Report of the use of hyperbaric oxygen therapy (HBO$_2$) in an unusual case of secondary infertility.

J. LEVERMENT, R. TURNER, M. BOWMAN AND C.J.COOKE

Department of Diving and Hyperbaric Medicine, Prince of Wales Hospital, Randwick, NSW, Australia 2031

Leverment J, Turner R, Bowman M, Cooke CJ. Case report on the use of hyperbaric oxygen therapy (HBO$_2$) in an unusual case of secondary infertility. Undersea Hyperb Med 2004; 31(2):245-250. We report the use of hyperbaric oxygen therapy (HBO$_2$) in the treatment of an unusual case of secondary infertility. The patient had failed to conceive after a 1-year period of in-vitro fertilization, during which oral sildenafil had also been administered. However she became pregnant after an IVF cycle and the use of adjunctive HBO$_2$ and sildenafil, which was administered intravaginally on this occasion. There is currently very little evidence to support the use of HBO$_2$ in this context. The possible mechanisms of action of HBO$_2$ in this case are discussed.

INTRODUCTION

This case report illustrates the use of hyperbaric oxygen therapy (HBO$_2$) for secondary infertility in a 32-year-old woman. The patient had developed endometrial scarring following a post-partum hemorrhage and uterine packing in 1998. Subsequent efforts to become pregnant failed despite natural attempts and in-vitro fertilization (IVF). After a 1-year period, our patient underwent a single IVF cycle with adjunctive HBO$_2$ and subsequently became pregnant. Following an uncomplicated pregnancy and elective Caesarean delivery, she gave birth to a healthy male infant. Secondary infertility is not a recognized indication for HBO$_2$. There however some theoretical rationale to suggest that HBO$_2$ may improve the condition of the endometrium for implantation particularly in the setting of chronic hypoxia. This case report describes a previously unreported use for HBO$_2$ that warrants further investigation.

Clinical History

This 32-year-old woman conceived naturally in 1997 but the delivery was complicated by obstructed labor necessitating an emergency Caesarean section. Intraoperatively she suffered a life-threatening post-partum hemorrhage secondary to an atonic uterus. Bleeding was controlled by intrauterine packs for 24 hours. She subsequently made an uneventful recovery and was discharged well from hospital.

In June 2000, the patient ceased contraception (the combined oral contraceptive pill). While menstrual cycles returned, mid-cycle bleeding occurred and she was unable to conceive. In March 2001, investigation for secondary infertility commenced. Basic reproductive hormone levels were normal. Diagnostic laparoscopy revealed scarr ed fallopian tubes and hysteroscopy showed that approximately 30% of the endometrium was scarred, particularly the fundus. This was thought to be due to her previous traumatic obstetric history.

Copyright © 2004 Undersea and Hyperbaric Medical Society, Inc. 245
In July 2001, stimulated IVF cycles were commenced. Fresh embryo transfer in October and frozen embryo transfers in December and January 2002 all failed. Trans-vaginal ultrasound repeatedly demonstrated an absence of the usual endometrial thickening noted during IVF and natural cycles. This was assumed to be secondary to previous endometrial trauma.

In February 2002, a repeat hysteroscopy confirmed previous findings and demonstrated calcification of approximately one third of the endometrium at the fundus (Fig 1. Compare a normal hysteroscopic view in Fig 2). A further IVF cycle with a fresh embryo transfer failed. Transvaginal ultrasound continued to show attenuated endometrium with an average thickness of 4mm.

Fig. 1 Hysteroscopy (February 2002) demonstrating calcified, scarred, thin endometrium.

Fig. 2. Normal endometrium on hysteroscopy.

After 11 months, frozen embryo transfers were commenced. The IVF unit’s usual endometrial preparation protocol was administered: oral ethinyl oestadiol from day 1 and additional progesterone vaginal pessaries from day 15. Adjunctive oral sildenafil was also administered, 25 mcg twice daily from day 10 to day 24. The endometrium again remained thin (<4mm) and the cycle was unsuccessful. The patient’s husband, a medical practitioner, then
performed an extensive literature search. This resulted in the idea to administer sildenafil intravaginally plus the hypothesis that HBO2 may assist endometrial development and subsequent embryo implantation. After discussion with several specialists in IVF and hyperbaric medicine, the couple presented for assessment in our hyperbaric unit. She was otherwise well and had no contraindications to HBO2. A second frozen embryo cycle was planned for May or June of 2002.

Because there is little evidence to support the use of HBO2 for the treatment of infertility, this issue was discussed carefully with the patient. Only theoretical reasons were given for a role of HBO2 in this case including the possibility that with HBO2 endometrial hypoxia in the setting of endometrial scarring could improve tissue oxygenation (1,2,3). HBO2 might also correct reproductive hormone level abnormalities in patients who have experienced recurrent miscarriage (4). Since the treatment rationale was tenuous and speculative, we decided to administer HBO2 as investigative treatment, and the patient and her partner were keen to proceed. One deciding factor was the ability to measure endometrial thickness with trans-vaginal ultrasound thus providing a clear and quantitative guide to the HBO2 treatment.

The risks and potential complications of HBO2 were explained and the patient gave written informed consent. She received 10 daily treatments at 2.0 ATA for 90 minutes (Royal Navy Table 10:90:10). These were given over day 1 to 10 of the IVF cycle. She had no problems with compression during any session.

During this cycle, a usual estrogen/progesterone protocol was administered plus sildenafil pessaries (25 mcg) on days 3 to 15. Transvaginal ultrasound on day 10 revealed an increased endometrial thickness to 6mm from previously recorded peaks of 4mm. Embryo transfer took place on day 20, on 11th June 2002. A single pregnancy was confirmed on 11th July 2002. A healthy male infant (3080g) was born by elective Caesarean section on 14th February 2003.

Discussion

There is little evidence for a treatment role of HBO2 in cases of poor endometrial thickening or in infertility generally. Our case report describes increased endometrial thickening and subsequent pregnancy following an IVF cycle with adjunctive HBO2. Previous IVF cycles had failed. There are several possible mechanisms by which HBO2 operated.

This patient had chronic uterine scarring on hysteroscopy. One could speculate that HBO2 restored normoxia in the endometrium, as it would in a chronically hypoxic wound (1). In these circumstances, normoxia promotes wound healing by creation of an oxygen tension gradient stimulating angiogenesis (1,2,3). In our patient, the fundus was particularly scarred and interestingly 85% of gestational sacs have been shown to implant in the fundus during an IVF/intracytoplasmic sperm injection program (5).

Some investigators have found a correlation between uterine blood flow and implantation and pregnancy rate (6). However, it is unlikely that HBO2 assisted implantation by this mechanism since various animal studies show that hyperoxic exposure actually causes reduced organ blood flow during hyperoxygenation as a result of vasoconstriction and cardiac output reduction secondary to increased afterload and bradycardia (7,8).

HBO2 has previously been used in the treatment of recurrent miscarriage (4). In this study, progesterone receptor levels, estrogen receptor levels and the estrogen:progesterone reception ratio during the secretory phase of the menstrual cycle were all found to be significantly higher in these patients. Hyperbaric oxygen appeared to normalize both hormonal levels and receptor ratio and an increased pregnancy rate followed. We did not measure hormone
receptor levels in this patient and this could have been useful in assessing a possible mechanism for HBO₂.

An abnormally high estrogen: progesterone receptor ratio has also been correlated with a bilaminar rather than trilaminar endometrium on ultrasound (9), and it is the trilaminar rather than bilaminar pattern that has been correlated with increased pregnancy rate (10). In our case, the endometrium did indeed have trilaminar appearance on ultrasound prior to successful implantation and pregnancy.

The importance of the endometrial thickness on ultrasound as a predictor of outcome in patients treated with IVF is well-established (9,10,11,12). A variety of “threshold” thicknesses of endometrium have been correlated with an increased pregnancy rate. Pregnancy has been found to be significantly greater when the endometrium is more than 10mm (11). No pregnancies or increased miscarriage rate has also been shown when endometrium was less than 9mm (9,12). Of particular relevance is a study that showed no pregnancy would occur if endometrial thickness was less than 6mm (10). In our patient, the endometrial thickness increased from an average thickness of 4mm to 6mm following an IVF cycle with adjunctive HBO₂ and a pregnancy was confirmed thereafter. Prior to HBO₂ no such increase was demonstrated.

Several regimens have been proposed to improve a poor endometrial response, including treatments with estrogens, low dose aspirin, transdermal nitric oxide and anti-fibrotic treatments. (13,14,15). In this particular patient sildenafil was used based on previous evidence (16,17). Sildenafil is thought to augment the vasodilatory effects of NO in the endometrium and thus increase uterine blood flow (16,17). Intravaginal sildenafil was thought to provide a method of administering NO closer to the target organ thus limiting the systemic side effects previously encountered with glyceryl trinitrate (GTN) patches. It may have been intravaginal sildenafil rather than HBO₂ that accounted for the endometrial thickening. The patient had used oral sildenafil during a previous cycle with no endometrial response. The relationship between the endometrium and HBO₂ requires further investigation.

Limitations of these Observations

Although this case report illustrates an intriguing potential new application of HBO₂, firm conclusions cannot be drawn. The route of sildenafil administration was simultaneously changed when HBO₂ was administered so a precise effect of HBO₂ cannot be determined confidently. Moreover, endometrial thickness is routinely measured only once so one could argue that the change was within measurement error. We offered several possible mechanisms of action by which HBO₂ could have facilitated IVF but none were actually tested. The hypothesis that HBO₂ could normalize reproductive hormone levels was based on patients with recurrent miscarriage rather than failed IVF. Finally the relevance of this case to most patients who undergo IVF is limited; poor quality ova or embryos are usually the cause of failure to conceive in IVF while the pathology underlying failure in this case was particularly unusual. Although its contribution to the broader field of hyperbaric medicine remains to be determined, this case highlights some fascinating aspects of secondary infertility.

SUMMARY

Poor endometrial development secondary to uterine trauma is a relatively rare cause for failure of IVF. In this case, HBO₂ may have contributed to the increase in endometrial thickness and subsequent pregnancy however this relationship is far from clear. Subsequent pregnancy
may otherwise have been co-incidental, related to the administration of trans-vaginal sildenafil, or due to a combination of both treatments. Interplay between HBO2 and sildenafil is an interesting possibility particularly when the vasoconstrictive effects of HBO2 are undesirable. This experience calls for systematic study of HBO2 and sildenafil in this area of infertility.

CONCLUSION

Hyperbaric oxygen therapy may conceivably have a role in individual cases of secondary infertility due to prior endometrial damage resulting in poor endometrial development. Further investigations are required.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Mike Bennett (MBBS, DA, FFARCSI, Dip DHM), Medical Director of Hyperbaric Unit, Prince of Wales Hospital, Randwick, Sydney, for his help and advice and Dr Warren Ambrosio (MB BS, FRANZCOG), Queensland Fertility Group Brisbane and Sydney IVF Limited for their provision of clinical information. The patient requested the following people be thanked: Dr Sarah Sharkey at Balmoral Naval Hospital, Dr Warren Ambrosio and Dr Geoffrey Sher (reproductive endocrinology, US) for their clinical input.

REFERENCES


