OBSTETRICS

# Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes

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Venous thromboembolism and adverse pregnancy outcomes are potential complications of pregnancy. Numerous studies have evaluated both the risk factors for and the prevention and management of these outcomes in pregnant patients. This consensus group was convened to provide concise recommendations, based on the currently available literature, regarding the use of antithrombotic therapy in pregnant patients at risk for venous thromboembolic events and adverse pregnancy outcomes.

**Key words:** pregnancy, thrombophilia, venous thromboembolism

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The incidence of pregnancy-related venous thromboembolism (VTE) is difficult to measure. The common symptoms and signs are nonspecific—dyspnea, tachypnea, peripheral edema, and leg pain—and are often associated with advanced, normal pregnancy, sometimes making the diagnosis difficult. Even when VTE is suspected, some practitioners are reluctant to use diagnostic tests because of fears of radiation exposure to the fetus. Consequently, the occurrence of VTE is probably underestimated in pregnant patients. Despite these difficulties, the incidence of VTE in pregnancy is reported to be 4- to 6-fold higher than in age-matched nonpregnant women,[1,2] and pulmonary embolism (PE) remains a frequent cause of maternal mortality.[2,3] Indeed, VTE is the leading cause of maternal death in both the United Kingdom and North America, with death from PE occurring in 2 in 100,000 deliveries in the United Kingdom[4] and representing 11% of maternal deaths in the United States.[5] Women who experience DVT during pregnancy are also more likely to have poor pregnancy outcomes. Furthermore, the risk of VTE extends to the postpartum period, with 50% of VTE cases occurring postpartum.[6]

After a firm diagnosis of VTE has been made in the pregnant patient, the perceived complications of antithrombotic therapy sometimes delay or inhibit its implementation. A pregnant patient's risk of having VTE develop is difficult to estimate and is dependent on numerous factors, some not readily identifiable by clinical history or examination. As a result, identifying the patient who would benefit from prophylaxis is difficult. A number of publications have addressed these problems, and some guidelines for prevention and treatment of VTE have been issued.[7-10] However, these guidelines are incomplete and are not always evidence based. The major reason for this deficiency is the relative paucity of well-designed, properly powered, randomized controlled trials in prevention and treatment of thromboembolism associated with pregnancy.

To define current consensus on these issues an expert meeting was organized by

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TABLE 1
**Grading of evidence according to the US Preventive Services Task Force[11]**

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| **Grade of evidence** | |
| I | Evidence obtained from at least 1 properly designed randomized controlled trial. |
| II-1 | Evidence obtained from well-designed controlled trials without randomization. |
| II-2 | Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. |
| II-3 | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence. |
| III | Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. |
| **Recommendation** | |
| A | Recommendation is based on good and consistent scientific evidence. |
| B | Recommendation is based on limited or inconsistent scientific evidence. |
| C | Recommendation is based primarily on consensus and expert opinion. |

Aventis Pharmaceuticals, a member of the Sanofi-Aventis group. In subgroups, 6 topics were discussed, including identification of the problem, risk assessment, options of prevention and counseling for VTE, options of prevention and counseling for poor obstetric history, practical management of anticoagulation and pregnancy, and anticoagulation in labor, postpartum and beyond. A round-table discussion of all topics by all participants followed, from which an original outline resulted. Based on the outline, this report was drafted, refined, and agreed on after multiple review rounds after the meeting was held. The working group maintained full and independent responsibility for content of the consensus document.

This report provides a concise update for practitioners in maternal and fetal health. Recommendations for the use of antithrombotic drugs in pregnancy are given throughout the report. Recommendation grades A to C and evidence levels I to III are based on the US Preventive Services Task Force grading of evidence (Table 1).[11] In brief, grade A recommendations and level I evidence come from randomized controlled trials with clear results; grade B recommendations and level II evidence come from well-designed nonrandomized studies with limited or inconsistent evidence; and level III evidence and grade C recommendations result from consensus opinions of respected experts and authorities based on clinical experience and descriptive studies.

## Pharmacologic Management of VTE in Pregnancy

Management of thrombosis in pregnancy remains a challenge. The anticoagulant drugs currently available for the prevention and treatment of VTE include warfarin, unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), factor-Xa inhibitors, and direct thrombin inhibitors.

Warfarin, a coumarin derivative, interacts with many other medications. Because of the physiologic changes associated with pregnancy as well as nausea and vomiting, it is difficult to attain stable anticoagulation with this drug. Use of the drug during the first trimester has been associated with spontaneous abortion and warfarin embryopathy, consisting of mental retardation, optic atrophy, microphthalmia, cataracts, ventral midline dysplasia, nasal hypoplasia, stippled bones and epiphyses, and central nervous system (CNS) abnormalities in approximately 4-5% of exposed fetuses. Frequencies of abnormalities up to 29% have been reported in patients requiring warfarin for mechanical heart valves.[12-14] Moreover, warfarin can cause CNS abnormalities after exposure at any stage during pregnancy. Warfarin readily crosses the placenta and results in fetal anticoagulation that is not readily reversible, resulting in an increased risk of intracranial hemorrhage.[15] Warfarin is minimally secreted into the breast milk and is therefore considered safe to use in breastfeeding mothers.[7,16] Treatment guidelines recommend postpartum anticoagulation with warfarin for 4-6 weeks with a target international normalized ratio (INR) of 2.0-3.0 (with overlap with UFH or LMWH until the INR $\geq$2.0).[7]

UFH has a short half-life and must be administered subcutaneously or via continuous infusion.[17] The current treatment guidelines recommend subcutaneous dosing of UFH every 12 hours; either as a low dose of 5000 U, to achieve target anti-Xa between 0.1 and 0.3 U/mL (moderate dosing), or to achieve target midinterval aPTT into the therapeutic range (adjusted dosing).[7] It requires frequent laboratory monitoring and dosage adjustment. Although UFH can be reversed by protamine sulfate, its use is complicated by the potential for bleeding complications (probably due to its effect on factor IIa resulting in inhibition of prothrombin activity and an anticoagulant effect). Although heparin-induced thrombocytopenia (HIT) is infrequently reported in pregnancy, it remains a concern, as up to 5% of individuals treated with standard heparin develop this complication, which is associated with a high thrombosis risk. Long-term use of UFH has been reported to cause osteoporosis, which is a concern in patients who require treatment throughout their pregnancy.[17] UFH is classified by the Food and Drug Administration (FDA) as a