorization marketed in France during pregnancy. Pharmacokinetic data nevertheless suggest a poorer cover of the nycthemerium.

5.4. Peripartum management

Childbirth is usually scheduled around 38 weeks, the risk of preeclampsia increases with the advancement of the pregnancy. In the peripartum period, aspirin is usually discontinued between 34 and 37 weeks WA to allow epidural analgesia under good conditions. The moment of stopping aspirin depends on the expected benefit, therefore the type of clinical history and risk of childbirth before term (whether delivery is spontaneous or induced). We have observed CAPS tables in the period of withdrawal of aspirin, especially in patients with APS with a history of arterial or even venous thrombosis. This leads us to limit maximum withdrawal of aspirin in this group of patients. In depending on the expected benefit of aspirin in these women, we It sometimes happens not to stop, or even to apply locoregional analgesia with aspirin. In our experience, heparin should only be withheld to allow epidural analgesia and childbirth in good conditions. It must be resumed immediately after due to postpartum thrombotic risk.[51] Some anesthetists offer a relay with unfractionated heparin in end of pregnancy, which, with a shorter half-life, allows shorten the window to stop anticoagulation.[17] Here again, the duration of this therapeutic window of anticoagulants is depend on the importance of the risk, therefore the type of history thrombotics. Postpartum, patients with an indication for long-term anticoagulants are treated with effective LMWH then, fairly quickly, by AVK with the same anticoagulation objective than before pregnancy. Breastfeeding on AVK is possible, under reserve of a regular supply of vitamin K in children (2 mg per orally per week). Fluindione (Préviscan®) is contraindicated due to a significant passage in the milk and possible changes in coagulation tests in patients with breastfed children. These reservations do not apply to warfarin (Coumadine®) which should therefore be favored in this context.[32.46] For patients with no indication for prolonged anticoagulation (SAPL with obstetric manifestations alone), preventive LMWH is prescribed within six weeks postpartum due to the increased risk of thrombosis in this period.[32] It is usually then proposed to continue treatment with low doses of aspirin to prevent thrombotic risk.[7,8,32] The reservations raised by the failure of aspirin for the prevention of thrombosis in subjects with APL biology without a history of thrombosis in a randomized placebo-controlled trial.[52] is unlikely to be extrapolated in the population of patients who have had obstetric manifestations of APS or in those with associated lupus.[7,32,53,54] In Indeed, in this randomized study, the number of patients with obstetric history was unclear and most importantly, the rate of thrombosis in the placebo group was surprisingly low (0%).[52] In contrast to these results, observational studies showed a clear protective effect of aspirin in female patients lupus with APL and in patients with obstetric APL.[7,32]

6. Monitoring

The follow-up of these high-risk pregnancies is based on multidisciplinary, associating obstetrician, internist doctor or rheumatologist, and anesthesiologist. We suggest, like others.[32] to carry out a follow-up initially monthly, then more closely at the end of pregnancy. The monitoring focuses on looking for warning signs of HELLP or pre-eclampsia (high blood pressure, proteinuria, oliguria, weight gain, edema, epigastric bar pain). At the same time, any unusual sign will be taken into account for look for the occurrence of thrombosis or signs of an attack lupus.

Treatment with LMWH during pregnancy does not require no monitoring of platelets as recommended by Afssaps in 2009.[25] As we have seen, if LMWH is used in a curative dose, anti-Xa activity can be monitored for of dose adjustment during pregnancy.[47] Above all, the biological monitoring will look for signs of preeclampsia and those heralds of HELLP, mainly in the second half of pregnancy (thrombocytopenia, hepatic cytolysis, hemolysis).

It is important to know that HELLP syndrome can sometimes precede the signs of preeclampsia. Note that the presence of APL may be associated with increased fetoprotein levels (possibly through placental insufficiency). The- fetoprotein being used in the blood test for trisomy 21, this leads to an underestimation of the risk of should be taken into account in the advice given to patients.[56] In addition to the three obstetric ultrasounds recommended in France, ultrasounds with Doppler are generally performed every month from four months, remembering that uterine Doppler abnormalities in the second trimester of pregnancy, in particular especially the presence of protodiastolic incisions (notches), are an important predictor of obstetric accidents.[27]

7. CONCLUSION

The prognosis of these pregnancies improved with a rate of successful pregnancies which is over 70%. This improvement is explained by an overall improvement in knowledge of the pathology by the various stakeholders, a better anticipation (preconception consultation) and by taking multidisciplinary burden of these high-risk pregnancies, including close obstetric monitoring and optimized treatment based on the patient's history. Different therapeutic protocols have been proposed with an undeniable advantage for the combination of low doses of aspirin and heparin.

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