CLINICAL ASSISTED REPRODUCTION

Haemodynamic Evaluation of Tubal and Male Factors of Infertility in Natural and Ovarian Stimulation Cycles

GHAZALA SIKANDAR BASIR,^{1,4} TINA POY WING LAM,² WAI-SUM O,³ and PAK CHUNG HO¹

Submitted: August 14, 2000

Accepted: October 13, 2000

Purpose: To determine the haemodynamic parameters in women with tubal and male factors of infertility and to investigate the effect of ovarian stimulation on the blood flow indices of the uterine and ovarian arteries.

Methods: Prospective evaluation of the pulsatility index (PI) and resistance index (RI) of the uterine and ovarian arteries in the tubal and male factors of infertility was done. Comparisons were made between the natural and ovarian stimulation cycles.

Results: In natural cycles, uterine PI was 3.55 ± 1.39 and RI was 0.95 ± 0.05 in tubal infertility. These were significantly lower (uterine PI = 4.13 ± 0.08 ; uterine RI = 0.99 ± 0.06) than the corresponding indices in patients with male factor infertility. After ovarian stimulation in tubal factor, uterine PI and RI were 2.62 ± 0.73 and 0.88 ± 0.08 and were similar (PI = 2.55 ± 0.62 , RI = 0.87 ± 0.06) to male factor infertility.

Conclusions: The data points to measurable differences in the uterine PI and RI between the tubal infertility and male infertility in the natural cycles. These differences were abolished after ovarian stimulation.

KEY WORDS: Assisted reproduction; Doppler haemodynamics; natural/ovarian stimulation cycles.

INTRODUCTION

In vitro fertilization and embryo transfer has been used to treat couples with a variety of infertility disorders. In clinical practice, majority of couples seeking assisted reproduction therapy are infertile for reasons of tubal and male factors. The success of treating fertility disorders depends on multiple factors. Apart from embryo quality, uterine conditions at the time of embryo transfer (ET) are of vital importance. Transvaginal color Doppler is a useful tool in the noninvasive evaluation of the uterine blood flow. Previous research by Goswamy (1) has shown that uterine blood flow is an important factor contributing to uterine receptivity. In literature, considerable heterogeneous studies exist on conception versus nonconception cycles (2,3) and spontaneous versus stimulation cycles (3,4) with respect to timing of Doppler ultrasound evaluation (5,6), ovarian stimulation protocols (7), and the probe and ultrasound machines used. However, current literature lacks studies on other confounding factors that might influence Doppler results. Could different factors of infertility present with different haemodynamic characteristics? The purpose of this study was to characterize utero-ovarian blood flow parameters associated with the tubal and male factors of infertility. We compared the uterine and ovarian arterial impedance indices measured as the pulsatility index (PI) and the resistance index (RI) in paired natural and ovarian stimulation cycles of 35 women with male infertility and tubal infertility to study (a) whether these indices were different in women with different causes of

¹ Department of Obstetrics and Gynecology, Queen Mary Hospital, The University of Hong Kong, Pokfulam, Hong Kong.

² Department of Diagnostic Radiology, Queen Mary Hospital, The University of Hong Kong, Pokfulam, Hong Kong.

³ Department of Anatomy Queen Mary Hospital, The University of Hong Kong, Pokfulam, Hong Kong.

⁴ To whom all correspondence should be addressed at Department of Obstetrics and Gynaecology, 6/F Professorial Block, Queen Mary Hospital, Pokfulam, Hong Kong. e-mail: gbasir@hotmail.com.

infertility and (b) the effect of ovarian stimulation on these indices.

MATERIALS AND METHODS

Seventy cycles of 35 women undergoing assisted reproduction treatment were studied. The indications for in vitro fertilization (IVF) treatment included tubal and male factors of infertility. The age range of the study population was 27–39 years (mean 33 ± 2.7 SD). Ethical approval for the study was obtained from the Ethics Committee of the Faculty of Medicine, The University of Hong Kong.

We compared the Doppler haemodynamic parameters of the uterine and ovarian arteries in paired cycles (natural and ovarian stimulation) of women undergoing assisted reproduction treatment. Twenty-two women were first evaluated in ovarian stimulation cycles and subsequently in natural cycles. All other women were first seen in natural cycles before the initiation of stimulation. There was an interval of at least 3 months between the natural and ovarian stimulation cycles. Women were evaluated in natural cycles when they underwent replacement of frozen thawed embryos. They had not received any steroid hormones or used a contraceptive device for at least 2 months prior to entering the study. The day of the Luteinizing hormone (LH) surge (designated as LH = 0) was determined by daily assays of serum oestradiol (E_2) and LH, starting 18 days before the next menstruation until the serum LH was found to be more than double the mean of the preceding values. In natural cycles, Doppler examination was performed when the women underwent replacement of frozen thawed embryos on day LH + 3.

Women in stimulation cycles were stimulated with the departmental standard protocol of ovarian stimulation (8) for in vitro fertilization and embryo transfer. These women underwent monitoring by assay of serum E_2 levels and serial transvaginal ultrasonographic scans during the follicular phase for the assessment of follicular growth. Human chorionic gonadotrophin (hCG, Pregnyl, Organon, The Netherlands) 10,000 IU was given when the mean diameter of the leading follicle was >18 mm and there were at least three follicles with a mean diameter of 16 mm or more. The day of hCG administration (day 0) was used as the reference for determination of the cycle day. As in natural cycles, Doppler evaluation was done on the day of embryo transfer.

All women recruited in the study were scanned transvaginally with color blood flow imaging approx-

imately an hour before embryo transfer. Doppler sonographic measurements were carried out using a Doppler US (Acumen XP128/10; Acuson Mountain View, CA, USA) machine equipped with a transvaginal transducer of 7 MHz. All scans were done by one operator experienced in the procedure. The women were studied between 8 and 9 am to exclude the effects of circadian rhythmicity on blood flow (5). Flow velocity waveforms were obtained from the ascending main branches of the uterine artery on the right and left side of the cervix in a longitudinal plane before it enters the uterus. Ovarian signals were obtained from within the ovarian parenchyma. The ovarian vessels studied were those detected in close proximity to the follicles or the corpus luteum. Because no significant differences were obtained in the Doppler velocimetry, indices between the left and right side of the uterine and intraovarian arteries, the data were combined and the average value of both arteries was used.

Statistical Analysis was performed using statistical package for Social Science (SPSS for Windows package release 5.0; SPSS Inc., Chicago, IL). The nonparametric Mann–Whitney U-test was used in the evaluation of the skewed data. All data are expressed as mean $\pm$ SD. A p value of <.05 was considered significant. Wilcoxon matched pairs signed rank sum test was used to estimate within-subject differences in natural and ovarian stimulation cycles.

RESULTS

In our center, the two most common factors of infertility in women undergoing assisted reproduction treatment were the tubal factor and the male related causes of infertility. In the present study, we compared cycles of tubal infertility ($n = 30$) with cycles of male factor infertility ($n = 40$). All male factor infertility were women with no significant gynecological abnormality on clinical evaluation.

The results of uterine artery Doppler velocimetry are shown in Table I. In natural cycles, the uterine artery PI and RI of women with tubal infertility were significantly lower than those of women with the male factor infertility. However, the difference was abolished after ovarian stimulation. Furthermore, there was no significant difference in the ovarian artery impedance values between the two groups of women in both natural and ovarian stimulation cycles.

When natural cycles were compared with ovarian stimulation cycles, the uterine and ovarian artery

Table I. Comparison of Doppler Velocimetry Indices in Women with Tubal and Male Factors of Infertility in Natural and Ovarian Stimulation Cycles

	Tubal infertility (<i>n</i> = 15) ^b	Male factor infertility (<i>n</i> = 20) ^b	<i>p</i> -Value ^a
<i>Natural cycles</i>			
Uterine PI	3.55 ± 1.39	4.13 ± 0.80	<.05
Uterine RI	0.95 ± 0.05	0.99 ± 0.06	<.05
Ovarian PI	1.00 ± 0.51	1.15 ± 0.81	<i>ns</i>
Ovarian RI	0.55 ± 0.24	0.61 ± 0.14	<i>ns</i>
<i>Ovarian stimulation cycles</i>			
Uterine PI	2.62 ± 0.73	2.55 ± 0.62	<i>ns</i>
Uterine RI	0.88 ± 0.08	0.87 ± 0.06	<i>ns</i>
Ovarian PI	0.85 ± 0.27	0.95 ± 0.67	<i>ns</i>
Ovarian RI	0.54 ± 0.11	0.56 ± 0.12	<i>ns</i>

^aMann-Whitney U-test.^bAll values are mean ± SD.

impedance values in ovarian stimulation cycles were all significantly lower than the corresponding values in natural cycles in both groups of women. There was no significant difference in the number of oocytes retrieved. Similarly, serum oestradiol concentration, endometrial thickness, and endometrial pattern on the day of hCG administration showed no statistically significant difference between the women with tubal and male factor infertility.

DISCUSSION

It has been reported in previous studies that uterine artery impedance correlates inversely with uterine receptivity for embryo implantation in IVF (9,10). In this study, we demonstrated a difference in the impedance to uterine blood flow in patients with different causes of infertility. When the uterine PI and RI of tubal factor were compared with those of presumably normal women (infertility due to male factor and no significant gynecological abnormality), the uterine PI and RI values in women with tubal infertility were significantly lower than those of normal women. A possible explanation for the decrease in PI and RI values seen in patients with tubal infertility might be that the scarring and inflammation associated with tubal blockage may result in increased uterine perfusion. This is in contrast to the study by Steer *et al.* (11), who found an increased PI value in women with tubal infertility when compared with that of normal women. However, in a subsequent study (12) the investigators found that women who had tubal occlusion exhibited greater endometrial perfusion than the controls.

It is believed that tubal blockage leads to altered endometrial perfusion. The suggested reason is that the

vascular circuit comprising the uterine and ovarian arteries and the corresponding veins allow counter-current exchange of material flowing through them. In addition, there is also the possibility of utero-tubal and tubo-ovarian vascular and perivascular anastomosis. This vascular pattern was reviewed by Verco (13,14), and it was found that altered vascular arrangement might also alter concentration of bioactive substances (e.g., ovarian steroids and prostaglandins) in such a way that uterine vessels are exposed to higher local levels than the circulating peripheral levels. The factors that resulted in tubal blockage would not only affect the tube but also disrupt the vascular communications along the tube (15,16). The more disruptive the tubal blockage, the more intensely vascular anastomosis might be established as a result of the healing process. Furthermore, the counter-current exchange of biological factors may be disturbed either because these factors did not enter the venous drainage or because the arterial supply is unable to deliver these factors to their target organs (12).

However, after ovarian stimulation the blood flow of the uterus and the ovaries was increased in both the tubal and male factor infertility, and the differences in perfusion disappeared. Therefore, in stimulation cycles the blood perfusion of the uterine and ovarian arteries was similar in both groups. The ovarian stimulation probably lowered the peripheral resistance to blood flow in both groups. It may be that the scarring and inflammation associated with tubal blockage already has low resistance to flow in natural cycles. Thus, even ovarian stimulation may not increase blood perfusion any further than would normally occur in response to endocrine changes.

To our knowledge, this is the first longitudinal study to compare the haemodynamics of tubal and male factors of infertility in natural and ovarian stimulation

cycles of the same women. Although the number of subjects in the study was small, the achievement of a statistical significance suggests a pronounced effect. Further studies are undoubtedly needed to substantiate these findings and to study the effect of these changes on the likelihood of embryo implantation.

REFERENCES

1. Goswamy RK, Steptoe PC: Doppler ultrasound studies of the uterine artery in spontaneous ovarian cycles. *Hum Reprod* 1988;3:721-726
2. Bassil S, Magritte JP, Roth J, Nisolle M, Donnez J, Gordts S: Uterine vascularity during stimulation and its correlation with implantation in in vitro fertilization. *Hum Reprod* 1995;10:1497-1501
3. Tekay A, Martikainen H, Jouppila P: Comparison of uterine blood flow characteristics between spontaneous and stimulated cycles before embryo transfer. *Hum Reprod* 1996;11:364-368
4. Coulam CB, Bustillo M, Soenksen DM, Britten S: Ultrasonographic predictors of implantation after assisted reproduction. *Fertil Steril* 1994;62:1004-1010
5. Zaidi J, Jurkovic D, Campbell S, Okokon E, Tan SL: Circadian variation in uterine artery blood flow indices during the follicular phase of the menstrual cycle. *Ultrasound Obstet Gynecol* 1995;5:406-410
6. Zaidi J, Jurkovic D, Campbell S, Pittrof R, McGregor A, Tan SL: Description of circadian rhythm in uterine artery blood flow during the peri-ovulatory period. *Hum Reprod* 1995;10:1642-1646
7. Favre R, Bettahar K, Granger G: Predictive value of transvaginal uterine Doppler assessment in an in vitro fertilization program. *Ultrasound Obstet Gynecol* 1993;3:350-353
8. Yeung SB, Lau YL, So WK, Ng HY, Chan TH, Ho PC: Assisted reproduction technology in Queen Mary Hospital: Ten years' experience. *Chin Med J Engl* 1997;110:444-447
9. Steer CV, Campbell S, Tan SL, Crayford T, Mill C, Mason BA, Collins WP: The use of transvaginal color flow imaging after in vitro fertilization to identify optimum uterine conditions before embryo transfer. *Fertil Steril* 1992;57:372-376
10. Cacciatore B, Simberg N, Fusaro P, Tiitinen A: Transvaginal Doppler study of uterine artery blood flow in in vitro fertilization-embryo transfer cycles. *Fertil Steril* 1996;66:130-134
11. Steer CV, Tan SL, Mason BA, Campbell S: Midluteal-phase vaginal color Doppler assessment of uterine artery impedance in a subfertile population. *Fertil Steril* 1994;61:53-58
12. Verco CJ, Carati CJ, Gannon BJ: Human endometrial perfusion after tubal occlusion. *Hum Reprod* 1998;13:445-449
13. Verco CJ: Mammalian oviduct vasculature and blood flow. *Archiv Biol Med Exp* 1991;24:229-239
14. Verco CJ: Fallopian tube anatomy, microanatomy, microcirculation and counter current exchange. In *The Fallopian Tube. Clinical & Surgical Aspects* in JG Grudzinskas, MG Chapman, T Chard, O Djahanbakhch (eds), London, Springer-Verlag, 1993, pp 3-15
15. Diamond E: Microsurgical reconstruction of the uterine tube in sterilized patients. *Fertil Steril* 1977;28:1203-1210
16. Eddy CA, Pauerstein CJ: Anatomy and physiology of the fallopian tube. *Clin Obstet Gynecol* 1980;23:1177-1193