Life-Threatening Thromboembolic Events and Ovarian Hyperstimulation Syndrome

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The paper by Tal et al. in this issue of *IMAJ* (*Israel Medical Association Journal)* [1] presents one of the most severe cases ever reported of vena cava occlusion 4 weeks after in vitro fertilization and embryo transfer. Ovarian hyperstimulation syndrome is a well-recognized complication of pharmacological stimulation of the ovaries following the administration of gonadotropins with an incidence as high as 30% [2]. It is characterized by "third spacing", initiated by increased capillary permeability. Taking into account the diameter of the enlarged ovaries and the amount of fluid shifted from the intravascular space, OHSS is classified as mild, moderate or severe. The severe form is reported in 1–2% of IVF cases, usually presents with ascites, pleural effusion, hypotension and oliguria and may result in potentially fatal complications such as thromboembolic phenomena (0.04–0.78%), renal failure and acute respiratory distress syndrome [3,4].

OHSS is also classified on the basis of the time of onset relative to the day of human chorionic gonadotropin administration or oocyte retrieval. Accordingly, occurrence of the syndrome 3–7 days after oocyte pick-up is considered early, and days 12–17 as late [5]. The early type is triggered by the hCG administration, and late OHSS by endogenous hCG of placental origin which continues to stimulate the ovaries after exogenous hCG levels have subsided. The late type usually occurs simultaneously with pregnancy [3,6].

It is assumed that the stimulated ovaries and consequently the associated increased estradiol levels create a prothrombotic state due to activation and exaggerated changes in the coagulation and fibrinolytic systems. The exact pathogenesis of this hypercoagulable condition is not fully understood, but an increase in coagulation factors and a decline in fibrinolysis markers have been observed [7].

Most cases of vascular thromboses are venous in origin but arterial events have also been described [8,9]. Arterial events seem to present earlier and concurrently with the hyperstimulation symptoms, whereas venous ones usually develop after the full-blown severe syndrome [8]. Chan and Dixon [7] recently demonstrated that while arterial thrombotic events presented on average 8.2 days after hCG administration and 10.5 days after embryo transfer, most venous thrombotic episodes presented 26.6 days following ovulation induction and 40 days after embryo transfer and usually days to weeks after the resolution of the OHSS symptoms.

The majority of thromboembolic events occur in unusual sites: more than half of the arterial cases involve the cerebrovascular system, and less than one-fourth involve the extremities [7]. The predominant sites of venous thrombosis are the veins in the neck and the upper extremities [7]. In the case reported in this issue, the patient was diagnosed with complete obstruction of the superior vena cava with thrombi in the brachiocephalic and jugular veins.

A review by Ou and Kau [10] included 65 women who had experienced thromboembolism after ovarian stimulation. Forty-seven percent of patients with intracranial thrombosis and 79% with thrombosis at other sites had a complete recovery. Patients with intracranial involvement showed a poorer prognosis.

A predisposing inherited thrombophilia has been documented in some women who developed these complications. Similar to the patient presented in the report by Tal et al. [1] heterozygosity to **a**ctivated protein C resistance was discovered later. Increased prevalence of thrombophilia in women with severe OHSS has been reported previously and an inherited thrombophilia was found in one-third of the patients who were tested for it [7]. Similarly, a fivefold increased risk for severe OHSS was observed in patients with homozygosity for MTHFR 677T and the prevalence of antithrombin and protein S deficiencies were significantly increased [11]. Despite these findings, whether to screen for thrombophilia in patients undergoing IVF treatment is still under debate [12].

Prophylactic anti-coagulation treatment is commonly administered to hospitalized patients with OHSS, although there are no randomized controlled studies supporting this approach. The

OHSS = ovarian hyperstimulation syndrome

hCG = human chorionic gonadotropin

American Society for Reproductive Medicine recommends venous support stockings and the consideration of heparin administration in severe cases. When symptoms prevent ambulation it is prudent to use an intermittent pneumatic compression device [13]. Thromboprophylaxis should be considered for an extended period after the resolution of the OHSS due to the possible late onset of venous events. When thromboembolism is diagnosed, treatment with optimal dose heparin or low molecular weight heparin is recommended and should be maintained throughout pregnancy. The patient discussed here had initially received heparin and tissue plasminogen activator, followed by coumadin treatment. However, there are few case reports regarding the use of thrombolysis during pregnancy. Although maternal outcomes were favorable, fetal effects remain unclear [14].

Pregnancy outcome in OHSS patients was discussed in only a few studies. Abramov and colleagues [15] reported a total clinical miscarriage rate of 29.8% in women with the severe form. Others found no difference in miscarriage rates between moderate to severe OHSS patients and the control group without the syndrome [16,17]. The patient presented here had a missed abortion discovered during her hospitalization period.

In conclusion, thromboembolic events in association with severe OHSS are a rare complication characterized by unusual anatomic sites and temporal differences between arterial and venous thrombosis. These events may unmask an underlying inherited thrombophilia. Therefore, thromboprophylaxis should be considered in women with severe OHSS and those with a history indicating a suspicion of thrombophilia. Since the late type of OHSS is being stimulated by endogenous hCG, termination of pregnancy is the definitive treatment in life-threatening situations.

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