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Effect Of Estradiol Progesterone Combination On Pregnancy In IVF-ICSI-ET Cycles

Östrodiol Progesteron Kombinasyonunun İVF – ICSI – ET Sikluslarında Gebe Kalmaya Etkisi

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Abstract

Objective: There are various treatment protocols in which different gonadotropins are used with or without pituitary down-regulation by using gonadotropin-releasing hormone (GnRH) agonists or antagonists. Since no single protocol suits every patient, the treatments should be individualized. Within the scope of this research, we aimed to elucidate the pregnancy rates achieved with progesterone and progesterone estradiol (E2) combination for luteal phase (LP) support in ICSI – ET cycles with ovarian hyperstimulation using GnRH analog were compared.
Method: This study evaluated 142 infertile couples aged between 20 and 40. The patients' admission histories and physical and pelvic examination findings were recorded. Basal serum FSH, LH, E2, prolactin, TSH, and free T3 – T4 levels were measured in each patient on the second or third day of the cycle. A long protocol with GnRH agonist was applied to all patients.
Results: Of the 142 patients in the study, 71 were randomized (1:1) to receive vaginally gel progesterone and transdermal estrogen for luteal phase support, and 71 to receive gel progesterone vaginally. When the cycles with and without pregnancy were evaluated independently of the groups, a significant difference was found in terms of female age, male age, and mean gonadotropin amounts used ($p<0.05$). When the E2 measurements in the group with and without a pregnancy were examined, no significant difference was found in the basal E2 level, the E2 level on the hCG day, and the early luteal phase, that is, on the day of embryo transfer ($p=0.788$, $p=0.735$ and $p=0.474$, respectively). However, E2 levels were higher in pregnant women.
Conclusion: In conclusion, data showing the superiority of one gonadotropin option over another in IVF/ICSI treatment cycles are insufficient. The choice of gonadotropin in controlled ovarian stimulation depends on the product's availability and should be based on ease of use and cost.

Keywords: Infertility, Pregnancy, In-Vitro Fertilization, Embryo Transfer, Luteal Phase.

Özet

Amaç: Gonadotropin salgılatıcı hormon (GnRH) agonistleri veya antagonistleri kullanılarak farklı gonadotropinlerin hipofiz down-regülasyonu ile veya olmadan kullanıldığı çeşitli tedavi protokolleri vardır. Her hastaya uyacak tek bir protokol olmadığı için uygulanacak tedaviler kişiye özel olmalıdır. Bu araştırma kapsamında, GnRH analoğu kullanılarak overhiperstimülasyonunun karşılaştırıldığı ICSI – ET sikluslarındaluteal faz (LF) desteği için progesteron ve progesteron estradiol(E2) kombinasyonu ile elde edilen gebelik oranlarının aydınlatılmasını amaçladık.
Yöntem: Bu çalışmada yaşları 20 – 40 arasında değişen 142 infertil çift değerlendirildi. Hastaların başvuru öyküleri, fizik ve pelvik muayene bulguları kaydedildi. Siklusun ikinci veya üçüncü gününde her hastada bazal serum FSH, LH, E2, prolaktin, TSH ve serbest T3 – T4 düzeyleri ölçüldü. Tüm hastalara GnRH agonisti ile uzun protokol uygulandı.
Bulgular: Çalışmadaki 142 hastadan 71'i luteal faz desteği için vajinal jel progesteron ve transdermal östrojen ve 71'i vajinal jel progesteron almak üzere randomize edildi (1:1). Gebelik olan ve olmayan sikluslar gruplardan bağımsız değerlendirildiğinde kadın yaşı, erkek yaşı ve kullanılan ortalama gonadotropin miktarları açısından anlamlı fark bulundu ($p<0.05$). Gebeliği olan ve olmayan grupta E2 ölçümleri incelendiğinde bazal E2 düzeyi,

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hCG günü E2 düzeyi ve embriyo transferi günü olan erken luteal fazda anlamlı fark bulunmadı (sırasıyla p=0.788, p=0.735 ve p=0.474). Bununla birlikte, hamile kadınlarda E2 seviyeleri daha yüksekti.
Sonuç: Sonuç olarak, IVF/ICSI tedavi sikluslarında bir gonadotropin seçeneğinin diğerine üstünlüğünü gösteren veriler yetersizdir. Kontrollü ovaryan stimülasyonda gonadotropin seçimi, ürünün mevcudiyetine bağlıdır ve kullanım kolaylığı ve maliyete dayanmalıdır.

Anahtar Kelimeler: İnfertilite, Gebelik, Tüp Bebek, Embriyo Transferi, Luteal Faz.

INTRODUCTION

Infertility is the inability of a couple of reproductive age to conceive despite at least one year of regular sexual intercourse without using any contraceptive method. Infertility affects 10 – 15% of couples of reproductive age (1). The standard evaluation is the demonstration of ovulation, adequate sperm production, and normal uterine cavity on hysterosalpingography and the demonstration of tubal patency. At the end of the unprotected 12-month period, 80% of the couples can get pregnant within the first six months, and only 10% of the remaining couples can get pregnant within the following six months (2). The prevalence and main causes of infertility, female infertility alone was responsible for one-third of the cases and male infertility alone in one-fifth. In addition, the problem was seen in men and women at a rate of 39% (3).

Ovulation disorders (32%) and tubal damage (26%) were the most common causes of female infertility. The rate of unexplained infertility is approximately 9%. If a cause can be identified, a general course of treatment becomes evident. The ovaries are in constant communication with other endocrine organs. It is undeniable that the uterus is also an endocrine organ. Therefore, it should be considered that an existing endocrine disorder in women may affect fertility to varying degrees (4).

The treatment approach is purely empirical in unexplained infertility since the underlying abnormality causing infertility cannot be revealed. The wait-and-see approach consists of ovulation induction (OI) with oral or injectable drugs, intrauterine insemination (IUI) alone or combined with ovulation induction, and in-vitro fertilization (IVF). It has been reported that the pregnancy rate per cycle is 8.7 – 11.4% with OI and IUI treatment with gonadotropins (5).

The first successful delivery after in-vitro fertilization was achieved by obtaining a single oocyte in a spontaneous ovulatory cycle and performing a single embryo transfer. However, the success rate of this method is low, and clinicians today have adopted ovarian stimulation strategies. that will ensure the synchronous development of many follicles (6). Controlled ovarian stimulation (COS) is the development of a large number of follicles in the same cycle with the aim of obtaining an ideal number and quality of oocytes from the ovaries within the scope of IVF. Increasing oocyte quality and live birth rates improving ovarian response, and reducing the risk of ovarian hyperstimulation in patients with ovarian reserve is the key (7).

There are various treatment protocols in which different gonadotropins are used with or without pituitary down-regulation by using gonadotropin-releasing hormone (GnRH) agonists or antagonists. Since there is no single protocol to suit every patient, the treatments to be applied should be individualized by considering the age of the woman, ovarian reserve, endocrine status, and related conditions such as endometriosis, polycystic ovary syndrome (PCOS) and ovarian cyst (8).

It has been shown that ovarian cysts that develop with GnRH agonists can be effectively prevented in the long protocol in which oral contraceptives (OCs) were added. It is also

known that with the addition of OCs, the pituitary is suppressed for a shorter time. Less gonadotropin is needed without affecting the number of oocytes obtained and pregnancy results. In addition, it is advantageous in that it enables the IVF treatment to be programmed and prevents the unintentional use of GnRH agonists in case of spontaneous pregnancy (9).

Within the scope of this research, we aimed to elucidate the pregnancy rates achieved with progesterone and progesterone estradiol (E2) combination for luteal phase (LP) support in ICSI – ET cycles with ovarian hyperstimulation using GnRH analog were compared.

METHOD

This study evaluated 142 infertile couples aged between 20 and 40. The patients' admission histories and physical and pelvic examination findings were recorded. Basal serum FSH, LH, E2, prolactin, TSH, and free T3 – T4 levels were measured in each patient on the second or third day of the cycle. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution, and informed consent has been obtained from all participants.

Patients with serum FSH levels of 10IU/ml and E2 below 80 pg/ml measured on the second or third day of menstruation were included. Ovarian volume and antral follicle count were determined by transvaginal ultrasonography (USG). The endometrial cavity and tuba were evaluated with hysterosalpingography. IVF – ICSI – ET was prepared considering the malefactor, age factor (38≤), unexplained factors, and tubal factor indications, as the causes of infertility may differ in the patients.

A long protocol with GnRH agonist was applied to all patients. The treatment was initiated subcutaneously with a GnRH analog on the 21st day of the previous cycle. Patients were called on the second or third day of the menstrual cycle to determine whether there was pituitary down regulation. The absence of follicular activity in transvaginal USG and serum E2 below 80 pg/ml were considered down-regulation. Ovulation induction was started with a combination of recombinant FSH (rFSH) or recombinant FSH/human menopausal gonadotropin (rFSH/hMG). In order to prevent premature LH surges, the dose of GnRH analog was reduced by half and continued until the day of hCG. The Gonadotropin dose was determined by the patient's age, weight, basal E2, FSY level, ovarian volume, and previous ovulation induction response, if any.

Oocyte retrieval was performed at 35 – 37 hours from the hCG dose. Patients randomly used vaginal progesterone gel alone or transdermal E2 in addition to progesterone gel. Those who received a combination of progesterone and E2 were called Group 1, and those who received only progesterone were called Group 2. The treatment was initiated on the day of oocyte retrieval and continued according to the β-hCG result. If β-hCG was negative, both treatments were discontinued. If β-hCG was positive, estradiol treatment was discontinued, and progesterone support was continued until the 12th gestational week

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data was given as descriptive values. For comparisons between groups, the “Independent Sample T–test” was used for two groups, and the “Pearson Chi-

Square Test" was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Of the 142 patients in the study, 71 were randomized (1:1) to receive vaginally gel progesterone and transdermal estrogen for luteal phase support, and 71 to receive gel progesterone vaginally. The malefactor was found in 38% (n=31) of the patients in the first group and 38% (n=27) in the second group. Unexplained infertility was detected in 43.7% (n=27) of the patients in the first group and 53.6% (n=38) in the second group. The tubal factor was observed in 9.9% (n=7) of patients in the first group and 2.8% (n=2) in the second group. Age factor was present in 5.6% (n=4) of the patients in the first group and 2.8% (n=2) in the second group. Both age factor and male factor were determined in 2.8% (n=2) of the patients in the first group and 2.8% (n=2) of the patients in the second group. IVF – ICSI – ET procedure applied (Table 1).

Table 1. Infertility reasons for both treatment groups (Group 1 & Group 2)

	Group 1		Group 2	
	n	**%**	**n**	**%**
Male Factor	27	38	27	38
Unexplainedinfertility	31	43,7	38	53,6
TubalFactor	7	9,9	2	2,8
Age Factor	4	5,6	2	2,8
Age Factor& Male Factor	2	2,8	2	2,8

Recombinant FSH (rFSH) was initiated in 71 patients in the first group. In addition to rFSH, hMG was started in 23 patients in the first group, and rFSH was started in 71 patients in the second group. testicular sperm extraction (TESE) was performed in 25.9% (n=7) of the patients in the first group and 48.1% (n=13) in the second group because of the male factor. There was no significant difference between the two groups in the study regarding female age, male age, and infertility duration (Table 2).

Table 2. The duration of the infertility period, female age, and male age within the study groups

	Group 1	Group 2	p-value
Female Age	30,92±4,77	31,13±4,748	0,792
Male Age	34,28±5,55	35,24±5,25	0,293
InfertilityPeriod	7,24±3,42	7,69±4,25	0,834

Between the two treatment groups, baseline FSH, mean gonadotropin dose, induction time, mature follicle level, E2 level on day hCG, number of oocytes, number of oocytes retrieved, number of fertilized oocytes, number of embryos transferred, endometrial thickness and E2 level on the day of transfer, and E2 levels on the β-hCG day revealed no significance. The basal E2 level (45.74±15.45) in the second group was statistically significantly higher than in the first group (p=0.005).

On the 12th day after embryo transfer, β-hCG positivity was 28.2% (n=20) in the first group and 25.4% (n=18) in the second group. When all patients were evaluated together, β-hCG

positivity was found on Day 12 in 38 (26.8%) of 142 patients, but there was no significant difference between the groups.

Considering the estradiol measurements, no clinically significant difference was found in the measurements on the hCG day, embryo transfer day, and the 12th day of the cycle (p=0.677, p=0.363, and p=0.777, respectively).

When the cycles with and without pregnancy were evaluated independently of the groups, a significant difference was found in terms of female age, male age, and mean gonadotropin amounts used (p<0.05). In the pregnant group, the ages of men and women are younger, and the amount of gonadotropin used is also lower.

When the E2 measurements in the group with and without a midwife were examined, no significant difference was found in the basal E2 level, the E2 level on the hCG day, and the early luteal phase, that is, on the day of embryo transfer (p=0.788, p=0.735 and p=0.474, respectively). However, E2 levels were higher in pregnant women (Table 3).

Table 3. The properties of groups with and without pregnancy

	Pregnancy (n=38)	No Pregnancy (n=104)	p-value
Basal FSH	6,71±1,35	7,13±1,83	0,198
Basal E2	42,84±13,32	42,05±16,09	0,788
Female Age	29,68±4,51	31,51±4,75	0,042
Male Age	33,11±4,58	35,37±5,57	0,027
Gonadotropin usage	1948,68±572,42	2271,59±749,93	0,017

DISCUSSION

The number and quality of oocytes and embryos are important determinants of success in any IVF-ICSI cycle. There are conflicting results in the literature of studies on serum E2 and serum progesterone (P4) values on hCG day, one of the factors affecting this parameter. On the day of human chorionic gonadotropin administration, the higher the E2 value, the higher the E2 value per follicle, oocyte, and M2 oocyte. Many studies state that the high level of E2 on the trigger day does not affect IVF results but has good or bad effects (10). Blazar et al. reported that continuing clinical pregnancy rates increase as serum E2 levels rise on the hCG day until they reach an approximate plateau of 2500 pg/ml. In addition, they also stated that the increase in the number of oocytes collected during ovum pick-up (OPU) is not always correlated with higher pregnancy rates (11).

High serum progesterone value impairs endometrial receptivity. It provides this negative effect through endometrial gene expression. Studies on IVF cycles with different COS protocols have shown that pregnancy rates are lower when the serum P4 value on the hCG day exceeds 1.5 ng/mL, and this has been evaluated in favor of premature luteinization (PL) (12).

There are also meta-analyses on the effect of estrogen supplementation on pregnancy rate. The first meta-analysis on this subject stated that E2 supplementation for luteal support did not positively contribute to pregnancy rates (13). The next meta-analysis on this topic was by Jee et al. in 2010, and similar results were published (14). Oral, transdermal, and vaginal E2 supplementation was evaluated in both agonist and antagonist cycles, and another meta-analysis involving 15 studies and 2.406 patients revealed that E2 supplementation was not significant in all routes of administration (15). However, it was reported that the transdermal

and vaginal routes should be examined better. Again, in a Cochrane review conducted in 2015, it was reported that supplementing the luteal phase with estrogen in addition to progesterone had no effect on pregnancy achievement, ongoing pregnancy, and abortion rates (16). Meta-analyses include agonist and antagonist cycles, and differences in estrogen administration routes and doses are noteworthy. More recent studies have investigated estrogen supplementation in the luteal phase for some specific patient groups, for example, in cases with a thin endometrium (17) and patients with low serum E2 per follicle (18). It has been shown that E2 support has no positive effect in both patient groups. Groups, patient characteristics, and E2 support must be homogenized for the event to become clear.

Many studies and meta-analyses are comparing GnRH agonist and antagonist treatment protocols. In the Cochrane review published in 2001, the newly applied fixed GnRH at that time when the antagonist protocol was compared with the standard GnRH agonist long protocol, a significant decrease was found in the incidence of severe ovarian hyperstimulation syndrome (OHSS), but lower pregnancy rates were reported with the antagonist protocol. However, pregnancy rates were found to be lower when compared to agonists (19). In 2011, a Cochrane meta-analysis comparing GnRH antagonist and agonist protocols reported no difference between the two protocols regarding live birth and ongoing pregnancy rates (20).

The 2016 updated review of this meta-analysis included 73 randomized controlled trials and found no difference in live birth rates (OR 1.02, 95% CI 0.85 to 1.23). On the other hand, the incidence of OHSS of all severity has been reported to be lower in GnRH antagonist protocols (OR 0.61, 95% CI 0.51 to 0.72). However, cycle cancellation due to poor ovarian response was higher in patients receiving GnRH antagonists than those receiving agonists (OR 1.32, 95% CI 1.06 to 1.65) (21). Similarly, Xiao JS et al. compared standard long agonist and antagonist protocols in expected responder patients. A systematic review, including randomized controlled trials, found that the incidence of OHSS was significantly lower in antagonist cycles. Still, there was no difference between ongoing pregnancy and live birth rates (22). Because LH and HCG bind and activate LH/HCG receptors, oocyte instead of endogenous LH in COS Bolus HCG ensures maturation.

A recently published Cochrane meta-analysis comparing recombinant and urinary HCG found no difference between the agents regarding live birth and ongoing pregnancy rates (23). However, HCG's half-life (days) is much longer than endogenous LH's (hours). Therefore, bolus injection of HCG may lead to the development of OHSS with the formation of multiple corpus luteum due to the prolonged luteotropic effect (23).

In a study comparing r-LH with a shorter half-life with urinary HCG, it was shown that a single dose of r-LH (15.000 – 30.000 IU) was as effective as HCG in achieving final oocyte maturation, with a significant reduction in the incidence of OHSS compared to HCG (24). GnRH agonists are ovulation-triggering agents that are an alternative to HCG and are increasingly popular. The GnRH agonist replaces the antagonist at the receptor level and stimulates the receptor, increasing the release of gonadotropins with a flare-up effect. For this reason, GnRH agonists are often used in antagonist protocols to induce ovulation. However, the gonadotropin released by the GnRH agonist is at lower levels than in the natural cycle.

CONCLUSION

In conclusion, data showing the superiority of one gonadotropin option over another in IVF/ICSI treatment cycles are insufficient. The choice of gonadotropin in controlled ovarian stimulation depends on the product’s availability and should be based on ease of use and cost.

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Conflict of interest: The authors declare that they have no competing interests.

Ethical Declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. Informed consent has been obtained from all participants.

Abbreviations

COS : Controlled ovarian stimulation

ET : Embryo transfer

E2 : Estradiol

FSH : Follicul stimulating hormone

GnRH : Gonadotropin-releasing hormone

HCG : Human corionic gonadotropin

HMG : Human menopausal gonadotropin

ICSI : Intracytoplasmic sperm injection

IUI : Intrauterine insemination

IVF : In-vitro fertilization

LH : Luteinizing hormone

LP : Luteal phase

OC : Oral contraceptives

OHSS : Ovarian hyperstimulation syndrome

OI : Ovulation induction

OPU : Ovum pick-up

PCOS : Polycystic ovary syndrome

PL : Premature luteinization

P4 : Serum progesterone

TESE : Testicular sperm extraction

REFERENCES

1. Ribeiro S, Sousa M. In Vitro Fertilisation and Intracytoplasmic Sperm Injection predictive factors: A review of the effect of female age, ovarian reserve, male age, and male factor on IVF/ICSI treatment outcomes. JBRA Assist Reprod. 2023;27(1):97-111. doi:10.5935/1518-0557.20220000

2. Garg N, Milad MP. Female sterilization reversal in the era of in-vitro fertilization. Curr Opin Obstet Gynecol. 2022;34(4):244-249. doi:10.1097/GCO.0000000000000802

3. Hanevik HI, Hessen DO. IVF and human evolution. Hum Reprod Update. 2022;28(4):457-479. doi:10.1093/humupd/dmac014

4. Hanevik HI, Hessen DO. In vitro-fertilisering – nye metoder, nye muligheter, nye mennesker [In vitro fertilisation – new methods, new possibilities, new people]. Tidsskr Nor Laegeforen. 2022;142(16). doi:10.4045/tidsskr.22.0578

5. Doyle N, Jahandideh S, Hill MJ, Widra EA, Levy M, Devine K. Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization: A Randomized Clinical Trial. JAMA. 2022;328(21):2117-2125. doi:10.1001/jama.2022.20438

6. Tome M, Zwahlen E. Lived experience of infertility and in vitro fertilisation treatment. Aust J Gen Pract. 2023;52(5):295-297. doi:10.31128/AJGP-09-22-6566

7. Jie H, Zhao M, Alqawasmeh OAM, et al. In vitro rescue immature oocytes - a literature review. Hum Fertil (Camb). 2022;25(4):640-650. doi:10.1080/14647273.2021.1876932

8. Doyle N, Jahandideh S, Hill MJ, Widra EA, Levy M, Devine K. Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization: A Randomized Clinical Trial. JAMA. 2022;328(21):2117-2125. doi:10.1001/jama.2022.20438

9. Doyle N, Jahandideh S, Hill MJ, Widra EA, Levy M, Devine K. Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization: A Randomized Clinical Trial. JAMA. 2022;328(21):2117-2125. doi:10.1001/jama.2022.20438

10. Zhou C, Yang X, Wang Y, et al. Ovulation triggering with hCG alone, GnRH agonist alone or in combination? A randomized controlled trial in advanced-age women undergoing IVF/ICSI cycles. Hum Reprod. 2022;37(8):1795-1805. doi:10.1093/humrep/deac114

11. Blazar AS, Hogan JW, Frankfurter D, Hackett R, Keefe DL. Serum estradiol positively predicts outcomes in patients undergoing in vitro fertilization. Fertil Steril. 2004;81(6):1707-1709. doi:10.1016/j.fertnstert.2003.10.039

12. Di M, Wang X, Wu J, Yang H. Ovarian stimulation protocols for poor ovarian responders: a network meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2023;307(6):1713-1726. doi:10.1007/s00404-022-06565-6

13. Gelbaya TA, Kyrgiou M, Tsoumpou I, Nardo LG. The use of estradiol for luteal phase support in in vitro fertilization/intracytoplasmic sperm injection cycles: a systematic review and meta-analysis. Fertil Steril. 2008;90(6):2116-25. doi:10.1016/j.fertnstert.2007.10.053

14. Jee BC, Suh CS, Kim SH, Kim YB, Moon SY. Effects of estradiol supplementation during the luteal phase of in vitro fertilization cycles: a meta-analysis. Fertil Steril. 2010;93(2):428-436. doi:10.1016/j.fertnstert.2009.02.033

15. Huang N, Situ B, Chen X, et al. Meta-analysis of estradiol for luteal phase support in in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril. 2015;103(2):367-373.e5. doi:10.1016/j.fertnstert.2014.10.029

16. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015;2015(7):CD009154. doi:10.1002/14651858.CD009154.pub3

17. Demir B, Dilbaz S, Cinar O, et al. Estradiol supplementation in intracytoplasmic sperm injection cycles with thin endometrium. Gynecol Endocrinol. 2013;29(1):42-45. doi:10.3109/09513590.2012.705381

18. Kasapoglu I, Düzok N, Şen E, Çakır C, Avcı B, Uncu G. Luteal oestradiol for patients with serum oestradiol levels lower than expected per oocyte. Hum Fertil (Camb). 2021;24(2):122-128. doi:10.1080/14647273.2019.1566647

19. Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. Cochrane Database Syst Rev. 2006;(3):CD001750. doi:10.1002/14651858.CD001750.pub2

20. Al-Inany HG, Youssef MA, Aboulghar M, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev. 2011;(5):CD001750. doi:10.1002/14651858.CD001750.pub3

21. Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev. 2016;4(4):CD001750. doi:10.1002/14651858.CD001750.pub4

22. Xiao JS, Su CM, Zeng XT. Comparisons of GnRH antagonist versus GnRH agonist protocol in supposed normal ovarian responders undergoing IVF: a systematic review and meta-analysis. PLoS One. 2014;9(9):e106854. doi:10.1371/journal.pone.0106854

23. Youssef MA, Abou-Setta AM, Lam WS. Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. Cochrane Database Syst Rev. 2016;4(4):CD003719. doi:10.1002/14651858.CD003719.pub4

24. European Recombinant LH Study Group. Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. J Clin Endocrinol Metab. 2001;86(6):2607-18. doi:10.1210/jcem.86.6.7599