JBRA Assisted Reproduction 2015;**19**(2):87-90
doi: 10.5935/1518-0557.20150019

Case Report

Improvement in Serum Anti-Müllerian Hormone Levels in Infertile Patients after Hyperbaric Oxygen (preliminary results)

Jesus Fernando Gallardo Pineda[1], Carlos Gerardo Salazar López Ortiz[1], Gonzalo de Jesus Siu Moguel[1], Carlos Roberto Eduardo Castro Lopez[2], Héctor Mondragón Alcocer[1], Sergio Téllez Velasco[1]

[1]HISPAREP Fertility Clinic, Hospital Español, México DF
[2]Multidisciplinary Diabetes Center México City (Hyperbaric Chamber)

ABSTRACT

Objective: To assess whether hyperbaric oxygen sessions elevate serum levels of anti-Müllerian hormone (AMH) in patients diagnosed with infertility with serum levels of less than or equal to 1 ng/dl AMH.
Methods: A study was performed on 4 patients diagnosed with infertility. Serum AMH level was measured at the beginning and end of hyperbaric oxygen sessions, and endometrial thickness was measured on endometrial cycle day 14 before and during the hyperbaric oxygen sessions.
Results: In two of the four patients, the serum AMH level increased by 40% and 116%. In one patient the serum AMH level was not elevated, with a serum AMH level before and after treatment of 0.1 ng/dl. The fourth patient became pregnant during the hyperbaric oxygen sessions. Endometrial thickness was not improved in any of our patients.
Conclusions: This study showed that hyperbaric oxygen sessions can increase serum AMH levels, with a significant increase of 116% in one case. Therefore, this therapy can be used as an alternative treatment for patients with serum AMH levels of less than or equal to 1 ng/dl and a limited number of eggs for IVF cycles but not for patients with serum AMH levels of less than or equal to 0.1 ng/dl, as we did not observe an increase in serum AMH level in patients with an initial AMH level of 0.1 ng/dl. This study did not demonstrate improvement in endometrial growth following hyperbaric oxygen sessions.

Keywords: Anti-Mullerian Hormone, Hyperbaric Chamber, Low Ovarian Reserve.

INTRODUCTION

In recent decades, there have been breakthroughs in the human reproductive field despite the fact that breakthroughs have only been occurring in a few branches of medicine. As an increasing number of patients with social issues and ideals postpone pregnancy, low ovarian reserve is more common. Great advances in reproductive medicine have occurred, mainly due to the discovery and development of highly complex techniques that accomplish what was long thought to be impossible. Furthermore, techniques such as ICSI and laboratory embryo development have helped treat problems in the indispensable organs of fertility, such as the fallopian tubes, and drugs for ovarian stimulation have been developed. This developments have undoubtedly marked a key stage in the advancement of reproductive treatment.

Despite these breakthroughs, a successful treatment has not been developed for patients with infertility issues who postponed pregnancy to later in life, and without a doubt, age is the main factor affecting fertility in such patients.

The ovary and development - The human ovary becomes functional during embryonic development. Oogenesis is a genetically determined chrono-event; at birth, women have a finite number of primordial follicles that form the ovarian reserve, and these follicles decrease gradually throughout reproductive life.

Menopause is the result of the depletion of these primordial follicles. Follicular loss clinically manifests as a state of hypergonadotropic hypogonadism, which culminates in reproductive failure. The ability to conceive is termed reproductive potential, and its decline is temporarily correlated with follicular depletion and impairment of oocyte quality, which act together to reduce the ovarian reserve (Vital-Reyes, 2010).

A quantitative morphological study of germ cells in 17 normal human fetuses revealed seven million germ cells at five months after conception; this study remains the basis of the current understanding of oogenesis in humans. The first meiotic division is initiated at approximately 15 weeks, and this indicates the transformation of oogonia into oocytes. This meiotic division is stopped in prophase once primordial follicles have formed (Baker, 1963).

Pituitary - At hypothalamic maturation, ovarian follicles are released and the menstrual cycle begins. This cycle is tightly regulated, and inhibitors of stimulatory effects result in the release of a single mature oocyte out of hundreds of thousands of primordial oocytes. This process is repeated month after month in most women, and a noticeable decrease in the quantity and quality of mature oocytes is observed in the fourth decade of life.

Infertility evaluation - Infertility evaluation is usually initiated after a year of regular unprotected intercourse without conception in women under 35 years of age and after six months of unprotected intercourse without conception in women over 35 years of age. However, infertility evaluation can be performed sooner for women with irregular menstrual cycles or known risk factors for infertility.

It is important to remember that multiple factors of both partners can contribute to a couple's infertility; therefore, a complete initial diagnostic evaluation should be performed to detect the most common causes of infertility (ASRM, 2012).

Among the many factors to consider when diagnosing infertility is the ovarian reserve, and there is no ideal test for reliably predicting the potential of pregnancy. This study focuses particularly on the hormone AMH, which reflects the size of the follicular pool and may be the best biochemical marker of ovarian function in a variety of clinical situations.

AMH is a member of the TGF-beta family and is expressed by the preantral follicles and antral follicles under 8 mm in diameter. In adult women, AMH levels gradually decrease with age as the pool of primordial follicles declines (Seifer *et al*., 2011), and AMH is undetectable at menopause (de Vet *et al*., 2002).

AMH level seems to be an early, reliable and direct indicator of a decline in ovarian function. It may also valuable for identifying ovarian follicular pool reduction in cer-

Received January 31, 2015
Accepted April 05, 2015

tain patients, including cancer patients (Broekmans *et al*., 2006) and patients who have experienced significant ovarian radiation injury or undergone ovarian surgery.

In patients who are planning to undergo in vitro fertilization (IVF), AMH level correlates with the number of oocytes retrieved after stimulation and is the best biomarker for predicting the ovarian response (Broekmans *et al*.; 2006; Nardo *et al*., 2009; Broer *et al.*, 2011). However, its diagnostic accuracy for predicting whether a child will be born alive is low, so it should not be used to exclude couples from IVF/ICSI (Iliodromiti *et al.,* 2014).

A review suggested the following general guidelines in regards to AMH level and IVF cycles (Toner & Seifer, 2013):

- AMH <0.5 ng/ml predicts ovarian response, with less than three follicles in an IVF cycle
- AMH <1.0 ng/ml predicts a probable limited oocyte stimulation cycle
- AMH >1.0 ng / ml and <3.5 ng / mL suggests good response to stimulation
- AMH >3.5 ng/ml predicts a vigorous response to ovarian stimulation and requires precautions to prevent ovarian hyperstimulation syndrome

Gnoth *et al.* (2008) studied 316 women in their 1st cycle of stimulation for IVF. For that study, age and FSH, inhibin B and AMH levels were evaluated. The cutoff point for AMH level to detect a poor response to stimulation was <1.26 ng/ml, with a sensitivity of 97% (<4 oocytes). Furthermore, AMH of <0.5 ng/ml predicted a very poor response (<2 oocytes) in 88% of cases considered but failed to correlate with the rate of pregnancy.

Hyperbaric Chamber - According to the Committee of Hyperbaric Oxygen Undersea and Hyperbaric Medical Society (UHMS), hyperbaric oxygen therapy involves the patient breathing 100% oxygen continuously or intermittently within a chamber at a pressure greater than 1.4 atmospheres absolute.

Importantly, exposure of isolated parts of the body to 100% oxygen or treatment in plastic or vinyl "chambers" is not considered hyperbaric oxygen therapy by the UHMS.

This technology has been used for over 200 years. It was originally used for treating diseases related to exposure to pressures beyond the atmospheric pressure (during diving and in mines, underground tunnels, etc.). Additionally, empirically, more enthusiasm than actual thorough scientific studies have indicated the use of "baths of compressed air" for the treatment of a variety of diseases, and the efficacy of this therapy for different diseases is unclear based on the currently available data; therefore, the enthusiasm for the use of this technology has decreased.

In 1960, based on the work of Ita Boerema and Brummelkamp, the first professor and cardiovascular surgeon at the University of Amsterdam, Netherlands concluded that hyperbaric oxygen therapy prolonged ischemic time to occlude large blood vessels and improve patient outcomes. He soon, along with other doctors, began scientific studies that demonstrated the possibility of using this technology for the treatment of different diseases caused by hypoxia (grafts, flap damage), infections (primarily anaerobic), lesions that have trouble healing (radiated tissue), and acute decreases in cell volume in Jehovah's Witnesses, as they cannot be treated with blood transfusion due to their religious beliefs (Luna Rodríguez, 2010).

Hyperbaric oxygen (HBO) serves as a primary or adjunctive therapy for a wide range of medical conditions.. Most of the benefits of HBO are the result of the gas concentration, volume and pressure. HBO is more commonly used in conditions of tissue hypoxia or to treat decompression sickness and air embolism, in which gas bubbles obstruct blood flow (Gill & Bell, 2004).

Therapeutic Functions for hyperbaric oxygen (Leach *et al*., 1998; Undersea & Hyperbaric Medical Society, 2005).

1. Air or gas embolism
2. Carbon monoxide poisoning
3. Decompression sickness
4. Clostridial myonecrosis (gas gangrene)
5. Crushing injury and other forms of trauma ischemia
6. Improved problem wounds, including diabetic wound healing
7. Severe anemia
8. Brain abscess actinomycotic
9. Necrotizing soft tissue infections
10. Refractory osteomyelitis
11. Radiation necrosis of the soft tissue and bone
12. Grafts and skin flaps committed

Increasing oxygen delivery - Henry's Law states that the amount of a gas dissolved in solution is ideally directly proportional to its partial pressure. Therefore, the dissolved oxygen concentration in plasma of 0.3 ml/dl at sea level (1.0 atm) increases to 1.5 ml/dl after administration of 100 percent oxygen, while the hyperbaric oxygen delivered at 3.0 atm has a dissolved oxygen content of 6 ml/dl. The latter figure is sufficient to meet the needs of tissue oxygen extraction at rest, regardless of the adequacy of the oxygen bound by hemoglobin. The capacity of OHB to increase oxygen content and independently meet the oxygen needs of resting tissue has led to its use under conditions of compromised oxygen supply, such as deep anemia, carbon monoxide poisoning, and acute and chronic ischemia (Leach *et al*., 1998; Wattel *et al.*, 1998; Hart *et al*., 1987; McLoughlin *et al*., 1999; Van Meter, 2005).

Technical - Multichamber cameras allow close monitoring of patients in critical conditions, while cameras in one chamber are appropriate for the treatment of chronic medical conditions in stable patients. Chamber pressure typically is maintained between 2.5 and 3.0 atm, and treatment lasts 45 to 300 minutes depending on the indication. An acute condition may require one or two treatments, while chronic medical conditions may require up to 30 or more sessions. Usually, hyperbaric oxygen therapy or oxygen therapy at normal air pressure is administered. Excess pressure of 2.8 to 3.0 atm, particularly during periods of hyperbaric exposure, dramatically increases the risk of both neurological and pulmonary oxygen toxicity. Helium/oxygen (heliox) and nitrogen/xygen (nitrox) mixtures are indicated only in certain cases of decompression sickness (Moon & Sheffield, 1997; Shupak *et al*., 1997).

Contraindications - The only absolute contraindication to HBO therapy is untreated pneumothorax. Relative contraindications include obstructive pulmonary disease, seizure disorders, respiratory and upper sinus infections, recent ear infections, thoracic surgery, uncontrolled fever, and claustrophobia (Toklu *et al*., 2008). Previously, it was believed that pregnancy is a contraindication to hyperbaric oxygenation (OHB), but it is now considered a suitable treatment for pregnant patients with carbon monoxide poisoning (Ernst & Zibrak, 1998).

Objective - The objective of this study was to assess whether hyperbaric oxygen sessions elevate serum levels of AMH in patients diagnosed with infertility with AMH serum levels of less than or equal to 1 ng/dl.

MATERIAL AND METHODS

This was an original study with a longitudinal, prospective design and with a level of evidence of III.

Informed consent was obtained and consultation by ex-

Table 1. Summary.

Patient	Age	Pre-treatment AMH level	Post-treatment AMH level	Antral follicle number before and after treatment	Endometrial thickness on day 14 of the endometrial cycle without HBO sessions	Endometrial thickness on day 14 of the endometrial cycle with HBO sessions	Percent increase in AMH level
1	40	1.0ng/dl	1.4ng/dl	4/6	7mm	7mm	40%
2	47	0.6ng/dl	1.3ng/dl	3/9	9.5mm	9mm	116%
3	46	0.1ng/dl	0.1ng/dl	1/1	6mm	6mm	0%
4	41	0.5ng/dl	Spontaneous pregnancy presented during the HBO sessions				

pert personnel was performed prior to enrollment in this study. The enrolled patients were diagnosed with infertility, were over 35 years of age, had serum AMH levels of less than or equal to 1 ng/dl, lacked chronic degenerative diseases and were undergoing hyperbaric oxygen therapy. For these patients, serum AMH levels were measured at the beginning and end of a series of 20 hyperbaric oxygen sessions. Each patient underwent 20 sessions of one hour each at 2 atmospheres over a period of 30 days.

Additionally, endometrial thickness was measured on day 14 of the endometrial cycle before the initiation of HBO and during the series of HBO sessions. Furthermore, antral follicles were counted before and after the series of HBO sessions.

This study was conducted at the HISPAREP fertility clinic/hospital in the Spanish Mexico Federal District in conjunction with the multidisciplinary diabetes center of the city of Mexico CEMUDI (hyperbaric chamber) from January to October 2014.

RESULTS

Table 1 summarizes the data.

Patient No. 1 had serum AMH levels of 1.0 ng/dl and 1.4 ng/dl before and after HBO treatment, respectively, and this represents a significant increase of 40%. No change in endometrial thickness was observed in this patient.

Patient 2 had serum AMH levels of 0.6 ng/dl and 1.3 ng/dl before and after HBO treatment, respectively, and this represents a significant increase of 116%. No change in endometrial thickness was observed in this patient.

Patient number 3 had serum AMH levels of 0.1 ng/dl and 0.1 ng/dl before and after HBO treatment, respectively; her AMH level did not increase after HBO. No change in endometrial thickness was observed in this patient.

At the beginning of the 16th HBO session, patient 4 had a serum AMH level of 0.5 ng/dl; therefore, as the patient had not shown improvement in her AMH serum level, was experiencing headaches that persisted with changing atmospheres, was not menstruating and had a positive pregnancy test, the HBO series was suspended.

DISCUSSION

We observed a significant increase in serum anti-Mullerian hormone level of up to 116% in patients undergoing hyperbaric oxygen therapy. Therefore, this therapy is an alternative treatment for patients diagnosed with low ovarian reserve.

No increase in serum anti-Mullerian hormone level was observed in patients presenting with extremely low serum AMH levels, as was the case for patient No. 3.

We conclude that hyperbaric chamber sessions do not help to increase endometrial thickness, but they do increase the antral follicular count.

Studies with more cases are required to support the findings of this study. We believe that HBO can be useful in the treatment of infertility in patients with low ovarian reserve, for whom there is currently no ideal treatment.

CONFLICT OF INTERESTS

No conflict of interest have been declared.

Corresponding author:
Jesus Fernando Gallardo Pineda
HISPAREP Fertility Clinic
Hospital Español, Mexico DF, Mexico
E-mail: gallardopineda@hotmail.com

REFERENCES

ASRM Practice Committee of American Society For Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. Fertil Steril 2012; 98: 302-7.

Baker TG. A quantitative and cytological study of germ cells in human ovaries. Proc R Soc Lond B Biol. Sci. 1963;158:417-33.

Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update 2006; 12: 685-718.

Broer SL, Dólleman M, Opmeer BC, Fauser BC, Mol BW, Broekmans FJ. AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. Hum Reprod Update 2011; 17:46-54.

de Vet A, Laven JS, de Jong FH, Themmen AP, Fauser BC. Antimüllerian hormone serum levels: a putative marker for ovarian aging. Fertil Steril 2002; 77:357-62.

Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med 1998; 339:1603-8.

Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. QJM 2004; 97:385-95.

Gnoth C, Schuring AN, Friol K, Tigges J, Mallmann P, Godehardt E. Relevance of anti-Mullerian hormone measurement in a routine IVF program. Hum Reprod. 2008; 23:1359-65.

Hart GB, Lennon PA, Strauss MB. Hyperbaric oxygen in exceptional blood-loss anemia. J Hyperb Med. 1987; 2:205-10.

Iliodromiti S, Kelsey TW, Wu O, Anderson RA, Nelson SM. The predictive accuracy of anti-Müllerian hormone for live birth after assisted conception: a systematic review and meta-analysis of the literature. Hum Reprod Update. 2014; 20:560-70.

Leach RM, Rees PJ, Wilmshurst P. Hyperbaric oxygen therapy. BMJ 1998; 317:1140.

Luna Rodríguez CL. Fundamento científico de la oxígenoterapia hiperbárica en el tratamiento del píe diabético infectado grave en medicina basada en evidencias. Med Int Mex. 2010; 26:374-82

McLoughlin PL, Cope TM, Harrison JC. Hyperbaric oxygen therapy in the management of severe acute anaemia in a Jehovah's witness. Anaesthesia. 1999; 54:891-5.

Moon RE, Sheffield PJ. Guidelines for treatment of decompression illness. Aviat Space Environ Med 1997; 68:234-43.

Nardo LG, Gelbaya TA, Wilkinson H, Roberts SA, Yates A, Pemberton P, Laing I. Circulating basal anti-Müllerian hormone levels as predictor of ovarian response in women undergoing ovarian stimulation for in vitro fertilization. Fertil Steril 2009; 92: 1586-93.

Seifer DB, Baker VL, Leader B. Age-specific serum anti-Müllerian hormone values for 17,120 women presenting to fertility centers within the United States. Fertil Steril 2011; 95:747-50.

Shupak A, Melamed Y, Ramon Y, Bentur Y, Abramovich A, Kol S. Helium and oxygen treatment of severe air-diving-induced neurologic decompression sickness. Arch Neurol 1997; 54:305-11.

Toklu AS, Korpinar S, Erelel M, Uzun G, Yildiz S. Are pulmonary bleb and bullae a contraindication for hyperbaric oxygen treatment? Respir Med 2008; 102: 1145-7.

Toner JP, Seifer DB. Why we may abandon basal follicle-stimulating hormone testing: a sea change in determining ovarian reserve using antimüllerian hormone. Fertil Steril 2013; 99:1825-30.

Undersea & Hyperbaric Medical Society. www.uhms.org (Accessed on August 09, 2005).

Van Meter KW. A systematic review of the application of hyperbaric oxygen in the treatment of severe anemia: an evidence-based approach. Undersea Hyperb Med 2005; 32:61-83.

Vital-Reyes VS. Evaluación de la reserva ovárica. Rev Mex Reprod 2010;2:89-95.

Wattel F, Mathieu D, Nevière R, Bocquillon N. Acute peripheral ischaemia and compartment syndromes: a role for hyperbaric oxygenation. Anaesthesia 1998; 53 Suppl 2:63-5.