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KLINIČKA EFIKASNOST GOSERELINA (ZOLADEX) U LEČENJU MIOMA MATERICE KOD INFERTILNIH PACIJENTKINJA

CLINICAL EFFICACY OF GOSERELIN (ZOLADEX) IN THE TREATMENT OF UTERINE MYOMAS IN INFERTILE PATIENTS

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Sažetak - U radu je ispitan uticaj goserelin acetata (Zoladex depo) 3,6 mg amp. U četvoromesečnoj primeni kod pacijentkinja sa miomima materice različite lokalizacije i veličine, a koje imaju probleme infertiliteta. Istraživanje je obuhvatilo 30 pacijentkinja starosne dobi od 22 do 42 godine podeljenih u dve grupe u zavisnosti od volumena mioma i materice. Prva grupa je obuhvatala pacijentkinje gde volumen mioma nije prelazio 70 ml, a materice 300 ml, dok su drugu grupu činile pacijentkinje gde volumeni mioma i materice prelazi ove vrednosti. Goserelin je aplikovan svakih 28 dana, četiri meseca, uz ultrazvučno praćenje pada volumena, dok je kod submukoznih mioma radjena kontrolna histeroskopija. Dobijeni razultati ukazuju na efikasnost goserelina u smanjivanju volumena mioma i volumena materice za više od 50% što odgovara podacima iz literature. Posebno se ističe kompletno iščezavanje mioma u prvoj grupi koje se kreće oko 60%. Praćene su serumske koncentracije FSH, LH i E2 pre i tokom primene goserelina, gde su multivarijatnom analizom varijanse ustanovljene statistički značajne razlike. Zabeležene su i nuspojave ovog leka koje su slične drugim GnRH analozima.
Ključne reči: Goserelin + terapijska primena; Miom + terapija lekovima; Neplodnost u žena + terapija lekovima

Summary *- This study investigated the efficacy of Zoladex depot 3.6 mg (goserelin acetate) during a 4-month treatment of infertile patients with uterine myomas of different size and location. The investigation comprised 30 patients aged 22 - 42 years, distributed into 2 groups regarding uterine and myoma volume. The first group included patients with uterine myomas less than 70 ml and uterus less than 300 ml. The second group included patients in whom these volumes exceeded the above mentioned values. Zoladex depot was administered every 28 days for 4 months with ultrasonographic follow-up of volume decrease, whereas patients with submucous myomas underwent control hysteroscopy. The obtained results point to efficacy of Zoladex in decreasing the volumes of both myomas and uterus by more than 50%, which correlates with literature data. Of particular interest is complete disappearance of myomas in about 60% of patients of the first group. Serum concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) were followed-up prior to and during Zoladex therapy where multivariate variance analysis showed statistically significant differences. The side effects were recorded and are similar to those of other GnRH analogues.*
Key words: *Goserelin + therapeutic use; Myoma + drug therapy; Infertility, Female + drug therapy*

Uvod

Miomi materice spadaju u najčešće solidne tumore reproduktivnog trakta žene. Poznato je da se samo u SAD izvodi godišnje 175.000 histerekotmija i 180.00 miomektomija zbog ove indikacije [1]. Većina autora ocenjuje da se nakon trideset pete godine života žene učestalost mioma kreće 25 - 30%, što bi značilo da svaka peta žena iznad trideset pete godine ima miom materice [2]. Po svojim karakteristikama benignog, oštro ograničenog glatkomišićnog tkiva materice, dobija nakon niza različitih naziva svoj pravi naziv *"myoma uteri"* od strane Virchowa koji takođe opisuje i njegovu histološku građu. Veličina i lokalizacija mioma determiniše i simptomatologiju koja se uglavnom odnosi na nekoliko kategorija: znaci pritiska tumora (bol, učestalost mokrenja,

Introduction

Uterine myomas are the commonest solid tumors of the female genital tract. It is well known that only in USA, 175.000 hysterectomies and 18.000 myomectomies are performed annually due to this indication [1]. It has been established by many authors that after 35 years of age myomas occur in 25 - 30% of women, which means that every fifth woman over 35 years of age has a uterine myoma [2]. It is a benign neoplasm of the uterine smooth muscle tissue, named variously until it was named "myoma uteri" by Virchow, who also described its histology. Size and location of myomas determines the symptoms which commonly include several categories: signs of tumor pressure (pain, frequent urination, constipation), irregular bleeding (menorrhagia, metrorrhagia) and re-

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Skraćenice

FSH	- folikulostimulirajući hormon
LH	- luteinizirajući hormon
E2	- estradiol
PRL	- prolaktin
PROG	- progesteron
GnRH	- gonadotropin rilizing hormon
KKS	- kompletna krvna slika
ŠUK	- šećer u krvi
AHM	- antihemoragični mehanizam

konstipacija), iregularno uterino krvarenje (menoragija, metroragija) i reproduktivne disfunkcije (infertilitet, rani pobačaji, prematuritet, distocija). Histerektomija se pokazuje kao jedino definitivno lečenje mioma materice. Uterina prezervacija abdominalnom klasičnom miomektomijom ili endoskopskom miomektomijom jeste alternativa, ali i rizik od ponovljenog hirurškog zahvata te se po literaturnim podacima kreće oko 50% [3].

Hormonska terapija u lečenju ovog tumora odnosi se na redukovanje simptoma i veličine mioma u cilju prezervacije uterusa kod pacijenata kod kojih je u pitanju sterilitet kao i kod onih koji na tome insistiraju ili pak postoje apsolutne kontraindikacije za operativni zahvat, kao i za uvođenje žena u menopauzu, a u poslednje vreme sve više kao alternativa u cilju uvođenja u definitivnu hiruršku interveciju koja će time dobiti bolji intra i postoperativni tok. Tako se na tržištu 80-ih godina pojavljuje upotreba GnRH analoga (*gonadotropin releasing hormone analoga*) koji pokazuju efikasnost u redukovanju volumena uterinih mioma i time i njihove simptomatologije. Njihovom kontinuiranom primenom u dužini ne više od 6 meseci, kako zbog potencijalnih komplikacija, tako i zbog visoke cene, prelazi se iz prve faze lečenja u drugu fazu: hirurgija ili menopauza. Tako Filicori i saradnici 1983. godine prikazuju prvi uspešan tretman mioma GnRH analozima, te zatim slede mnogobrojni autori koji prikazuju efikasnu upotrebu GnRH analoga u rešavanju ovog problema [4].

Mehanizam delovanja GnRH analoga na smanjenje volumena fibroidnih tumora uterusa nije sasvim razjašnjen. Poznato je da su uterini miomi estrogenzavisni tumori sa više estrogenskih receptora što potvrđuje njihov porast u veličini tokom trudnoće, kao i pad tokom puerperijuma ili menopauze. Tako prolongirano hipoestrogenemijsko stanje izazvano primenom GnRH agonista može dovesti do involucije ovog tumora. Takođe je zapaženo da regresija može biti i posledica smanjene koncentracije kako cirkulišućeg estradiola, tako i EGF (*epidermal growth factor*) i IGF (*insulin growth factor*) [5]. Histološka istraživanja ukazuju da kod GnRH tretiranih uterinih fibroida dolazi do porasta celularne atrofije i nekroze za razliku od netretiranih tumora, a da pri tom nije nađena razlika u vaskularnim promenama, edemu i fibrozi.

Abbreviations

FSH	- Follicle stimulating hormone
LH	- Luteinizing hormone
E2	- Estradiol
PRL	- Prolactin
PROG	- Progesterone
GnRH	- Gonadotrophin-releasing hormone
KKS	- Complete blood count
ŠUK	- Blood sugar
AHM	- Antihemorrhagic factor

productive dysfunctions (infertility, early miscarriage, prematurity, dystocia). Hysterectomy is the only definitive therapy of uterine myomas. Preservation of uterus by classic abdominal myomectomy or endoscopic myomectomy is an alternative, but according to literature data the risk of repeated surgical procedure is around 50% [3].

Hormone therapy in treatment of these tumors tends to reduce the symptoms and size of myomas in the aim of preserving the uterus in infertile patients, as well as in those who insist on it, or there are absolute contraindications to surgery, as well as onset of menopause, while recently it is more and more an alternative to definitive surgical procedure with better intra and postoperative course. In the 80-ies, GnRH (gonadotrophin releasing hormone) analogues appeared on the market, showing efficacy in reducing the volume of uterine myomas and so their symptomatology. Their continual use for no longer than 6 months, due to potential complications and high cost, leads to the second phase of treatment: surgery or menopause. That is how Filicori and associates presented the first successful treatment of myomas by GnRH analogues in 1983. After that a great number of authors reported about the efficacy of GnRH analogues in solving this problem [4].

The mechanism of action of GnRH analogues on reducing the volume of uterine fibroids has not been completely explained. It is well known that uterine myomas are estrogen-dependent tumors with several estrogen receptors, which is confirmed by their growth during prenancy and decrease during puerperium or menopause. Thus, prolonged hypoestrogenic state caused by GnRH agonists may lead to involution of tissue tumors. It has also been noted that regression may be the consequence of decreased concentrations of both circulating estradiol and epidermal growth factor (EGF) and insulin-like growth factor (IGF) [5]. Histologic examinations revealed that in uterine fibroids treated by GnRH there is an increased cellular atrophy and necrosis, in contrast to nonuterine tumors, but at the same time there is no difference in vascular changes, edema and fibrosis.

Goserelin acetat (Zoladex depo) 3,6 mg jeste sintetski dekapeptid GnRH analoga koji svojim direktnim dejstvom na hipofizu dovodi do prologiranog hipoestrogenemijskog stanja koje može dovesti do skvrčavanja tumora [6]. Dobro je poznat dvostruko dozno zavisni efekat GnRH analoga na hipofizu, gde male doze aktiviraju gonadotropne ćelije, a veće doze postepeno blokiraju hipofizu i time reverzibilno suprimiraju gonade, što je i omogućilo njihovu kliničku primenu poznatu kao "metod medikamentozne kastracije". Tako se primenom goserelina nakon prvobitne stimulacije i porasta nivoa FSH i LH, a time i estradiola u prvih 24 h, dolazi do brzog izostanka odgovora na sledeću stimulaciju, tzv. pojavu desenzitacije ili "*down* regulacije" hipofiznih GnRH receptora koji svoj maksimum supresije dostižu 21 dan od momenta aplikacije leka. Time se postižu postmenopauzalne vrednosti estradiola i zadržavaju tokom šestomesečnog tretmana ovim lekom. Različiti autori prikazuju svoje rezultate šestomesečnog tretmana goserelinom (6 depo 3,6 mg inj.), nakon čega sledi hirurška procedura koja se pokazala mnogo kvalitetnijom za pacijenta kako u signifikantno kraćem trajanju operativnog zahvata, tako i u manjem intraoperativnom gubitku krvi, manjoj potrebi za nadoknadu krvi, kraćem hospitalnom boravku i manjem broju postoperativnih komplikacija [7].

Cilj rada bio je ispitivanje uticaja goserelin amp. 3,6 mg u četvoromesečnoj primeni kod pacijenata sa dijagnostokovanim miomom materice različite veličine i lokalizacije, potom odredjivanje serumskih koncentracija FSH, LH i E2 pre i tokom primene leka, evaluacija rezultata, te izvođenje zaključaka o njegovoj ciljanoj i opravdanoj upotrebi.

Materijal i metode

U istraživanje je uključeno 30 pacijenata sa problemima infertiliteta i dijagnostikovanim uterinim miomom. Kod odabranih pacijenata prethodno je uzeta anamneza, podaci o dosadašnjem lečenju, urađeni ginekološki i ultrazvučni pregledi, kod pojedinih i histeroskopija, te uzeta paleta laboratorijskih (KKS, ŠUK, AHM, urin) i biohemijsko-hormonskih analiza (lipidni status, FSH, LH, PRL, E2 i PROG). Terapija goserelin amp. 3,6 mg započeta je neposredno nakon završene menstruacije, te nastavljana u razmacima od 28 dana četiri meseca, i to subkutano 2-3 cm ispod pupka, uz prethodnu lokalnu infiltraciju lidokaina 1%. Ultrazvučno je praćen pad volumena mioma i uterusa, a kod pacijenata sa submukoznim miomima nakon terapije urađena kontrolna histeroskopija. U radu je korišćen ultrazvučni aparat ALOKA SSD 1200 i vaginalna sonda od 3,5 MHz. Volumen mioma je izračunat po formuli $4/3\ \pi r^3$. Takođe je kontrolisan i hormonski status (FSH, LH i E2) tokom terapije. Zabeležene su i nuspojave ovog leka. Rezultati su statistički (t-test, MANOVA - ponovljena me-

Zoladex depot 3.6 mg (goserelin acetate implant) is a synthetic decapeptide of GnRH analogue which directly affects the hypophysis and causes a prolonged hypoestrogenic state which leads to tumor shrinkage [6]. Double-dose dependent effects of GnRH analogues on hypophysis are well known - little doses activate gonadotropic cells, whereas greater doses gradually block the hypophysis and thus reversibly gonadal suppression. That is why their clinical application is known as a "method of medical castration". After initial increase of FSH and LH le-vels and thus estradiol in the first 24 hours, use of Zoladex causes fast lack of response to the next stimulation - so called desensitization or "down-regulation" of hypophyseal GnRH receptors and their maximal suppression occurs on 21st day from drug administration. This causes postmenopausal values of estradiol, which are prolonged by a 6-month Zoladex treatment. Numerous authors have presented their results obtained by 6-month Zoladex therapy (6 depot 3.6 mg, s.c. monthly) which is followed by a surgical procedure which has proved to be much better for the patients due to a significantly shorter surgery, less intraoperative blood loss and less need for blood replacement, shorter hospital stay and less postoperative complications [7].

The purpose of this study was to investigate the efficacy of Zoladex depot 3.6 mg during a 4-month treatment of patients with diagnosed uterine myomas of different size and location; follow-up of serum concentrations of FSH, LH and E2 prior to and during Zoladex therapy; evaluation of results and making conclusions about its targeted and justified use.

Material and methods

The investigation comprised 30 infertile patients with diagnosed uterine myomas. Patients included into this investigation underwent a thorough examination starting with anamnestic data on previous treatments, gynecological and ultrasound examinations, in some cases hysteroscopy was performed, as well as a great number of laboratory examinations (KKS, ŠUK, AHM, urine) and biochemical-hormonal analyses (lipid status, FSH, LH, PRL, E2 and PROG). Zoladex depot 3.6 mg. therapy started after completed menstruation and was administered every 28th day during 4 months subcutaneously 2 - 3 cm below the umbilicus with previous local infusion of 1% lidocaine. Volume decrease of myomas and uterus was followed-up ultrasonographically, whereas after therapy patients with submucous myomas underwent control hysteroscopy. All patients were examined using a sonographic scanner (ALOKA SSD 1200) and a 3.5 MHz vaginal probe. The myoma volumes were calculated after the formula $4/3\ \pi r^3$. Hormonal status was also followed-up during therapy (FSH, LH, and E2) and side effects were established.

renja, Šefeov test kontrastiranja) i grafički obrađeni programskim paketom *Statistica for Windows* 5.1.

Rezultati

Prema definisanim ciljevima istraživanja izvršena je analiza i statistička obrada prikupljenih rezultata kod 30 pacijentkinja.

Ispitivane pacijentkinje bile su u starosnoj dobi 22-42 godine. Prosečna starost je bila 31 godina.

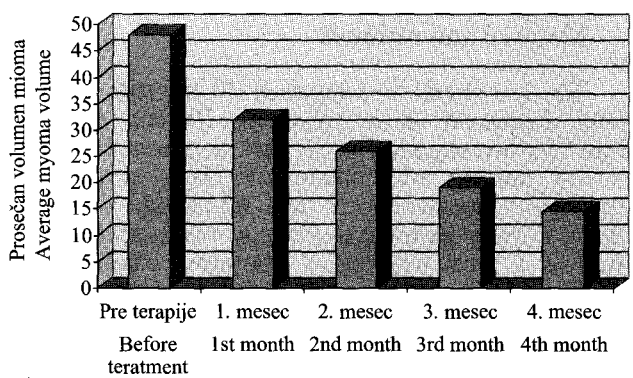
Od ukupno 30 pacijentkinja kod 13 se radi o primarnom bračnom sterilitetu, dok kod 17 o sekundarnom bračnom sterilitetu.

Od ukupno 17 pacijentkinja sa dijagnozom sekundarnog steriliteta 6 pacijentkinja ima jedno dete nakon čega su registrovani uterini miomi, dok je 9 pacijentkinja imalo u anamnezi više od dva sponatna pobačaja, a 2 pacijentkinje jedan spontani pobačaj.

Od ukupno 30 pacijentkinja kod 5 pacijentkinja nađeni su isključivo subserzni miomi, kod 10 isključivo intramuralni miomi, kod 7 submukozni miomi, dok je kod 8 pacijentkinja postojalo više mioma kombinovane lokalizacije.

Pacijentkinje su podeljene u dve grupe radi boljeg prikaza efikasnosti leka: I grupa - pacijentkinje kod kojih miomi ne prelaze volumen od 70 ml izračunat po datoj formuli, a materica ne prelazi volumen od 300 ml, bez obzira na lokalizaciju mioma. N=20; II grupa - pacijentkinje kod kojih miomi prelaze volumen od 70 ml i materica prelazi 300 ml N=10.

Smanjivanje volumena mioma i materice tokom četvoromesečne terapije goserelin amp. 3,6 mg prikazano je na slikama 1-4.



Slika 1. Volumen mioma tokom četvoromesečne terapije (I grupa)

Fig. 1. *Myoma volume during a 4-month treatment (Group I)*

Kao što je grafički prikazano na prethodnim slikama, uočava se statistički značajan pad volumena mioma i volumena materice u obe grupe pacijentkinja - u prvoj grupi pacijenata $t = 3,02$; $p<0,01$ i u drugoj grupi $t = 2,85$; $p<0,01$.

Hormonalni profil pacijentkinja i kretanje koncentracija hormona u krvi tokom terapije goserelinom određivan je Elisa testom, i to za sledeće hormone:

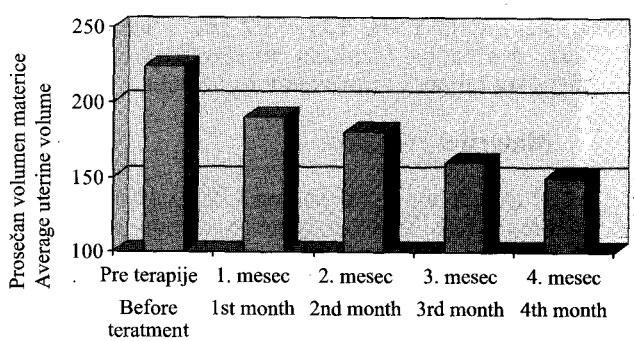
Results of investigation were statistically analyzed (t-test, MANOVA for repeated measures, Scheffe test for multiple comparison) and graphically processed by means of Statistica for Windows 5.1.

Results

According to the purpose of this research, a statistical analysis of obtained results was performed in 30 patients.

The investigated patients were 22 - 42 years of age. The average age was 31 years. Out of 30 patients, there were 13 with primary infertility and 17 with secondary infertility.

Of 17 patients with secondary infertility, 6 patients had one child after which uterine myoma was diagnosed, while 9 patients had more than two spontaneous miscarriages and 2 patients had one spontaneous miscarriage. Out of 30 patients, 5 had subserous myomas, 10 had intramural myomas, and 7 had submucous myomas, whereas 8 patients had several myomas of combined location. In order to establish the efficacy of Zoladex, patients were divided into two groups. Group I: patients with uterine myomas less than 70 ml (volume was calculated after the above-mentioned formula) and uterus less than 300 ml, regardless of myoma location. N = 20. Group II: Patients in whom the volumes of myomas and uterus exceeded 70 ml and 300 ml, respectively. N=10.

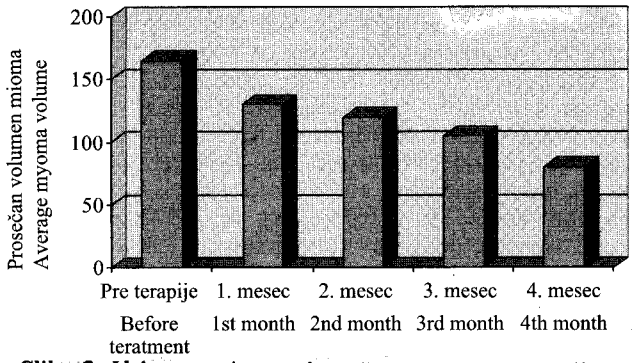


Slika 2. Volumen materice tokom četvoromesečne terapije (I grupa)

Fig. 2. Uterine *volume during a 4-month treatment (Group I)*

Volume decrease of myomas and uterus during a 4-month Zoladex depot 3.6 mg therapy is presented in Figures 1-4. Graphic representations clearly show a statistically significant decrease in volume of both myomas and uterus in both groups of patients: in the first group $t=3.02$; $p<0.01$ and in the second group $t=2.82$; $p<0.01$.

The hormonal profile of patients and hormone concentrations in blood during Zoladex therapy were established by Elisa test, for the following hormones: FSH, LH and E2. These concentrations were evalua-

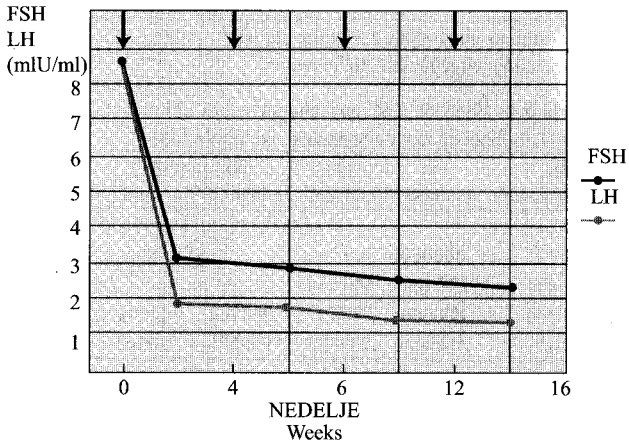


Slika 3. Volumen mioma tokom četvoromesečne terapije (II grupa)

Fig. 3. *Myoma volume during a 4-month treatment (Group II)*

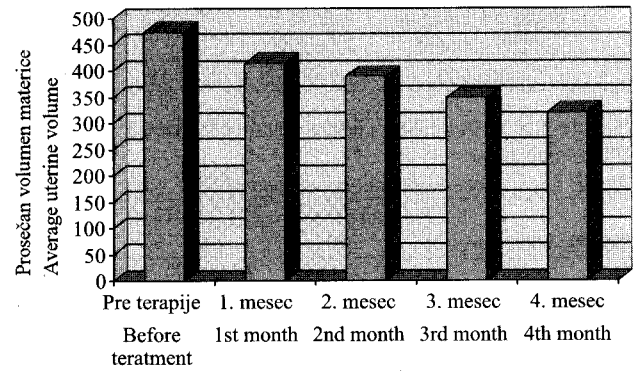
FSH, LH i E2. Koncentracije ovih hormona su određivane pet puta: prva analiza je sprovedena treći dan ciklusa (bazalna vrednost), nakon čega je sledila I ampula goserelina peti dan ciklusa, druga analiza dve nedelje nakon prve ampule goserelina, treća analiza dve nedelje nakon druge ampule goserelina, četvrta analiza dve nedelje nakon treće ampule gose- relina i peta analiza hormona nakon četvrte ampule goserelina. Razmak između datih ampula goserelina je iznosio četiri nedelje. Grafički je prikazan strelicom momenat davanja goserelina kao i prosečne serumske koncnetracije FSH, LH i E2 tokom četvoromesečne primene goserelina (slika 5 i 6).

Multivarijatna analiza varijanse za ponovljena merenja (3 zavisne varijable/5 nivoa ponovljenih merenja) pokazala je da postoji statistički značajna razlika (p=0,000001 [tabela 1.a]) u prostoru serumskih nivoa sva tri posmatrana hormona pre započete terapije goserelinom i u toku njegove primene.



Slika 5. Prosečne serumske koncentracije FSH i LH tokom četvoromesečne primene goserelina (strelice označavaju aplikaciju goserelina)

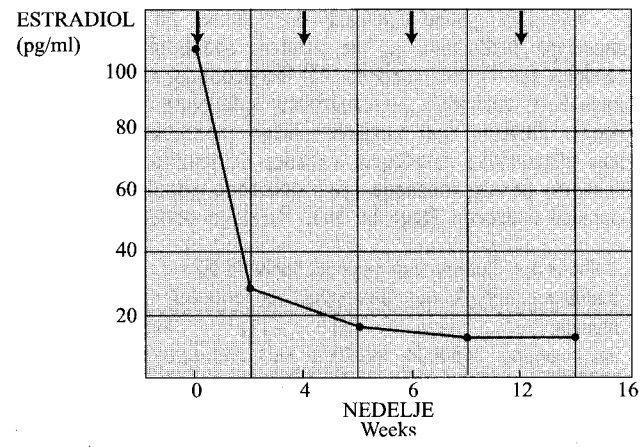
Fig. 5. *Serum concentrations of FSH and LH during a 4 month treatment with Zoladex (arrows indicate aplications of Zoladex)*



Slika 4. Volumen materice tokom četvoromesečne terapije (II grupa)

Fig. 1. *Uterine volume during a 4-month treatment (Group II)*

ted 5 times: the first analysis was performed on the third day of the cycle (basal value), the first subcutaneous injection of Zoladex was administered on the 5th day of cycle; the second analysis was performed two weeks after the first Zoladex administration; the third analysis was performed two weeks after the second Zoladex administration; the fourth two weeks after the third administration and the fifth hormonal analysis was performed after the fourth Zoladex administration. Zoladex was administered monthly, every 28 days. Figures 5 and 6 show the moments of Zoladex administration as well as average serum concentrations of FSH, LH and E2 during the 4-month therapy. Multivariate variance analysis for repeated measures (3 dependant variables/5 levels of repeated measures) showed that there was a statistically significant difference (p=0.000001 - Table 1a) regarding serum levels of all three examined hormones prior to, during and following Zoladex therapy.



Slika 6. Prosečna serumska koncentracija estradiola tokom četveromesečne primene goserelina (strelice označavaju aplikaciju goserelina)

Fig. 6. *Serum estradiol concentrations during a 4 month treatment period with Zoladex*

Tabela 1.a. Multivarijatni F (Wilksova Lambda) - ukupni
Table 1.a. *Multivariate F (Wilks Lambda) - total*

	Wilksova Lambda *Wilks Lambda*	Raovo R *Raos R*	df 1	df 2	p
1	0,100163	13.47562	12	18	.000001

Tabela 1.b. Aritmetičke sredine serumskih nivoa FSH, LH i E2 po merenjima
Table 1.b. *Mean serum concentrations of FSH, LH and E2*

	Raovo R/*Raos R* (12,18)=13.48; p<.0000		
Merenje/*measurement*	FSH	LH	E2
0	8.634000	8.606667	106.8200
1	3.150000	2.056667	28.3040
2	2.866667	1.770000	16.1133
3	2.470000	1.356667	12.7633
4	2.346667	1.286667	12.5167

Posebno je testirano da li je došlo do statistički značajne razlike za svaki od hormona posebno. Rezultati pokazuju da su i razlike u okviru serumskih koncentracija FSH i LH pre i tokom primene goserelina, takođe statistički značajne (tabela 2).

Tabela 2. Glavni efekat Zoladexa (ponovljeni faktor)
Table 2. *Main effect of Zoladex (repeated factor)*

Varijabla *variable*	MS efekat *MS effect*	MS greška *MS Error*	F (df1,2) 4,116	p
FSH	213.74	4.1506	51.49588	.000000
LH	296.04	4.4468	66.57380	.000000
E2	49193.73	996.1970	49.38153	0

*istaknute su statistički značajne razlike
**statistically significant differences*

Šefeov test kontrastiranja pokazao je da postoji statistički značajna razlika serumskih nivoa FSH i LH između prvog merenja (pre primene goserelina) i svih ostalih merenja (tabela 3.a i tabela 3.b). Razlike serumskih nivoa ova dva hormona merenih u toku primene goserelina nisu statistički značajne (tabela 3a i tabela 3b).

Multivarijatna analiza varijanse za ponovljena merenja pokazala je da postoji statistički značajna razlika (p=0,000 [tabela 2]) serumskog nivoa E2 pre započete terapije goserelinom i tokom njegove primene. Šefeov test kontrastiranja pokazao je da postoji statistički značajna razlika serumskog nivoa E2 između prvog merenja (pre primene goserelina) i svih ostalih merenja (tabela 3c). Razlike serumskih nivoa

Tabela 3.c. Šefeov test: zavisna variabla E2
Table 3.c. *Scheffe test: dependent variable E2*

Merenja	{1}	{2}	{3}	{4}	{5}
measurements	106.8200	28.30400	16.11333	12.76333	12.51667
0 {1}					
1 {2}	.000000				
2 {3}	.000000	.692557			
3 {4}	.000000	.461153	.996574		
4 {5}	.000000	.444491	.995488	1.000000	

*istaknute su statistički značajne razlike
**statistically significant differences*

We have also investigated if there were statistically significant differences regarding each hormone separately. Our results showed that differences regarding serum concentrations of FSH and LH prior to and during Zoladex therapy were also statistically significant (Table 2). Scheffe test revealed that there was a statistically significant difference in serum levels of FSH and LH between the first analysis (prior to Zoladex therapy) and all other analyses (Tables 3a and Table 3b). Differences in serum levels of these two hormones evaluated during Zoladex therapy were not statistically significant (Table 3a and Table 3b).

Multivariate variance analysis for repeated measures showed that there was a statistically significant difference (p=0.000 - Table 2) in E2 serum level prior to and during Zoladex therapy. Scheffe test showed that there was a statistically significant difference regarding E2 serum level between the first analysis (prior to Zoladex therapy) and all the other analyses (Table 3c). Differences in serum levels of this hormone during Zoladex therapy were not statistically significant (Table 3c).

Adverse events during therapy are presented in Table 4. It must be pointed out that 36.6% of patients had withdrawal bleeding after the first administration of Zoladex in the interval from the 17th to 28th day. Hypersensitivity to this drug was not recorded (Table 4).

Tabela 3.a - Šefeov test: zavisna variabla FSH
Table 3.a *- Scheffe test: dependent variable FSH*

	{1} 8.634000	{2} 3.150000	{3} 2.866667	{4} 2.470000	{5} 2.346667
0 {1}					
1 {2}	.000000				
2 {3}	.000000	.990309			
3 {4}	.000000	.795547	.966112		
4 {5}	.000000	.675516	.912594	.999623	

*istaknute su statistički značajne razlike
**statistically significant differences*

Tabela 3.b. Šhefeov test: zavisna variabla LH
Table 3.b. *Scheffe test: dependent variable LH*

Merenja	{1}	{2}	{3}	{4}	{5}
measurements	8.606667	2.056667	1.770000	1.35667	1.286667
0 {1}					
1 {2}	.000000				
2 {3}	.000000	.991114			
3 {4}	.000000	.798827	.965282		
4 {5}	.000000	.735775	.939506	.999965	

*istaknute su statistički značajne razlike
**statistically significant differences*

Discussion

This study presents results of a 4-month therapy with Zoladex depot 3.6 mg (subcutaneous application) in treatment of uterine myomas of different size and location in 30 patients with primary or secondary infertility.

ovog hormona merene u toku primene goserelina nisu statistički značajne (tabela 3c).

Nuspojave tokom terapije prikazane su u tabeli 4. Treba naglasiti da je 36,6% pacijentkinja imalo probojno krvarenje nakon prve ampule goserelina u razmaku od 17. do 28. dana. Osetljivost na ovaj lek nije zapažena (tabela 4).

Tabela 4. Nuspojave tokom terapije
Table 4. *Side effects during treatment*

Nuspojave tokom terapije *Side effects during treatment*	Broj pacijenata *no. of patients*
Probojno krvarenje/*withdrawal bleeding*	11 (36,6%)
Valunzi vrućine i znojenja *Hot flushes and sweating*	22 (73,3%)
Suvoća vagine/*vaginal dryness*	5 (16,6%)
Promene raspoloženja u formi depresije *Mood changes including depression*	4 (13,3%)
Uvećanje i nadutost dojki *Increase in breast size*	6 (20%)
Povišenje arterijskog krvnog pritiska *Hypertension*	5 (16,6%)
Glavobolje/*headaches*	8 (26,6%)
Opadanje kose/*hair loss*	1 (3,33)

Diskusija

U radu su prikazani rezultati četvoromesečne terapije goserelin amp. 3,6 mg u subkutanoj primeni na postojeće miome materice različite lokalizacije i veličine kod 30 pacijentkinja sa problemima primarnog ili sekundarnog steriliteta.

Dobijeni rezultati prikazuju efikasnost ovog leka u smanjivanju volumena, kako mioma tako i materice, za više od 50%, što se slaže sa rezultatima raznih autora [8]. Prikazana je bolja efikasnost ovog leka kod pacijentkinja sa manjim volumenom mioma (do 70 ml) i materice (do 300 ml) gde je u 60% došlo do kompletnog iščezavanja mioma, potvrđeno kontrolnim nalazima histeroskopije i ultrazvukom, što će imati udela u rešavanju problema infertiliteta. Kod pacijentkinja gde su miomi prelazili 70 ml i matеrica 300 ml volumena, stopa pada je sporija, nema kompletnog iščezavanja mioma, ali se goserelin takođe pokazao efikasnim jer je došlo do smanjivanja volumena za oko 50% od početne vrednosti, što za te pacijente predstavlja ulazak u drugu fazu hirurške intervencije miomektomije ili eventulano histerektomije. Od 10 pacijenata ove grupe kod 6 pacijenata je urađena miomektomija, kod jedne pacijentkinje histerektomija a tri pacijentkinje su odustale od operativnog zahvata. Multivarijatna analiza varijanse serumskih koncentracija FSH, LH i E2 pokazala je statistički značajan pad ovih koncentracija dve nedelje nakon ordinirane prve ampule goserelina, i na tim nivoima se održavala tokom četvoromesečne terapije. Menstrualni ciklus je uspostavljen u proseku 46. dan nakon poslednje ampule goserelina. Nuspojave nastale u toku ove terapije slažu se sa podacima iz literature i slični su sa ostalim GnRH analozima [9]. Probojno krvarenje koje se javilo u 11 pacijentkinja (36,60%) može biti posledica sporije hormonske supresije što može biti predmet sledećeg istraživanja.

Zaključak

Goserelin 3,6 mg pokazao se kao efikasan lek u terapiji mioma materice, različite veličine i lokalizacije, te time ima udela u rešavanju problema infertiliteta, ili predstavlja dobru pripremu za što kvalitetniju hiruršku intervenciju.

The obtained results point to efficacy of this drug in decreasing the volume of both myomas and uterus by more than 50%, which correlates with results of numerous authors [8]. Higher efficacy of this drug was established in patients with smaller volume myomas (up to 70 ml) and uterus up to 300 ml, where complete disappearance of myomas occurred in 60% of patients. This has been confirmed by control hysteroscopy and ultrasound, being of particular importance in solving problems of infertility. In patients with myomas exceeding 70 ml and uterus 300 ml, the rate of decrease was slower, there was no complete disappearance of myomas, but Zoladex also proved to be efficient due to volume decrease by about 50% from the initial value which is important for patients fulfilling the condition for the second phase - surgical procedure of myomectomy or possibly hysterectomy.

Out of 10 patients from this group, 6 patients underwent myomectomy, 1 patient hysterectomy, whereas 3 patients refused surgery. Multivariate variance analysis of serum concentrations of FSH, LH and E2 showed a statistically significant decrease of these concentrations two weeks after first administration of Zoladex and remained unchanged during 4 months of therapy. The menstrual cycle resumed 46 days following the last application of Zoladex on average. Side effects of this therapy correlate with literature data and are similar to other GnRH analogues [9]. Withdrawal bleeding occurred in 11 patients (36.60%) and might be the consequence of slow hormonal suppression and remains an issue for future investigations.

Conclusion

Zoladex depot 3.6 mg proved to be an efficient drug in the treatment of uterine myomas of different size and location, and thus in treatment of infertility, as well as a good preparation for quality surgical procedures.

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