FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol.15, No 1, 2008, pp. 24 - 27 UC 613.888:[618.14:612.15]

COLOR DOPPLER MEASUREMENTS OF UTERINE ARCUATE BLOOD FLOW IN PATIENTS ON ORAL CONTRACEPTION

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Summary. *The aim of this study is to determine if there are differences in vascular impedance of uterine arcuate arteries between spontaneous ovulatory cycles and cycles in which monophasic combination containing 0,03 mg ethynilestradiol and 2 mg dienogest was administered for contraception. Twenty two patients were included: 11 patients on oral contraceptives, 11 patients with spontaneous ovulatory cycles. Ultrasound examinations, using 7 MHz endovaginal transducer with color Doppler imaging and pulsed spectral analysis, were performed after 15 days of therapy in patients on oral contraceptives and in periovulatory period in the second group. The mean ages were similar – 23 ± 5.65 years in the group on oral contraceptive and 28 ± 5.09 years in the group with spontaneous ovulatory cycles (p = 0.20465). Pulsatily index was lower in the group with spontaneous ovulatory cycles (0.98±0.255 vs. 2.38 ± 0.127, p = 0.00038). Resistance index was lower in the group with spontaneous ovulatory cycles (0.59 ± 0,054 vs. 0,795 ± 0,007, p = 0,000145), also as S/D ratio (2.59 ± 0.247 vs. 4,9 ± 0.14, p = 0.000182). There were no significant differences in peak systolic velocity between group on oral contraception and spontaneous ovulatory cycles (17 ± 9.89 cm/sec. vs. 8.5 ± 3.33 cm/sec, p = 0.21728). Vascular impedance of uterine arcuate arteries was higher in patients on oral contraception containing 0.03 mg ethynilestradiol and 2 mg dienogest than in patients with spontaneous ovulatory cycles.*

Key words: *Color doppler, oral contraception, dienogest*

Introduction

In few past years, color Doppler (CD) and color Doppler energy (CDE) imaging and measurements of intrauterine and intraovarian blood flow became very popular among many investigators in reproductive endocrinology. There are many articles about significance of these measurements in spontaneous ovulatory and anovulatory cycles, in controled ovarian hyperstimulation for in vitro fertilization, but only a few articles regarding CD and CDE energy imaging in cycles with oral contraception (OC). The aim of this study is to determine if there are differencies in vascular impendance of uterine arcuate arteries between spontaneous ovulatory cycles and cycles in which monophasic combination containing 0.03 mg ethynilestradiol and 2 mg dienogest was administered for contraception

Method

Twenty two patients were included: eleven on oral contraceptive (monophasic combination containing 0.03 mg ethynilestradiol and 2 mg dienogest) and eleven with spontaneous ovulatory cycles. Color Doppler measurements were performed after 15 days of therapy in patients on OC and in periovulatory period in the second group. The ultrasound examinations were performed on color Doppler ultrasound system Acuson 128 XP 10i (Mountain View, US), with 7 MHz endovaginal transducer. All examinations have been done between 8:00 and 10:00 a.m. to avoid circadian variation in blood flow. CD imaging was used for mapping the uterine arcuate arteries. The sample gate was positioned on the blood vessel, after which the pulse wave was started. Measuring was performed when the minimum of three clear waveforms was obtained. Pulsatile index (PI), resistance index (RI), S/D ratio and peak systolic velocity (v max) were measured. The same investigator (R.K.) performed all ultrasound exams.

Statistic significance was tested on commercial software by Student's t-test and t-test with Cohren and Cox corrective approximate method for small samples, when it was appropriate.

Results

The mean ages were similar: 23 ± 5.65 years in the group on OC and 28 ± 5.09 years in the group with spontaneous ovulatory cycles (p=0.20465).

Pulsatily index (PI), resistance index (RI) and S/D ratio in uterine arcuate arteries were statistically significant lower in the group of patients with spontaneous ovulatory cycles then in the group of patients on oral contraception containing ethynilestradiol (0.03 mg/day) and dienogest (2 mg/day). There were no significant

Table 1. Color Doppler measurements of uterine arcuate blood flow in group of patients on oral contraceptive containing ethynil estradiol and dienogest and in the group of patients with spontaneous ovulatory cycles

	PI	RI	S/D	V max (cm/sec)
Group of patients with spontaneous ovulatory cycles n = 11	0.98 ± 0.255	0.59 ± 0.054	2.59 ± 0.247	17.0 ± 9.89
Group of patients on oral contraceptive n = 11	2.38 ± 0.127	0.795 ± 0.007	4.9 ± 0.14	8.5 ± 3.33
p	0.00038*	0.000145*	0.000182*	0.21728

* statisticaly significant difference ($p < 0.05$)

differences in peak systolic velocity (v max) between group on OC and spontaneous ovulatory cycles (table 1).

Discussion

The monophasic combination containing ethynilestradiol 0.03 mg/day and dienogest 2 mg/day administered for contraception is safe and well tolerated. Similar combination 2 mg estradiol valerate and 2 mg dienogest) is the first combined preparation containing progestogen with antiandrogenic activity that is used as hormone replacement therapy (1,2). Deienogest is also used in the therapy of endometriosis.

Estrogen has vascular effects: on vasotonus, coagulation and atherogenesis.Vasodilatatory action of estrogens are related to estrogen - induced beneficial effect on nitric oxide (NO) synthesis, modulating the synthesis of prostacyclin and endothellin, and blocking calcium channels (3). Nitric oxide is potent vasodilatator and has antiaggregatory, antiproliferative, anti – inflammatory and antioxidative effects (4). Estrogens also down regulate angiotensin gene expression and synthesis of plasminogen activator inhibitor-1 (3). Estrogens downregulate cytokines, cell adhesion molecules (anti/inflammatory action) and thrombocyte aggregation/adhesion, which delay atherogenesis in combination with inhibition of vascular smooth muscle cell proliferation and antiatherogenic changes in serum lipids and lipoprotein profile (3). Estrogen increases markers of fibrinolytic activity (5). Oral estradiol induces hypercoagulability, but transdermal estradiol has no such effects (5). This explains the positive vascular effects of estrogen: vasodilatation (6), increase of fibrinolytic activity, and delay of atherogenesis (3).

Progesterone antagonizes effects of estrogen: beneficial effect on NO synthesis, function of antioxydative enzymes and vasodilatation (6). This could explain the fact that clinical studies found no reduction in cardiovascular pathology with estrogen and progesterone combination used for hormone replacement therapy (7). The results of other study are different: the vascular effects of dienogest used in postmenopausal hormone replacement therapy might not be clinically relevant, at least not in healthy women (8). The exact role of progestin addition must be determined by further studies.

Oral contraceptive containing dienogest (2mg/day) and ethynilestradiol (0.03 mg/day) has no clinically significant effects on coagulation, carbohydrate metabolism; serum lipid and lipoprotein content (9-11). In healthy women this combination slightly stimulated both procoagulation and fibrinolysis and there are no disturbances in haemostasis (12).

Dienogest protects of endometrial proliferation and has progestagenic potency that is stronger than progestogenic potency of any other progestogen (13). Dienogest is used in the therapy of endometriosis, after extirpation of endometrioma and in the therapy of uterine bleeding, and strong oral endometrial activity is explained by its good pharmacokinetic profile (14,15).

In available literature there are no data regarding the effects of ethynilestradiol/dienogest combination used for oral contraception on uterine vasculature. It is already said that estrogen is vasorelaxant and it seems that progestagens may attenuate vascular effects of estrogen. Dienogest has low antiestrogenicity according to studies of SHBG levels and vasodilatation markers (13).

Anti-angiogenic action of dienogest has been found during in vitro studies with cultured human microvascular endothelial cells (16). This could be used in the therapy of endometriosis, where angiogenesis has very important role (17). Direct vascular effects of dienogest are less studied, and there are only few data regarding the impact of dienogest on blood flow measurements (18). Results of our present investigation support thesis that dienogest could exert the effect on intrauterine blood flow: the resistance to uterine arcuate arteries blood flow, measured by color Doppler, is higher in cycles with dienogest / ethynilestradiol than in spontaneous ovulatory cycles. In animal experiments (with mares), it was found that the LH deficiency during anovulatory season led to reduction in perifollicular blood flow and intrafollicular concentrations of estradiol, IGF-1, inhibin – A and VEGF (19). Oral contraceptives cause anovulation and in our present investigation the reduction of blood flow in uterine arcuate arteries in OC users was found. It seems logical that anovulation caused by oral contraceptives and consecutive reduction of blood flow could partly explain the reduction in endometrial implants during the treatment of endometriosis with oral contraceptives, especially

with these containing dienogest. Our further investigations are in progress.

Conclusion

Vascular impedance of uterine arcuate arteries was higher in patients on OC, containing 0,03 mg ethynilestradiol and 2 mg dienogest, than in patients with spontaneous ovulatory cycles.

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KOLOR DOPPLER MERENJA PROTOKA KRVI KROZ ARTERIJE ARKUATE UTERUSA U PACIJENTKINJA NA ORALNOJ KONTRACEPCIJI

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Kratak sadržaj: *Cilj ovog ispitivanja je da se odredi da li postoje razlike u vaskularnoj impedanci arteriola arkuata uterusa izmedju spontanih ovulatornih ciklusa i ciklusa u kojima je korištena monofazna kombinacija, koja sadrži 0,03 mg etinilestradiola i 2 mg dienogesta, data u svrhu kontracepcije. Dvadeset dve pacijentkinje su uključene u ovo ispitivanje: 11 na oralnoj kontracepciji, 11 sa spontanim ovulatornim ciklusima. Ultrazvučni pregledi, uz korištenje endovaginalne sonde od 7 MHz sa kolor Doppler prikazom i pulsnog Dopplera, su sprovedeni posle 15 dana terapije u pacijentkinja na oralnoj kontracepciji i u periovulatornom periodu u drugoj grupi. Izmedju ove dve grupe nije bilo razlika u životnom dobu - 23±5,65 godina u grupi na oralnoj kontracepciji i 28 ± 5,09 godina u grupi sa spontanim ovulatornim ciklusima (p = 0,20465). Pulsatilni indeks je bio niži u grupi sa spontanim ovulatornim ciklusima*

(0,98±0,255 prema 2,38 ± 0,127, p=0,00038). Indeks rezistence je bio niži u grupi sa spontanim ovulatornim ciklusima (0,59 ± 0,054 prema 0,795 ± 0,007, p=0,000145), takodje i S/D odnos (2,59±0,247 prema 4,9±0,14, p=0,000182). Nije bilo signifikantne razlike u maksimalnoj brzini protoka u sistoli izmedju grupe na oralnoj kontracepciji i spontanih ovulatornih ciklusa (17±9,89 cm/sec prema 8,5±3,33 cm/sec, p=0,21728). Vaskularna impedanca uterusnih arterija arkuata je viša u pacijentkinja na oralnoj kontracepciji koja sadrži 0,03 mg etinilestradiola i 2 mg dienogesta, nego u pacijentkinja sa spontanim ovulatornim ciklusima.

Ključne reči: *Kolor Dopler, oralna kontracepcija. dienogest*