Internal jugular vein thrombosis in patients with ovarian hyperstimulation syndrome

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Objective: To describe a case of bilateral internal jugular vein thrombosis complicating ovarian hyperstimulation syndrome (OHSS).

Design: Case report.

Setting: Internal medicine ward in a teaching hospital.

Patient: A 28-year-old nulliparous woman undergoing IVF.

Intervention(s): Ultrasonographic Doppler of the neck veins was performed because of pain and swelling in the neck, and bilateral jugular vein thromboses were detected. Laboratory evaluation revealed activated protein C resistance caused by factor V Leiden mutation. Low-molecular-weight heparin (enoxaparin) was administered for the remainder of the pregnancy and for 6 weeks after delivery.

Main Outcome Measure: Resolution of jugular venous thromboses documented by ultrasonographic Doppler and normal progression of pregnancy.

Result(s): The patient delivered healthy twins at term. There were no complications arising from the jugular vein thromboses or the low-molecular-weight heparin treatment.

Conclusion(s): Unusually located venous thrombosis should prompt an evaluation for a hypercoagulable state. The high prevalence (4%-7%) of factor V Leiden mutation in most Western populations and the mutation's potential contribution to thrombotic complications in OHSS suggest that screening for this abnormality in women undergoing IVF may be indicated. (Fertil Steril 1998;69:140-2. ©1998 by American Society for Reproductive Medicine.)

Key Words: Ovarian hyperstimulation, thrombosis, factor V Leiden, low-molecular-weight heparin
tient, we detected a newly described underlying pro-
thrombotic state, activated protein C resistance (3) that is
caused by a mutation in the factor V gene. The mutant
clotting factor V that results, known as factor V Leiden, is
resistant to degradation by the activated form of the clotting
factor inhibitor, protein C. This hereditary abnormality may
have contributed to the development of the unusual venous
thrombosis that occurred in our patient. We also describe
successful treatment of the thrombosis with low–molecular-
weight heparin (enoxaparine).

CASE REPORT

A 28-year-old woman had been treated for primary infer-
tility for 4 years. During her second IVF treatment cycle, she
was prepared for follicle aspiration using GnRH-a (3.75 mg,
Decapeptyl; Ferring AB, Malmo, Sweden) and menotropins
(Metrodin; Teva Pharmaceuticals, Petach Tiqva, Israel). Af-
ter 10 days of ovarian stimulation requiring a total dose of 36
ampules, the patient developed 14 follicles ranging in diam-
er from 15 to 22 mm. Her estradiol level was 2,812 pg/mL.

Follicle aspiration was performed 34 hours after admin-
istration of 10,000 µg of hCG (Chorigon; Teva Pharma-
ceuticals), and 16 oocytes were recovered; 15 of these oocytes
were injected with use of intracytoplasmic sperm injection,
and 9 were fertilized. Two days later, six embryos were
transferred. More than the usual three to four embryos were
implanted at the patient’s request to increase the chance of
conception and because of the couple’s desire for twins.

Institutional Review Board approval was not necessary
for any aspect of the treatment that this patient received. The
stimulation protocol and the ET were carried out according
to the accepted standard of practice in our IVF unit, and the
hormonal therapy was administered according to this stan-
dard. Informed consent for all aspects of the protocol was
obtained. Enoxaparin is registered for use by the Israeli
Ministry of Health and was not considered experimental in
this case.

Ten days later, the patient was admitted because of ovar-
ian enlargement, ascites, and signs of pleural effusion. Lab-
oratory studies revealed hemoconcentration (hematocrit,
58%), severe hypoalbuminemia (albumin level, 2.4 mg/dL),
and increasing β-hCG levels. The patient was treated with
IV fluids, including Haemaccel (Behringwerke AG, Mar-
burg, Germany), and abdominal paracenteses. Her condition
rapidly improved, and she was discharged 5 days later.

Ten days later, she was readmitted because of complaints
of pain and bilateral fullness in the neck and in the left axilla.
A duplex Doppler study revealed occlusion of the right and
left internal jugular veins. The subclavian veins were patent.
Laboratory testing for a prothrombotic state showed normal
protein C antigen levels and activity, normal total and free
protein S levels, and normal levels of antithrombin III. Tests
for lupus anticoagulant activity in the patient’s plasma were
negative, as was an enzyme-linked immunoassay for anti-
phospholipid antibodies. A test for activated protein C resis-
tance was positive with a ratio of 1.2 (normal, >2). Protein
C resistance-based DNA testing revealed that she was ho-
mozygous for factor V 1691 G to A mutation (factor V
Leiden mutation).

Treatment with IV unfractionated heparin was started,
and the patient’s baseline partial thromboplastin time was
prolonged twofold to threefold. The patient’s cervical and
axillary symptoms decreased markedly within 24 hours.
After 3 days, treatment was changed to low–molecular-
weight heparin (enoxaparin; 40 mg) by subcutaneous injec-
tion every 12 hours. The patient continued to feel well, and
her pregnancy proceeded normally. Treatment with enoxapa-
rin was continued until 36 weeks of gestation, when the dose
was reduced to 20 mg/d in anticipation of a twin delivery at
36–37 weeks. One week later, she delivered healthy male
twins. Treatment with enoxaparin and warfarin sodium was
begun 12 hours after delivery, and warfarin sodium treat-
ment alone was continued for 6 weeks. Repeat duplex Dop-
pler examination of the jugular veins performed 3 months
postpartum revealed recanalization and normal flow bilat-
erally.

DISCUSSION

Hereditary thrombophilia is defined as an underlying ten-
dency toward venous thrombosis caused by a functional
abnormality in proteins regulating the coagulation cascade.
An emerging concept in the study of hypercoagulable states
is the synergistic effect of multiple hereditary risk factors in
a single individual. Similarly, the coexistence of hereditary
and acquired or environmental factors markedly increases
the predisposition to venous thrombosis (3).

Among the most prevalent acquired risk factors for
thrombosis are those associated with elevated levels of cir-
culating estrogens, e.g., pregnancy or oral contraceptive
(OC) ingestion. The risk for the development of venous
thromboembolism in women homozygous for factor V Lei-
den mutation who use estrogen-containing OCs may be 38
times higher than in women not bearing this mutation. Like-
wise, activated protein C resistance increases the risk of
pregnancy-related venous thrombosis (4).

Patients developing OHSS are at even greater risk for
thrombosis because of the increased hematocrit and mark-
edly elevated estrogen levels that accompany this syndrome.
However, even in these patients the incidence of thrombosis
is low, suggesting that an additional risk factor, such as an
inherited or acquired hypercoagulable state, may need to be
present for thrombosis to occur.

The unusual location of the thromboses in this patient
remains unexplained because no local anatomical alterations
were detected in the cervical region or at the level of the
thoracic inlet. The occurrence of thrombosis in unusual
anatomical locations, however, is characteristic of venous thrombosis in patients with underlying thrombophilia such as activated protein C resistance (3).

Low-molecular-weight heparins are a group of drugs derived from unfractionated or standard heparin. Their clinical utility has been demonstrated in deep vein thrombosis prophylaxis for orthopedic, surgical, and medical patients. Low-molecular-weight heparin also is effective in the treatment of established deep vein thrombosis. Low-molecular-weight heparins have been used successfully in pregnancy and are particularly suited for use in this setting because low-molecular-weight heparins do not cross the placenta, appear to cause less osteoporosis during long-term use than standard heparin, and do not require routine laboratory monitoring.

In this case, we were able to demonstrate the successful use of a low-molecular-weight heparin in the treatment of an unusual case of deep vein thrombosis associated with OHSS in a patient homozygous for factor V Leiden. Further studies are necessary to evaluate the role of inherited thrombophilia in the development of thrombosis in patients with OHSS. If patients developing thrombosis as a complication of OHSS are predominantly those with underlying thrombophilia, then screening for such disorders, especially prevalent disorders such as activated protein C resistance, may be considered in patients undergoing IVF.

References