CASE REPORTS

Upper limb thrombosis associated with assisted conception treatment

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Three cases of upper limb deep venous thrombosis occurring in association with assisted conception treatment are presented. The accepted argument that lower limb thrombosis occurring in cases of complicated or severe hyperstimulation syndrome represents the likeliest thrombo-embolic disorder in this situation is questioned. Key words: assisted conception/human/ovarian hyperstimulation syndrome/ovulation induction/thrombosis

Introduction

Deep venous thrombosis is recognized as a potential complication of assisted conception treatment (Royal College of Obstetricians and Gynaecologists, 1995). A number of factors are believed to have a contributory role in this situation, namely high concentrations of oestrogen, relative venous stasis in the legs resulting from obstructive effects of enlarged ovaries and the haematological and anatomical consequences of ovarian hyperstimulation syndrome (OHSS); intravascular hypovolaemia, haemoconcentration, ascites further reducing venous return and prolonged periods of debility and immobility.

It has been of interest therefore that in >1000 cycles of assisted reproduction treatment carried out in this hospital there have been four confirmed cases of thrombo-embolic disease directly related to treatment, but of these, three have been upper limb and neck venous thromboses. The fourth case (not reported here) was of pulmonary embolism from unknown primary source but believed to be of lower limb origin. Upper limb venous thrombosis in the general population is rare as a spontaneous event and results either from congenital anatomical abnormality causing venous obstruction or unusual position or exercise; so-called effort thrombosis. More commonly compression from tumour is the main aetiological factor or exercise; so-called effort thrombosis. More commonly arterial thrombusation syndrome/ovulation induction/thrombosis

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Three cases of upper limb deep venous thrombosis occurring in association with assisted conception treatment are presented. The accepted argument that lower limb thrombosis occurring in cases of complicated or severe hyperstimulation syndrome represents the likeliest thrombo-embolic disorder in this situation is questioned. Key words: assisted conception/human/ovarian hyperstimulation syndrome/ovulation induction/thrombosis

Case 1

This 34 year old woman [weight 80.8 kg, body mass index (BMI) 30 kg/m2], with no previous or family history of thrombo-embolism, presented for in-vitro fertilization (IVF) following 3 years primary infertility of unexplained origin. She was treated with buserelin nasal spray (Suprefact; Hoechst UK Ltd., Hounslow, UK) 800 µg/day for 6 weeks, to suppress pituitary gonadotrophin secretion. For the last 12 days she also received Metrodin 3 ampoules i.m./day [follicle stimulating hormone (FSH) 225 IU; Serono, Welwyn Garden City, UK] producing 23 follicles at 16–20 mm diameter. A maximum oestrogen >12 500 pmol/l was recorded on the day of human chorionic gonadotrophin (HCG) administration. 10 000 IU HCG (Pregnyl; Organon, Cambridge, UK) was administered 48 h prior to egg collection and 13 oocytes were retrieved from 18 follicles. Two 4-cell embryos were transferred 2 days later and she received two doses of HCG (2000 IU) 48 h apart, for luteal support. Three days later she complained of abdominal pain, distension and nausea and vomiting. Blood tests confirmed haemoconcentration (haemoglobin 17.8 g/dl) and hypo-osmolarity (serum osmolarity 284 mmol/kg). She developed bilateral pleural effusions and marked ascites. Two units (1000 ml) of human albumin solution gave her significant symptomatic relief and a diuresis. The benefit was short-lived and 48 h later she underwent peritoneal tap draining 9 l of ascites over 36 h. She re-established satisfactory fluid balance over the following 4 days and was discharged home, fully mobile, 17 days from embryo transfer having received s.c. heparin (5000 IU, twice daily) throughout her hospital admission. Two weeks later, 5 weeks post embryo transfer, she complained of neck and arm pain. Clinical examination revealed a swollen tender left arm with palpable basilic venous cord suggestive of venous thrombosis. This was confirmed by Doppler ultrasound scan showing thrombus in the left axillary vein. She was promptly treated with 5000 IU heparin i.v. followed by an infusion of 40 000 IU heparin/24 h and subsequently by 12 500 IU twice daily s.c. heparin. Pelvic ultrasound scan at 7 weeks gestation (5 weeks post embryo transfer) confirmed a viable singleton intrauterine pregnancy.
She was safely delivered of her daughter by emergency Caesarean section after spontaneous labouring at term. She continued s.c. heparin to 8 weeks postnatally. A full thrombophilia screen (factor V Leiden, AT III, Protein C and S, lupus inhibitor and anticardiolipin antibodies) was negative.

**Case 2**

A 34 year old female weighing 71 kg (BMI 23 kg/m²) presented for gamete intra-Fallopian transfer (GIFT) following 4 years of primary unexplained infertility. She had previously used the combined oral contraceptive pill for 7 years without incident and had previously undergone three cycles of GIFT elsewhere.

There was no history suggestive of previous personal or familial thrombo-embolism although her mother subsequently died of pulmonary embolism. She received Eugynon 30 (levonorgestrel 250 µg, ethinyl oestradiol 30 µg; Schering Health, Burgess Hill, UK) for 1 month then Suprefact (Hoechst) nasal spray (buserelin 200 µg four times per day) and Pergonal 2 amoules [FSH 150 IU, luteinizing hormone (LH) 150 IU] i.m. per day, resulting in the development of 30 follicles (16–20 mm) after 12 days. On the 12th evening she received 5000 IU HCG (Profasi, Serono) i.m. The maximum recorded oestradiol was 7337 pmol/l. GIFT was performed 2 days later resulting in a singleton intrauterine pregnancy. Gestone (progesterone 50 mg/day i.m.; Ferring, Feltham, UK) was prescribed for luteal support until 12 weeks gestation. She developed no symptoms of OHSS.

Six weeks following GIFT she complained of a painful swollen left neck, examination revealing a swollen, tender supraclavicular fossa, and distended brachial veins. Doppler ultrasound scan confirmed thrombus in the left jugular, subclavian, and brachiocephalic veins. She was treated with 5000 IU loading dose heparin i.v. followed by an infusion of 30 000–48 000 IU/24 h for 7 days followed by subcutaneous heparin 25 000 IU twice daily until successful delivery of her daughter at 35 weeks gestation. Heparin was continued for 6 weeks postnatally. Review 11 weeks postnatally showed development of collateral circulation bypassing the left jugular vein.

Despite the family history, she had a negative thrombophilia screen, other than slightly raised anticardiolipin antibodies [IgG anticardiolipin 23.9 GPL U/ml (normal <10 GPL U/ml), IgM anticardiolipin 5.3 MPL U/ml (normal <10 MPL U/ml)] on one occasion (previous IgG anticardiolipin 4.6 GPL U/ml and IgM anticardiolipin 8.9 MPL U/ml) associated with no other features of the antiphospholipid syndrome [prothrombin time 12.2 s (normal 10.9–15.1 s), activated partial thromboplastin time 27.7 s (23.4–36.4 s), fibrinogen 3.3 g/l (1.5–4.0 g/l), functional protein S 108% (60–140%), functional antithrombin III 119.9%, functional protein C 130.6%].

**Case 3**

A 35 year old female smoker weighing 65 kg (BMI 24 kg/m²) had previously taken the combined oral contraceptive pill uneventfully and presented with 5 years primary unexplained infertility. GIFT was performed uneventfully following a stimulation regime similar to that described in case 2 with a maximum recorded oestradiol on the day of HCG administration, of 14 600 pmol/l. Nine oocytes were collected from 10 follicles and three oocytes were replaced. She received prophylactic s.c. heparin on the day of egg retrieval, commencing pre-operatively (3×5000 IU). HCG luteal support (2000 IU×2) was prescribed. Four weeks later a positive pregnancy was reported but ultrasound scan showed an empty uterus and there was a suspicion of a left tubal pregnancy. Laparoscopy confirmed the diagnosis and partial salpingectomy was performed at laparotomy. Pathological examination of the tube confirmed the ectopic gestation.

Three weeks following her discharge, she was admitted to a general medical ward with acute painful swelling of her right arm and occlusion by thrombus of the right proximal subclavian vein was demonstrated by venography. She was given heparin (35 000 IU/day) and warfarin with good symptomatic relief and discharged on warfarin (5 mg/day).

Eight weeks later, right-sided chest veins were still distended. She remained amenorrhoeic and was discovered to have an ongoing intrauterine pregnancy dated at ultrasound scan to the GIFT treatment, confirming a heterotopic pregnancy. She continued on warfarin to 29 weeks gestation converted to s.c. heparin 10 000 IU twice daily and was delivered of a healthy boy at term. She was again administered with warfarin until 8 weeks postnatally. Thrombophilia screen performed subsequently has proved negative.

**Discussion**

Current practice in this unit is to provide peroperative s.c. heparin (5000 IU, single dose) in women undergoing oocyte retrieval under general anaesthetic (GIFT mainly) and during hospitalization with symptomatic OHSS (heparin s.c. 5000 IU twice daily), as these have been the times of perceived greatest risk. It can be seen that not only are these thromboses occurring in unusual sites contrary to the arguments of presumed aetiologies but also that they are occurring well after the assumed peak periods of risk and in two cases without the development of OHSS. In none of these women was there evidence of thrombophilia (although case 2 exhibited raised anticardiolipin antibodies on one occasion there was no other evidence of the antiphospholipid syndrome), and therefore the cause of their thromboses goes largely unexplained. Similar observations have been discussed previously by Mills et al. (1992) but any discussion is unsatisfactory given the lack of knowledge surrounding the relevant haematological changes which must be occurring. Further research is needed to identify these changes, and in the meantime both clinicians and patients must be made aware of the risks (Stewart et al., 1997).

**References**


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