

CHANGE DYNAMICS OF DOMINANT AND NONDOMINANT UTERINE ARTERY AND OVARIAN ARTERY IN STIMULATED CYCLES IN INFERTILE WOMEN

Vekoslav Lilić, Aleksandra Tubić-Pavlović, Goran Lilić

Clinic of Gynecology and Obstetrics, Clinical Center Niš

Summary. *Our aim was to investigate hemodynamic changes in the uterine artery, its branches and in ovarian artery, and to establish their significance in infertility investigation. In the prospective study in the period January-December 2005, 90 infertile women in their generative age were monitored by color Doppler method in the same number of cycles. Hemodynamic changes in the uterine and ovarian artery at the dominant and non dominant side were monitored on certain cycle days (XI, XIV and XX cycle days) according to the following parameters: Pi (pulsatile index), Ri (resistance index) and Vmax (maximal flow velocity). The quality of endometrial receptivity was determined based on the EPDA (Endometrial Power Doppler Area). With Mann Whitney U test it was established that there is a significant difference in the obtained hemodynamic parameters among the dominant and non dominant ovarian artery on day XI of the cycle (Pi-3.17, Ri-2.90 and 4.51, Vmax-2.81) in all three groups of the examinees, and on day XIV, Vmax was markedly higher in pregnant women (Vmax-2.49) and in the group of women with spontaneous cycles (Vmax-2.89). Statistically significant difference among the dominant and non dominant uterine artery was found only in pregnant women on XX cycle day (Pi-2.05, Ri-2.49, Vmax 2.89) for each of those three parameters. The frequency of ovulation was higher on the right side (70%) compared to the left side (30%) of blood vessels. The measurement of hemodynamic changes in uterine and ovarian arteries can be of use to the doctor in infertility studies, in the correction of ovulation inducers and in pregnancy prediction.*

Key words: *Infertility, color Doppler, hemodynamic parameters*

Introduction

Ovarian and uterine ultrasonography is one of the standard methods of monitoring of ovulation induction. Its value is based on the ability to characterize the number, size, growth, location and disappearance of follicles, as well as to detect the changes in the uterus, endometrium, its depth and texture. More recently, together with standard monitoring, the flow measurements through the ovarian and uterine blood vessels are used, aiming at provision of the best possible conditions for a successful cycle outcome, especially in infertile women. The control of the pulsatile index (Pi), resistance index (Ri) and maximal flow velocity (Vmax) established the difference among the dominant and non dominant side in both uterine and ovarian artery. The dominant side of an artery is the side with the leading follicle, i.e. with the *corpus luteum* in the second phase of the cycle. In primates, ovulation depends on the constant changes occurring with similar frequency in the left and right ovaries. Some studies demonstrate that ovulation is more frequent in the right ovary (70%) compared to the left (30%). Out of 10 pregnancies, in 7 the ovulation was right-sided. Our aim was thus to better determine hemodynamic changes in ovarian and uterine artery of the dominant and non dominant side, the statistical signifi-

cance and possible importance of the side of ovulation for cycle success. Quality of the endometrium was also studied in all three groups monitoring the EPDA in the second phase of the cycle (fields inside endometrium to endometrial-myometrial border within which power Doppler signals occur). Since cost-benefit is an important issue today, it is sufficient to perform only ultrasound folliculometry, and determination of hormones in the blood is not rational any more, except for basal hormonal levels. It is believed that adequately performed ultrasound folliculometry correlates well with the blood levels of estradiol, so this analysis is no longer needed (1). Many papers (2,3,4) demonstrate that at least 6 mm of endometrial depth is necessary for a cycle to be successful, but again there are cases in the literature in which the depth of 4 mm was measured in successful ART proceedings. However, endometrial depth is not the only factor of importance for a proceeding to be successful. Today, a number of parameters are thought to be involved, such as cytokines, LIF (leukemia inhibitory factor), CSF-1 (colony stimulating factor), various integrins, MUCI, glycodelin, the role of which in implantation is not completely elucidated (5).

Material and Methods

Our prospective study in the period January-December 2005 at the Clinic of Gynecology and Obstetrics in Nis enrolled 90 infertile women in their generative age, divided into 3 groups with the same number of cycles monitored. The first group comprised 70 women with stimulated cycles, out of which 10 resulted in pregnancy (the second group) and 20 women with spontaneous, natural cycles comprised the third group. The patients were aged from 25 to 36 years. Before the enrollment into the study they were investigated according to the commonly used protocol at the Dept. for Infertility. The inclusion criteria were:

- Idiopathic infertility
- Dysovulatory cycles
- Partner with hypospermia

Most frequently used for ovulation induction was clomiphene citrate, metformin tablets in combination with clomiphene citrate as well as gonadotropins.

All measurements on uterine and ovarian arteries were performed on color Doppler ultrasound Accuson 128XP by vaginal approach, in the morning hours in order to avoid circadian rhythm influence, with vaginal 7MHz probe. The measurements were performed on XI, XIV and XX cycle days. The obtained parameters: pulsatile index (Pi), resistance index (Ri) and maximal flow velocity (Vmax) were entered into the table and statistically processed by Mann Whitney U test.

Results and Discussion

Uterine and ovarian arteries were divided into dominant (where the leading follicle is, or the *corpus luteum* in the second phase) and non dominant side.

Table 1. demonstrates the tested difference among the hemodynamic parameters of dominant and non dominant ovarian artery by Mann Whitney U test. The highest, statistically significant differences are seen on day XI between dominant and non dominant ovarian artery, especially in stimulated cycles (Wmax-2.81, Pi-2.90 i Pi-3.17, Ri-4.51), and did not result in pregnancy.

Table 1. The tested difference among the hemodynamic parameters in dominant and nondominant ovarian artery

Examined parameters	Group	Z value		
		XI day	XIV day	XX day
Pulsatile index (Pi)	I	3.17**	0.67	1.83
	II	1.28	0.21	2.24*
	III	2.90**	0.48	1.45
Resistance index (RI)	I	4.51***	0.64	1.87
	II	0.81	0.47	1.68
	III	1.21	1.47	2.74**
Maximal flow velocity (V max.)	I	2.81**	0.41	0.41
	II	0.10	2.78**	0.74
	III	1.29	2.64**	0.49

Level statistical significance (Mann Whitney U Test):
* p<0.05 ** p<0.01 *** p<0.001

Vmax is markedly higher especially on day XIV (Vmax-2.64 i Vmax-2.78) and then on day XX of the cycle in pregnant women and in spontaneous cycles (Pi-2.24, Ri-2.74) which did not result in pregnancy. It is obvious that the ovarian artery on the leading follicle side has a different trend of change of hemodynamic parameters, especially in cycles resulting in pregnancy. The flow velocity in ovarian artery doubled from XI-XIV days in cycles resulting in pregnancy, from 0.12 m/sec to 0.23 m/sec, and in spontaneous cycles from 0.12 m/sec to 0.21 m/sec.

Table 2. demonstrates the tested difference among the hemodynamic parameters, by cycle days, of dominant and non dominant uterine artery also by Mann Whitney U test. Hemodynamic changes of uterine artery are, as it seems, also influenced by the side of ovulation, since there too is a significant difference between the dominant and non dominant side, especially on XX day in cycles resulting in pregnancy (Pi-2.05, Ri-2.49, Vmax-2.89). The difference in Pi of ovarian and uterine artery on the ovulation side, in contrast to the contralateral side, demonstrates that uterine artery is involved in supplying with blood and in the changes of vascular impedance. The changes in hemodynamic parameters in both uterine and ovarian artery are more similar between the spontaneous cycles and cycles resulting in pregnancy. This demonstrates that for the implantation and cycle success the value of hemodynamic parameters was certainly important, ie. that it is necessary to achieve the milieu as close to natural as possible in order for a cycle to result in pregnancy (6).

Table 2. The tested difference among the hemodynamic parameters in dominant and nondominant uterine artery

Examined parameters	Group	Z value		
		XI day	XIV day	XX day
Pulsatile index (Pi)	I	1.74	1.57	1.75
	II	0.07	0.59	0.40
	III	0.81	0.97	2.05*
Resistance index (Ri)	I	1.82	0.70	1.86
	II	1.14	1.35	0.54
	III	0.33	1.62	2.49*
Maximal flow velocity (V max.)	I	1.41	1.49	0.83
	II	0.94	0.05	0.71
	III	0.69	0.41	2.89**

Level statistical significance (Mann Whitney U Test):
* p<0.05 ** p<0.01 *** p<0.001

The opinions differ as to the level of influence of these changes regarding the indication of receptivity of an endometrium, since subendometrial flow is more important for implantation (demonstrated by the papers of a number of authors) (7,8). The values of hemodynamic parameters of uterine artery are not applicable to spiral arteries since the characteristics of blood vessels change in their branching through the myometrium and endometrium (9).

Table 3. Resistance index (Ri) values in dominant uterine artery

Days of cyclus	Stimulated cycles without pregnancy		Spontaneous cycles without pregnancy		Stimulated cycles with pregnancy	
	$\bar{X} \pm SD$	Medial	$\bar{X} \pm SD$	Medial	$\bar{X} \pm SD$	Medial
XI	0.74 ± 0.11	0.76	0.82 ± 0.08	0.82	0.75 ± 0.04	0.75
XIV	0.87 ± 0.44	0.80	0.74 ± 0.07	0.75	0.70 ± 0.09	0.67
XX	0.80 ± 0.04	0.81	0.70 ± 0.08	0.70	0.64 ± 0.04	0.64

Mann Whitney U Test

Table 4. Resistance index (Ri) values in nondominant uterine artery

Cycle days	Stimulated cycles without pregnancy		Spontaneous cycles without pregnancy		Stimulated cycles with pregnancy	
	$\bar{X} \pm SD$	Medial	$\bar{X} \pm SD$	Medial	$\bar{X} \pm SD$	Medial
XI	0.80 ± 0.07	0.78	0.90 ± 0.27	0.88	0.76 ± 0.09	0.77
XIV	0.76 ± 0.19	0.82	0.77 ± 0.07	0.78	0.74 ± 0.26	0.77
XX	0.79 ± 0.15	0.79	0.69 ± 0.16	0.72	0.75 ± 0.07	0.75

Mann Whitney U Test

In addition to the parameter measurements, it was interesting to see whether the implantation success depends on the ovulation side. The ratio of right-sided to left-sided ovulations is 70% vs 30%, which agrees with other authors' papers (10). Out of 10 registered pregnancies, in 7 the ovulation was right-sided and in 3 left-sided. Clinical significance of the ovulation side in a normal menstrual cycle is not clear, but in 2000 Fukuda et al. (11) demonstrated that right-sided ovulation favours the pregnancy compared to left-sided ovulation. The explanation for this could be that changes in vascularization, especially on the left side, have slower venous drainage and that in the ovary in question some mediators are accumulated with negative effects on the ovulation preparation and implantation. The results of various papers are contradictory and our sample was too small to allow assessment of statistical significance (11). Table 3 demonstrates the values of resistance index (Ri) of dominant uterine artery, and Table 4 the values of Ri of nondominant uterine artery. It can be seen that Ri values in uterine artery on both dominant and nondominant side are below 0.80 in the middle of luteal phase, with strong diastolic component, especially in cycles resulting in pregnancy, which agrees with other authors' reports (11,12). The measurements demonstrated that the patients with pulsatile index (Pi) in the range 2.00-2.99 had maximal chances for pregnancy. Thus measured Pi highly correlates with estradiol level and with endometrium which would be biopsied at this point for histology studies (12,13).

Color Doppler measurements demonstrate that corpus luteum undergoes the process of neoangiogenesis

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via the changes of the vascular flow during its development, and undergoes regressive changes during its origination. The typical sign is the "ring of fire" – very intense vascular changes in the wall of this circular formation. This space starts to grow from the midluteal phase and is being reduced during menstruation (13).

As for the subendometrial level, the presence and absence of EPDA (endometrial power Doppler area) is also interesting; it is defined as the space of up to 5 mm from the myometrial/endometrial junction. This space is important since if there is a higher number of signals, more than 5 on power Doppler, this could mean good endometrial receptivity. In our study there was a large number of cycles with registered EPDA – those were especially the ones resulting in pregnancy.

Conclusion

Various parameters are investigated within the studies of cycle characteristics in infertile women, such as the thickness of endometrium, Doppler measurements of uterine and ovarian arteries and subendometrial flow. In this prospective study measuring hemodynamic parameters with color Doppler, it was established that the pulsatile index (Pi) values ranging from 2.00 to 2.99 and resistance index (Ri) midcycle values in uterine artery below 0.80 have prognostic significance regarding pregnancy predictions.

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DINAMIKA PROMENA DOMINANTNE I NEDOMINANTNE ARTERIJE UTERINE I ARTERIJE OVARIKE U STIMULISANIM CIKLUSIMA INFERTILNIH ŽENA

Vekoslav Lilić, Aleksandra Tubić-Pavlović, Goran Lilić

Klinika za ginekologiju i akušerstvo, Klinički centar Niš

Kratka sadržaj: Cilj rada je bio da se ispituju hemodinamske promene u arteriji uterini, njenim granama, kao i arteriji ovarici i utvrdi njihov značaj u ispitivanju infertiliteta. U prospektivnoj studiji u periodu januar - decembar 2005. godine, metodom color doplera, praćeno je 90 infertilnih žena, u isto toliko ciklusa, u generativnoj dobi. Bile su podeljene u tri grupe. Praćene su hemodinamske promene arterije uterine i arterije ovarike dominantne i nedominantne strane po danima ciklusa (XI, XIV i XX dan ciklusa), parametrima: Pi (pulsatilni indeks), Ri (indeks otpora) i V max. (maksimalna brzina protoka). Kvalitet receptivnosti endomerijuma određivan je na osnovu pojave EPDA (Endometrial Power Area). Mann Whitney U Testom je utvrđeno da postoji stastički značajna razlika u dobijenim vrednostima ispitivanih hemodinamskih parametara između dominantne i nedominantne arterije ovarike XI dana ciklusa (Pi-3,17, Ri-2,90 i 4,51, Vmax-2,81) kod sve tri grupe pacijentkinja, da bi već XIV dana V max bila značajno viša u grupi gravidnih žena (Vmax-2,49) ali i u grupi žena sa spontananim ciklusima (Vmax-2,89). Stistički značajna razlika između dominantne i nedominantne arterije uterine postoji samo kod grupe gravidnih žena XX dana ciklusa (Pi-2,05, Ri-2,49, Vmax-2,89) za sva tri parametra. Učestalost ovulacija je veća desno (70%) u odnosu na levu stranu (30%) krvnih sudova. Merenje hemodinamskih promena u arteriji uterini i arteriji ovarici može koristiti lekaru u ispitivanju infertiliteta, u korekciji induktora ovulacije, kao i u predikciji trudnoće.

Ključne reči: infertilitet, color Doppler, hemodinamski parametri