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Estrogen in Luteal Phase Support: Effects on IVF-ICSI Antagonist Protocol Pregnancy Results

Luteal Faz Desteğinde Östrojen: IVF-ICSI Antagonist Protokolde Gebelik Sonuçları Üzerine Etkisi

Cemre Alan, Hüseyin Görkemli

Necmettin Erbakan University Meram Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Turkey

Abstract

Aim: This study aimed to investigate the effect of luteal phase support (LPS) with estradiol in addition to progesterone on pregnancy outcomes in patients who underwent ovulation induction with GnRH antagonist protocol in in vitro fertilization- intracytoplasmic sperm injection (IVF-ICSI).

Material and Method: This retrospective study was carried out at IVF Unit of our faculty. The study enrolled 128 patients undergoing ICSI on an antagonist protocol for controlled ovarian hyperstimulation. Study group administered 7.8 mg transdermal estradiol (E2) daily in addition to progesterone for LPS (n=64). Control group administered only progesterone for LPS (n=64). All women received 200 mg progesterone 3x1 intravaginal daily and 50 mg progesterone intramuscular injection per two days for LPS. Blood samples were drawn 12 days after embryo transfer for β-hCG. If the result is negative, treatment was discontinued, if positive, estradiol was discontinued and progesterone support was continued until the 10th week of gestation. Pregnancy outcomes were the main endpoint.

Results: There was no difference between groups in terms of biochemical pregnancy, clinical pregnancy, abortus and ongoing pregnancy rates.

Conclusion: In our study, the use of estrogen for luteal phase support in GnRH antagonist protocol did not show any difference on pregnancy outcomes.

Keywords: Luteal phase support, estradiol, GnRH antagonist, ICSI

Öz

Giriş: Bu çalışma GnRH antagonist protokolle IVF-ICSI yapılan hastalarda luteal faz desteğinde (LFD) progesterone ek olarak östradiol verilmesinin gebelik sonuçlarına etkisini incelemeyi amaçlamaktadır.

Gereç ve Yöntem: Bu retrospektif çalışma fakültemizin Yardımla Üreme Teknikleri Ünitesi' nde yapılmıştır.Tıp Fakültesi Yardımla Üreme Teknikleri Merkezinde yapılmıştır. Çalışmaya GnRH antagonist protokolle kontrollü ovaryan stimülasyon uygulanacak 128 hasta katılmıştır. Çalışma grubuna LFD'de progesterona ek olarak günlük 7.8 mg transdermal estradiol (E2) uygulanmıştır (n=64). Kontrol grubu LFD için sadece progesteron kullanmıştır (n=64). Tüm kadınlara LFD' de günlük 200 mg progesteron 3x1 intravajinal ve gün aşırı 50 mg progesteron intramuskuler uygulanmıştır. β-hCG için kan örnekleri embryo transferinden 12 gün sonra alınmıştır. Sonuç negatifse tedavi sonlandırılmış, pozitifse estradiol sonlandırılıp progesteron desteği gebeliğin 10. Haftasına kadar sürdürülmüştür. Gebelik sonuçları esas hedef olarak belirlenmiştir.

Bulgular: Gruplar arasında biyokimyasal gebelik, klinik gebelik, abortus ve devam eden gebelik oranları açısından fark bulunamadı.

Sonuç: Çalışmamızda GnRH antagonist protokol LFD'de östrojen kullanımı gebelik sonuçları üzerinde farklılık göstermedi.

Anahtar Kelimeler: Luteal faz desteği, estradiol, GnRH antagonist, ICSI

Corresponding *(İletişim)*: Cemre Alan, Department of Obstetrics and Gynecology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Turkey
E-mail *(E-posta)*: drcemrealan@gmail.com
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INTRODUCTION

The stimulated IVF cycles are associated with the largely defective luteal phase.[1] In assisted reproductive techniques (ART) in order to optimize endometrial receptivity, progesterone supplementation is frequently administered throughout the luteal phase.[2] Luteal phase support (LPS) in ART includes drug treatment to increase implantation. However, there is no consensus on the optimal treatment scheme.[3] Natural estradiol is added as a pretreatment to the GnRH antagonist cycle.[4]

Earlier studies show that follicle stimulating hormone (FSH) intra-cycle elevations can be effectively prevented by utilizing the natural negative feedback on the hypothalamus-pituitary-over axis induced by E2, follicle synchronization can be increased and eventually more coordinated follicle development can be achieved, resulting in more mature oocytes being collected.[5,6] Follicular development and granulosa cell proliferation are increased by estrogens and FSH.[7] Decrease of mid-luteal estradiol levels under only progesterone treatment might be associated with a decrease in pregnancy rates. Also women with mid-luteal estrogen fall might suffer from luteal vaginal bleeding which may be associated with implantation failure.[8] During embryo implantation, the primary factors necessary for endometrial receptivity are ovarian steroids; estrogen and/or progesterone which act primarily through their respective nuclear receptors.[8] The studies aiming to evaluate estrogen administration in LPS so far have reached questionable results.

To our knowledge, there are many studies examining the effect of estrogen on LPS in IVF- ICSI cycles. This study aimed to investigate the effect of luteal phase support (LPS) with estradiol in addition to progesterone on pregnancy outcomes in patients who underwent ovulation induction with GnRH antagonist protocol. However, this study is unique in that it investigated the effect of "transdermal" estradiol on pregnancy outcomes in only "GnRH antagonist" cycle.

MATERIAL AND METHOD

Patients

This retrospective observational study included 128 women undergoing ICSI on a GnRH antagonist protocol at reproductive medicine center of IVF Unit of our faculty between January 2005 and December 2015.

The inclusion criteria were as follows: i) women aged between 20-44 years old, ii) women with an early follicular phase serum FSH level of less than 15 IU / L, iii) women who underwent for the first or second IVF cycle, iv) women with a serum E2 level below 4000 pg / ml on the day of hCG injection v) no diagnosed chronic rheumatologic and cardiological disease.

Control group consisted of 64 women who were administered i.m. and vaginal progesterone for LPS; study group consisted of 64 women who were administered transdermal E2 in addition to this treatment. ICSI indications included: tubal factor, male factor, age, endometriosis and unexplained infertility. Patients in the GnRH antagonist cycle received transdermal (7.8 mg daily) E2 in the luteal phase in addition to routine treatment. The LPS was continued until 12 days after embryo transfer.

It was determined randomly which patient would be given estradiol in luteal phase support. Each patient was included in the study for a single cycle. The number of embryo transfers was at least 1, at most 2 for each patient.

Treatment Protocol

Ovarian stimulation was performed with subcutaneous (SC) injection of FSH (Puregon® 300 IU MSD- follitropin beta, Germany), starting with a dose of 150-450 IU on Day 2 of the menstrual cycle. The dose of FSH is adjusted according to the body mass index (BMI), the response of antral follicles, basal FSH, and previous ovulation, if any. When needed, FSH doses were changed starting from the fourth day of stimulation based on ultrasound findings and E2 blood levels. A GnRH antagonist (Cetrotide; Merck-Serono Pharmaceuticals, Italy) was administered at a dose of 250µg 0.5mL/day starting when the lead follicle reached 13-14mm in diameter, until the day of hCG injection.

Ovulation was induced by a SC injection of 250 mcg of recombinant hCG (Ovitrelle, Merck-Serono Pharmaceuticals, Italy) when three follicles of at least 18 mm in diameter were observed on ultrasound examination. Oocyte pickup was performed 34 to 36 hours after hCG injection. ICSI was performed in all metaphase II oocytes. All patients underwent embryo transfer with ultrasound guidance on Day 3.

Luteal Phase Support

Supplementation with intravaginal progesterone 600 mg daily (3x200 mg) (Progestan ® 200 mg, Koçak Farma, Turkey) and 50 mg intramuscular (Progynex ® 50 mg, Koçak Farma, Turkey) per two days were administered to all patients on the day of oocyte retrieval.

The LPS of 64 patients who constituted the control group was planned in this way. In the study group, 64 patients received 7.8 mg estradiol transdermal form (Climara ® forte 7.8 mg/ 25 cm^2, Bayer, Turkey) to be replaced daily in addition to the treatment above. Transdermal route of estrogen was preferred to prevent the first pass effect in the liver. After 12 days of embryo transfer, serum β-hCG test was performed in all patients. If the outcome was negative, treatment was discontinued. If positive, estradiol was discontinued and progesterone supplementation was continued until the 10th week of gestation. Clinical pregnancies were detected with the confirmation of a fetal heartbeat on transvaginal ultrasound examination.

Embryo transfer

ICSI was routinely performed in all fertilization procedures. Embryos were cultured until the day of transfer (Day 2,3 or 5 due to development of embryos) in HEPES buffered

medium before transfer. The same embryologist performed all embryology procedures and embryo assessments in this study. All women received one or two embryos categorized as Time Table Slow (TTS), Time Table Normal (TTN) or Time Table Good (TTG). Embryo transfers were performed two, three or five days after oocyte retrieval. The patients were instructed to have a full bladder to provide for an acoustic window to visualize the uterus in preparation for the ultrasound-guided embryo transfer. Each patient was placed in the lithotomy position without anesthesia or sedation. The embryo transfers were performed with a Wallace® Sure-Pro® Embryo Replacement Catheter with soft obturator (23 cm), and abdominal ultrasound was performed using a 5 MHz probe (GE Logiq 400 Pro Series, General Electric Company, Pewaukee, WI).

Laboratory methods

Serum LH, E2, and β-hCG levels were determined by chemiluminescence immunoassay (ADVIA Centaur® CP Immunoassay System, Siemens). Serum FSH levels were determined by the solid phase two-stage chemiluminescence immunoassay method on the IMMULITE® 2000 immunoassay System (Siemens device).

Statistical method

Statistical analyses were performed with SPSS 16.0 for Windows (IBM SPSS Statistics, Chicago, IL, USA). Pearson's Chi-square or Fisher's exact test was used to analyze the exact variables. Independent sample t-test was used to analyze the variables with normal distribution. Mann-Whitney U-test was used to evaluate the variables without normal distribution.

Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). A p-value < 0.05 was considered to indicate a statistically significant difference for all the statistical tests.

RESULTS

Data of 132 patients were obtained. It was observed that four patients discontinued the treatment voluntarily. The remaining 128 women were included in the study. No drug-related side effects were reported in this study. **Table 1** summarizes the patient and cycle characteristics.

Mean age was older in study group than control group (p<0.001). Mean day 2 FSH, LH and E2 values were higher in study group than control group (p=0.015, p=0.024, p=0.001, respectively). There was significant difference between two groups with respect to the numbers of embryos transferred, day of embryo transfer and OPU day endometrium thickness (p=0.002, p<0.001, p=0.001, respectively) (**Table 1**). However, transferred embryo quality did not differ between groups (p=0.890). Similarly, both groups gave comparable rates of (+) β-hCG results on the 12th day after embryo transfer with %39.1 in study group and %45.3 in control group (p=0.474).

Patients with β-hCG (+) result in the study were classified with respect to their clinical status. Patients with β-hCG (+) result but no gestational sac (GS) on ultrasound (USG) were identified as biochemical pregnancy; patients with GS and fetal heart beat (FHB) on ultrasound were identified as clinical pregnancy; patients who reached the 16th gestational week according to the last menstrual period and had FHB (+) fetus on USG were identified as ongoing pregnancies; patients who aborted after GS or FHB was seen on USG were identified as abortus. There was no significant difference between groups in terms of biochemical pregnancy, clinical pregnancy, ongoing pregnancy and abortus rates (**Table 2**).

Table 1. Patient and cycle characteristics

	Study group	Control group	p value
BMI*	22.06±1.75	22.28±1.66	0.516**
E2 value on OPU day* (pg/mL)	1463.81±1031.1	1252.36±1092.06	0.056**
Oocyte count*	6.91±4.01	6.87±3.84	0.996**
Progesterone value of patients whom β-hCG* (+)	41.60±13.84	36.41±11.86	0.328**
Average daily gonadotropin dose used* (IU)	177.73±21.88	175.39±20.65	0.590**
Duration of induction until β-hCG day* (days)	10.00±0.8	10.02±0.83	0.911**
Age*	32.92±5.51	29.06±5.55	<0.001**
Day 2 FSH value* (mIU/mL)	6.81±3.22	5.67±2.25	0.015**
Day 2 LH value* (mIU/mL)	5.22±8.45	3.17±1.48	0.024**
Day 2 E2 value* (pg/mL)	43.56±30.08	28.69±9.94	0.001**
Number of embryos transferred*	1.58±0.5	1.83±0.38	0.002**
Day of embryo transfer*	3.23±1.11	3.88±1.05	<0.001**
Endometrium thickness on OPU day* (mm)	9.53±2.2	8.30±0.94	0.001**

*Data are presented as mean ± SD, ** P-value for Mann-Whitney U test

Table 2. Comparison of groups in terms of pregnancy achievement

	Study group	Control group	Total	p value
Biochemical pregnancy*	3 (4.7%)	6 (9.4%)	9	0.300**
Clinical pregnancy*	22 (34.4%)	23 (35.9%)	45	0.853**
Ongoing pregnancy*	20 (31.2%)	21 (32.8%)	41	0.850**
Abortus *	2 (3.1%)	2 (3.1%)	4	1.000**

* Data are presented as n (%). ** P-value for Pearson Chi-Square test.

DISCUSSION

Stimulated IVF cycles are usually associated with abnormal luteal phase.[1] If hormone supplementation is not performed in the luteal phase of an IVF cycle, serum E2 and progesterone levels usually reduce to low levels. The decrease in sex steroids in the luteal phase is in association with reduced implantation and pregnancy rates.[9] Different doses and types of LPS treatments were developed to increase the probability of pregnancy. According to studies on pregnancy outcomes, the optimal balance between E2 and progesterone is necessary for the normal progression of early pregnancy. Estrogens in the form of 17 β-E2 or E2 valerate are used in LPS with the view that estrogen deficiency occurs after oocyte retrieval.[10] Estrogen

can be administered orally, intravaginally or transdermally. In this study, transdermal route was preferred to avoid hepatic metabolism which eliminates the majority of oral administration.

According to Tavaniotou and Devroey, the luteal phase duration was shortened in the cycles induced by GnRH antagonist compared to the natural cycles, the LH level decreased in the luteal phase and the level of progesterone increased. Low LH levels and shortened luteal phase suggest the LPS in GnRH antagonist protocol.[11] Studies investigating the use of estrogen in LPS to increase the success of the GnRH antagonist protocol are more frequently seen in recent years.

In the present study, addition of transdermal E2 to luteal progesterone in GnRH antagonist cycles did not give beneficial effects on pregnancy outcomes. Although the control group was younger and the number of embryos transferred was higher, quality of the transferred embryos and the pregnancy results did not differ between groups. Endometrial receptivity may had played a role in this. Because the double wall thickness of endometrium on OPU day was higher in the study group than control group.

Fatemi et al. studied luteal hormone profiles in GnRH antagonist cycles for the first time, and they suggested that addition of E2 to progesterone for LPS was not associated with a significant effect in the endocrine profile of the luteal phase.[3]

Transdermal or vaginal route of estrogen is preferred to prevent the first pass effect in the liver. Serna et al. used transdermal E2 in patients who underwent GnRH long agonist or antagonist protocol; no improvement in pregnancy or implantation rates were observed in their study.[12]

In a prospective randomized controlled study of Engmann et al., patients who underwent ovulation induction with long GnRH agonist, GnRH antagonist and microdose GnRH agonist protocol were analyzed for the benefit of luteal vaginal estrogen administration. There was no significant difference in clinical pregnancy rates between groups in microdose GnRH agonist and GnRH antagonist protocols.[13] In the same study, other randomized studies,[14-16] which resulted in increased pregnancy rates after luteal E2 support, are reported to be studies incluiding more than one cycle of the same patient. This can be considered as one of the limitations of these studies.

Gelbaya et al. examined 10 randomized controlled trials conducted between January 1960 and March 2007 in a meta-analysis; the women who underwent IVF-ICSI with the GnRH agonist or antagonist protocol were compared in terms of ongoing pregnancy and implantation rates per embryo transfer; there was no statistically significant difference between the groups who administered progesterone alone and progesterone plus E2 in LPS.[17] Similar to our study, it was found that there was no advantage of E2 supplementation in addition to progesterone in LPS in terms of pregnancy rates.

In the meta-analysis of Kolibianakis, three randomized controlled trials mentioned above[3,12,13] were examined.[18] Patients were compared in terms of β-hCG positivity rate, clinical pregnancy rate and live birth rate per patient and no difference was found between the groups.

In a meta-analysis by Jee et al. a total of 9 randomized controlled trials including patients undergoing IVF-ICSI with GnRH agonist and GnRH antagonist cycles were analyzed; the patients were compared in terms of clinical pregnancy rate per patient, clinical pregnancy rate per embryo transfer, implantation rate, ongoing pregnancy rate per patient, clinical abortion rate and ectopic pregnancy rate. In terms of all IVF results, there was no difference between the progesterone-treated group and the progesterone-plus E2 group in LPS. In this meta-analysis, 3 studies using GnRH antagonist cycle were examined, and similar pregnancy results were observed between the two groups.[19]

In the systematic review made by van der Linden et al. and published in Cochrane database, studies including various ovulation induction protocols (clomiphene citrate, gonadotropins, GnRH agonist, their combinations or antagonist protocol) were examined; they described that the addition of estrogen or hCG to progesterone did not improve the results.[20]

In a retrospective study conducted by Chang et al., poor responder patients in the GnRH antagonist protocol whom had no E2 supplementation were compared with whom had E2 supplementation in two different protocols (In one group, oral estradiol valerate 4 mg / day was started on the 21st day of the cycle and given to the 3rd day of menstruation; in the other group it was continued until hCG day) during LPS. The cycle cancellation rate was found to be significantly lower in the group with E2 supplementation in the luteal phase. The number of oocytes collected in the luteal estrogen given group was found to be significantly higher. In addition, the number of normal fertilized embryos and good quality embryos were found to be higher in luteal E2 given group, although not statistically significant. When two luteal E2 given group was compared with each other, there was no significant difference between the groups in terms of embryological data, but the rates of ongoing pregnancy were found to be higher in the group that continued to be given E2 until the day of hCG.[4]

Studies with GnRH agonist and antagonist protocol suggest that there may be differences in the luteal phase dynamics in these two protocols. However, in a comparative study by Friedler et al., GnRH agonist and antagonist cycles have been shown to have similar luteal hormone profiles under the same LPS (vaginal micronized progesterone).[21]

Similar to this current study, Madkour et al. showed no beneficial effect of luteal estrogen support in GnRH antagonist protocol on pregnancy outcomes. They used 4 mg oral E2 daily.[8]

In the systematic review conducted by Pinheiro et al., they evaluated 4 prospective studies which focus on luteal estradiol support in GnRH antagonist protocol. The studies included in this systematic review used oral and transdermal route for estrogen administration. Only one study showed higher implantation rate in E2 group than study group; but there was no difference in pregnancy results.[22,23]

Huang et al. reported that E2 addition with oral route during luteal phase does not improve IVF/ICSI outcomes in GnRH agonist and antagonist cycles in their meta-analysis, adding future studies are needed to investigate other administration routes.[24]

Scheffer et al. mentioned on different routes of estrogen administration in GnRH antagonist protocol. They compared oral, transdermal patch and transdermal gel form of luteal estrogen support in GnRH antagonist protocol. All groups administrated estrogen and there was no difference in pregnancy rates between groups.[25]

Çakar et al. compared luteal administration of micronized E2 and vaginal progesterone with vaginal progesterone alone. There was no difference between groups in terms of clinical pregnancy rates, early pregnancy loss rates, incidence of luteal vaginal bleeding and implantation rates.[26]

Kasapoğlu et al. reported that independently from the embryo quality, altered E2 levels associated with dysfunctional folliculogenesis could impair endometrial receptivity. Therefore, E2 administration for LPS could be reasonable in a specific subgroup of patients. They evaluated pregnancy outcomes of patients who had a ratio of serum E2 levels on the hCG day to the number of oocytes retrieved (estradiol /oocyte ratio – EOR) levels of <100 pg/ml of estradiol undergoing antagonist ICSI cycles. One randomized group received oral estradiol (4 mg/d) plus vaginal progesterone and other group received only vaginal progesterone. Implantation rate following transfer of a single embryo and clinical pregnancy rates per embryo transfer did not differ between groups. So, they claimed that they conducted the study to find out which patient subgroup could get benefit from luteal E2 supplementation but additional estradiol did not provide further benefit to their study population.[27]

Some previous studies compared GnRH long agonist cycles in terms of LPS; progesterone alone versus progesterone and E2.[12,13] Some other studies made same comparision in GnRH antagonist cycles.[3,13,23] Different routes of E2 were used for administration in previous studies.[3,4,8,12,13] Our study is different with using transdermal E2 in LPS in GnRH antagonist protocol. In our study, the addition of transdermal E2 to progesterone in luteal phase did not show any beneficial effects on pregnancy outcomes.

This study has several limitations. Due to the limited sample and retrospective nature, the groups were not homogeneously distributed. Anyway, embryo quality was similar between groups. Long term pregnancy follow-up records and number of live births are needed to express IVF success.

CONCLUSION

In conclusion, according to this current study the addition of transdermal estradiol to progesterone in LPS in GnRH antagonist cycle does not improve pregnancy outcomes. For a more objective evaluation, prospective studies comparing the numbers of live births with larger samples, demographic characteristics, and more homogeneous distribution are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Necmettin Erbakan University Faculty of Medicine Ethics Committee (Date: ……. , Decision No: 2016/503).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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