International Journal of Medical and Health Research
ISSN: 2454-9142, Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 2; Issue 9; September 2016; Page No. 84-88

The comparison of GNRH agonist administration versus vaginal progesterone on serum progesterone in luteal phase in ovarian hyperstimulation and intrauterine insemination cycles in unexplained infertility

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Abstract
Background and aim: Luteal phase supplementation allows programming of treatment cycles in this trial we compared the effect of GnRH agonist administration with vaginal progesterone on serum progesterone in luteal phase in control ovarian hyperstimulation and intrauterine insemination cycles. Methods and materials: In this clinical trial 242 patients with UEI (unexplained infertility) candidate for ovarian stimulation and intrauterine insemination referring to infertility ward of Mirza khuchak khan Hospital were recruited. The patients were randomized into two groups (group A or Progesterone group) and (B or GnRH agonist group).The luteal phase was routinely supplemented in 121 patients (group A) with 400mg/day/vaginally of natural micronized progesterone starting 1 days after the IUI (intrauterine insemination) for two weeks. In B group (121 patients) a single dose of GnRH agonist (triptorelin 0.1mg) subcutaneously was injected 4 days after IUI. Then serum progesterone level was compared 10 days after IUI in two groups. Results: Totally we evaluated 240 patients with mean age 28.42±4.02 (20-38). The mean serum level progesterone in A group was 33.45±18.12ng/ml and in B group was 32.50±23.82ng/ml and the difference between two groups was not significant (p=0.72). Also, regarding results of IUI, we found BHCG positive in 20 patients in vaginal group and 19 patients in GnRH group (p=0.86). Moreover, clinical pregnancy was detected in 15 patients in vaginal progesterone group and in 15 patients in GnRH group (p=NS). Conclusion; the GnRH agonist showed comparable effect with vaginal progesterone on luteal phase supporting in patients with unexplained infertility.

Keywords: GnRH agonist, vaginal progesterone, controlled ovarian hyperstimulation, intrauterine insemination, in vitro fertilization, unexplained infertility

1. Introduction

Implantation of the embryo into the endometrium of uterine is a critical phase in the reproductive development and in the initiation of pregnancy. The hormones (Estrogen & Progesterone) balance is very important in implantation; therefore, adequate concentrations of these hormones are essential for adequate endometrial maturation before embryo implantation [1-3]. Embryonic implantation occurs in the luteal phase and a normal luteal phase is characterized by a normal hormonal environment, normal progesterone secretion by the corpus luteum and adequate endometrial secretory transformation [4]. Corpus luteum function is dependent on LH stimulation and LH-dependent on GNRH secretion [5].

In normal condition, in the luteal phase, corpus luteum secretes progesterone and helps for establishing and maintaining pregnancy [6]. Supraphysiologic serum steroid concentrations might adversely affect LH secretion via feedback mechanisms, which in turn results in premature luteolysis and defective progesterone secretion [5]. In assisted reproduction cycles suppression of the pituitary luteinizing hormone (LH) release by gonadotropin-releasing hormone (GnRH) analogs, decreased the progesterone level. Hence, luteal phase supplementation is recommended in controlled ovarian stimulation (COS) and intrauterine insemination (IUI) [1-3].

Luteal phase supplementation or the support is common practice in infertility treatment to improve the embryo implantation rate, clinical pregnancy rate (CPR) and delivery rate, remarkably. To achieve these aims, natural progesterone and HCG (Human chorionic gonadotropin) as two therapeutic agents, are regularly used to support the luteal phase [7]. The mechanism of the presumed beneficial effect of luteal phase agonist administration is poorly defined. It is hypothesized that GNRH agonist may support the corpus luteum by stimulating the secretion of luteinizing hormone by pituitary gonadotropic cells, or by acting directly on the endometrium through the locally expressed receptors [8].The benefits of a single low-dose administration of a GNRH agonist at the time of implantation 6 days after fertilization have been recently reported in ICSI and oocyte donation cycles by Tesarik *et al*., [8, 9]. Due to patient comfort and effectiveness, the intravaginal progesterone supplementation has gained wide application as a first-choice luteal-support treatment and there is the solid body of evidence in previous reports that indicated vaginal progesterone is at least as effective as IM (intramuscular) progesterone at providing luteal support in induced cycles [10, 11].

Luteal phase supplementation allows programming of treatment cycles, which helps to organize more efficiently the activities of in vitro fertilization (IVF) centers, and has emerged as the standard of care in most centers worldwide.

Hence, in this study we compared the effectiveness of GnRH agonist with vaginal progesterone as luteal phase supplementation on progesterone serum level and pregnancy rate in control ovarian stimulation and intrauterine insemination cycle.

2. Methods and materials

This study was designed a single-center, randomized, controlled trial to compare the effect of a subcutaneously GnRH agonist (triptorelin) administration versus vaginal progesterone on serum progesterone in the luteal phase and pregnancy rate in ovarian hyperstimulation and IUI cycles in unexplained infertility patients.

The study protocol was approved by ethical committee of Tehran University of Medical sciences (registration code. IRCT201205159762N1). Furthermore, the study procedure was explained to all patients and written informed consent was taken.242women who were candidates for IUI referring to the infertility center of Mirza khuchak khan Hospital (Tehran, Iran) were included in the study.

The inclusion criteria were as follow: age<40years old, FSH<10 U/ml, normal prolactin levels, normal thyroid function, normal uterine cavity and bilateral tubal patency assessed by hysterosalpingography (HSG) and/or laparoscopy during 6 month ago, regular menstrual cycles with mid-luteal progesterone>10ng/ml in previous cycles and duration of infertility at least 1 years for each case. Furthermore, in sperm analyzes: ≥20 million sperms/cc,>50% motility,>30% normal morphology based on WHO criteria.

Exclusion criteria: The ovarian surgery history, single ovary, polycystic ovary (PCO) in sonography, hypogonadism hypogonadotropic.

After enrollment in the study, transvaginal ultrasonography was performed for patients on day 3 of the cycle and clomiphene 100mg/daily was started from 3rd day to 7th day of menstrual cycles and on days 7 – 8 of the cycle HMG (Menogon, Ferring, Germany) at a dose of 75 IU per day. Ovarian response was assessed based on transvaginal sonography finding at the 10th day of each cycle. If a leading follicle with a mean diameter >18 mm was detected at the transvaginal ultrasound scan, 1000 IU of HCG (Choriomon INC, Switzerland) was administered intramuscularly. When >3 follicles >18mm were detected by ultrasound on the day of HCG administration, the cycle was canceled.

Semen samples were taken by masturbation and collected in sterile containers. After liquefaction of the fresh ejaculate semen, the volume, concentration, and motility were assessed according to World Health Organization criteria. Swim-up was the preferred method for semen preparation because the lower limit of total sperm number was >20milion/ml and the basal total sperm motility was>50%and normal morphology >30%in all of the infertile couples who were included in the study. In the swim-up technique, one-fourth of the semen was taken into a tube and sperm medium containing human serum albumin (Sperm Rinse, Vitrolife, Kungsbacka, Sweden) was added to the semen in a 1:1 proportion. The supernatant was separated after 10 min of centrifugation at 600g.we added 0.25ml of sperm medium over the pellet at a 45 angle; incubation was then performed at 37C for 1 h. After the procedure, sperm concentration, sperm motility, and sperm morphology were evaluated and semen was stored in an incubator at 37 C until the time of insemination.

IUI procedure and luteal phase support

A single insemination was performed 36 hours after HCG injection, in both groups using a catheter (Cook, IUI catheter, Australia) inserted through the cervix. The procedure was performed in the dorsal lithotomy position, with the cervix exposed using a bivalve speculum. The cervix was cleaned with a dry sterile swab and the insemination catheter connected to a 2ml syringe was gently passed through the cervical canal. When it reached the uterine fundus level, the sperm suspension contained in the syringe was expelled. The women remained in the supine position for 15-20 minutes following insemination. Then the patients were randomized by a computer-generated randomization program in two groups (group A or Progesterone group) and (B or GnRH agonist (triptorelin) group).

The luteal phase was routinely supplemented in group A with 400mg/day/vaginal progesterone (Cyclogest, Actavis, UK) 1 day after the IUI procedure for two weeks.

In B group a single dose of triptorelin 0.1mg (Decapeptide, Ferring, Germany) subcutaneously was injected 4 days after IUI. Then serum progesterone level was measured 10 days after IUI in two groups. Fourteen days after the insemination, a quantitative serum value of B-HCG was obtained, as a result of >10IU/ml considered to be positive. When B-HCG was positive a second B-HCG test and a primary transvaginal ultrasound were performed 2 weeks later (21 days after insemination).Pregnancy was defined as a positive B-HCG result after an IUI cycle. Clinical pregnancy was considered when the embryonic sac was seen by vaginal ultrasound from the fifth week of pregnancy.

3. Statistical analysis

Data were expressed as the mean ± SD; continuous variables were compared with Student's t-test. The x2-test was used to compare clinical outcome between the two groups. The analysis was carried out using the statistical package for social sciences (SPSS Inc., USA) (version 20). $P < 0.05$ was considered significant.

4. Results

Totally we evaluated 240 patients with mean age 28.42±4.02 (ranged 20-38) years in this trial. The mean serum level progesterone in A (progesterone group) was 33.45±18.12ng/ml and in B (GnRH or triptorelin group) was 32.50±23.82ng/ml and the difference between two groups was not significant (p=0.72).Moreover, pregnancy sac was detected in 15patients in vaginal progesterone group and in 15 patients in GnRH group (p=NS).also, regarding results of IUI, BHCG positive was detected in 20 patients in vaginal group and in 19 patients in GnRH group (p=0.86). Furthermore, the mean endometrial thickness was 7.43±1.39mm in group A and 7.20±1.42mm in group B and difference between two groups was not significant. (Table 1, 2).

Table1: Demographic and anthropomorphic findings in two groups

variables		Mean	SD	P value
age	*A	28.2167	4.20521	0.42
	*B	28.6333	3.83906	
count of sperm	A	60.4750	34.02223	0.88
	B	61.0917	32.50365	
motility of sperm	A	60.6833	18.68131	0.91
	B	56.8250	16.46267	
morphology of sperm	A	46.3917	21.42813	0.33
	B	43.8250	19.93463	
FSH(IU/l) on day3	A	6.2783	2.20542	0.23
	B	5.9792	1.61437	
LH(IU/l) on day3	A	6.9950	3.82084	0.77
	B	7.1467	4.22810	
duration of infertility	A	4.2500	2.60977	0.77
	B	4.1500	2.89203	
mid luteal progesterone(nmol/l)	A	33.4533	18.12315	0.72
	B	32.5058	23.82477	
leading follicle	A	1.9500	1.12907	0.16
	B	1.7667	.91425	
antral follicular count	A	13.7083	4.28677	0.40
	B	14.1833	4.60541	
endometrial thickness(mm)	A	7.4325	1.39767	0.21
	B	7.2033	1.42911	
Type of infertility	A	Primary	96(79%)	0.001
		Secondary	25(21%)	
	B	Primary	91(75%)	
		Secondary	30(25%)	

*A =progesterone group, *B =GnRH or triptorelin group

Table 2: Pregnancy rate and clinical pregnancy rate in progesterone and GNRH agonist groups

	Group A (progesterone), n=120	Group B (triptorelin), n=120	p
Pregnancy rate rate %	20/120 (16.6%)	19/120 (15.8%)	NS
Clinical pregnancy rate%	15/120 (12.5%)	15/120 (12.5%)	Ns

5. Discussion

The luteal phase is the result of intermittent stimulation of the corpus luteum by the pituitary luteinizing hormone, and it is different in ART cycles compared with natural cycles. Luteal phase deficiency is a common feature of cycles resulting from stimulation of follicular development [4] and leads to a decreased embryo implantation rate, a lower pregnancy rate, and an increased miscarriage rate when pregnancy's established [7]. In normal ovulatory women, physiological feedback mechanisms ensure the presence of only one or two dominant follicles. These mechanisms are disturbed, however, in stimulated IUI cycles with a multimolecular ovarian response, leading to high levels of steroids (progesterone and estradiol). Together with inhibin A, this results in the suppression of pituitary LH and FSH secretion to very low levels [12]. The low levels of LH may result in a lack of corpus luteum support, which causes low progesterone levels and a short luteal phase in this cycles [13, 14]. The outcome of intrauterine insemination (IUI) cycles is largely dependent upon the quality of the luteal phase of the menstrual cycle. A good quality luteal phase requires optimum follicular development, ovulation and production of a corpus luteum with adequate luteinization of granulosa cells [15]. Controlled ovarian hyperstimulation is a technique commonly utilized with assisted reproductive technologies. It has the advantage of increasing the number of oocytes available for fertilization, thus improving pregnancy rates per stimulated cycle [16]. The reasons for luteal deficiency are not yet fully understood. To cope with this problem, luteal phase support can be provided by HCG or progesterone. According to some reports, GNRH agonist administration can support the luteal phase [8, 9]. It seems that luteal phase support by GNRH agonist have any adverse effect, but caution is recommended until more details on the effect of luteal phase GNRH agonist administration are available. Desensitization is related to the extent of exposure and dose of GNRH, and perhaps short-acting and low-dose GNRH agonist could have an agonistic effect without inducing desensitization. Thereby producing a stimulatory secretion of LH by pituitary gonadotropic cells and maintaining progesterone and E2 levels without the need of additional progesterone [17, 18].

IUI is a softer; more patients' friendly and inexpensive treatment option for couples undergoing supported reproduction compared with other treatment techniques in this field [19]. IUI is applied worldwide as a cost-effective and, in some cases, a successful first line of treatment [20, 21], and some studies indicated that the success rates of IUI in patients with unexplained infertility were similar to those attained with IVF/ICSI methods [22].

In this clinical trial, we compared GNRH agonist and vaginal progesterone in luteal phase supporting in IUI cycles. The mean serum level progesterone 10 days after IUI in vaginal progesterone group was 33.45±18.12ng/ml and in GnRH group was 32.50±23.82ng/ml and the difference between two groups

was not significant (p=0.72). The pregnancy occurred in 20 patients in vaginal group and in19 patients in GNRH group and difference between two groups was not significant (p==0.86).The success of any form of ART technique depends on careful patient selection, proper treatment allocation, and adequate oocyte recruitment, in this case, the patients in our study were properly matched and the difference between demographic data in two groups as age, duration of infertility and type of infertility was not significant. In this trial we signified no difference between two groups regarding serum progesterone 10 days after IUI, pregnancy rate, however, we could not show the pregnancy improvement rate, because we did not include a control group to compare the results of pregnancy rate in supported and unsupported patients in this survey. Significant differences in mid-luteal progesterone and pregnancy rate were not found among women with GNRH agonist administration compared with the vaginal progesterone group. A similar study reported that administration of 0.1mg of the GNRH agonist (triptorelin) at the time of implantation versus placebo did not improve pregnancy outcome in intrauterine insemination cycles [23].

Regarding the effectiveness of GnRH analogs during IUI cycles, Pirad *et al* in a study indicated that intranasal administration of buserelin (GnRH antagonist) may be effective in follicular maturation activating and providing luteal phase support in patients undergoing assisted reproduction techniques (ART) [18]. Furthermore another study by Oliveira *et al*. signified that the luteal-phase single-dose GnRH-a administration can increase implantation rate in all cycles and CPR per transfer and ongoing pregnancy rate in cycles with GnRH-antagonist ovarian stimulation protocol [24]. The mentioned studies in this article signified supported patients were superior to unsupported, regarding pregnancy outcomes, however, Eskandar in a study specified that the primary outcomes in supported patients were not superior to those of the control group and the different between supported and control groups was not significant. Therefore, the author concluded that GnRH agonists may be used in IUI cycles to prevent the occurrence of premature LH surges during ovarian stimulation, but clinical and ongoing pregnancy or live birth are not affected by the GnRH agonist administration. Moreover, they declare, the frequency of negative outcomes, such as ectopic pregnancies and miscarriage was not different in two groups [25].

This was an uncontrolled study that limits the ability to compare the results of pregnancy outcomes with unsupported luteal phase, so, further controlled trials will answer the question regarding whether these agents (Estrogen & progesterone) are true condition modifiers.

Conclusion; the GnRH agonist showed comparable effect with vaginal progesterone on luteal phase supporting in patients with unexplained infertility.

6. Acknowledgements

We would like to thank the nursing, administrative and secretarial staff of the gynecology department and clinic at Vali-Asr hospital for their contribution to the maintenance of our patient record without which this project would have been impossible.

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