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IVF/ICSI in Polycystic Ovary Syndrome, a Prospective Randomized Study: A Comparison of Oral Contraceptive-Supported Early and Conventional Antagonist Initiation Protocols

Polikistik Over Sendromunda IVF/ICSI, Prospektif Randomize Çalışma: Oral Kontraseptif Destekli Erken ve Konvansiyonel Antagonist Başlama Protokollerinin Karşılaştırılması

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This manuscript was previously presented as a poster under the title "Early GnRH-antagonist initiation does not improve pregnancy rates of PCOS cases undergoing IVF/ICSI: A prospective randomized study" at the American Society for Reproductive Medicine (ASRM) Congress, held between October 17-21, 2015; Baltimore, Maryland.

ABSTRACT

Objective: This study aimed to evaluate the effectiveness of early initiation of the GnRH antagonist protocol following oral contraceptive pretreatment compared to the conventional initiation in PCOS patients undergoing IVF. **Material and Methods:** A total of 24 PCOS patients were randomized into two groups: the early antagonist group, where GnRH antagonist was initiated on the first day of stimulation, and the conventional group, where the antagonist was introduced when the lead follicle reached a size of 13-14 mm. Key outcomes assessed included the number of oocytes retrieved, fertilization rates, implantation rates, and clinical pregnancy rates. **Results:** Patients in the early antagonist group required significantly higher doses of the GnRH antagonist ($p < 0.05$) and had a slightly thinner endometrial thickness compared to the conventional group ($p=0.043$). However, no significant differences were found between the groups regarding the number of oocytes retrieved ($p=0.140$), fertilization rates ($p=0.311$), implantation rates ($p=0.210$), or clinical pregnancy rates ($p=0.682$). Both protocols were found to be safe, with no cases of OHSS reported in either group. **Conclusion:** Early initiation of the GnRH antagonist following oral contraceptive pretreatment does not significantly improve IVF outcomes in PCOS patients compared to conventional initiation. While early initiation may have specific benefits in cycle scheduling, it requires higher doses of antagonists and could potentially affect endometrial receptivity. Further research is warranted to identify patient subgroups that might benefit from tailored protocols.

Keywords: Polycystic ovary syndrome; *in vitro* fertilization; GnRH antagonist protocol; ovarian stimulation

ÖZET

Amaç: Bu çalışma, oral kontraseptif ön tedavisini takiben GnRH antagonist protokolünün erken başlatılmasının, konvansiyonel başlatma ile karşılaştırıldığında, PCOS hastalarında IVF etkinliğini değerlendirmeyi amaçlamaktadır. **Gereç ve Yöntemler:** Toplam 24 PCOS hastası rastgele iki gruba ayrıldı: erken antagonist grubu (GnRH antagonisti stimülasyonun ilk gününde başlatıldı) ve konvansiyonel grup (antagonist, önde gelen folikül 13-14 mm boyutuna ulaştığında başlatıldı). Değerlendirilen temel sonuçlar arasında toplanan oosit sayısı, fertilizasyon oranları, implantasyon oranları ve klinik gebelik oranları yer aldı. **Bulgular:** Erken antagonist grubundaki hastalar, anlamlı derecede daha yüksek dozda GnRH antagonisti gereksinimi gösterdi ($p < 0.05$) ve konvansiyonel gruba kıyasla hafifçe daha ince endometrium kalınlığına sahipti ($p=0.043$). Ancak, iki grup arasında toplanan oosit sayısı ($p=0.140$), fertilizasyon oranları ($p=0.311$), implantasyon oranları ($p=0.210$) veya klinik gebelik oranları ($p=0.682$) açısından anlamlı fark saptanmadı. Her iki protokol de güvenli bulundu ve hiçbir hastada OHSS vakası bildirilmedi. **Sonuç:** Oral kontraseptif ön tedavisini takiben GnRH antagonistinin erken başlatılması, PCOS hastalarında IVF sonuçlarını konvansiyonel başlatmaya kıyasla anlamlı şekilde iyileştirmemektedir. Erken başlatma, siklus programlamasında belirli avantajlar sağlayabilse de, daha yüksek dozda antagonist kullanımını gerektirmekte ve endometrial reseptiviteyi potansiyel olarak etkileyebilmektedir. Belirli hasta alt gruplarının bireyselleştirilmiş protokollerden fayda sağlayıp sağlayamayacağını belirlemek için daha ileri araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Polikistik over sendromu; *in vitro* fertilizasyon; GnRH antagonist protokolü; ovaryan stimülasyon

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Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders, affecting approximately 10% of women of reproductive age.[1] Characterized by hyperandrogenism, chronic anovulation, and polycystic ovarian morphology, PCOS is a complex condition associated with metabolic disturbances such as insulin resistance and hyperinsulinemia.[2] These metabolic irregularities contribute to abnormal ovarian function, often leading to infertility and suboptimal outcomes in assisted reproductive technologies (ART) like in vitro fertilization (IVF).[3]

The diagnosis of PCOS is commonly based on the Rotterdam criteria established in 2003. According to these criteria, a diagnosis requires the presence of at least two of the following: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovarian morphology on ultrasound, while excluding other etiologies such as congenital adrenal hyperplasia or androgen-secreting tumors.[4]

Due to the heterogeneous nature of PCOS, patients show variable responses to ovulation induction in ART. One major challenge during ovarian stimulation in PCOS patients is the risk of premature luteinization and ovarian hyperstimulation syndrome (OHSS), both of which can compromise IVF outcomes. To mitigate these risks, gonadotropin-releasing hormone (GnRH) antagonists are commonly utilized to prevent premature luteinizing hormone (LH) surges. GnRH antagonist protocols have been shown to be effective alternatives to the long GnRH agonist protocols, with advantages such as a shorter treatment duration, reduced injections, and a lower risk of OHSS.[5,6]

Despite the widespread use of GnRH antagonists, there remains ongoing debate regarding the optimal timing of antagonist initiation. Traditional protocols typically initiate the antagonist when the leading follicle reaches a size of 13-14 mm or when serum estradiol levels exceed 300-350 pg/mL. However, recent studies have investigated the potential benefits of earlier initiation, including starting the antagonist on the first day of ovarian stimulation. Recent meta-analyses have further explored the effectiveness of GnRH antagonist protocols compared to long GnRH agonist protocols in PCOS patients, emphasizing the advantages of lower OHSS risk, reduced treatment duration, and cost-effectiveness.[6-8] Kolibianakis et al. demonstrated that early initiation of GnRH antagonists could lead to improved follicular synchronization and hormonal regulation without compromising pregnancy rates.[9] This has been supported by studies highlighting that GnRH antagonist protocols, when optimized, achieve comparable clinical outcomes with fewer complications.[10-12] An additional strategy to enhance synchronization and suppress early follicular phase LH elevations in PCOS patients involves pretreatment with oral contraceptives (OCs). Recent studies suggest that OC pretreatment followed by GnRH antagonist protocols improves synchronization and reduces premature LH surges without compromising IVF success rates.[13-15] The ability to reduce complications, including suboptimal ovarian responses, makes this approach particularly valuable in ART.[16]

In this study, we aim to compare the outcomes of PCOS patients undergoing IVF using two different GnRH antagonist initiation protocols following OC pretreatment: early initiation (on the first day of ovarian stimulation) versus conventional initiation. By analyzing clinical, hormonal, and pregnancy-related outcomes, this study seeks to determine whether early antagonist initiation provides significant advantages in optimizing IVF success rates in PCOS patients. Given the growing body of literature suggesting that GnRH antagonist protocols can achieve comparable or superior outcomes to traditional approaches, this study also aims to validate whether tailored OC pretreatment and timing of antagonist initiation can further refine IVF outcomes.

MATERIAL AND METHODS

STUDY DESIGN AND PATIENT SELECTION

This prospective, randomized controlled study was conducted at the Department of Obstetrics and Gynecology, Ankara University, between December 2007 and December 2010. Ethical approval for the study was obtained from the local ethics committee (Protocol ID: 145-4396 on 19/01/2009), and written informed consent was obtained from all participants. The study was conducted in accordance with the uni-

versal ethical standards of the Declaration of Helsinki.

A total of 30 patients diagnosed with polycystic ovary syndrome (PCOS) and presenting with infertility were included. The inclusion criteria were: diagnosis of PCOS based on the Rotterdam criteria (presence of at least two of oligo- or anovulation, clinical/biochemical hyperandrogenism, or polycystic ovarian morphology), age under 38 years, and fewer than two prior IVF attempts. Patients were excluded if they had male factor infertility, significant endocrine or metabolic disorders, or endometriotic cysts.

RANDOMIZATION AND GROUP ALLOCATION

Patients were randomly assigned to one of two groups using sealed envelopes containing single and double numbers. Group 1 (n=12) received oral contraceptive (OC) pretreatment followed by early initiation of the GnRH antagonist on the first day of ovarian stimulation. Group 2 (n=12) received OC pretreatment with conventional initiation of the GnRH antagonist when the lead follicle reached a diameter of 13-14 mm or serum estradiol exceeded 350 pg/mL.

PRETREATMENT AND OVARIAN STIMULATION PROTOCOLS

All patients received pretreatment with a combined oral contraceptive (drospirenone 3 mg and ethinylestradiol 0.03 mg) for 21 days in the cycle preceding ovarian stimulation. Ovarian stimulation began on cycle day 2 or 3 with recombinant follicle-stimulating hormone (rFSH) at doses ranging from 150 to 200 IU per day (Gonal-F, Merck Serono or Puregon, Schering Plough). The GnRH antagonist used was either cetrorelix (Cetrotide, 0.25 mg/day) or ganirelix (Orgalutran, 0.25 mg/day).

MONITORING AND TRIGGERING OF OVULATION

Follicular development and endometrial thickness were assessed via transvaginal ultrasonography on days 1-2, 5-6, and the day of human chorionic gonadotropin (hCG) administration. Hormonal profiles, including serum FSH, LH, estradiol, and progesterone, were measured at each visit. Ovulation was triggered with 250 µg recombinant hCG (Ovitrelle, Merck Serono) when at least three follicles reached ≥18 mm.

OOCYTE RETRIEVAL, FERTILIZATION, AND EMBRYO TRANSFER

Oocyte retrieval was performed 35-36 hours after hCG administration using transvaginal ultrasound-guided aspiration. All mature oocytes underwent intracytoplasmic sperm injection (ICSI). Fertilization was assessed 18 hours post-ICSI, and embryos were graded based on morphological criteria on days 2 and 3. One or two embryos were transferred on day 2 or 3 based on the embryo quality and patient preference.

OUTCOME MEASURES

The primary outcomes were the implantation rate and clinical pregnancy rate. Secondary outcomes included the number of oocytes retrieved, metaphase II oocytes, fertilization rate, endometrial thickness, and rates of premature luteinization and ovarian hyperstimulation syndrome (OHSS).

DEFINITION OF PREMATURE LUTEINIZATION

Premature luteinization was defined as serum LH ≥10 IU/L or progesterone ≥1.2 ng/mL on the day of hCG administration. For further analysis, a secondary threshold of progesterone ≥1.9 ng/mL was also considered based on literature variations.

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 24. Continuous variables were compared using the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test or Fisher's exact test where appropriate. A p-value <0.05 was considered statistically significant.

The following outcomes were assessed: duration of ovarian stimulation, total rFSH and GnRH antagonist doses, serum estradiol and endometrial thickness on the day of hCG administration, number of mature oocytes (metaphase II), fertilization rate, number of high-quality embryos, implantation and clinical pregnancy rates, and incidence of OHSS.

RESULTS

PATIENT CHARACTERISTICS

A total of 30 patients meeting the inclusion criteria were initially enrolled in the study, but 24 patients completed the treatment and were included in the final analysis. Demographic characteristics, including age, body mass index (BMI), duration of infertility, and previous IVF or intrauterine insemination (IUI) attempts, were similar between the early antagonist initiation group and the conventional group.

The mean age of patients in the early antagonist group was 27.0 years, compared to 27.5 years in the conventional group (p=0.538). Both groups had a similar duration of infertility, with means of 5.0 years and 5.5 years, respectively (p=0.931). The BMI values were also comparable between groups (24.6 vs. 24.5 kg/m², p=0.862), and previous IVF attempts did not differ significantly (mean=2 for both groups, p=0.600) (Table 1).

TABLE 1: Baseline characteristics of the study groups

Characteristic	Early antagonist Group (n=12)	Conventional Group (n=12)	p value
Age (years)	27.0	27.5	0.538
Duration of infertility (years)	5.0	5.5	0.931
BMI (kg/m²)	24.6	24.5	0.862
Previous IVF attempts	2	2	0.600

OVARIAN STIMULATION AND HORMONAL PROFILES

Patients in the early antagonist group required significantly higher doses of GnRH antagonists compared to the conventional group (9.5 mg vs. 6.0 mg, $p < 0.05$). However, no significant differences were observed in the total rFSH dose (1456 IU vs. 1293 IU, p=0.419), stimulation duration (10 days for both groups, p=0.330), or peak estradiol levels (3610 pg/mL vs. 2614 pg/mL, p=0.564) (Table 2).

TABLE 2: Stimulation and hormonal data

Parameter	Early antagonist Group	Conventional Group	p value
Stimulation duration (days)	10.0	10.0	0.330
Total rFSH dose (IU)	1456	1293	0.419
Total antagonist dose (mg)	9.5	6.0	**<0.05**
Peak estradiol (pg/mL)	3610	2614	0.564
Endometrial thickness (mm)	9.15	11.5	**0.043**

OOCYTE RETRIEVAL AND EMBRYO DEVELOPMENT

No significant differences were observed in the number of oocytes retrieved (16.5 vs. 12.5, p=0.140), number of metaphase II oocytes (15.5 vs. 11.0, p=0.155), fertilization rates (47% vs. 54.5%, p=0.311), or the number of high-quality embryos on day 2 (2.5 vs. 2.0, p=0.704) or day 3 (3.0 vs. 3.0, p=0.561) (Table 3).

TABLE 3: Oocyte and embryo data

Parameter	Early antagonist Group	Conventional Group	p value
Oocytes retrieved (n)	16.5	12.5	0.140
Metaphase II oocytes (n)	15.5	11.0	0.155
Fertilization rate (%)	47.0	54.5	0.311
High-quality embryos (Day 2)	2.5	2.0	0.704
High-quality embryos (Day 3)	3.0	3.0	0.561

IMPLANTATION AND PREGNANCY OUTCOMES

The implantation rate was higher in the early antagonist group (36.0%) compared to the conventional group (20.7%), although this difference was not statistically significant (p=0.210). Similarly, the clinical pregnancy rates were 50.0% in the early group and 41.7% in the conventional group (p=0.682), while live birth rates were identical (33.3% in both groups, p=1.000) (Table 4).

TABLE 4: Implantation and pregnancy outcomes

Outcome	Early antagonist Group	Conventional Group	p value
Implantation rate (%)	36.0	20.7	0.210
Clinical pregnancy rate (%)	50.0	41.7	0.682
Live birth rate (%)	33.3	33.3	1.000
Multiple pregnancy rate (%)	25.0	8.3	0.590

PREMATURE LUTEINIZATION AND OHSS

Premature luteinization, defined as serum progesterone levels ≥1.2 ng/mL, was observed in 4 patients in the early antagonist group and 3 patients in the

TABLE 5: Premature luteinization

Parameter	Early antagonist Group	Conventional Group	p value
Progesterone ≥1.2 ng/mL (n)	4	3	0.098
LH ≥10 IU/L (n)	0	0	-

conventional group, but this difference was not statistically significant (p=0.098). No cases of OHSS were reported in either group (Table 5).

LH LEVELS OVER TIME

LH levels were monitored throughout the stimulation period in both groups (Figure 1). The early antagonist group exhibited a slight initial increase in LH levels, from 3 IU/L on day 1 to a peak of 9

IU/L on day 9, followed by a decline to 5 IU/L by day 13. In the conventional group, LH levels peaked at 8 IU/L on day 9 and returned to 4 IU/L by day 13. No statistically significant differences in LH levels were observed between the groups (p >0.05).

ESTRADIOL LEVELS OVER TIME

Estradiol levels increased progressively over the course of stimulation in both groups (Figure 2). The early antagonist group demonstrated a rapid rise, reaching 1,800 pg/mL on day 7 and peaking at 3,600 pg/mL on day 13. The conventional group showed a more gradual increase, with levels reaching 1,600 pg/mL on day 7 and peaking at 3,300 pg/mL on day 13. Despite the earlier peak in the early antagonist group, no statistically significant differences in peak estradiol levels were found (p >0.05).

PROGESTERONE LEVELS OVER TIME

Progesterone levels showed a gradual increase during stimulation (Figure 3). The early antagonist group experienced slightly higher levels of progesterone towards the end of the stimulation period, rising from 0.5 ng/mL on day 1 to 2.5 ng/mL on day 13. In the conventional group, levels increased from 0.4 ng/mL on day 1 to 2.2 ng/mL by day 13. However, the difference was not statistically significant (p >0.05) and did not indicate an increased risk of premature luteinization.

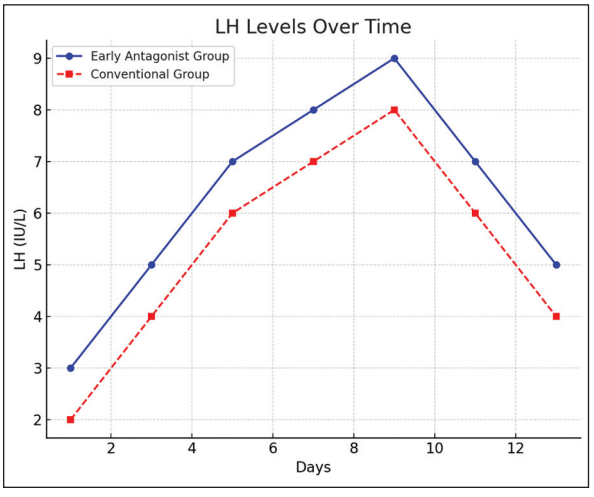

FIGURE 1: LH levels over time

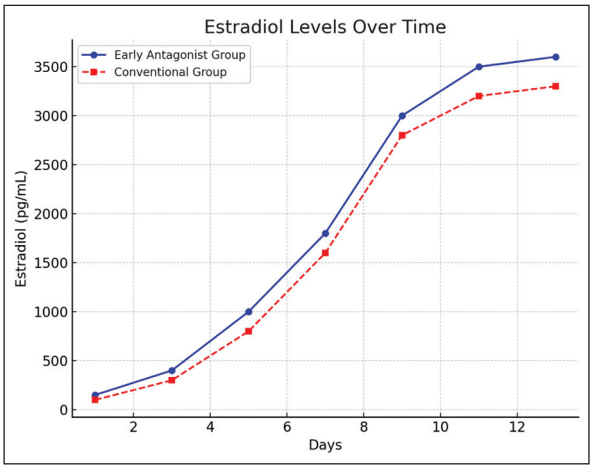

FIGURE 2: Estradiol levels over time

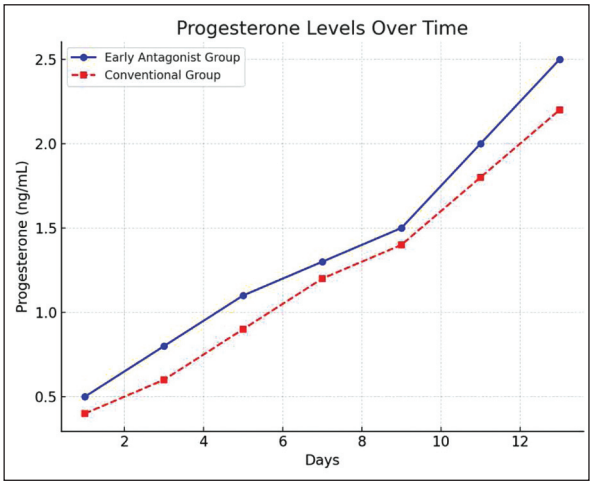

FIGURE 3: Progesterone levels over time

These results indicate that early initiation of the GnRH antagonist does not significantly improve IVF outcomes compared to conventional initiation but may require higher doses of GnRH antagonists and lead to slightly thinner endometrial thickness.

DISCUSSION

This study aimed to evaluate the impact of early versus conventional initiation of GnRH antagonist protocols following oral contraceptive pretreatment on IVF outcomes in PCOS patients. The results demonstrated that while early initiation required higher doses of GnRH antagonists and led to slightly thinner endometrial thickness, the overall clinical outcomes, including implantation rates, clinical pregnancy rates, and live birth rates, were not significantly different between the two groups.

INTERPRETATION OF KEY FINDINGS

One key finding was that patients in the early initiation group required significantly higher total doses of GnRH antagonist. This is consistent with previous studies that suggest early initiation may increase antagonist requirements due to prolonged suppression of endogenous gonadotropin activity.[9] Recent studies have further highlighted the variability in antagonist dose requirements among PCOS patients and emphasized the need for individualized dosing protocols.[10,12,17]

Despite the increased dose, this did not translate into improved clinical outcomes, suggesting that early initiation may not provide a clear advantage over conventional protocols in terms of pregnancy success.

Although some studies have suggested that early initiation of GnRH antagonists may enhance implantation rates by improving follicular synchronization and hormonal balance, our findings did not demonstrate a significant advantage in implantation or pregnancy rates.[9,13] This discrepancy may be attributed to differences in study populations, stimulation protocols, or endometrial receptivity factors, highlighting the need for further investigations to identify patient subgroups that may benefit from early antagonist initiation

This finding is supported by research from Huirne et al., who indicated that while flexible protocols help cycle control, they do not consistently improve clinical outcomes.[11]

The slight reduction in endometrial thickness observed in the early antagonist group is another notable finding. Griesinger et al. in their study emphasize the role of optimal endometrial thickness in achieving higher implantation and live birth rates.[18]

COMPARISON WITH PREVIOUS LITERATURE

Our results align with those of Hwang et al. and Kadoura et al., who reported no significant differences in pregnancy outcomes when comparing early and conventional GnRH antagonist initiation.[8,13] However, some studies have suggested that early initiation could improve follicular synchronization.[9,19] Baerwald et al. in their research on suboptimal ovarian responses in PCOS patients also underscores that follicular synchronization does not always lead to improved clinical outcomes, which is consistent with our findings.[20]

The estradiol and progesterone profiles observed in both groups provide additional insights. The early antagonist group exhibited a more rapid rise in estradiol levels, which could be attributed to early follicular recruitment. However, this did not lead to a higher number of mature oocytes or improved fertilization rates, suggesting that the timing of antagonist initiation alone may not be sufficient to enhance follicular development. This conclusion is supported by Hamdine et al. who found no consistent improvement in pregnancy outcomes with early antagonist initiation.[21]

CLINICAL IMPLICATIONS

This study demonstrates that conventional GnRH antagonist protocols remain highly effective without the need for early initiation. While early initiation may be beneficial in select cases, such as patients with poor cycle scheduling flexibility, its routine use may not be justified given the higher antagonist dose requirement and potential impact on endometrial thickness. Tilborg et al. and Marca et al., in their studies, have also emphasized that selecting protocols tailored to patients' ovarian reserve and response is a more

appropriate approach, a perspective that our findings support as well.[22,23]

Additionally, the absence of OHSS in either group highlights the safety of both protocols in PCOS patients, who are typically at higher risk for this complication. The careful monitoring of estradiol levels and tailored dosing strategies likely contributed to minimizing this risk, underscoring the importance of individualized treatment protocols.

LIMITATIONS AND FUTURE DIRECTIONS

This study has several limitations. The relatively small sample size may have limited the statistical power to detect subtle differences in clinical outcomes. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings. Future research with larger, multicenter trials is needed to confirm these results and explore the potential benefits of early antagonist initiation in subgroups of PCOS patients, such as those with poor ovarian reserve or previous IVF failure.

Another area for future investigation is the long-term impact of early antagonist initiation on cumulative live birth rates, as this study focused primarily on outcomes from a single cycle. Understanding how different protocols affect cumulative success rates could provide a more comprehensive assessment of their clinical utility.

Future studies should also address the following questions: Does early antagonist initiation benefit patients with low ovarian reserve more significantly than conventional initiation? Are there specific hormonal thresholds that predict better outcomes with early initiation? How does early initiation impact patients undergoing repeated IVF cycles? Addressing these questions may help refine current protocols and provide better tailored treatments.

CONCLUSION

In conclusion, early initiation of the GnRH antagonist following oral contraceptive pretreatment does not appear to significantly improve IVF outcomes in PCOS patients compared to conventional initiation. While it may offer some benefits in cycle scheduling, the higher antagonist dose requirement and potential impact on endometrial thickness should be carefully considered. Future studies should specifically focus on patients with poor ovarian reserve or previous IVF failures to determine whether tailored protocols could enhance cumulative pregnancy outcomes.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Murat Sönmezer;* ***Design:*** *Murat Sönmezer, Evren Koçbulut;* ***Control/Supervision:*** *Murat Sönmezer;* ***Data Collection and/or Processing:*** *Evren Koçbulut;* ***Analysis and/or Interpretation:*** *Evren Koçbulut;* ***Literature Review:*** *Evren Koçbulut, Ahmet Kurt;* ***Writing the Article:*** *Evren Koçbulut, Ahmet Kurt;* ***Critical Review:*** *Ahmet Kurt.*

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