Review Article

Upper body venous thrombosis associated with ovarian stimulation: Case report and review of the literature

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Summary

Thromboembolic events are a serious complication of assisted conception treatment. Thrombosis may be either arterial or venous but the latter is far more common. This phenomenon is more frequent in the lower limb, but several cases of upper extremity thrombosis have been described in the literature. Although the aetiology of these thromboembolic disorders is not fully understood, the mechanism is thought to be due to a hypercoagulable state associated with haemostasis and thrombophilia. Predisposing factors seem to be hyperoestrogenism, ovarian hyperstimulation syndrome, a hereditary hypercoagulable state and multifoetal pregnancy. We report a case of superior sagittal sinus thrombosis that developed in a patient following successful assisted conception in the absence of evident risk factors. In the current literature, the site of thrombosis, possible predisposing factors, oestrogen levels, number of foetuses, maternal and foetal outcomes, and management of thrombosis were analysed.

Key words: Cerebral venous thrombosis; Ovulation induction; OHSS; Thrombophilic state.

Introduction

Thrombotic events are a potential complication of assisted conception treatment [1] especially if ovarian hyperstimulation syndrome (OHSS) is present. Significant OHSS complicating assisted reproduction technology (ART) is quoted to occur at a rate of between 2-6% [2], and a thromboembolic accident is considered to be a dangerous and unpredictable manifestation of this syndrome, with an incidence of 0.04% [3].

Thrombosis may be either arterial or venous but the latter is far more common (25% vs 75%) [4]. The unusual characteristics of these cases are their occurrence in young women in particular, and their localisation in uncommon sites, especially the extremity of the upper body [5, 6].

The pathogenesis of OHSS-associated vascular thrombosis is not fully understood. Several theories have been hypothesised, such as haemoconcentration and subsequent hyperviscosity, modifications of thrombin-antithrombin III and plasminα2-antiplasmin complexes [7], increased levels of factor V, platelets, fibrinogen, profibrinogen, fibrinolytic inhibitors and thromboplastin [8].

Recently several authors have reported some cases of venous thrombosis in the upper body that occurred in women with a hereditary thrombophilic state in the presence or not of OHSS and modifications of the haemocoagulation system.

In this paper we report a case of superior sagittal sinus thrombosis that developed in a patient following successful assisted conception, without any clinical evidence of OHSS and in the absence of a hereditary condition of hypercoagulability. The current literature is reviewed.

Literature search

A MEDLINE literature search, starting from 1995, was conducted using the following keywords: ovarian stimulation, in vitro fertilization, thrombosis, ovarian hyperstimulation syndrome (OHSS). The site of thrombosis, possible predisposing factors, estrogen levels, number of foetuses, maternal and foetal outcomes, development of OHSS and treatment of thrombosis were analysed.

Case report

A 30-year-old primigravida in her 10th week of pregnancy was admitted to the Neurological Department of the University Hospital complaining of severe headaches, vomiting and bilateral amaurosis. The patient had suffered from ovulatory dysfunction and had undergone ovarian stimulation with gonadotrophin-releasing hormone agonist (Decapepty®Ipsen, Biotech,-France) and recombinant FSH (Puregon®Organon, The Netherlands) in a specialised private medical centre. After ovulation induction, with 5,000 UI

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of HCG (Pergonal®Serono, Italia), the patient underwent intrauterine homologous insemination and the luteal phase was supported by 100 mg IM progesterone daily (Prontogest,AMSA, Italia). In the sixth week ultrasonography showed a viable quadruplet pregnancy, with ovaries not enlarged and absence of ascites. The patient was informed that she could have a selective abortion but she refused. During the hospital stay, neurological and clinical examinations were normal, while papilloedema was revealed by an ophthalmologic check-up. Laboratory tests revealed a haematocrit of 38%, haemoglobin of 12.6 g/dl, WBC count 14 x 10^3/µl, and platelet count 338 x 10^3 /µl. Electrolytes, liver function tests, prothrombin time and partial thromboplastin time were normal. Serum albumin was 38.5 g/l and urinary output was 1.4 l/day. Vaginal ultrasonography showed four embryos whose crown-rump length corresponded to ten weeks, normal-sized ovaries and absence of ascites. Magnetic resonance imaging (MRI) of the brain showed in T1-weighted images an increased signal in the transverse left venous sinus and in the superior sagittal sinus. Screening for antithrombin III, Leiden V factor, prothrombin gene mutation, protein C and S deficiency, anti-cardiolipin IgG, lupus anticoagulant activity and hyperhomocysteinemia were negative. Intravenous heparin (5,000 UI every 4 hr) was commenced without delay; nevertheless a further MRI showed a slow progression of the thrombosis.

The patient was informed of her condition and she requested termination of her pregnancy as she was worried about her well-being.

Dilatation and curettage were performed and the patient was discharged after four days but continued anticoagulant treatment with low-molecular-weight heparin. Several neurological checks showed progressive improvement of her condition.

Discussion

We reviewed 17 papers concerning 26 patients who had experienced a thrombotic event of the upper body (Table 1). The research was limited to the last nine years in order to focus our attention on the hereditary thrombophilic state. Indeed, the study of some thrombophilic factors such as V Leiden and prothrombin 3' UTR mutations and their association with thromboembolic events have been evidenced recently. By analysing these cases we tried to gain a better understanding of the possible oetiology of this event, evaluating the correlation between thrombosis and predisposing factors such as hyperestrogenism, OHSS and thrombophilia in each patient.

Hyperoestrogenism. Endogenous oestrogens, which are increased in pregnancy and puerperium, are associated with a higher risk of thromboembolism, and intracranial thrombosis is the most common type of ischaemic strokes during pregnancy [22, 23].

Elevated levels of estrogens during pregnancy determine an increase in the haematological concentration of factors VII, VIII, IX, X, XII, fibrinogen and a reduction of protein S and AT III levels [24-26]. The result of these modifications appears to be a relative thrombophilic state.

Table 1. — *Reported cases of upper body thrombosis associated with ovarian stimulation.*

Author	Principal Venous Site	Foetuses	Thrombophilia	OHSS	PCOS	Treatment	Outcome	Estrogen
Hocke *et al.* [9]	Internal jugular	3	NR	III	Yes	Heparin	Favourable	4818 pg/ml
Hocke *et al.* [9])	Iinternal jugular	6	NR	III	Yes	Heparin	Favourable [a]	NR
Hocke *et al.* [9])	Superior sagittal sinus	2	NR	III	Yes	Heparin	Favourable	NR
Hignett *et al.* [6]	Internal jugular	2	NC (V, II)	III	No	Heparin	NR	17225pmol/l
Hollemaert *et al.* [10]	Subclavian	2	V	III	NR	Heparin	NR	NR
Horstkamp *et al.* [11]	Internal jugular	2	V	III	No	Heparin	Favourable	27317 pmol/l
Moutos *et al.* [12]	Internal jugular	2	NC (V, II, H)	III	No	Heparin	NR for 1 fetus	3120 pg/ml
Stewart *et al.* [13]	Axillary	1	NC (II, H)	III	No	Heparin	Favourable	12500 pmol/l
Stewart *et al.* [13]	Internal jugular	1	IgG anticardiolipin	No	No	Heparin	Favourable	7337 pmol/l
Stewart *et al.* [13]	Subclavian	1	NR	No	No	Heparin	Favourable	14600 pmol/l
Ellis *et al.* [14]	Internal jugular	2	V	III	No	Heparin	Favourable	2812 pg/ml
Aboulghar *et al.* [4]	Cortical	1	NC (V, II, H)	II	No	Heparin	Miscarriage	2100 pg/ml
Aboulghar *et al.* [4]	Cortical	NR	NC (V, II, H)	II	No	Heparin	NR	2800 pg/ml
Tang *et al.* [15]	Cortical	1	NC (II, H, IgG)	III	No	Heparin	Abortion	20808 pmol/l
De Mola *et al.* [16]	Internal jugular	1	NC (II, H)	II	No	Heparin	Favourable	NR
De Mola *et al.* [16]	Subclavian	1	NC (II, H)	II	No	Heparin	Favourable	NR
Belaen *et al.* [17]	Internal jugular	2	NC (II, H)	II	No	Heparin	Favourable	2069 pg/ml
Arya *et al.* [3]	Internal jugular	3	No	III	Yes	Heparin	Favourable [b]	NR
Arya *et al.* [3]	Internal jugular	2	V	No	Yes	Heparin	Favourable	NR
Arya *et al.* [3]	Internal jugular	2	PS, II	No	Yes	Heparin	Miscarriage	NR
Arya *et al.* [3]	Internal jugular	2	No	III	No	Heparin	Favourable	NR
Arya *et al.* [3]	Internal jugular	1	No	III	No	Heparin	PROM at 28w	NR
Ulug *et al.* [18]	Internal jugular	2	NC (II)	No	No	Heparin	Favourable	2502 pg/ml
Mc Gowen *et al.* [19]	Internal jugular	2	V, II	No	NR	Heparin	Favourable	NR
Ou *et al.* [20]	Superior sagittal sinus	1	NC (V,II)	II	Yes	Thrombec.	Favourable	3707 pg/ml
Berker *et al.* [21]	Internal jugular	2	No	III	NR	Heparin	Favourable	NR
Our case	Superior sagittal sinus	4	No	No	Yes	Heparin	Abortion	1980 pg/ml

NR = not reported; NC = not complete (unreported factors in brackets); H = homocysteinemia; V = V Leiden; II = prothrombin gene mutation; PS = protein S deficiency; [a] 2 double foetal reduction + miscarriage of 1 foetus; [b] Miscarriage of 1 foetus.

Ovulation induction with gonadotrophin administration, giving rise to higher estrogen levels, further increases the risk of thromboembolic disease [7]. Aune *et al.* showed that ovarian stimulation is associated with a significant increase in fibrinogen levels and in clot lysis time, as well as with a decrease in AT III concentration, implying an alteration of the coagulation balance [27].

Ovarian hyperstimulation syndrome. The development of OHSS, which affects haemoconcentration as result of fluid escaping to the extravascular compartment, worsens this hypercoagulable condition [28].

Kodama and colleagues, performing prospective tests on 23 women admitted with severe OHSS in IVF cycles, showed a lower concentration of α2 plasmin inhibitor, increased levels of plasmin-α2antiplasmin complexes and a higher concentration of D-dimers [29]. Some studies have shown neutrophil-induced thrombogenic effects on endothelial cells and the possibility of endothelial damage by activated polymorphonuclear leucocytes as a result of stress-induced leucocytosis in OHSS [30, 31].

Balasch *et al.* found that the tissue factor expression by monocytes was induced by severe OHSS suggesting its possible role in thrombogenesis [32]. All these reports confirm that OHSS determines a hypercoagulation condition which is an important risk factor for ART-related venous thrombosis.

Possible conditions predisposing the development of severe OHSS include serum oestrogen levels of more than 10,000 pmol/l or 3,000 pg/ml at HCG daily administration and polycystic ovary syndrome (PCOS) [33].

In our review OHSS accounted for 20 out of 27 cases (74.1%): five of these patients showed high oestrogen levels, three suffered from PCOS, two had both risk factors, four (20%) developed OHSS without any risk factor and in six cases (30%) the presence of predisposing factors was only partially reported.

Among the seven patients who did not develop OHSS, four women had a potential risk for this syndrome: we observed three cases with PCOS and one case with oestrogen levels above the cut-off point.

All patients had undergone a GnRH-based protocol for ovarian stimulation: in 12 cases it was followed by administration of HMG, in five by recombinant FSH, in four by highly purified folliculotropin and in six cases the drugs used for the stimulation were not reported. In all cases, HCG was used to induce ovulation. It should be noted that the use of prophylactic measures for OHSS was not reported in the literature reviewed.

Thrombophilia. Recently, some authors have focussed their attention on the role of hereditary thrombophilia as a cause of upper body thrombosis. Major thrombophilias comprise protein S (PS), protein C (PC) and antithrombin III (AT III) deficiency, antiphospholipid syndrome, hyperhomocysteinemia correlated or not with a methylene tetrahydrofolate reductase (MTHFR) gene mutation, expression of factor V Leiden and prothrombin 3'UTR mutation. Protein S deficiency is a recognized risk factor for venous thrombosis, affecting 4.3% of thrombophilic patients [34] and its prevalence is estimated as between 0.026% and 0.13% in the general population [35]. Family-based studies have reported a 5-8.5 fold higher risk of thrombosis among affected relatives of PS-deficient patients when compared with unaffected relatives [36, 37]. Protein C deficiency is detectable in 0.2-0.4% of the general Caucasian population [34], in 4.8% of selected patients with venous thrombosis [34], and its relative risk for venous thrombosis is 6.5-fold higher [38]. Anithrombin III deficiency increases the risk of venous thrombosis by 5-fold [38] and its prevalence is 0.02-0.16% in the general population [34]. Overall, rare deficiencies of natural coagulation inhibitors (AT, PC, and PS) are detectable in less than 1% of the general population. Antiphospholipid antibodies are found among young, apparently healthy control subjects at a prevalence of 1-5% for both anticardiolipin antibodies and lupus anticoagulant antibodies [39]. Prospective studies have shown an association between antiphospholipid antibodies and venous thrombosis [40]. Hyperhomocysteinemia increases the risk of cerebral venous thrombosis by 4-fold [41] and it is determined by low levels of folate, vitamin B12, vitamin B6 or by MTHFR gene mutation. Approximately 10% to 13% of the white population are homozygous for this mutation [42]. Case control studies have shown a relative risk of 2.5 and 1-fold for hyperhomocysteinemia and MTHFR gene mutation, respectively [43, 44]. Factor V Leiden, resulting in activated protein C resistance, occurs with a frequency of 2-4% in the general population and of 40-60% for those with a personal or family history of thrombosis [45]. The G to A mutation at nucleotide 20210 in the 3' untranslated region of the prothrombin gene is found in 6% of unselected patients with deep venous thrombosis and the rate in the Caucasian population is approximately 2% [46]. The Leiden Thrombophilia Study [47] found that heterozygosity for factor V Leiden and the prothrombin gene mutation increase the risk of developing a deep venous thrombosis 7.9-fold and 2.8-fold, respectively, compared with normal individuals. This relative risk increases to over 40 for a combination of these two mutations [47] and 40-80 for Leiden homozygosis [48]. Moreover, it has been shown that mutations in the prothrombin gene and the factor V gene are associated with cerebral vein thrombosis [49].

The simultaneous presence of the above-mentioned mutations and OHSS might enhance the risk of cerebrovascular thrombosis [50].

Seven out of all cases reported showed a hereditary condition: four of these patients were carriers of factor V gene mutation (V Leiden), one of prothrombin gene mutation associated with factor V Leiden, one of Ig G antiphospholipid and one of protein S deficiency associated with prothrombin gene mutation. However, a complete screening for hereditary thrombophilia was not reported in 55.5% of the cases examined. One could assume that some of these women who had a thrombotic accident in the absence of OHSS might be carriers of an unscreened thrombophilic condition. Five patients resulted negative for all hereditary thrombophilic factors and four of them developed a thrombotic event

probably related to the presence of OHSS. The fifth case was our patient who developed cerebral thrombosis, in the absence of a hereditary thrombophilic state and without OHSS, probably related to the presence of PCOS and to ovarian induction resulting in a quadruplet pregnancy.

To summarise: 17 patients had only OHSS as a risk factor for thrombosis, three had OHSS and thrombophilia, four had only thrombophilia, two without OHSS underwent partial thrombophilic screening and one case (our patient) was negative either for OHSS or for a complete thrombophilic screening.

Site of thrombosis. As regards the localisation of thrombosis, we found that it affected the internal jugular vein in 17 cases, the cerebral veins in six, the subclavian vein in three and the axillary vein in the remaining one. There is no clear explanation for the tendency to produce thrombi in these unusual sites. In particular, in cases of internal jugular thrombosis – the most frequently found in our survey – there are usually local predisposing factors such as catheterisation, tumour compression or IV drug abuse [51]. However, where there is a lack of local causes, the upper body location may be the result of the above-mentioned haematological changes.

Although venous thrombosis is not usually fatal unless accompanied by significant pulmonary embolism, the recanalization of vessels may be disabling; particularly when the upper body is involved [52]. Cerebral venous thrombosis is the most serious, with a mortality rate of between 5% and 30% [53], and it is even more dangerous if thrombosis occurs in the cerebral sinus. However, this site is not frequently affected and, besides our patient, only two other cases of superior sagittal sinus have been reported. In spite of heparin treatment, termination of pregnancy was required in our patient due to a worsening of the cerebral condition, while in the other patients a cerebral thrombectomy or heparin treatment improved the neurological condition and allowed the pregnancy to go its course. Fortunately, radiological technologies such as angiography and MRI, enable early diagnosis and thus treatment can be given promptly to achieve a favourable maternal outcome. No case of maternal death was reported.

Pregnancy outcome. With regard to obstetric prognosis, the pregnancy had a regular course in 17 women, two pregnancies ended in miscarriage, two patients required elective termination, one underwent selective abortion in a sextuplet pregnancy, one had a miscarriage of one of three foetuses and the foetal outcome was not reported in the remaining four cases. None of the newborns were found to have either congenital anomaly or neonatal morbidity and mortality.

Conclusion

Our case is the first one reported in the literature of upper body venous thrombosis occurring in the absence of any risk factor. It is probable in this case that thrombosis was due to the modifications brought on by a strong stimulating protocol and by the resultant quadruplet pregnancy, which represents an additional risk for thrombosis *per se.* In all the other cases however, a hereditary or acquired predisposing factor to thrombosis was present. Since thrombosis represents one of the most severe complications of thrombophilia or OHSS, especially when it occurs in cortical veins, a decrease in the incidence of OHSS and screening for a hereditary condition might be useful to reduce the number of venous thrombotic events.

With regard to this, the following are some general rules that could be applied:

1) *Screening for a hereditary thrombophilic condition.* In the presence of a condition of thrombophilia, patients should be fully briefed about their heightened risk of developing thrombosis by undergoing ART, and administration of low weight heparin should be started early on and continued throughout the first trimester or for the entire pregnancy [54];

2) *OHSS prevention.* Although conflicting reports have been published since these measures were suggested, some of them seem to be useful: a) Controlled ovarian stimulation using the lowest effective dose, making allowance for age, body mass index and PCOS [33]; b) Hormonal and/or ultrasonographic coasting [33, 55]; c) Cycle cancellation before HCG administration [56]; d) A single bolus of GnRH agonist to trigger ovulation in a GnRH antagonist-based protocol [57, 58]; e) Intravenous administration of concentrated human albumin at the time of oocyte retrieval [59, 60];

3) *OHSS management.* In addition to the replacement of plasma volume to alleviate haemoconcentration and a careful clinical, sonographic and laboratory evaluation [33], prophylactic low-weight heparin should be given throughout the first trimester, because short-term measures may not be sufficient [6, 13, 54, 61];

4) *Thrombosis management.* Supportive treatment with optimal-dose heparin is recommended because it enables the thrombotic event to be resolved without any negative effects on the pregnancy and on foetal well-being [54].

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