Short Communication

Internal jugular vein thrombosis following ovarian hyperstimulation syndrome

Tina FLEMING[1], Gavin SACKS[2] and Justin NASSER[3]

[1]*Department of Obstetrics and Gynaecology, St George Hospital,* [2]*IVF Australia, Kogarah, New South Wales, and* [3]*Go Health Group, Benowa, Queensland, Australia*

Two cases of women who developed internal jugular vein (IJV) thrombosis associated with ovarian hyperstimulation syndrome (OHSS) are reported in this article. There are 27 cases of IJV thrombosis associated with *in vitro* fertilisation (IVF) reported in the literature, and in 78% of cases, this outcome was following OHSS. The hypercoagulable state of OHSS increases the risk of venous thromboembolism, and the IJV appears to have a preponderance in uncommon-site thrombosis.

Key words: internal jugular vein thrombosis, *in vitro* fertilisation, ovarian hyperstimulation syndrome.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a syndrome of ovarian enlargement and acute fluid shift from the intravascular space, usually following ovarian stimulation for *in vitro* fertilisation (IVF). Associated complications include renal failure, hypovolaemic shock, venous thromboembolism, respiratory distress syndrome and death. OHSS is self-limiting, and treatment is primarily supportive with an aim to reduce the incidence of associated complications.

Venous thromboembolism associated with OHSS can be atypical and requires a high degree of suspicion for rapid diagnosis and treatment. We present two cases of internal jugular vein (IJV) thrombosis following OHSS, which we believe to be the first reported from Australia. IJV thrombosis is generally considered a rare phenomenon, most commonly associated with intravenous drug use and central venous catheterisation.[1] A literature review was undertaken to assess predisposing factors and fetal outcomes in cases with OHSS.

Case One

The first woman, a 32-year-old Gravida 2 Para 1, presented to the Emergency Department with progressive abdominal distension and shortness of breath 8 days following embryo transfer for unexplained secondary infertility of 4 years duration. She had a previous term vaginal delivery, which was spontaneously conceived with the same paternity. She was otherwise well with no significant previous medical history and was a nonsmoker. Specifically, she had no family or personal history of thrombophilia.

Clinical examination revealed mild tachycardia and tachypnoea, bilateral absent air entry to the lower pulmonary zones, and a moderately distended abdomen with shifting dullness to percussion. Blood profile indicated hyperkalaemia associated with haemoconcentration (haematocrit 0.50). Coagulation profile was normal. Quantitative beta-hCG was 38 IU/L. Transabdominal ultrasonography confirmed the diagnosis of OHSS with moderate free fluid and markedly enlarged ovaries.

She was admitted for monitoring of fluid balance and was administered prophylactic low-molecular weight heparin for the duration of her admission, in addition to the use of compression TED stockings. Symptoms of OHSS improved without the requirement for paracentesis or pleurocentesis. There was rapid normalisation of serum biochemistry in the ensuing 24 h, and haemoconcentration resolved (haematocrit 0.33). She was discharged to the care of her private obstetrician four days after admission with the evidence of a rising beta-hCG, consistent with a viable pregnancy. Transabdominal ultrasound attended by her private obstetrician 5 days later suggested a twin gestation.

She represented to the Emergency Department 1 week after discharge with dyspnoea and pleuritic right-sided chest pain. Doppler ultrasonography on the day of admission suggested no evidence of thrombus in lower limb or pelvic vessels, or inferior vena cava. While the clinical suspicion of pulmonary embolus was high, she declined computer-tomography pulmonary angiography (CTPA), and a decision was made to proceed to commencement of therapeutic low-molecular weight heparin (enoxaparin

Correspondence: Dr Tina Fleming, Obstetrics and Gynaecology Registrar, St George Hospital, Kogarah, NSW, Australia.
Email: tinaannemartino@gmail.com

Received 14 August 2011; accepted 4 November 2011.

sodium, 1.5 mg/kg daily, *Sanofi-Aventis Australia*) without diagnostic pulmonary imaging.

One day after admission, she developed a painful swelling of the left side of her neck. Doppler ultrasonography revealed an IJV thrombosis. No inherited thrombophilias were detected. She was discharged on day four after admission on therapeutic dose low-molecular weight heparin and low-dose aspirin.

Pregnancy progress ultrasound attended privately 1 week after discharge showed two embryonic poles at 13.5 and 7.5 mm, respectively, with no cardiac activity identified in either. A missed miscarriage was diagnosed, and curettage was performed with temporary suspension of anticoagulation. Haematologist consultation recommended continuation of anticoagulation for a period of 6 months.

Case Two

The second case was, a 30-year-old nulliparous woman with a background history of unexplained infertility and factor V Leiden heterozygosity. In recognition of the known thrombophilia, she was commenced on prophylactic low-molecular weight heparin (enoxaparin sodium, 40 mg daily) prior to the initiation of ovarian stimulation for IVF, during which oestradiol levels were as high as 10 973 pmol/L, and 27 eggs were harvested. The anticoagulation was continued after the fresh embryo transfer.

The woman developed symptoms consistent with mild OHSS 8 days following embryo transfer, however, did not seek medical attention. She reported abdominal bloating and discomfort, in addition to a 7 kg weight gain. The symptoms spontaneously resolved within 6 days, and excess fluid weight was shed during this timeframe. She had a positive pregnancy test and continued to comply with prophylactic low-molecular weight heparin.

At 7 weeks gestation, she presented to the Emergency Department with right-sided neck pain and swelling. Doppler ultrasonography demonstrated a right IJV thrombosis. As there were no respiratory symptoms, a CTPA was not indicated. Peripheral vessels on Doppler ultrasound were unremarkable. Pelvic ultrasound confirmed a viable intrauterine 6 week singleton embryo.

Table 1 Case reports of IJV thrombosis in pregnancy

Author	Country of origin	Predisposing factors	Ovarian hyperstimulation syndrome	Pregnancy outcome
Ayhan[4]	Turkey	No	Yes	Miscarriage
Ellis[8]	Israel	APC resistance	Yes	Successful (twins)
Raw[19]	UK	No	Yes	Not recorded
Bedarida[5]	Germany	No	Yes	Successful
Belaen[6]	Belgium	No	Yes	Not recorded
Kitao[14]	Japan	No	Yes	TOP
Moutos[17]	USA	No	Yes	Successful
Berker[7]	Turkey	No	Yes	Successful (twins)
Schanzer[16]	USA	No	Yes	Not recorded
Arya[1]	UK	No	Yes	1 × IUFD at 24/40, 1 × liveborn CS 31/40
Arya[2]	UK	FV Leiden heterozygote	No	Successful (twins)
Arya[2]	UK	Protein S deficiency	No	Miscarriage
Arya[2]	UK	No	Yes	Successful
Arya[2]	UK	No	Yes	Successful
El-Ghazali[1]	UK	No	Yes	Not recorded
Ulug[22]	Turkey	No	No	Successful (twins)
Jeduason[13]	UK	No	Yes	Not recorded
Ergas[9]	Israel	APC resistance	Yes	Miscarriage
Ergas[9]	Israel	FV Leiden heterozygote	Yes	Successful
McGowan[16]	UK	FV Leiden heterozygote and P3UTR heterozygote	No	Successful (twins)
Fournet[10]	USA	No	Yes	Successful (twins)
Hignett[11]	Canada	No	Yes	Successful (twins)
Horstkamp[12]	Germany	APC resistance	Yes	Successful (twins)
Stewart[20]	UK	IgG anticardiolipin	No	Successful
Alasiri *et al.*[3]	Canada	No	Yes	Not recorded
Leibman *et al.*[15]	Israel	No	Yes	Not recorded
Thomas *et al.*[21]	UK	Protein S deficiency and P3UTR heterozygote	No	IUFD at 24/40

IUFD, Intrauterine fetal demise; CS, caesarean section; TOP, termination of pregnancy; APC, activated protein C; FV, Factor V; P3UTR, Prothrombin 3′ UTR mutation.

Haematological and biochemical profiling performed at this time was unremarkable with a haematocrit of 0.37.

The woman was hospitalised for analgesia and commenced on therapeutic low-molecular weight heparin (enoxaparin sodium, 1.5 mg/kg daily, *Sanofi-Aventis Australia*). She was discharged on day four and anticoagulation continued for the duration of her ongoing pregnancy.

Discussion

Venous thrombosis is a rare but serious complication of the hypercoagulable state conferred by OHSS. Several factors contribute to the thrombophilia of OHSS, including haemoconcentration, leucocytosis, thrombocytosis, altered coagulation and reduced fibrinolysis.[2] In a case review by Nelson *et al.*,[18] 81% of all upper extremity deep vein thrombosis coexistent with OHSS occurred in the IJV.

A Medline search spanning from 1991 to the current day was undertaken using the following keywords: OHSS, IJV thrombosis, IVF, ovarian hyperstimulation and thrombosis. All English case reports of IJV thrombosis associated with OHSS were selected for analysis. There were 27 reported cases of IJV thrombosis reported by 22 authors (Table 1). The addition of these Australian cases makes 29 cases reported worldwide since the first case described by Fournet *et al.*[10] in 1991. Interestingly, only half of the reported cases were published in journals pertaining to obstetrics and gynaecology, highlighting the need for multidisciplinary care in patients affected by this condition.

Of the case studies, the 78% of women who developed thrombus of the IJV following IVF also experienced OHSS. All women with IJV thrombosis in the absence of OHSS had a coexisting thrombophilia. Heterozygous Factor V Leiden and Activated Protein C deficiency accounted for two-thirds of the congenital thrombophilia; however, those with genetic predisposition for thrombus formation accounted for only 33% of all cases.

Ovarian hyperstimulation syndrome is known to be more common in patients with multiple pregnancies. Similarly, IJV thrombosis seems to be associated with multiple births, with 47% of cases reported being associated with a twin pregnancy. Indeed, the first case reported here is an example of severe OHSS and IJV thrombosis associated with a twin gestation. While that case unfortunately ended as a miscarriage, the miscarriage rate in all reported cases of IJV thrombosis is no higher than would be expected. There are also no reported long term consequences for the mothers.

Conclusion

The hypercoagulable state of OHSS increases the risk of venous thromboembolism, and the IJV appears to have a particular preponderance in uncommon-site thrombosis. OHSS is an independent risk factor for all thromboembolic events, and it is recommended that prophylactic anticoagulation be considered for all patients with severe disease. In women who have OHSS on a background of known thrombophilia, we recommend therapeutic doses of anticoagulation. Management of IJV thrombosis involves a high degree of suspicion for early diagnosis, and multidisciplinary specialist involvement. With appropriate treatment the prognosis appears to be good. Nevertheless, it is incumbent on IVF units to endeavour to treat this iatrogenic condition by primary prevention in reducing the incidence of OHSS.

References

1 El-Ghazali AM, Hill D. Internal jugular vein thrombosis due to ovarian hyperstimulation syndrome. *J Laryngol Otol* 2005; **119**: 737–739.

2 Arya R, Shehata H, Patel RK *et al.* Internal jugular vein thrombosis after assisted conception therapy. *Br J Haematol* 2001; **115**: 153–155.

3 Alasiri SA, Case AM. Thrombosis of subclavian and internal jugular veins following severe ovarian hyperstimulation syndrome: a case report. *J Obstet Gynaecol Can* 2008; **30** (7): 590–597.

4 Ayhan A, Urman B, Gurgan T *et al.* Thrombosis of the internal jugular vein associated with severe ovarian hyperstimulation syndrome. *Aust NZ J Obstet Gynaecol* 1993; **33**: 436–437.

5 Bedarida GV, Hoffmann U, Tato F. Jugular vein thrombosis with severe local and systemic inflammation in a woman with ovarian hyperstimulation syndrome. *J Thromb Haemost* 2006; **95**: 1035–1037.

6 Belaen B, Geerinckx K, Vergauwe P, Thys J. Internal jugular vein thrombosis after ovarian stimulation. *Hum Reprod* 2001; **16**: 510–512.

7 Berker B, Demirel C, Satiroglu H. Internal jugular vein thrombosis as a late complication of ovarian hyperstimulation syndrome in an ICSI patient. *Arch Gynecol Obstet* 2004; **270**: 197–198.

8 Ellis MH, Nun IB, Rathaus V *et al.* Internal jugular vein thrombosis in patients with ovarian hyperstimulation syndrome. *Fertil Steril* 1998; **69**: 140–142.

9 Ergas D, Levin D, Elbirt D *et al.* Internal jugular vein thrombosis following mild ovarian hyperstimulation syndrome in women with factor V Leiden mutation. *Am J Med Sci* 2006; **332** (3): 131–133.

10 Fournet N, Surrey E, Kerin J. Internal jugular vein thrombosis after ovulation induction with gonadotropins. *Fertil Steril* 1991; **56** (2): 354–356.

11 Hignett M, Spence JE, Claman P. Internal jugular vein thrombosis: a late complication of ovarian hyperstimulation syndrome despite mini-dose heparin prophylaxis. *Hum Reprod* 1995; **10** (12): 3121–3123.

12 Horstkamp B, Lubke M, Kentenich H *et al.* Internal jugular vein thrombosis caused by resistance to activated protein C as a complication of ovarian hyperstimulation after in-vitro fertilisation. *Hum Reprod* 1996; **11** (2): 280–282.

13 Jesudason WV, Small M. Internal jugular vein thrombosis following ovarian hyperstimulation. *J Laryngol Otol* 2003; **117**: 222–223.

14 Kitao K, Ohara N, Funakoshi T *et al.* A late complication of thrombosis in internal jugular vein and subclavian vein in a

pregnant woman with ovarian hyperstimulation syndrome. *Acta Obstet Gynecol Scand* 2006; **85**: 116–118.
15 Leibman Y, Ayalon M, Steiner IP. Internal jugular venous thrombosis after in vitro fertilization. *J Emerg Med* 2009; **37** (1): 29–31.
16 McGowan B, Kay L, Perry D. Deep vein thrombosis followed by internal jugular vein thrombosis as a complication of in vitro fertilisation in a woman heterozygous for the prothrombin 3 UTR and factor V leiden mutations. *Am J Hematol* 2003; **73**: 276–278.
17 Moutos D, Miller M, Mahadevan M. Bilateral internal jugular venous thrombosis complicating severe ovarian hyperstimulation syndrome after prophylactic albumin administration. *Fertil Steril* 1997; **68**: 174–176.
18 Nelson S, Greer A. Artificial reproductive technology and the risk of venous thromboembolic disease. *J Thromb Haemost* 2006; **4**: 1661–1663.
19 Raw D, Collins M. Internal jugular vein thrombosis and ovarian hyperstimulation syndrome. *J R Soc Med* 2007; **100**: 339–340.
20 Stewart J, Hamilton P, Murdoch A. Thromboembolic disease associated with ovarian stimulation and assisted conception techniques. *Hum Reprod* 1997; **12** (10): 2167–2173.
21 Thomas RV, Reid W, Perry DJ. Internal jugular vein thrombosis following in-vitro fertilization in a woman with proteinS deficiency and heterozygosity for the prothrombin 3′ UTR mutation despite anticoagulation with heparin. *Blood Coagul Fibrinolysis* 2001; **12** (6): 487–489.
22 Ulug U, Aksoy E, Erden H *et al.* Bilateral internal jugular venous thrombosis following successful assisted conception in the absence of ovarian hyperstimulation syndrome. *Eur J Obstet Gynecol Reprod Biol* 2003; **109**: 231–233.