# Case-based discussion on the implications of exogenous estrogens in hemostasis and thrombosis: the obstetrician's view

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**This is the obstetrician's view on 3 different clinical scenarios involving bleeding and thrombotic disorders. In the first scenario, an 18 year old with a history of heavy menstrual bleeding since menarche presents with abdominal pain and ultrasound findings suggestive of a hemorrhagic ovarian cyst. The association with an underlying bleeding disorder is recognized. The goals of management, which are controlling hemorrhage and preserving fertility, are stated. Ovarian suppression, the most effective method to prevent recurrent hemorrhagic ovarian cysts, is outlined. Long-term management of heavy menstrual bleeding with hormonal contraception is described. In the second scenario, the same patient returns 5 years later for a preconception visit. The potential risks to an unborn baby with von Willebrand disease (VWD) are addressed. The natural rise in von Willebrand factor (VWF) during pregnancy is discussed, but the fact that women with VWD do not achieve the same VWF levels as women without VWD is emphasized and the implications are presented. In anticipation of pregnancy, the need for nonhormonal management of heavy menstrual bleeding and hemorrhagic ovarian cysts is mentioned. In the third and final scenario, the patient's cousin with factor V Leiden seeks consultation regarding the risks of thrombosis with in vitro fertilization. The steps of assisted reproductive technology are described. The strategies to prevent venous thromboembolism by preventing ovarian hyperstimulation and reducing the likelihood of multiple gestation are detailed.**

**Learning Objectives**

- Appreciate the role of underlying bleeding disorders in the formation of hemorrhagic ovarian cysts
- Describe the peripartum management of von Willebrand disease
- Have a better understanding of the process of assisted reproductive technology and the associated risk of venous thromboembolism

## Clinical case: part 1

The patient is an 18 year old with heavy menstrual bleeding since starting menses at age 14 who develops severe abdominal pain with a 2-g drop in hemoglobin. Laboratory tests reveal hemoglobin 8.6 g%, von Willebrand factor (VWF):RCo 0.32 IU/mL, VWF:Ag 0.38 IU/mL, factor VIII:C 0.49 IU/mL, PFA collagen/epi 186 seconds, collagen/adenosine 5′-diphosphate 178 seconds, normal VWF multimers, and a bleeding score =5 (based on menorrhagia, bleed with dental extraction, bruising, and epistaxis). Family history includes heavy menses in her mother, maternal aunt, and maternal grandmother. Her abdomen is diffusely tender to palpation with guarding and rebound tenderness. Ultrasound reveals a 4.4 × 4.0 × 3.6-cm right ovarian mass with both cystic and solid components.

## The obstetrician's view

To the obstetrician, this an acute problem of severe abdominal pain superimposed on a chronic problem of heavy menstrual bleeding (accompanied by anemia with a hemoglobin of 10.6). Acute abdominal pain in a young woman has a broad differential diagnosis, but with the drop in hemoglobin, the ultrasound findings are most consistent with a hemorrhagic ovarian cyst. Other ovarian masses with a cystic and solid component include an endometrioma (an ovarian mass owing to endometriosis), an ovarian teratoma (a dermoid cyst), another benign tumor (such as a fibroma), or a malignant tumor.[1] Other ovarian masses can bleed, but they are less likely to bleed than a functional ovarian cyst arising from an ovarian follicle or a postovulatory corpus luteum. Bleeding is much more likely in a young woman with an underlying bleeding disorder. Hemorrhagic ovarian cysts have been reported in women with von Willebrand disease (VWD), hemophilia, afibrinogenemia, factor X deficiency, and factor XIII deficiency or other rare isolated clotting factor deficiencies.[2] Bleeding with a hemorrhagic ovarian cyst may be confined to the ovary but may also occur intraperitoneally or retroperitoneally. A massive retroperitoneal hemorrhage, presumably owing to ovulation, was reported in a woman with combined factor II, VII, IX, and X deficiency.[3] Hemorrhagic ovarian cysts have also been reported in women using anticoagulant therapy, particularly in women on the higher doses used with mechanical heart valves.[4]

The goals of management of hemorrhagic ovarian cysts are to control hemorrhage and preserve fertility. In the hemodynamically unstable patient, salpingo-oophorectomy may be required to control hemorrhage. In the hemodynamically stable patient, a more conservative approach is warranted. The patient's vital signs and clinical condition, including

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hemoglobin levels, should be closely monitored, and serial ultrasounds should be performed. As opposed to other ovarian masses, hemorrhagic ovarian cysts will undergo transformation and resolve with time, confirming the diagnosis. Another threat to fertility other than salpingo-oophorectomy is ovarian torsion, which can cause ovarian necrosis. Any ovarian mass can increase the ovary's susceptibility to torsion. If the diagnosis is uncertain or torsion of the ovary is suspected, diagnostic laparoscopy may be required. If there is torsion, untwisting the ovary is necessary to preserve fertility. In the interim, the expectation is that the hematologist will address and treat the patient's systemic bleeding condition, whereas the obstetrician monitors for postoperative bleeding.

The most effective way to prevent hemorrhagic ovarian cysts and protect future fertility is to suppress ovulation. Suppression of ovulation can be achieved with a combined hormonal contraceptive.[5] Combined hormonal contraceptives contain an estrogen and a progestin (synthetic progestogen) and come in the form of a pill (taken daily), a patch (changed weekly), or an intravaginal ring (changed monthly). Progestin-only pills incompletely suppress ovulation.[6] The levonorgestrel intrauterine device results in little if any systemic absorption of progestin, and although very effective at reducing menstrual blood flow, it does not suppress ovulation[7] and therefore, does not suppress formation of hemorrhagic ovarian cysts.[6]

The long-term management of the young woman's heavy menstrual bleeding depends on her desire for future fertility.[8] She may not want to become pregnant now but might desire childbearing in the future. Before therapy, there should be determination as to whether the patient has any other explanation for her heavy menstrual bleeding in addition to suspected VWD, such as a uterine/endometrial abnormality or a disorder of ovulation. This patient seems to be ovulating, and her ultrasound did not reveal any uterine abnormalities. Testing would be performed to exclude *Chlamydia* or gonorrhea as a cause of an endometrial abnormality.

First-line therapy for the management of heavy menstrual bleeding in women with or without an underlying bleeding disorder and without a history of thromboembolism is hormonal therapy. Two randomized trials have shown that a combined hormonal contraceptive (estradiol valerate and dienogest) is more effective than placebo in reducing menstrual blood flow (69% vs 6%[9] and 64% vs 8%, $P < .001$[10]). Two randomized trials have found that the levonorgestrel intrauterine device is even more effective than combined hormonal contraceptives in reducing menstrual blood flow (83% vs 68%, $P = .002$[11] and 87% vs 35%, $P = .013$[12]), but the levonorgestrel intrauterine device does not protect the patient against recurrent hemorrhagic ovarian cysts. Tranexamic acid has also been shown in multiple trials to reduce menstrual blood loss by ~50%, but it too provides no protection against recurrent hemorrhagic ovarian cysts. The best option for this patient would be a combined hormonal contraceptive (pill, patch, or intravaginal ring).

## Clinical case: part 2

The (same) patient returns 5 years later to re-establish care and is now seeking your advice on becoming pregnant. She is worried about bleeding if she stops her combined hormonal contraceptive to become pregnant. She is also worried about bleeding during and after delivery.

## The obstetrician's view

During any preconception visit, the obstetrician should develop a plan for the fetus and a plan for the mother. This patient should receive comprehensive prepregnancy evaluation and counseling[13] as well as receive specific information about VWD during conception, pregnancy, delivery, and postpartum for both herself and her future child. The obstetrician should ascertain whether the patient's partner has any history of bleeding. Because she seems to have type 1 VWD, which is inherited in an autosomal dominant fashion, unless her partner is also affected, the chance that the baby would inherit VWD is 50%. An elective cesarean delivery is not required for babies at risk for VWD, but during labor, invasive fetal procedures should be avoided. Cesarean delivery, however, would be preferred to operative vaginal delivery (forceps or vacuum). At delivery, umbilical cord blood can be obtained and sent for a von Willebrand panel, but a definitive diagnosis should be postponed, because normal VWF levels at birth do not rule out VWD. Nonetheless, if the infant is male and the parents desire circumcision, the procedure should be postponed until VWD is ruled out.

VWF levels increase during pregnancy. At the end of pregnancy, VWF levels are ~250% of normal, and FVIII levels are 140% to 150% of normal.[14] Although levels increase in women with VWD, levels do not increase to the same levels achieved by women without VWD.[14] Nonetheless, in a prospective study of women referred for management of VWD during pregnancy, half required no treatment, because levels were at least 50% of normal.[14] The patient can be reassured that women with these levels are no more likely to bleed during or after delivery than women without VWD. If the patient's levels are >50% at the time of delivery, the obstetrician can treat the patient like any other patient and expect that she would be a candidate for a regional anesthetic. Were the patient's VWF level <50% at 36 weeks gestation, she would be at a greater risk of bleeding at delivery and postpartum, but this risk can be mitigated by obstetric measures to minimize bleeding from the uterus. The patient should deliver at a center with maternal-fetal medicine consultation and with a hemophilia treatment center or center with similar expertise in hemostasis. The patient should receive treatment with VWF concentrate at the time of delivery.

After delivery, postpartum bleeding gradually ceases over ~6 weeks.[14] During this time, clotting factor levels decline exponentially and reach baseline about 3 weeks postpartum.[14] Nonsteroidal anti-inflammatory drugs, which are prescribed universally postpartum, should be avoided. Tranexamic acid may be used to prevent excessive bleeding.[15]

In anticipation of pregnancy, the patient will need to stop her combined hormonal contraceptive. She should be reassured that heavy menstrual bleeding can be managed with the antifibrinolytic hemostatic agent tranexamic acid. Typical regimens are 1.0 g 4 times per day or 1.3 g 3 times per day during menstruation (up to 5 days).[16] There are no data on preventing hemorrhagic cysts other than with ovarian suppression, but because there is an association with the formation of hemorrhagic ovarian cysts among women with bleeding disorders and among women on anticoagulation, correction of abnormal coagulation should minimize the chance of recurrence. The hematologist may be able to provide recommendations for a hemostatic agent at the time of ovulation.

## Clinical case: part 3

Two years later, she returns for her annual appointment at the bleeding disorders center, and she brings her 28-year-old cousin who is heterozygous for factor V Leiden (FVL) mutation, is planning to undergo in vitro fertilization in several months, and seeks a second opinion regarding risk of thrombosis with the procedure.

## The obstetrician's view

If the cousin is planning to undergo in vitro fertilization, she and her partner have already been evaluated by a reproductive endocrinologist/infertility specialist. Presumably, not only the cousin but also, her

partner have been queried to ascertain any personal or family history of genetic disorders, including clotting disorders. The couple should be aware of the inheritance of FVL in their offspring. If the partner has FVL or another clotting disorder, the couple should be aware of the possibility of homozygosity for FVL or compound heterozygosity in their offspring. Although most clotting disorders are not life limiting, the couple should be aware that, for certain mutations, there is preimplantation genetic testing of embryos.[17] At the time of formal consultation, the patient should be reassured that, based on available data, FVL does not increase or decrease her chances of a successful pregnancy with assisted reproductive technology (ART).[18]

ART cycles include multiple steps.

1. Suppression of spontaneous ovulation with a gonadotropin-releasing hormone (GnRH) agonist, a GnRH antagonist, or combined hormonal contraceptive pills (less common)
2. Controlled ovarian hyperstimulation with gonadotropins, particularly with follicle-stimulating hormone (natural or unstimulated cycles are possible but result in lower pregnancy rates, and therefore, they are rarely used, accounting for <1% of the total in vitro fertilization cycles in the United States[19])
3. Oocyte maturation with exogenous human chorionic gonadotropin (hCG) as the trigger (hCG is chemically very similar to luteinizing hormone, the natural regulator of ovulation[20]) or a GnRH agonist (such as leuprolide), which allows endogenous luteinizing hormone to act as the trigger
4. Follicle aspiration (oocyte retrieval)
5. In vitro fertilization of the retrieved egg with spermatozoa
6. Embryo transfer

In women who undergo ART cycles, the risk of thrombosis is increased in both successful and unsuccessful cycles.[21] Studies using the Swedish medical birth register have found that, in successful pregnancies, women who undergo in vitro fertilization have an increased risk of venous thromboembolism (VTE) during pregnancy of 4- to 5-fold compared with spontaneous conceptions,[22,23] particularly during the first trimester, with an absolute risk of VTE during the first trimester of 0.2%.[22] This is compared with the absolute risk of VTE during the entire gestation of spontaneously conceived pregnancies of 0.05% to 0.2%.[24] The risk of VTE is 100-fold if ovarian hyperstimulation syndrome (OHSS) develops.[22]

Strategies to prevent VTE include prevention of OHSS and reduction in the likelihood of multifetal gestation. OHSS, which develops in 1% to 5% of ART cycles,[25] is an iatrogenic complication of the injection of hCG used to finalize oocyte maturation and/or trigger oocyte release. OHSS results in arteriolar vasodilation, increased capillary permeability, shifts from the intravascular to the extravascular compartment, hyponatremia, and hemoconcentration.[25] In severe cases, women can develop ascites, pleural effusion, electrolyte disturbances, and thromboembolism.[25] Natural or unstimulated in vitro fertilization cycles do not result in OHSS.[26] Mildly stimulated cycles are less likely to result in OHSS, but they are also less likely to result in a successful pregnancy.[26] Other strategies that have been shown to reduce the risk of OHSS are as follows.[25]

1. A protocol that uses a GnRH antagonist to suppress ovulation
2. A GnRH agonist (such as leuprolide) that allows endogenous luteinizing hormone to act as the trigger for oocyte maturation (instead of hCG as the trigger), especially for patients at high risk for OHSS based on their history and/or serum estradiol levels
3. A dopamine agonist at the time of hCG trigger
4. Metformin in patients with polycystic ovarian syndrome
5. Low-dose aspirin
6. Cryopreservation of embryos with transfer later

By reducing the possibility of multifetal gestation, transfer of a single embryo, as opposed to multiple embryos, also reduces the risk of OHSS.[27] Multifetal gestation doubles the risk of VTE in pregnancy,[24] and therefore, transfer of a single embryo not only reduces the risk of VTE conferred by OHSS but also, reduces the risk of VTE owing to multifetal gestation itself.

There are 2 randomized trials of low-dose aspirin to prevent OHSS. The rationale for the use of low-dose aspirin is that it may reduce platelet activation, which in the setting of elevated levels of vascular endothelial growth factor, may result in the release of histamine, serotonin, platelet-derived growth factor, lysophosphatidic acid, or other substances that promote OHSS.[28] In the first study,[29] subjects were randomized to aspirin 100 mg and 10 to 30 mg of prednisolone per day vs neither medication. Subjects who received the combination had an incidence of severe OHSS of 1.7% vs 6.5% ($P = .03$) in those who did not receive the combination. In the second study,[28] subjects at high risk for OHSS based on a prior history of OHSS, the presence of polycystic ovarian syndrome, or age under 30 years old were randomized to aspirin 100 mg/d vs no medication. Those who received aspirin had a 0.25% incidence of severe OHSS vs 8.4% ($P < .001$) in those who did not receive aspirin.

If a patient does develop severe OHSS, the American Society of Reproductive Medicine recommends prophylactic anticoagulation from the time of diagnosis through the first trimester of pregnancy, and the American Society of Hematology (ASH) 2018 Guidelines for Management of Venous Thromboembolism: Venous Thromboembolism in the Context of Pregnancy also suggest the same.[25,30] If a patient does not develop OHSS, prophylactic anticoagulation may or may not be recommended depending on the patient's other risk factors for thrombosis. If there is a recommendation for anticoagulation, the patient should be aware that anticoagulation does not decrease the chances of a successful pregnancy (but anticoagulation does not increase the chances of a successful pregnancy either).[18] The ASH VTE in pregnancy guidelines suggest against prophylactic anticoagulation for unselected women undergoing ART. In general, a reasonable strategy is to recommend prophylactic anticoagulation during ART cycles for patients who should receive prophylactic anticoagulation during pregnancy.[30] In the case of this patient who is heterozygous for FVL, in the absence of other compelling risk factors, she would not receive prophylactic anticoagulation during pregnancy[30] and would not require prophylactic anticoagulation during ART.

For the patient who is on lifelong anticoagulation or receiving prophylactic anticoagulation, the anticoagulant should be held before and after oocyte retrieval. In 1 paper regarding ART in women with systemic lupus erythematous and antiphospholipid syndrome, the authors recommended holding heparin 12 to 24 hours before retrieval and resuming heparin 6 to 12 hours after retrieval.[31] There is actually little guidance on this subject, but the gauges of needles used for oocyte retrieval (16-19)[32] are associated with bleeding in the target organs of anticoagulated animals.[33] For patients on low-molecular weight heparin, our practice has been to hold anticoagulation 24 hours before and after egg retrieval.

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