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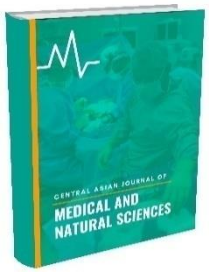

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Female Aging and Superovulation Induction for IVF

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Abstract: In this study the efficacy of the recombinant and urinal gonadotropin usage in women of late reproductive age during ovarian stimulation with the gonadotropin-releasing hormone (GnRH) antagonists has been investigated.

Keywords: in-vitro fertilization, ovarian stimulation, reproductive age.

Introduction

Research on factors contributing to infertile marriages has shown that in almost every second couple (44.3-52.7%) the infertility is caused by the pathology of woman’s reproductive system, in 6.4-19.4% of cases it is caused by the pathology of man’s reproductive system and in 34.2 – 38.7% of couples the infertility is due to pathology in both spouses [1,5].. Age is an important factor influencing the effectiveness of in-vitro fertilization and embryo transfer procedures as it determines the quantity of retrieved oocytes, quality of transferred embryos and number of successful pregnancies. Administration of complex IVF and embryo transfer procedures in women older than 38 years of age significantly improves the efficacy of fertilization and allows women to try to use their own ovarian reserve to full extent. Insufficient effectiveness of the methods to recover natural human fertility has started development of new supplementary reproductive techniques, in particular in-vitro fertilization method, the effectiveness of which varies between 28.5 to 32.5% [2,3Therefore, in recent years more attention has been given to refinement of the extracorporeal fertilization methods in order to increase their effectiveness [3,4,5].

Fujimoto et al. have studied a group of women over 40 years of age and found that only 16% of women between the age of 40 and 42 years gave birth to healthy newborns, whereas women over 43 years could not become pregnant (6). Such factors as the duration of infertility, age of a spouse, age at the beginning of the marriage, history of surgical operations on the uterus were statistically insignificant. The authors have concluded that positive results can be achieved in women between 40 and 42 years of age given they have low levels of the follicle stimulating hormone (FSH), normal menstrual cycle and no history of surgical operations on ovaries.

In summary, despite increasing administration of supplementary reproductive techniques that can facilitate pregnancy conception in almost every 3rd infertile couple, a development of new methods to increase the effectiveness of expensive in-vitro fertilization and embryo transfer procedures remains highly relevant. The effectiveness of IVF, i.e. occurrence of pregnancy conception, currently does not exceed 35-40%, moreover, about one third of the induced pregnancies usually ends with the abortion on early stages. The causes of negative results very often remain unknown. Therefore, further research is needed on the possibilities to improve the effectiveness of in-vitro fertilization by optimizing examination and preparation of women with endocrine forms of infertility.

The aim of the study: to investigate the effectiveness of the recombinant and urinal gonadotropin usage in women of late reproductive age during ovarian stimulation with the gonadotropin-releasing hormone (GnRH) antagonists.

Participants and methods

The protocol of ovarian stimulation with the GnRH antagonists has been used in this study.

From the 2-4 day of the menstrual cycle the 1st group of patients (main group) was given a recombinant FSH –Gonal-F (Merck Serono, Italy) (Fig.1). The 2nd group was given a urinary FSH – Menopur (Ferring, Germany) (Fig.2).

The initial dose of the gonadotropin in both groups was 150-250 IU depending on the measures of ovarian reserve. The duration of the usage varied from 6 to 16 days in the 1st group and from 6 to 12 days in the 2nd group. The daily dosage was corrected depending on the follicles' growth measured on ultrasound scanning Ultrasound monitoring was performed on the 1st day of the beginning of ovarian stimulation, on the 5-6 day of stimulation and further every other day till the day when the ovulatory dose of the human chorionic gonadotropin (HCG) was given.

GnRH antagonists – Orgalutran (Merck, USA) were given subcutaneously in daily dose of 0.25 mg after the leading follicle had reached 13-14 mm in diameter. The trigger of final follicular maturation, i.e. the ovulatory dose of the HCG – Ovitrelle (6500 IU) (Serono, Switzerland) was given after at least 3 follicles had become >17 mm in diameter.

All patients received Utrogestan 600 mg per day intravaginally until positive or negative results of pregnancy test were obtained. Pregnancy tests were made by measuring blood levels of β-subunits of the HCG on the 14th day after the embryo transfer. Test results were considered positive if β-subunits levels were >20 IU/l (biochemical pregnancy). Ultrasound examination to confirm presence of clinical pregnancy was performed on the 21st day after the embryo transfer and further management strategy was determined.

Results

Duration of ovarian stimulation in the recombinant gonadotropin group (main group) was significantly longer than in the group that received urinary gonadotropin (comparison group). Specifically, in the main group the duration of stimulation was 9.3±0.2 days, whereas in the comparison group it was 8.6±0.3 days. Additionally, in the comparison group the trigger of final follicle maturation was given earlier than in the main group (on the 10.5±0.3 and 11.4±0.2 day respectively, $p<0.05$)

Ultrasound monitoring revealed that during gonadotropic stimulation the number of growing follicles was higher in the main group – 7.5±0.5 and 5.7±0.5 in the main and comparison groups respectively ($p<0,05$).

There were no statistically significant differences between the two groups in the quantities of retrieved

oocytes, overall dose of gonadotropins taken by women, numbers and days of ovarian punctures.

Table 1. Measurements of the gonadotropic ovarian stimulation in patients of both groups (M±m)

Measurement	Main group	Comparison group	p
Summary dose of gonadotropins, in IU	2035,4±93,9	1947,6±131,4	
Duration of stimulation, in days	9,3± 0,2	8,6± 0,3	<0,05
Number of growing follicles	7,5± 0,5	5,7± 0,5	<0,05
Day of triggering the final follicular maturation, in days of menstrual cycle	11,4± 0,2	10,5± 0,3	<0,05
Frequency of ovarian puncture, in %	97,8	93,8	
Day of ovarian puncture, in days of menstrual cycle	13,3± 0,3	12,8± 0,3	
Average number of retrieved oocytes	6,4±0,5	5,6±0,7	
Frequency of ovarian punctures with zero oocytes retrieved, in %	7,6	6,3	
Frequency of stopped cycles of stimulation due to the absence of follicular growth, in %	1,1	0	

Table 2. Correlation of the ovarian response to stimulation with age and hormone levels (M±St)

Parameter	low ovarian response	4 or more oocytes retrieved	P
Age, in years	38,8±0,5	37,6±0,3	<0,05
FSH levels on the 2nd day of menstrual cycle, in nmol/l	7,8±0,4	6,4±0,2	<0,01
Anti-Mullerian hormone (AMH)	1,2±0,2	2,2±0,2	<0,005

Chances of obtaining a sufficient or ‘weak’ response of ovaries in women of late reproductive age are presented in Table 2. of retrieving 4 or more oocytes were higher in the main group (OR=1,35,p<0,05).

Table 3. Chances of retrieving a certain number of oocytes in women of late reproductive age

Number of oocytes retrieved during the puncture	Study groups		OR	p
	Main	Comparison		
1-3	32	13	-	>0,05
	34,8%	41,9		
4 and more	60	18	1,35	<0,05
	65,2%	58,1%		

During the measurement of the b-HCG blood levels on the 14th day after the embryo transfer, biochemical pregnancy was detected in 18 (24%) women from the main group and in 9 (32.1%) women from the comparison group. After 1-2 weeks during the ultrasound scanning a fetus was observed in 21.3% (16) of women from the main group and in 28.6% (8) of women from the

comparison group. Differences in pregnancy onsets between the two groups were not statistically significant.

Table 4. Effectiveness of the carried out treatment in two study groups

Pregnancy rate		Main group	Comparison group	Total
Biochemical pregnancy	n	18	9	27
	%	24	32,1	25,9
Presence of the fetus on ultrasound scans (implantation coefficient)	n	16	8	24
	%	21,3	28,6	23,3
Single child delivery	n	7	4	11
	%	9,3	14,3	10,7
Twins delivery	n	1	0	1
	%	1,3	0	0,9
Abortion	n	2	0	2
	%	12,5	0	8,3

Dynamic relationships between the FSH, AMH and pregnancy onsets in 3 age groups of women are presented in Fig1. It is noteworthy that in a subgroup of women between 37-39 years of age the frequency of pregnancy onsets was higher than in two other subgroups (34-37 years and 40-43 years).

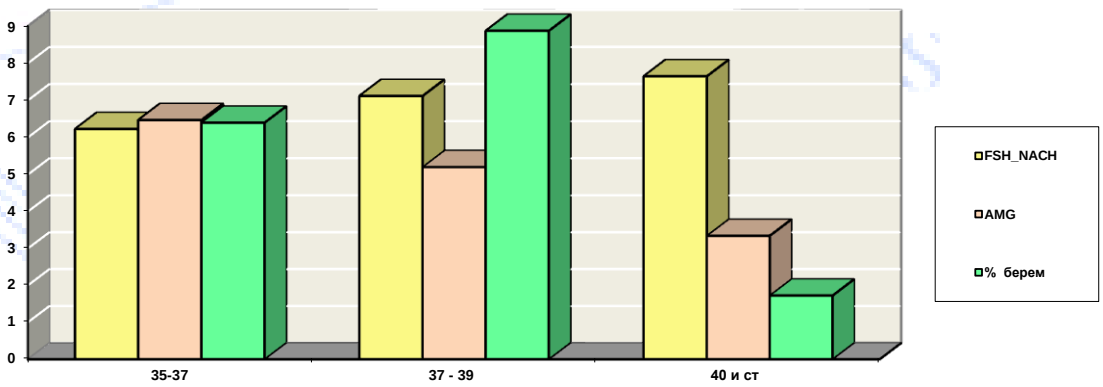

Fig.1. Dynamic relationships between the blood levels of FSH, AMH and the frequency of pregnancy in 3 different age groups.

Complex assessment of pregnancy prognosis after the ECF/ECF+ICSI programme in women of late reproductive age. A scale to assess overall probability of clinical pregnancy in women of late reproductive age undergoing ECF/ECF+ICSI programme was developed using the classification tree method. 3 points was a transition score that can be considered as a threshold. The probability of clinical pregnancy in women who score 4-5 points was 21.8 times higher than in women who have 0-3 points; at 6-7 points the probability increased by 120 times ($p<0.001$) in comparison with patients who have 0-3 points.

In order to assess probabilities of biochemical pregnancy the following scale has been developed:

Table 5. The prognostic index scale of clinical pregnancy prediction in women of late reproductive age undergoing the ECF/ECF+ICSI programme

Parameter	Value	Point
Age, in years	Age ≥ 40	0
	Age < 40	1
History of induced abortions	Present	0
	Absent	1
Ovarian function insufficiency	Present	0
	Absent	1
History of tubectomy	One-sided	0
	No	1
	Two-sided	2
FSH, in IU/l (on the 2ndd.m.c.)	≥6,5	0
	4,5- 6,5	1
	< 4,5	2

Table 6. The prognostic index scale of biochemical pregnancy prediction in women of late reproductive age undergoing the ECF/ECF+ICSI programme

Parameter	Value	Point
Age, in years	Age ≥ 40	0
	Age <40	1
History of induced abortions	Present	0
	Absent	1
Ovarian function insufficiency	Present	0
	Absent	1
Chronic salpingo-oophoritis	No	0
	Yes	1
Duration of embryo cultivation	2, 4, 5 days	0
	3 days	1
FSH, in IU/l (on the 2ndd.m.c.)	FSH ≥6,5	0
	4,5≤ FSH <6,5	1
	FSH <4,5	2

Similarly, to the previous scale, 3 points was a transition score that can be considered as a threshold. The probability of biochemical pregnancy in women who score 4-5 points was 20 times higher than in women who have 0-3 points ($p<0.001$); at 6-7 points the probability increased by 159 times in comparison with patients who have 0-3 points.

Conclusions

The quantity of retrieved oocytes and quality of in-vitro fertilization and cultivation show negative correlation with the basal levels of FSH and positive correlation with AMH. Inhibin B blood levels are correlated with the quantity of class ‘C’ embryos on the 3rd day after fertilization.

In patients of late reproductive age recombinant FSH and urinal gonadotropin are equally effective in stimulation of ovaries, fertilization of oocytes and successful pregnancy conceptions.

In patients who were given urinal gonadotropin, on the day of triggering the final maturation of oocytes the levels of the luteinizing hormone were 2 times lower than in women who were given recombinant FSH.

Use of urinal gonadotropin was characterized by shorter duration of stimulation. Also, the thickness of the endometrium during the embryo transfer to the uterus was higher in the urinal gonadotropin group.

The frequency of pregnancy onsets was dependent on the overall score on the prognostic index scale of clinical pregnancy prediction in women of late reproductive age undergoing the ECF/ECF+ICSI programme. 3 points is a transition score that can be considered as a threshold.

The probability of clinical pregnancy in women who score 4-5 points was 21.8 times higher than in women who have 0-3 points; at 6-7 points the probability increased by 120 times ($p<0.001$) in comparison with patients who have 0-3 points.

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