

# Advances in Hematology

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*Current Developments in the  
Management of Hematologic Disorders*

## Bleeding and Hypercoagulable Problems in Women

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### **What bleeding problems are experienced by women?**

In general, women have more symptoms of bleeding, primarily due to menses, surgical procedures, and issues related to pregnancy. At menarche and at perimenopause, hormonal changes often lead to irregular menses and predispose women to increased bleeding. Also, older women are more likely to have anatomic abnormalities, such as fibroids, that can increase the risk of bleeding.

The biology of these problems is not well understood or studied. The hemostatic changes that take place during menopause are not well known, in terms of either thrombotic risk or bleeding risk. Both men and women have an increased risk of blood clots with aging, but whether menopausal women have a higher risk has not been studied.

### **What is the goal of hormone replacement therapy?**

Initially, the primary goal of hormone replacement therapy (HRT) was to prevent cardiovascular disease in postmenopausal women. However, studies have now shown that postmenopausal women who receive oral conjugated estrogen do not have a lower incidence of cardiovascular disease. HRT does help prevent osteoporosis, and also decreases the vasomotor symptoms of menopause. For treatment of vasomotor symptoms HRT is usually needed only on a short-term basis.

### **What types of clotting problems are associated with HRT at menopause?**

This question continues to be evaluated in clinical trials. The recently completed HERS and WHI studies evaluated the introduction of HRT in postmenopausal women, as secondary and primary prevention, respectively. A new clinical trial is currently evaluating perimenopausal women and earlier introduction of HRT. This randomized, controlled study of 900 women, entitled the Kronos Early Estrogen Prevention Study (KEEPS), will examine the effects of estrogen initiated earlier than in WHI. Among other objectives, progression of atherosclerosis will be evaluated, and blood will be collected in order to identify hemostatic changes in the perimenopause. This study should provide clarity about

the changes that occur at the time of menopause, and the effect of HRT at this time.

### **How are HRT and thrombosis related?**

HRT is associated with an increased risk of venous thrombosis. HRT further increases the risk of venous thrombosis in women who are predisposed to this condition. In addition, for women who have an inherited thrombophilia and who experience blood clots, HRT is associated with an earlier occurrence of clotting. The clotting effects of HRT are particularly enhanced in women who are heterozygous or homozygous for Factor V Leiden, but also in women with other thrombophilias.

The HERS study, which evaluated HRT as secondary prevention of cardiovascular disease, found a 50% increased risk of cardiovascular risk in the first year of treatment. The question, in these women with pre-existing atherosclerotic lesions, is whether an increased tendency for clot formation (enhanced by HRT) would result in an acute occlusive event due to blood clot formation on the existing lesions.

### **How is hormonal therapy used to treat bleeding problems, and what are the side effects?**

Generally, oral contraceptives (OCs) are used in women with bleeding disorders such as von Willebrand disease. For heavy menses, use of OCs is a mainstay of treatment and is often effective in decreasing menstrual blood flow. Women with heavy menses may stay on OCs throughout their menstruating years, except when pregnant.

Whether this use of OCs is associated with long-term risk of atherosclerotic or other disease is yet unknown. We assume that the bleeding disorder confers some protection against the potential risks of oral contraception as these women age. This question is an important topic for future study.

### **What bleeding and clotting risks are associated with pregnancy, and why?**

Pregnancy is associated with a 5- to 8-fold higher risk of venous thrombosis, compared to nonpregnant women. One of

the reasons for this increased risk may be factor VIII levels, which are a risk factor for venous thrombosis, and are increased during pregnancy.

Women with thrombophilia have an increased risk of thrombosis during pregnancy, and particularly in the postpartum period. Based on an individual's history and the type of thrombophilia, prophylactic or therapeutic anticoagulation, usually as low molecular weight heparin, may or may not be given during pregnancy or postpartum. Most women experience few side effects from anticoagulation during pregnancy, probably because they are generally young and healthy.

In general, women have fewer symptoms of bleeding during pregnancy, and women with mild bleeding problems do not have specific difficulties during pregnancy. For the majority of women with von Willebrand disease or who are carriers of hemophilia A, factor VIII (and von Willebrand factor) levels typically normalize by the end of pregnancy. It is our practice to confirm this in the third trimester so that if Caesarean section, epidural anesthesia, or other procedures are needed at delivery, they can be done without delay.

Factor VIII levels decrease postpartum, with varying timing among women. Some women experience postpartum hemorrhage, and based on a small amount of data, it appears that women who experience postpartum hemorrhage once are more likely to experience it after future pregnancies.

### **What thrombotic disorders are associated with pregnancy loss?**

Women who have inherited thrombophilias are more likely to have an increased risk of pregnancy loss. This loss occurs after 10–11 weeks of gestation; the time the vasculature is established. For women with recurrent loss, anticoagulation is being explored as a potential prophylactic approach. Recent studies have suggested that prophylactic enoxaparin (Lovenox, Aventis) at a dose of 40 mg/day significantly improves pregnancy outcomes.

### **Are the bleeding and clotting risks associated with pregnancy due to hormonal changes?**

Hormonal changes are responsible for these problems, but the underlying biology is not well understood. Studies on OCs, pregnancy, and HRT have identified many changes in coagulation, so the cause is most likely multi-factorial.

There is one consistent finding among many studies: acquired activated protein C (APC) resistance. Studies have documented an approximately 2-fold greater risk of venous thrombosis in women using third-generation OCs compared to second-generation formulations. This finding was surprising because initially the risk of thrombosis observed with OCs was thought to be solely associated with estrogen, but third-generation OCs have less estrogen than the second-generation compounds. However, the third-generation preparations have new synthetic progestins APC resistance is greater in women taking the third-generation OCs compared to second-generation products.

This resistance may explain, for example, why women with Factor V Leiden, a inherited condition producing APC re-

sistance, have a much higher risk of thrombosis during hormonal treatment. Several studies have evaluated the relationship between oral contraception and the risk of venous thrombosis in women who have Factor V Leiden. Bloemenkamp et al evaluated the effect of third-generation OCs in women who were carriers of the Factor V Leiden mutation and found an approximately 50-fold higher risk of venous thrombosis compared to women not taking OCs. In studies that included primarily second-generation agents, that increased risk was 20- to 30-fold. These findings are consistent with the idea that the acquired APC is related to the risk of venous thrombosis.

### **What agents to treat coagulation problems in women are on the horizon?**

Better anticoagulants for thrombosis are awaited, although the role such agents will have in specific treatment for women is unclear. Some new anticoagulants may not be suitable for use in pregnancy if they cross the placenta. Fondaparinux (Arixtra, Organon/Sanofi-Synthelabo), approved for prophylaxis in orthopedic procedures, probably does not cross the placenta, and may be a good drug for further study in pregnancy given its longer half-life and probable lack of risk of heparin-induced thrombocytopenia, compared to low molecular weight heparin compounds. There are no agents on the horizon that would specifically counter hormonal effects on coagulation.

### **What clinical trials, other than KEEPS, are ongoing in this area?**

There are ongoing trials for the prevention of pregnancy loss. In one study thrombophilic women are being randomized to receive either low molecular weight heparin, aspirin, or placebo. The previously reported study did not include a placebo, and it is possible that instead of enoxaparin having a positive effect on pregnancy outcome, aspirin was detrimental. The inclusion of a placebo arm will help further define the efficacy of these approaches. Another study is examining whether a defined thrombophilia will impact the efficacy of low molecular weight heparin on pregnancy outcomes. Women with pregnancy loss, but without a defined thrombophilia, are being randomized to low molecular weight heparin, aspirin, or placebo.

### **Suggested Reading**

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