Hyperbaric Oxygenation as a Possible Therapy of Choice for Infertility Treatment

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Abstract

Endometrial sonographic and color doppler features can be used to predict the occurrence of pregnancy in natural or stiumlated cycles. Implatation will usually onlytake place if the endometrium has reach a certain stage of vascularisation and development. The aim of this study was to evaluate endometrial devalopment – endometrial thickness and reflectivity , subendometrial, endometrial and uterine perfusion, after hyperbaric oxygenation, using transvaginal color doppler. During a three years period 32 women with unexplained infertility were entered into a randomised study. The patients were treated in multiplaced HAUX chamber at pressure of 2,3 ATA during 70 minutes, 7 days consecutively begining with day 5th of menstrual cycle.The evaluation of effects of hyperbaric oxygen therapy was carried out by transvaginal color doppler sonography which was continuously used starting from 8th day of menstrual cycle untyl the ovulation in the cycles when the therapy was applied , one month before and one month after the therapy. Folliculometry in the cycles when hyperbaric oxygen therapy at 2,3 ATA was applied, indicated an excellant response of endometrium. Thickness of endometrium at the time of ovulation was 11,0 ± 2,6mm. Desirable quality of endometrium was significantly better in the cycle when HBO therapy had been applied ($p< 0,001$). The doppler flowmetry of the uterine arterys indicated that the uterine blood vassel resistance was slightly higher than expected. Mapping of subendometrial blood vessels in the cycles covered by hyperbaric oxygen therapy showed the intensive capillary network of endometrium with low resisstance $Ri< 0,45$. The oxygen used under higher pressure – oxygen as a drug , may have an extraordinary significance for better outcome of pregnancy implantation by improving endometrial receptivity. If endometrial receptivity is conditioned by adequate vascularisation and oxygenation, then hyperbaric oxygen therapy is the treatment of choice.

KEY WORDS: endometrial receptivity, hyperbaric therapy, infertility

Introduction

The issue of infertility is, more or less, the problem existing in the whole world. Generally, every sixth couple has the problem of fulfillment of desired reproduction and needs an assistance of qualified personnel. One of the causes of infertility in women is certainly the problem of endometrial receptivity, i.e. quality of uterine mucosa where the future embryo will be implanted. Given that the programs of in vitro fertilization (IVF) result in high percentage of high-quality embryos which are replaced to uterus by embryotransfer (ET), their implantation into endometrium and fulfillment of desired pregnancy is expected. Yet, a large number of embryos fails to implant for unknown reasons, and instead of expected pregnancy, hemorrhage occurs as the sign of menstrual cycle and failure of implantation. Many factors affect the quality of this dynamic tissue: anatomy of the cavum and uterus as a whole, optimal hormonal status, absence of endometrial waves, and one of the most important factors is the quality of vascularization and oxygenation. Many drugs have been used for improvement of blood supply to uterus, and accordingly to subendometrium, but there have been no favorable results. Many medicaments, which have been used for vasodilatation and increased blood supply, that is, blood volume supplying the endometrium, have been effective only if endothelium had been preserved, and the effects have been still short-term and negligible. Knowing the physiological basis of hyperbaric therapy and its effects to different tissues and cells, and especially to tissues in hypoxia, we assumed that the increased volume of dissolved oxygen in hyperbaric conditions might have favorable effect to cells multiplying intensively, as in case of endometrium. Only adequately developed endometrium will allow for implantation of blastocyst and development of pregnancy. Considering that the conception is affected by many factors, it is extremely important to observe each of them separately. The most powerful instrument for noninvasive diagnostics of quality of endometrium is by, all means, transvaginal color Doppler sonography. Owing to most modern ultrasonographic apparatuses, we are able to analyze different sonographic parameters for evaluation of quality of endometrium as well as to monitor the blood flow through the entire uterus, all the way to subendometrial spiral arteries and capillaries. We are aware of the fact that, for a long time, one of the most important factors of prediction of endometrial quality has been its thickness only, and therefore, the thickness less than 7 mm at the time of ovulation is almost incompatible with pregnancy. In addition, the quality of texture and reflectivity of endometrium are analyzed, thus inadequate appearance of endometrium (grade C) is incompatible with gestation. The introduction of color Doppler procedures has revealed that the change of uterine arterial resistance as well as the absence of adequate capillary network in subendometrium at the time of ovulation is incompatible with pregnancy. Today, by transvaginal color Doppler sonography and analysis of hormonal status, it is possible to assess with high probability the quality of endometrium – endometrial receptivity.

Objective

The objective of this study was to evaluate the effects of hyperbaric oxygen – hyperoxia to vascularization of uterus and subendometrium as well as the quality of endometrium using transvaginal color Doppler sonography.

Materials and Methods

A part of study, which has been still under way, as a part of the project, was carried out at the University Clinic of Gynecology and Obstetrics "Narodni front", Belgrade, at the Institute for Hyperbaric Medicine in Banjica and the Institute of Physiology, Faculty of Medicine, Belgrade. A total of 32 women were analyzed, aged from 24 to 34 years, who presented to the institution with the problem of infertility of unknown etiology. Before the initiation of therapy, all patients underwent complete diagnostic procedures and analyses that could clarify the primary problem. Moreover, the male infertility as the cause was ruled out. The study included the patients who had no earlier history of assisted reproductive techniques (ART), and who used only moderate stimulants of ovulation during the natural intercourse. The patients agreed to recommended therapy in hyperbaric chamber on voluntary basis. The patients were treated in multi-placed HAUX chamber at pressure of 2,3 ATA during 70 minutes, 7 days consecutively beginning with day 5^{th} of menstrual cycle . The evaluation of effects of hyperbaric oxygen therapy was carried out by transvaginal color Doppler sonography which was continuously used starting from 8^{th} day of menstrual cycle. until the ovulation in the cycle when the therapy was applied, one month before and one month after the therapy. Ten patients who underwent such therapy at pressure of 1 ATA were treated and analyzed in the same way. London Gynecology and Fertility Center Criteria were used as a standard for evaluation of quality of endometrium.Criteria : Grade A – optimal,Grade B – moderate, Grade – C bad ,sonographics findings (1). The uterine

artery flow was monitored and pulse index (Pi), resistance index (Ri) and systolic/diastolic ratio were determined, as well as the mapping of capillary vascular bed of subendometrium in the aforementioned cycles.v

Results and Discussion

As seen in Table 1, the desired sonograph of endometrium could not be visualized even at the time of ovulation, in the majority of patients (91,2%, Grades C and around 8% Grade B). Such findings of transvaginal sonography definitely correlated with low probability of future pregnancy. Observing the thickness of endometrium as an isolated parameter in the cycle prior to therapy, poor prognostic result was also obtained, i.e. 7,7 mm ± 1,6. The analysis of findings of folliculometry in the cycle when hyperbaric oxygen therapy at 2,3 ATA was applied, as illustrated in Table 2, indicates an excellent response of endometrium to hyperoxia and significant result in view of achieving an optimal quality in preovulatory and ovulatory period in 82,9% to 84,8 % of patients. Moreover, observing separately the thickness of endometrium at the time of ovulation – 11,1 mm ± 2,6 – we may say we have a good prognostic factor. Desirable quality of endometrium was good and significantly better in the cycle when HBO therapy had been applied ($p<0,001$). In addition, endometrial waves were noted only in 2% of patients, while early optimal form of endometrium, which was not in correlation with the size of follicles, was noted in 1,9% of patients. As expected, the patients who, upon suggestion of EUBS, were treated as the controls and received hyperbaric oxygen therapy at 1 ATA, had no increase of thickness or desired sonographic appearance of endometrium at the time of ovulation, $p>0,05$. The analysis of Doppler flowmetry of the left and right uterine arteries indicated that the uterine blood vessel resistance was slightly higher than expected in the cycle before therapy, Pi = 3,1; Ri = 0,81; and S/D = 3,7. During the application of therapy, the resistance became lower but it was not significant, and the mean value was Pi <3; Ri = 0,85; S/D =3,5. Power color-Doppler mapping of subendometrial blood vessels is particularly significant for evaluation of adequate vascularization of endometrium. In the cycles where sonographic appearance of endometrium failed to achieve desirable quality – i.e. Grade A, before therapy and during therapy at 1 ATA, the mapping of subendometrium could visualize almost complete absence of capillary network or presence of separate capillaries with marked resistance Ri = 0,65 , what led us to conclude that neoangiogenetic process was missing or was not adequate. In the cycles covered by hyperbaric oxygen therapy at 2,3 ATA, the mapping showed the intensive capillary network of endometrium with low resistance Ri < 0 ,45, as the result of intensive neoangiogenetic processes. The analysis of the obtained results confirms that inadequate thickness and appearance of endometrium, i.e. its poor quality, correlates to a high percentage with poor endometrial receptivity. Endometrial receptivity, other than sonographic characteristics, is characterized by vascularization of the uterus, and particularly of the endometrium (1,2,3). In so far such conditions are fulfilled in spontaneous cycle without any therapy or in cycle during therapy, and the patient has well-timed sexual intercourse with her partner whose findings are normal, the pregnancy is guaranteed to a high percentage. The stimulation of cell division of basal endometrium is achieved under elevated pressure, by increasing the volume of dissolved oxygen in circulation, i.e. hyperoxia, and maximal hemoglobin saturation in arterial and venous blood flow. The action of hormones and optimal vascularization and oxygenation, in proliferative phase of cycle, brings about the dynamic changes in view of increased thickness of endometrium

Days of menstrual cycles	9	10	11	12	13	14	15
Grade C (%)	96,5	97,3	92,4	93,1	90,4	91,2	91,2
Grade B (%)	3,5	2,7	7,6	6,9	7,2	7,3	8,8
Grade A (%)	0,0	0,0	0,0	0,0	2,4	1,5	0,0

TABLE 1. Endometrial quality before HBO therapy

Days of menstrual cycles	9	10	11	12	13	14	15
Grade C (%)	52,8	55,9	47,1	22,2	25,9	17,1	16,2
Grade B (%)	47,2	42,2	60,3	62,4	47,8	36,5	38,5
Grade A (%)	0,0	1,9	2,6	15,4	26,3	46,4	45,3

TABLE 2. Endometrial quality during the HBO on 2.3 ATA

and its so-called maturation and preparation for probable future implantation of fertilized blastocyst (4,5,6,7). In patients undergoing therapy by hyperoxia, because of physiological characteristics of oxygen which is used as a drug according to strictly defined protocol, the therapy is initiated from the follicular phase of a cycle, but the exact day is defined individually depending upon subjective characteristics of the patient herself. The therapy should begin not later than day 5 of the menstrual cycle during regular cycle, and the first three therapies should proceed one after another, and, if possible, all therapies (5 at minimum) should be carried out successively. We insist on continual therapy in phase I of a cycle and in preovulatory period because we think that it is necessary to maintain high level of dissolved oxygen as well as to provide support for neoangiogenetic processes in subendometrium (8,9,10,11). Moreover, we believe that adequate oxygenation of the uterus *in toto* is important for prevention of smooth uterine musculature contractions and development of endometrial waves which may interfere with the process of implantation and nidation. In comparison with medicaments having been used until these days for improvement of vascularization, the application of hyperbaric oxygen therapy is advantageous over drugs in any aspect. Essentially, it is the question of healthy population having problems of infertility, not expecting the problem of blood vessels. Experience has taught us that the problem of microcirculation at the uterine level is frequent cause of nonpregnancy. Maybe the problem related to endothelium or microcoagulopathy affects the infertility. The action of drugs, which is dependent upon the endothelium and quality of capillary system, is surpassed by employment of this method. The oxygen used under higher pressure – oxygen as a drug, may have an extraordinary significance for better outcome of pregnancy implantation.

Conclusion

Endometrial receptivity is a significant factor among a series of conditions determining the future pregnancy. It is conditioned by regular anatomy of the uterus and its cavity, optimal hormonal status as well as by optimal vascularization and oxygenation. The application of hyperbaric oxygen provides, in so far the first two factors were accomplished, an optimal quality of endometrium and adequate subendometrial vascularization and oxygenation. If endometrial receptivity is conditioned by adequate vascularization and oxygenation, then hyperbaric oxygen therapy is the treatment of choice.

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