Thromboembolic disease associated with ovarian stimulation and assisted conception techniques

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Introduction

The incidence of thromboembolic disease associated with assisted reproductive techniques is considered to be extremely rare. From reviews of these techniques it is often inferred that lower limb deep venous thrombosis (DVT) is the most likely thromboembolic phenomenon to be encountered and the reasons outlined are reduced venous return secondary to enlarged ovaries and, particularly in the case of ovarian hyperstimulation syndrome (OHSS), the added factors of immobility and ascites (Kaaja et al., 1989; Royal College of Obstetricians and Gynaecologists, 1995). These anatomical features, compounded by high oestrogen concentration and, in OHSS, haemoconcentration and reduced circulating blood volume, are thought to explain the aetiology and pathogenesis.

The aim of this paper is to show that this view is probably too simplistic to explain the problem fully and that it may be more significant than previous authors have suggested. The emphasis is on the need for further research into the aetiology and pathogenesis of this complication such that appropriate measures can be taken to avoid it.

Case reports

As has been suggested from the case reports presented elsewhere, this type of review may oversimplify the problems and neglect important alternative sites. In addition OHSS, although an important aetiological factor, need not be present and indeed stimulation for ovulation induction as opposed to assisted conception may also be a risk factor. These suggestions have been revealed from an extensive search of the world literature, starting from Medline searches. A total of 54 cases of thromboembolic disease have been reported since 1964 (Table I) in association with ovulation induction and assisted conception treatment [33% in association with ovulation induction (Crooke et al., 1964; Mozes et al., 1965; Humbert et al., 1973; Nwosu et al., 1974; Schenker and Weinstein, 1978; Dumont et al., 1980; Dalrymple et al., 1982; Bouliet et al., 1989; Neau et al., 1989; Rajah et al., 1991; Waterstone et al., 1992; Ayhan et al., 1993; Inbar et al., 1994)] including one case where two episodes were associated with clomiphene use alone (Benshushan et al., 1995). There was also one case where clomiphene was used in a man to improve spermatogenesis (Chamberlain and Cumming, 1986). Of the 54 cases 66% were associated with OHSS and 84% of those where it was recorded, with pregnancy. One fatality has been reported (Mozes et al., 1965) although in many cases the outcome has not been specifically recorded. However, although the majority of thromboses reported were venous sites (75%), 60% of these were in upper limb, neck and head veins; with an associated 4–12% risk of pulmonary embolism (PE) (Burihan et al., 1993; Horattas et al., 1988), compared with lower limb DVT or PE. The remaining 25% were arterial thromboses and were mostly intracerebral (Mozes et al., 1965; Humbert et al., 1973; Dumont et al., 1980; Neau et al., 1989; Rizk et al., 1990; Kermode et al., 1993; Inbar et al., 1994; Thill et al., 1994; Kodama et al., 1995).

Although the factors described above may promote lower limb thromboses, the pathogenesis of the remainder remains obscure. Spontaneous arterial thrombosis, although common in the elderly in the form of strokes, is rare in young women. Similarly, upper limb venous thromboses are unusual without local trauma, including central venous catheterisation, or compression (Burihan et al., 1993) and represent only 4% of the incidence of DVT in the general population (Horattas et al., 1988). If Virchow’s triad of causative factors is considered, lower limb venous thrombosis could be explained by reduced venous drainage alone. However, with a lack of local causes, upper limb and arterial thromboses must be the result of haematological changes. This introduces the potential phenomenon of the ‘hypercoagulable state’.

Key words: assisted reproduction/human/ovarian hyperstimulation syndrome/ovulation induction/thrombosis
### Table I. Summary of reported cases of thromboembolic disorders associated with ovarian stimulation

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Treatment</th>
<th>OHSS</th>
<th>Pregnancy</th>
<th>Predisposing factors</th>
<th>Site of thrombus</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper extremity DVT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayhan et al. (1993)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>L internal jugular vein</td>
<td>14 days post HCG</td>
</tr>
<tr>
<td>Rajah et al. (1991)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Internal jugular vein</td>
<td>21 days post HCG</td>
</tr>
<tr>
<td>Ong et al. (1991)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>PE-L internal jugular vein</td>
<td>27 days and 40 days post HCG</td>
</tr>
<tr>
<td>Waterstone et al. (1992)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>R transverse sinus, internal cephalic vein and vein of Galen</td>
<td>20 days post HCG</td>
</tr>
<tr>
<td>Boulieu et al. (1989)</td>
<td>Ovulation induction</td>
<td>No</td>
<td>Yes</td>
<td>Costoclavicular nipping</td>
<td>L (internal jugular and) subclavicular veins</td>
<td>37 days after ovulation</td>
</tr>
<tr>
<td>Boulieu et al. (1989)</td>
<td>IVF</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>R venous innominate trunk</td>
<td>28 days from OR</td>
</tr>
<tr>
<td>Boulieu et al. (1989)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>R jugular and subclavian veins</td>
<td>32 days post HCG</td>
</tr>
<tr>
<td>Mills et al. (1992)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Subclavian vein</td>
<td>50 days post HCG</td>
</tr>
<tr>
<td>Waterstone et al. (1992)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Internal jugular vein</td>
<td>50 days post HCG</td>
</tr>
<tr>
<td>Hignett et al. (1995)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>R jugular vein</td>
<td>42 days post HCG</td>
</tr>
<tr>
<td>Waterstone et al. (1992)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>R jugular, subclavian and axillary veins</td>
<td>47 days post embryo transfer</td>
</tr>
<tr>
<td>Waterstone et al. (1992)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>R humeral and internal jugular veins</td>
<td>40 days post HCG</td>
</tr>
<tr>
<td>Stewart et al. (1997)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td>Activated protein C resistance</td>
<td>L axillary vein</td>
<td>37 days post HCG</td>
</tr>
<tr>
<td>Hocke et al. (1995)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Superior sagittal sinus</td>
<td>15 days post embryo transfer</td>
</tr>
<tr>
<td>Hocke et al. (1995)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>R internal jugular vein</td>
<td>30 days post HCG</td>
</tr>
<tr>
<td>Hulinsky and Smith (1995)</td>
<td>GIFT</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>R external jugular vein</td>
<td>38 days post HCG</td>
</tr>
<tr>
<td>Hocke et al. (1995)</td>
<td>GIFT</td>
<td>No</td>
<td>Yes</td>
<td>Laparotomy for ectopic pregnancy</td>
<td>R subclavian vein</td>
<td>51 days post HCG</td>
</tr>
<tr>
<td>Stewart et al. (1997)</td>
<td>GIFT</td>
<td>No</td>
<td>No</td>
<td>Mother died from PE later</td>
<td>L jugular, subclavian and brachiocephalic veins</td>
<td>44 days post HCG</td>
</tr>
<tr>
<td><strong>Lower limb DVT or PE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chamberlain and Cumming (1986)</td>
<td>Clomiphene</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>PE, male on clomiphene</td>
<td>N/A</td>
</tr>
<tr>
<td>Benshushan et al. (1995)</td>
<td>Clomiphene</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>R DVT</td>
<td>N/A</td>
</tr>
<tr>
<td>Crooke et al. (1964)</td>
<td>Ovulation induction</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Saphenous vein</td>
<td>Previous DVT and PE, post-operatively</td>
</tr>
<tr>
<td>Schenker and Weinstein (1978)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>No</td>
<td>DVT; thrombophlebitis</td>
<td>Previous DVT and PE, post-operatively.</td>
<td></td>
</tr>
<tr>
<td>Schenker and Weinstein (1978)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>No</td>
<td>DVT, thrombophlebitis</td>
<td>Previous DVT on clomiphene</td>
<td></td>
</tr>
<tr>
<td>Nwosu et al. (1974)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>L superficial phlebitis and PE</td>
<td>11 days post HCG, and 46 days post HCG</td>
</tr>
<tr>
<td>Dalrymple et al. (1982–3)</td>
<td>Ovulation induction</td>
<td>No</td>
<td>No</td>
<td>Previous R DVT and PE post-operatively.</td>
<td>L femoral and external iliac veins. Common iliac and distal veins</td>
<td></td>
</tr>
<tr>
<td>Thill et al. (1994) and Aurousseau et al. (1995)</td>
<td>IVF</td>
<td>No</td>
<td>No</td>
<td>spontaneous PE</td>
<td>PE</td>
<td>6 days post HCG</td>
</tr>
<tr>
<td>Huong et al. (1996)</td>
<td>IVF</td>
<td>No</td>
<td>No</td>
<td>Laparotomy. Sepsis</td>
<td>Inferior vena cava, L renal vein</td>
<td>2 weeks after treatment</td>
</tr>
<tr>
<td>Kligman et al. (1995)</td>
<td>IVF</td>
<td>No</td>
<td>Yes</td>
<td>Mixed connective tissue disease.</td>
<td>DVT</td>
<td></td>
</tr>
<tr>
<td>Boulieu et al. (1989)</td>
<td>IVF</td>
<td>No</td>
<td>Yes</td>
<td>Low protein S</td>
<td>L, popliteal and iliofemoral phlebitis</td>
<td>70 days after ovulation</td>
</tr>
</tbody>
</table>

continued.
Table I. Continued

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Treatment</th>
<th>OHSS</th>
<th>Pregnancy</th>
<th>Predisposing factors</th>
<th>Site of thrombus</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boulieu et al. (1989)</td>
<td>IVF</td>
<td>No</td>
<td>Yes</td>
<td>Previous superficial phlebitis of lower limb. Family history of thromboembolic disease</td>
<td>R phlebitis (iliofemoral vein) and inferior vena cava</td>
<td>42 days after ovulation</td>
</tr>
<tr>
<td>Kaaja et al. (1989)</td>
<td>IVF</td>
<td>Yes</td>
<td>Yes</td>
<td>Laparotomy 5 days post HCG</td>
<td>L posterior fibular veins</td>
<td>24 days post HCG</td>
</tr>
<tr>
<td>Stewart et al. (unpublished)</td>
<td>GIFT</td>
<td>Yes</td>
<td>Yes</td>
<td>'Kinking' of internal carotid arteries</td>
<td>R femoral artery, L popliteal artery, PE and L femoral vein</td>
<td>15 days from last injection</td>
</tr>
<tr>
<td>Inbar et al. (1994)</td>
<td>Ovulation induction</td>
<td>No</td>
<td>No</td>
<td>R middle cerebral artery</td>
<td>L anterior cerebral artery</td>
<td>7 days post HCG</td>
</tr>
<tr>
<td>Mozes et al. (1965)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>No</td>
<td>L internal carotid artery and probably L vertebral artery</td>
<td>R middle cerebral artery</td>
<td>5 days post HCG</td>
</tr>
<tr>
<td>Humbert et al. (1973)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>Yes</td>
<td>L anterior cerebral artery</td>
<td>R middle cerebral artery</td>
<td>1 day post HCG</td>
</tr>
<tr>
<td>Dumont et al. (1980)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>Yes</td>
<td>'Kinking' of internal carotid arteries</td>
<td>R internal carotid artery</td>
<td>36 days post HCG</td>
</tr>
<tr>
<td>Neau et al. (1989)</td>
<td>Ovulation induction</td>
<td>Yes</td>
<td>Yes</td>
<td>Smoker. Previous L popliteal arterial thrombosis after IVF</td>
<td>Aorta, subclavian artery</td>
<td>7 days post HCG</td>
</tr>
<tr>
<td>Thill et al. (1994) and</td>
<td>IVF</td>
<td>No</td>
<td>Yes</td>
<td>Smoker. Previous L popliteal arterial thrombosis after IVF</td>
<td>R middle cerebral artery</td>
<td>14 days post HCG</td>
</tr>
<tr>
<td>Aurousseau et al. (1995)</td>
<td>IVF</td>
<td>No</td>
<td>Yes</td>
<td>Smoker. Previous L popliteal arterial thrombosis after IVF</td>
<td>R middle cerebral artery</td>
<td>30 days post HCG</td>
</tr>
<tr>
<td>Kermode et al. (1993)</td>
<td>GIFT</td>
<td>Yes</td>
<td>No</td>
<td>L internal carotid artery and R internal iliac vein</td>
<td>Middle cerebral artery 13 days post HCG</td>
<td>11 days post HCG</td>
</tr>
<tr>
<td>Rizk et al. (1990)</td>
<td>GIFT</td>
<td>Yes</td>
<td>Yes</td>
<td>Bilateral external iliac and femoropopliteal arteries</td>
<td>Bilateral external iliac and femoropopliteal arteries</td>
<td>17 days post HCG</td>
</tr>
<tr>
<td>Choktanasiri and Rojanasakul (1995)</td>
<td>GIFT</td>
<td>Yes</td>
<td>Yes</td>
<td>Bilateral external iliac and femoropopliteal arteries</td>
<td>Bilateral external iliac and femoropopliteal arteries</td>
<td>17 days post HCG</td>
</tr>
</tbody>
</table>

OHSS = ovarian hyperstimulation syndrome; DVT = deep venous thrombosis; L = left; R = right; PE = pulmonary embolism; IVF = in-vitro fertilization; OR = oocyte retrieval; HCG = human chorionic gonadotrophin; GIFT = gamete intra-Fallopian transfer; AT = anti-thrombin.

‘Hypercoagulable state’

This term has been used to refer to any haematological changes resulting in increased risk of thrombogenesis. The natural assumption in the case of assisted conception and ovulation induction is that raised oestrogen concentration is to blame.

Hyper-oestrogenism

Evidence that administration of exogenous oestrogens promotes thrombogenesis is undisputed although it is dose (Inman et al., 1970) and preparation (Bonnar 1987) dependent, hence the recent controversy surrounding combined oral contraceptive pill (COCPP) use (McPherson, 1996). The role of endogenous oestrogens is less clear. Pregnancy is a hyperoestrogenic state associated with an increased risk of thromboembolism [3–12 per 1000 pregnancies (de Swiet 1989)], with maximum concentrations of endogenous oestradiol reaching 22.53–127 nmol/l (O’Leary et al., 1991). There are recognized haematological changes associated with pregnancy, predominantly increased concentrations of factors VII, VIII, IX, X and XII and fibrinogen (Strauss and Diamond, 1963), presumed in part to be an oestrogen effect, also a reduction of the concentration of protein S (Comp et al., 1986; Boerger et al., 1987) and a reduction in fibrinolytic activity including antithrombin (AT) III (Schafer, 1985; Wright et al., 1988). The result appears to be a relative thrombophilia. Of the reported cases of thromboembolic disease associated with ovulation induction and assisted conception, 72% were in pregnancy cycles; although this may be considered an explanation in part, it is important to note that thrombosis in pregnancy is much more likely to occur at term and post-partum when anatomical factors also play a role. The pregnancy-associated thromboses reviewed here occurred almost exclusively in first trimester. Also antenatal arterial thrombosis is rare in pregnancy, as is upper limb venous thrombosis; three cases are reported associated with pregnancy; one associated with AT III deficiency (Mackie et al., 1978), one in third trimester (Ben-Shlomo et al., 1992) and one at 12 weeks gestation in a molar pregnancy (Årstad et al., 1980). Lower limb DVT greatly predominates.

The most useful study of the effects of endogenous oestrogen on coagulation has been performed by Kim et al. (1981), when the coagulation parameters of seven women undergoing ovulation induction treatment were measured. They reported...
a rise in fibrinogen concentration that correlated well with the rise in oestradiol concentration as the cycle progressed. There were no significant changes in prothrombin time (PT) or activated partial thromboplastin time (APTT) but there was a significant rise in factor VIIIIR.VWF (von Willebrand factor) and reduction of AT III, signifying a relative hypercoagulable state. The drawback of this study with regard to many of the cases discussed here is that measurements were concluded after human chorionic gonadotrophin (HCG) administration and therefore were not representative of the times at which many women appear to experience thromboembolic complications of treatment.

Aune et al. (1991) reported that ovarian stimulation for IVF induced a hypercoagulable state. They considered 12 IVF cycles, measuring whole blood clotting time (WBCT), whole blood clot lysis time (CLT), antithrombin III (AT III), plasma fibrinogen and factor VII, both before stimulation and after HCG administration, at the ‘peak’ of oestradiol concentration. Their findings showed a significant increase in fibrinogen and reduction in AT III concentration and a significant increase in CLT over this time, implying a disruption of the balance of coagulation and thrombolysis leading to a relative increase in coagulability. In contrast Lox et al. (1995) claim to have excluded the hypercoagulable state in IVF cycles. They assessed coagulation parameters up to 14 days post HCG. They noted significant correlations of certain factors with changes in oestradiol and in PT and APTT; however, none of these changes were out with their laboratory’s normal ranges and they concluded therefore that these changes could not constitute a promotion of coagulability and challenged others’ findings on that basis. Colburn and Buonassisi (1978) suggested that endothelial cells expressing oestrogen hormone receptors may specifically contribute to thrombotic events locally, e.g. by changes in platelet–endothelial interactions.

If hyperoestrogenism alone is responsible for the risk of thromboembolic disease in the reported cases, then it is interesting that in many cases the thromboembolic event is diagnosed some time after the expected peak oestradiol concentration (around the time of HCG administration). Perhaps in some cases, for example, OHSS prolongs the risk period in some way. Mills et al. (1992) suggested this could result from the prolonged hepatic dysfunction secondary to OHSS, described by Ryley et al. (1990). Bremme et al. (1994), although only assessing the period of stimulation and immediately afterwards, suggest that a decrease in factor VII and increase in free protein S may be thrombo-protective at high concentrations of endogenous oestradiol. Perhaps this phenomenon contributes to the delay in thrombogenesis if the fall in oestradiol is prolonged.

Ovarian hyperstimulation syndrome

Delvigne et al. (1993) estimated a prevalence of thromboembolic disease of one in 128 women exhibiting severe OHSS, and severe, complicated OHSS is reported to account for 0.56–6.5% of cases (Pride et al., 1990). Invoking OHSS as the major cause of thrombogenesis in this group of cases, however, is difficult, firstly because it does not occur in all cases, but also because over three decades and international boundaries, it is likely that the definition of OHSS and its diagnosis has varied widely, particularly preceding any form of clinical and biochemical grading of the condition. In addition in our case of OHSS and others reported, the development of thrombosis appears to have occurred after clinical resolution of the syndrome. As has been discussed previously OHSS certainly predisposes to lower limb DVT. How it contributes to thromboses in other sites is less clear but presumably by the promotion of a hypercoagulable state.

Few studies have been carried out to examine the haematological changes occurring during ovarian stimulation complicated by OHSS. Importantly, as with the studies discussed above, they have not been extended much beyond the administration of HCG and certainly not into early pregnancy where women appear to be at greatest risk. In addition none seem to give conclusive evidence of thrombophilia. Kodama et al. (1995) performed prospective tests on 23 women admitted with severe OHSS in IVF cycles. Of these women, 14 became pregnant in these cycles and one developed thrombosis of the right middle cerebral artery ~2 weeks following HCG. Samples were taken once only, ~9 days (9.2 ± 4.6) after HCG administration, and they were able to show that at the time of sampling the woman developing the thromboembolism had a decreased concentration of α2 plasmin inhibitor, an increased concentration of plasmin–α2 antiplasmin complexes and higher concentration of D-dimers than the other patients with uncomplicated OHSS. These results cannot be considered representative because of the limited sampling. In addition the differences shown, by virtue of the timing of sampling and occurrence of thromboembolism, may represent active coagulopathy as opposed to any predisposition to thrombosis.

Phillips et al. (1975) reported that two women, receiving human menopausal gonadotrophins (HMG) for ovulation induction and suffering from severe OHSS, exhibited increased concentrations of factor V, platelets, fibrinogen, profibrinolysin and fibrinolytic inhibitors suggestive of increased risk of thrombosis. Todorow et al. (1993) performed a retrospective study assessing the changes in vWF in OHSS. They measured vWF-associated antigen (vWF:ag) and ristocetin cofactor activity (an indicator of vWF function). They found that women subsequently developing OHSS showed an increase in vWF:ag which persisted into the luteal phase following embryo transfer, where a decline was seen in unaffected women. Kaaja et al. (1989) had suggested that raised vWF could result from increased platelet adhesion potentiated by haemoconcentration and therefore could be an indicator of impending OHSS development. Todorow implied that, by measuring vWF:ag, OHSS could be predicted with its concomitant risk of thrombosis.

Although studies have shown neutrophil-induced thrombogenic effects on endothelial cells (Pintucci et al., 1993; Kolpakov et al., 1994), and although Germoud et al. (1996) have introduced the possibility of endothelial damage by activated polymorphonuclear leukocytes as a result of stress-induced leukocytosis in OHSS, neither have been further substantiated. Balasch et al. (1996) found that tissue factor expression by monocytes was induced by the plasma of nine
women with severe OHSS and suggest that this may play a role in thrombogenesis in this condition.

Recently, important conditions which could potentiate the risk of thrombosis under conditions of relative hypercoagulability have been described — the thrombophilias.

**Thrombophilia**

The major thrombophilias comprise protein C, protein S and AT III deficiencies and the antiphospholipid syndrome, but by far the most important, described by Koster et al. (1993) and Bertina et al. (1994), is expression of factor V Leiden, resulting in activated protein C resistance. This condition, described in 5% of the Dutch population, has a similar incidence in the UK, and has a significant bearing on thromboembolic disease in all areas, e.g. the additional risk of DVT in a COCP user with factor V Leiden is 25 per 10 000 woman-years (Vandenbroucke et al., 1996).

Only the most recently reported cases in the above series have specifically been investigated for thrombophilia. Horstkamp et al. (1996) reported a case where activated protein C resistance was subsequently exposed as a predisposing factor. Kligman’s case (Kligman et al., 1995) was specifically related to AT III deficiency. Huong et al. (1996) have reported a case of inferior vena cava and left renal vein thrombosis in a cycle of IVF complicated by known mixed connective tissue disease associated with features of systemic lupus erythematosus (SLE) including raised antiphospholipid antibodies. Bénifla et al. (1994) reported reduction in protein S in their case; however, this did not persist after delivery and was believed to be pregnancy-related, whilst one of the cases reported by Boulieu et al. (1989) was found to have reduced protein S concentration even after delivery. Otherwise findings have been negative or unreported.

**Other predisposing factors**

Thill et al. (1994) (and Aurousseau et al., 1995), in reporting three cases of thromboembolic disease in the absence of OHSS, argued that this is unlikely to occur without another predisposing factor. They stated that the coagulation changes related to hyperoestrogenism may not be enough to precipitate thrombosis alone and that by virtue of the biochemical and circulatory changes of severe OHSS, thromboembolism is precipitated. In their cases, other predisposing factors, previous DVT, ‘kinking’ of the internal carotid arteries and peritonitis were used to explain the occurrence of thromboembolism in these women. Boulieu et al. (1989) described a case of phlebitis of the right axillary and subclavicular veins in association with costoclavicular ‘nipping’ of the subclavicular vein. Five cases (Dalrymple et al., 1982–3; Boulieu et al., 1989; Thill et al., 1994; Benshushan et al., 1995; Stewart et al., 1997) had either a personal or family history of thromboembolic disease without evidence of familial thrombophilia.

**Site of thrombosis**

There is no clear explanation for the propensity to produce thromboses in unusual sites in these women where there appear to be no specific local effects. In particular, central venous catheterisation is not a prominent feature in the reported cases. It is possible that lower limb DVT is under-reported as it is ‘expected’, and thus alternative sites are disproportionately represented. It seems likely that multiple sites could be affected in the same woman although most cases report only one site or an extended site as opposed to two distinct thromboembolic events (PE excluded as a secondary event). Exceptions are reports by Kermode et al. (1993) and Mozes et al. (1965). Arterial and venous thromboses may be found to have different pathogeneses as the timing of these events appear to differ. Although the appearance of thrombosis is delayed in relation to clinical events when the reported cases are reviewed overall, it is of interest that arterial thrombosis appears to occur much earlier than venous thrombosis in the timescale of events. The mean timing, from HCG administration, of the occurrence of venous thrombosis in the case reports reviewed is 38 days, and of arterial thrombosis 14 days. It is clear that arterial thrombosis may result in serious sequelae particularly as most were intracranial in origin. Stroke may have severe long-term disability as an outcome if survived. The one reported death occurred in this group (Mozes et al., 1965), whilst dysphasia and hemiparesis (Kermode et al., 1993), motor deficit of the upper limb (Neau et al., 1989) and coma, tetraplegia and aphasia (Humbert et al., 1973) have been the long-term outcomes recorded for some cases. Venous thrombosis is not usually fatal unless accompanied by significant pulmonary embolism or other thromboembolic events causing end organ damage. It is important to note, however, that although recanalization of vessels after DVT occurs as does the development of collateral vessels, there can be significant long-term morbidity following venous thrombosis which again may be disabling particularly in the upper limb. Tilney et al. (1970) reported that in a series of 48 cases of upper extremity DVT, 74% had residual disability up to 6 years later in the form of persistent discomfort, exercise-induced cramp, cold hand and weakness.

**Conclusion**

Reported here have been cases of thromboembolic disease of an unusual nature and without specific aetiologies. It is hoped that by reviewing these cases, it has been brought to notice that this is a significant problem in relation to all methods of assisted conception treatment involving superovulation and ovulation induction. Significant research is required in order to elucidate the expected ‘normal’ coagulation changes occurring through treatment cycles and into early pregnancy including those cycles complicated by OHSS. In this way it is to be hoped that specific risk factors can be identified along with definition of the pathogenesis, such that these complications can be anticipated and thus avoided.

At present best advice includes selecting out women who may be at greatest risk: those with a family history of thromboembolic disease, those developing OHSS and those in whom pregnancy is achieved. Serious thought must be given to the use of screening for thrombophilias. A recent article suggests that this is not cost-effective in COCP users.
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