

Subarachnoid haemorrhage in pregnancy after *in vitro* fertilisation with egg donation: a case report and review of the literature

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Abstract: We report a rare case of *in vitro* fertilisation (IVF) with egg donation complicated by a subarachnoid haemorrhage (SAH). Haemostatic changes related to IVF are known to increase risk of venous thrombosis; however, less is known regarding the risk of arterial events such as cerebrovascular accidents (CVA). Matrix metalloprotease-9 (MMP-9) upregulated in IVF patients may have a role in arterial aneurysm formation, which is the most common cause of SAH. Further research is required to assess the benefit of screening for risk of CVA and the best way to manage this in the IVF population. This may have implications for the ethics of offering certain procedures such as egg donation to women with pre-existing risk factors.

Keywords: aneurysm, CVA, fertility, IVF, pregnancy, SAH, thrombosis

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Introduction

Changes in haemostatic parameters during pregnancy are well known to increase the risk of venous thrombotic events.¹ *In vitro* fertilisation (IVF) procedures have been observed to exacerbate this, possibly due to utilisation of exogenous gonadotropins which produce a more hypercoagulable state.² The risk of thrombosis conveyed by venous aneurysms is such that IVF patients with such vascular malformations have been recommended antenatal anticoagulation or even prophylactic surgical correction.³ Compared with venous thrombosis, however, less is known regarding the risk of arterial events such as cerebrovascular accidents (CVA) in this population.

CVA such as subarachnoid haemorrhage (SAH) are most commonly caused by rupture of a pre-disposing cerebral aneurysm or arteriovenous malformation (AVM). This is the case in both pregnant women and the general population.⁴ Whether the incidence of aneurysmal SAH is higher in pregnant women, however, is contested.⁵ In the United Kingdom, for example, SAH has been reported to occur in 8-31 per 100,000 pregnancies and risk is highest in the

third trimester. This is likely due to the haemodynamic and hormonal changes occurring with advancing gestation, such as increasing blood pressure and the level of circulating oestrogen.^{6,7} Studies have found that risk factors for SAH in pregnancy besides underlying vascular pathology include African American descent, hypertension, obesity, chronic headaches and conditions of hypercoagulability such as sickle cell disease.^{6,8} Conclusions from these studies regarding the risk conveyed by age and twin pregnancies, however, are conflicting.

As far as we are aware, IVF procedures have not been associated with an increased risk of SAH in pregnancy. It is also not yet established whether the mechanisms underlying venous aneurysm formation in women who have undergone IVF could be the same as those leading to arterial dilatation and increased risk of CVA in this population. To our knowledge, there are no other reports published of SAH in women with an IVF pregnancy, or of whether such procedures augment the risk conveyed by other factors such as hypertension. Thus, we present the clinical background and course of one patient who experienced a SAH in

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the third trimester of her pregnancy with dichorionic diamniotic (DCDA) twins following IVF with donor eggs.

Case report

We report a case of a 50-year-old primigravida with a history of IVF who was diagnosed with a SAH at 33⁺⁴ weeks gestation. She underwent IVF at a private clinic, which resulted in a successful dichorionic diamniotic (DCDA) twin pregnancy. The patient had a body mass index (BMI) of 36.5 and was a nonsmoker. She began treatment with a STAT dose of a gonadotropin-releasing hormone (GnRH) analogue and continued on a daily regimen of oral and vaginal oestradiol, aspirin, folic acid and vitamin D supplementation. Two frozen embryos, from donor eggs fertilised with her partner's sperm 5 days beforehand, were transferred following sonographic assessment of the patient's endometrium. The patient remained on the same drug regimen with the addition of progesterone suppositories to reduce risk of pre-term labour. A successful pregnancy was confirmed 12 days following the embryo transfer. At approximately 4 weeks gestation, the patient was started on nifedipine owing to a background of mild, chronic hypertension. Her blood pressure remained controlled for the remainder of the pregnancy and she did not develop pre-eclampsia. During the third trimester, the patient was also diagnosed with gestational diabetes mellitus, and this was managed with dietary modifications alone.

At 31⁺⁶ weeks, abdominal ultrasound scan showed normal amniotic fluid volumes, arterial Dopplers

and placental sites. Both foetuses had normal anatomy, movement and growth on the 77th and 61.5th percentiles. The patient was scheduled for elective caesarean section at 37 weeks; however, at 33⁺⁴ weeks, she presented with a 1-week history of headache, nausea and vomiting. The headache had peaked in severity and caused a transient loss of vision, prompting her to seek medical attention. On admission, she had a blood pressure of 174/43 and required assistance to mobilise. There was no facial droop or evidence of diplopia, nystagmus or photophobia. Power, tone, sensation and coordination of all her limbs were normal. Bedside echocardiogram showed no right heart strain and her blood tests were within normal range. There was no protein in her urine. The patient had an urgent magnetic resonance imaging (MRI) head scan which demonstrated an extensive SAH involving the prepontine cistern (Figure 1a), the right sylvian fissure (Figure 1b), interpeduncular (Figure 1c) and ambient (Figure 1d) cisterns. There was a suspicious focal dilation in the bifurcation of the right middle cerebral artery (MCA), suggestive of an aneurysm causing the bleed and area of ischaemia (Figure 2). The patient was urgently started on nimodipine to reduce the risk of arterial vasospasm and transferred to a neurosurgical team at a specialist hospital. Here, she had computed tomographic (CT) (Figure 3) and magnetic resonance angiography (MRA) head scans (Figure 4) which confirmed an aneurysm of the right MCA.

Prior to further intervention, a joint decision was made between the neurosurgical and obstetrics teams to deliver the patient by caesarean section and this went ahead without complication.

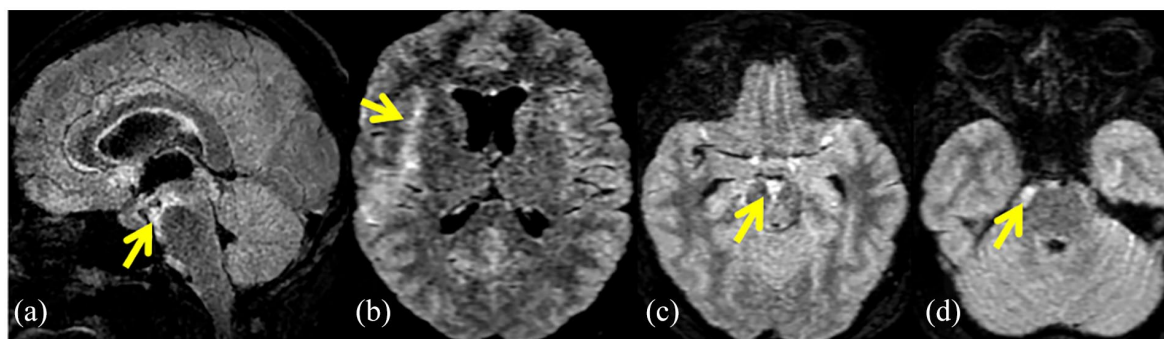


Figure 1. Sagittal and axial T2W FLAIR MRI head: high signal intensity consistent with acute subarachnoid blood in the prepontine cistern (a), right sylvian fissure (b), interpeduncular (c) and ambient (d) cisterns (arrows).

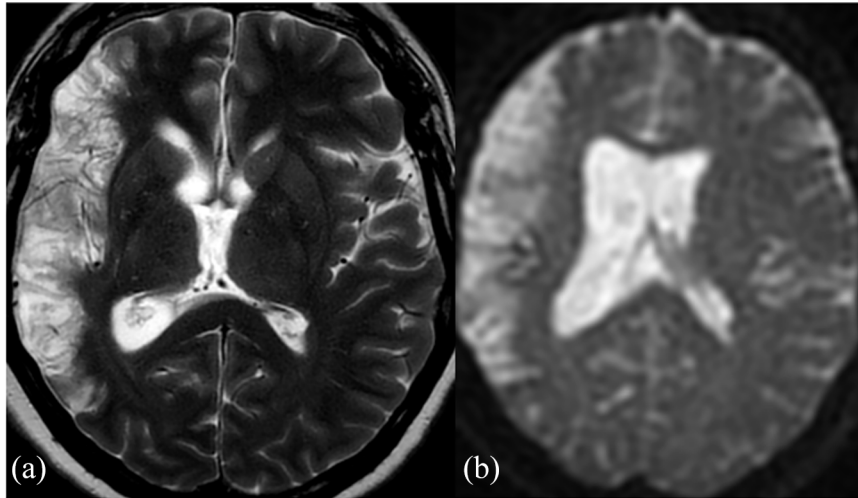


Figure 2. Axial T2W (a) and DWI (b) MRI head: high signal intensity in the right frontoparietal cortex MCA territory consistent with acute ischaemia.

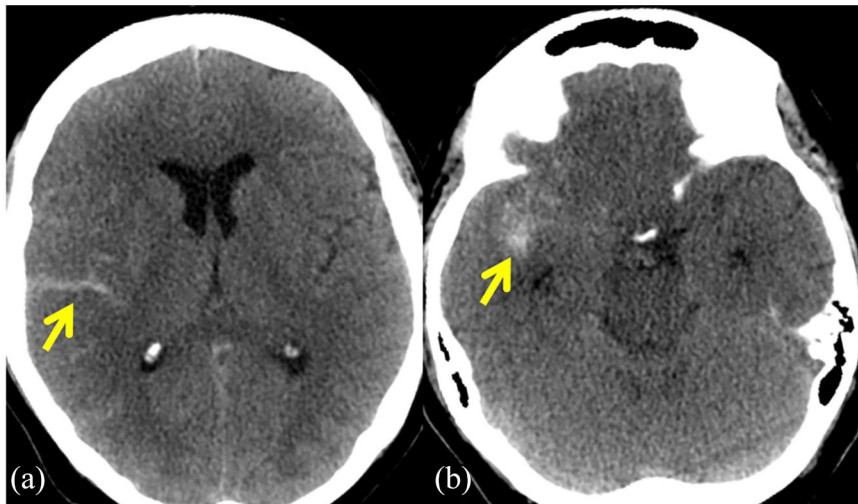


Figure 3. Axial non-contrast CT head (a and b): high density in right sylvian fissure (arrows) consistent with subarachnoid blood.

Following delivery, she underwent endovascular coiling of the aneurysm which unfortunately resulted in thrombosis of the M1 segment of the MCA. This was immediately treated with thrombectomy and the endovascular procedure was abandoned. Secondary to the thrombus, the patient sustained complete left-sided hemiparesis, mild dysarthria and a small degree of confusion. After repeat imaging, the procedure was rescheduled and the aneurysm was successfully

treated with endovascular coiling during this attempt.

While in hospital, the patient also received psychotherapy to improve her cognitive function, and her weakness was resolving by discharge. Two months following the coiling procedure, she and her twins remain clinically well. The patient has regained power in her left arm and leg and has no residual facial droop. She reports



Figure 4. Volume rendered image MR angiogram of the Circle of Willis: right M1 segment of MCA aneurysm (arrow).

some slurring of words at times when she is tired; however, she has recovered her cognition in full.

Discussion

It is well known that changes in haemostasis increase the risk of venous thrombosis during pregnancy.¹ Changes related specifically to IVF have been observed to increase this threefold compared with spontaneous conception. This holds even in the absence of ovarian hyperstimulation syndrome (OHSS)⁹; a severe complication of some IVF procedures resulting in fluid shift and haemoconcentration.¹⁰ The risk of thrombosis conveyed by IVF can also be secondary to exogenous gonadotropins, which result in a hypercoagulable state of reduced serum protein C, protein S, antithrombin and increased thrombomodulin.² In keeping with this, use of antenatal anticoagulation has increased the rate of live births following IVF owing to a perceived beneficial effect on embryonic implantation.^{11,12} Compared with thrombosis, however, far less is known regarding the risk of arterial pathology in women undergoing IVF.

Worldwide, CVA are estimated to occur in every 34 of 100,000 births.⁴ These are mostly haemorrhagic strokes such as SAH and occur as a result of a ruptured cerebral aneurysm or AVM. Such vascular pathology remains the most common cause of SAH in pregnant women as well as the

general population. Compared with nonpregnant women, however, the incidence of SAH has been reported to be up to 5 times higher in pregnancy.¹³ It occurs most frequently in the third trimester, suggesting the involvement of haemodynamic and hormonal changes. Besides an underlying vascular malformation, evidenced associations with SAH in pregnancy include African American descent, hypertension, obesity, chronic headaches and conditions of hypercoagulability such as sickle cell disease. Some studies, however, have found no increased incidence of SAH in pregnancy, and there is paucity of data regarding the potential risk conveyed by either twin pregnancy or IVF procedures.⁵

To our knowledge, this is the first case reported of a SAH in a woman with history of IVF conception. She had the well-established risk factors for SAH of a right MCA aneurysm, hypertension and a high BMI.^{6,8} Other factors may have included being female, age between 45 and 55 years, primiparity, pregnancy and her gestation in the third trimester.^{14,15} It is not possible, however, to exclude the possibility that the patient's IVF medications or procedures contributed to her risk of aneurysmal development or rupture. More research is required to investigate the mechanism potentially underlying this, such as the upregulation of matrix metalloprotease-9 (MMP-9). This appears to be raised in the serum of IVF patients compared with spontaneously pregnant controls

and has been found to contribute to venous aneurysm formation.^{16,17} It may be that MMP-9 also leads to degeneration in arterial walls, resulting in aneurysm development and therefore greater risk of SAH in this population.⁴

The risk of associated thrombosis is significant to the extent that anticoagulation, or even surgical correction, has been recommended for women with venous malformations undergoing IVF.³ Further investigation is required to assess whether similar precautions should apply to those with risk factors for CVA and the benefit of screening women undergoing IVF for underlying arterial pathology. It may be necessary, for example, to inform women about these risks when consenting them for IVF. These include the potential need for investigation using ionising intracranial imaging and the possible complications of conservative or neurosurgical management, as demonstrated by the subject of this case report. Such risks may be unacceptable to some women, and it may even be unethical to offer IVF to high-risk cases.

Although the clinical course of SAH does not appear to differ between pregnant and nonpregnant women, the method of delivering women at risk of SAH requires evaluation on a case-by-case basis at present.¹⁸ This is due to a lack of large population studies or guidelines to inform this decision. Some groups have suggested a therapeutic algorithm to simplify the management of SAH in pregnancy which considers the gestation, radiation exposure and location of an aneurysm to advise treatment and timing of delivery.⁵ Further work, however, is required to develop recommendations for the standardised management of CVA in pregnant women and in particular those undergoing IVF.¹⁹

Conclusion

Compared with venous thrombosis, little is known regarding the risk of arterial events such as SAH in women undergoing IVF. MMP-9 upregulated in IVF patients may have a role in arterial as well as venous aneurysm formation, increasing their risk of such CVA. Further research is required to assess the benefit of screening for vascular malformations, the risk of CVA and the safest way to manage this in the IVF population.

Author contributions

The project was conceived by MH. The manuscript was written by NH, with revision and intellectual input from SC and MH. Radiology images included were produced and annotated by SL. Consent from the patient was obtained by NH. All authors have read and approved the manuscript.

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Consent for publication

Written consent for publication of the personal information and photographs contained in this report was granted by the patient.

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