



## Prevention of Thrombosis during Pregnancy

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Anticoagulant therapy is indicated for many conditions involving the cardiovascular system, such as deep vein thrombosis and chronic atrial fibrillation, and for thrombosis prophylaxis in patients with mechanical heart valves. For rheumatologists and general practitioners, interest in anticoagulant therapy arose following the description of the antiphospholipid syndrome, also known as Hughes' syndrome. In APS, in addition to arterial and venous thromboembolic complications, without other identifiable causes of thrombophilia, obstetric complications may also occur. These include recurrent fetal losses, premature deliveries and consecutive early abortions, when anatomic and chromosomal causes are excluded [1]. These manifestations of APS can be avoided when full oral anticoagulation is maintained for life. Anticoagulation during pregnancy remains a controversial subject. Oral anticoagulants cross the placenta freely and may have teratogenic effects (if used in the embryonic period) and fetal hemorrhages (when used close to delivery). Heparin has a better safety profile but is less efficacious. In this review of the literature on anticoagulation during pregnancy and through analysis of the experience with this therapy in other conditions, we suggest a reevaluation of the present obstetric management of APS.

### Oral anticoagulants

Concern regarding the use of oral anticoagulants during pregnancy began in the 1950s with the first reports of teratogenicity related to coumadin. Although the series published in 1960 overestimated the incidence of teratogenicity, pregnancy became contraindicated in women requiring permanent anticoagulation [2]. Additional experience with oral anticoagulation during pregnancy became available in the 1970s, when women with mechanical heart valves who were taking coumadin became pregnant despite the medical contraindication [3].

Oral anticoagulants are inhibitors of the  $\gamma$ -carboxylation of the vitamin K-dependent coagulation factors. Its absorption by the gastrointestinal tract is good and its bioavailability is not affected

during pregnancy [4,5]. Daily oral administration and monitoring by INR facilitate treatment adhesion and long-term use.

Coumadin teratogenicity is characterized by bone dysplasias, nasal hypoplasia, defects in the fusion of bones, microphthalmia, optic atrophy and cataracts [6,7]. We now know that these alterations can only occur when the fetus is exposed to coumadin during the first trimester of pregnancy, particularly between the sixth and eighth week [8]. The real incidence is about 4–6%. The pathogenic mechanism of coumadin embryopathy is unknown. It was believed initially that micro-hemorrhages in the fetal cartilages were responsible for the defects, but since the immature fetal liver does not produce coagulation factors before the 12th week of pregnancy this hypothesis is unlikely [9]. In animal models it was not possible to demonstrate teratogenicity resulting from coumadin use during pregnancy. The role of vitamin K deficiency in the skeleton formation is also unknown [10].

Neurologic malformations may occur when the fetus is exposed to coumadin during the second or third trimesters [11]. The Dandy-Walker syndrome is characterized by corpus callosum agenesis, hydrocephaly and myelomeningocele [12]. These alterations may be attributed to fetal hemorrhage; however the exact incidence of this syndrome is unknown since it has only been described in isolated case reports [13]. Fetal and placental hemorrhage is probably another risk factor that was overestimated in the initial reported series. Sarelli et al. [14] surveyed 60 pregnancies and found only one case with histopathologic documentation. Chan et al. [15], reviewing 1,294 cases in the literature, noted a 2% incidence of placental hemorrhages. This complication may be avoided by substituting coumadin with heparin close to the due date [15,16].

### Heparin

The anticoagulant action of heparin is through enhancement of the antithrombin-III effect. Unfractionated heparins do not cross the placenta and impose no risk of embryopathies [17]. Its plasmatic half-life is short and its bioavailability is relatively unpredictable. During the pregnancy course progressively increasing dosages of heparin are necessary to obtain the same anticoagulant effect [14].

Unfractionated heparin may be administered subcutaneously or intravenously. During pregnancy it is generally used subcutaneously in dosages varying between 5,000 and 20,000 UI every 8–12 hours.

APS = antiphospholipid syndrome

The need for IV or SC administration is one of the disadvantages of heparin. In the course of 37 weeks of use, bruises and local infections occur frequently and patients must be well informed of these side effects before starting therapy. Some authors recommend IV heparin for 5–10 days until the anticoagulation target is reached. Monitoring for maintaining the partial thromboplastin time at therapeutic levels (2.0 to 2.5 times the control) is not always simple, and in order to acquire a true level of anticoagulation the PTT must be obtained 6 hours after the last injection [1]. For women who require more than 8,000 UI every 8 hours, the intravenous route is safer. Furthermore, a resistance to heparin was noted in women with mechanical heart valves [3].

The use of heparin for a prolonged period is associated with an increased risk of mineral bone mass loss. Five studies demonstrated the occurrence of osteopenia in one-third of the patients who used heparin during pregnancy. The risk of osteoporosis and fracture was found to be lower, occurring in only 2% of the patients. Osteopenia seems to be reversible when heparin is withdrawn. The maximal exposure time necessary for the development of osteopenia is not known [18–20], however bone mass loss may reach 10% of the total bone mass during 9 months of heparin exposure and the recovery may take up to 2 years.

Another adverse effect of heparin is thrombocytopenia, which may occur early or late during its usage. The mechanism of thrombocytopenia is formation of platelet thrombi, also called white thrombi, which may cause either platelet consumption or vascular occlusions. The thrombocytopenia may be severe, causing bleeding and increasing the maternal mortality rate. When the platelet count is below 50,000, heparin withdrawal is obligatory [21,22].

Low molecular weight heparins can be used safely during pregnancy, with no risk to the fetus. Although more costly than the unfractionated heparins, they have several advantages such as a longer half-life, which allows a single daily dose, and lower risk of bleeding and thrombocytopenia [23,24]. The efficacy and safety of the low molecular weight heparins during pregnancy have been demonstrated in women with congenital and acquired thrombophilias [25].

### **Anticoagulation in pregnant women with mechanical heart valves**

Cardiology studies compared three different forms of anticoagulation therapy in pregnant women with mechanical heart valves: a) heparin between 6 and 12 weeks of pregnancy with coumadin during the second and third trimesters, b) oral anticoagulant throughout the pregnancy, and c) heparin throughout the pregnancy. Most of the published studies were not well controlled, making a definite consensus even harder. However, the investigations did identify the factors determining whether the anticoagulation intensity should be increased or diminished: namely, mechanical heart valve localization, quantity and model. The presence of atrial fibrillation and ventricular function was not

identified [14,26,27]. Nonetheless, the conclusions of these studies provided important information on anticoagulation during pregnancy.

Thrombosis of the mechanical heart valve and thromboembolism were the major causes of maternal mortality in all studies. The incidence was considerably greater during the period of heparin usage. The group of patients who used heparin throughout their pregnancy had the highest mortality rate and a 10% maternal incidence of thromboembolism [17,28]. The incidence of abortions was high in all patient groups, ranging from 24 to 50%. Among the patients who used heparin throughout the pregnancy the frequency of abortions was slightly lower. In a review of 1,325 pregnant patients taking anticoagulation because of mechanical heart valves, embryopathy was detected in 4%. All the cases of embryopathy occurred when the oral anticoagulants were used between the 6th and 12th weeks of gestation. Central nervous system malformations were not detected [15].

Fetal and placental hemorrhages occurred in 2.5% of the cases, 80% during spontaneous delivery [13]. A high incidence of preterm deliveries (55–70%) in the group of patients with valve disease determined the decision to replace coumadin with heparin after the 35th week of pregnancy. Some authors recommend pregnancy interruption at 36 weeks by cesarean section to avoid hemorrhage of spontaneous delivery [14,15]. None of the studies confirmed the efficacy of LMWH for the prevention of thromboembolism and mechanical heart valve thrombosis.

### **Treatment and prevention of deep vein thromboses**

For patients who develop DVT or pulmonary thromboembolism during pregnancy, the current recommendation is subcutaneous heparin every 12 hours in a sufficient dose to keep the PTT ratio at 2–2.5 times the control, until the pregnancy is over [29]. After delivery the heparin is replaced by coumadin. For DVT prophylaxis in patients at risk, subcutaneous heparin 5,000–10,000 IU is used every 12 hours. Recent studies demonstrated the efficacy and safety of LMWH for the treatment and prevention of DVT and pulmonary emboli during pregnancy [30]. To the best of our knowledge, no studies have evaluated coumadin for these indications.

### **Antiphospholipid antibody syndrome [Table 1]**

Patients with APS have an increased risk of fetal loss and other obstetric complications, as well as arterial and venous thromboses during pregnancy. Despite being a treatable cause of fetal loss, treating APS during pregnancy is still controversial, mainly due to the scarcity of controlled clinical trials [31–34]. To date, the schemes evaluated include the use of aspirin in anti-platelet aggregating dosages, heparins, prednisone and intravenous gammaglobulin. The use of prednisone was demonstrated to be ineffective in a prospective well-controlled study [35]. The LMWH were equivalent to the unfractionated heparins for the prevention of

PTT = partial thromboplastin time

LMWH = low molecular weight heparins

DVT = deep vein thrombosis

**Table 1.** Antiphospholipid antibodies and APS: current recommendations for preventing complications during pregnancy according to previous history

Past history	Low IgG or IgM aCL	Moderate or high aCL or positive LA
No thrombosis or fetal loss:	Observe only	Observe only or low dose ASA
Thrombosis*	Low dose ASA	Low dose ASA + heparin or LMWH
Fetal loss only	Low dose ASA**	Low dose ASA + heparin or LMWH
Fetal loss on low dose ASA	Low dose ASA + heparin or LMWH#	Low dose ASA + heparin or LMWH + IVIG
Recurrent abortions	Low dose ASA	Low dose ASA + heparin or LMWH

\* Those who had cerebral vascular accidents have a worse prognosis and may be advised against pregnancy or require a more intense anticoagulation and IVIG.

\*\* Investigate other causes such as hyperhomocysteinemia and activated protein C resistance.

aCL = anticardiolipin antibodies, LA = lupus anticoagulant, ASA = acetyl salicylic acid, IVIG = Intravenous immunoglobulin.

fetal reabsorption in animal models of experimental APS [36]. The current recommendation is to use unfractionated heparin or LMWH, in addition to baby aspirin [34,35,37]. It is important to remember that due to the presence of lupus anticoagulant, the PTT ratio of the patient may be altered. We therefore recommend that a basal PTT ratio be obtained for every patient before initiating heparin therapy, and the therapeutic range must be 1.5–2.0 times the basal PTT ratio. The anti-platelet and heparin scheme yielded a significant improvement in APS obstetric results, and the pre-treatment index of 19% fetal survival increased to 70% after treatment. However, the frequency of preeclampsia, fetal wastage and restriction of intrauterine growth remained higher than in the normal population control [38]. There is a consensus in the literature that a good interaction among the high risk pregnancy medical teams, together with closely followed prenatal care to assure fetal well-being, improve both the pregnancy and the APS prognosis. A preliminary report from our group demonstrated the efficacy and safety of the use of coumadin between 14 and 36 weeks of pregnancy in patients with APS [39].

## Conclusion

Treatment for thrombosis prevention in hypercoagulable states during pregnancy is still controversial. The initial overestimated risk of coumadin embryopathy determined its contraindication during pregnancy. The therapeutic disadvantages of heparin and the high mortality rate due to thromboembolism among pregnant women with mechanical heart valves prompted new trials with oral anticoagulants. The experience acquired by cardiologists demonstrated oral anticoagulants to be efficacious and safe during pregnancy. A new therapeutic approach to APS during pregnancy, using heparin with aspirin in the beginning and the end of pregnancy, and coumadin with aspirin between 14 and 36 weeks of pregnancy, appears to improve treatment compliance since it is more convenient and less costly than the present scheme. The role of hydroxychloroquine as a safe anti-platelet aggregating agent to be used in APS pregnancy, as well as other new coagulation-acting agents, remains to be investigated. Prospective well-controlled studies are necessary to evaluate their efficacy and safety.

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