Clinical Investigation / Araştırma

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What should be the strategy in case of a big follicle at the start of the cycle? Shall we start the stimulation or postpone it to the next cycle?

Siklus başlangıcında büyük folikül saptanması durumunda strateji ne olmalıdır? Stimülasyona başlanmalı mı yoksa bir sonraki siklusa mı ertelenmeli?

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Abstract

Objective: This study facilitates decision-making when an antral follicle diameter >15 mm is detected at the beginning of the menstrual cycle in poor responder (POR) patients.

Materials and Methods: Eighty-three POR patients with at least one leading follicle with a diameter of 15 to 24 mm on the 2nd-4th days of the menstrual cycle were assessed.

Results: The mean age of females was 40.1±4.8 (26-45), and the mean partners' age was 42.1±7.8 (26-65). Fifty-one (61.4%) women underwent an oocyte pick-up procedure 36 h after the first ultrasonographic examination on the 2nd-4th days of the menstrual cycle. Gonadotrophin stimulation was initiated in 32 (38.6%) patients. Among women in whom oocyte retrieval was performed, an oocyte was obtained in 49 (59.75%) patients. In 13 of 49 patients (26.5%), no mature oocytes were obtained. Fertilized 2pn embryos were obtained in 18 of 33 patients (54.5%). Among the fertilized embryos, 12 were good, six were moderate, and two were of poor quality. Following the frozen embryo transfer procedure, one of the two patients experienced a clinical pregnancy.

Conclusion: Patients with POR are still difficult to manage both clinically and therapeutically. Since every oocyte is valuable and important, patients should be carefully followed up. Our research will be directed by the need to rule out a physiological ovarian cyst when large antral follicles appear at the beginning of the cycle. The clinician should give them a chance.

Keywords: Poor responder, diminished ovarian reserve, big antral follicle

Öz

Amaç: Bu çalışmada, zayıf over yanıtlı (ZOY) kadınlarda menstrüel siklusun başlangıcında antral folikül çapı >15 mm saptanması durumunda karar vermeyi kolaylaştırmayı amaçladık.

Gereç ve Yöntemler: Menstrüel siklusun 2.-4. günlerinde, çapı 15-24 mm arasında olan en az bir önde giden folikülü olan ZOY tanısı konulan 83 kadın değerlendirildi.

Bulgular: Ortalama kadın yaşı 40,1±4,8 (26-45), ortalama partner yaşı 42,1±7,8 (26-65) idi. Elli bir (%61,4) katılımcıya siklusun 2.-4. günlerinde ilk ultrasonografik incelemeden 36 saat sonra oosit toplama işlemi yapıldı. Katılımcıların 32'sine (%38,6) gonadotropin stimülasyonu başlandı. Oosit toplama yapılan, 49 (%59,75) kadından oosit elde edildi. Kırk dokuz hastanın 13'ünde (%26,5) matür oosit elde edilemedi. ICSI yapılan 33 hastanın 18'inde

PRECIS: The emergence of big antral follicles at the beginning of the menstrual cycle should not be misdiagnosed as a physiological ovarian cyst and should be given a chance.

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(%54,5) 2pn embriyo elde edildi. Döllenen embriyolardan 12'si iyi kalitede, 6'sı orta kalitede ve 2'si kötü kalitede idi. İki hastaya dondurulmuş embriyo transferi yapıldı ve bir hastada klinik gebelikle sonuçlandı.

Sonuç: ZOY'li hastaların klinik yönetimi ve tedavisi zordur. Hastalar dikkatle takip edilmelidir; her oosit çok değerli ve önemlidir. Menstrüel siklusun 2.-4. günlerinde büyük antral foliküllerin ortaya çıkması fizyolojik over kisti ile karıştırılmamalı ve oosit elde edilebilecek folikül olabileceği göz önünde bulundurulmalıdır. Klinisyen büyük antral folikül için bir şans vermelidir.

Anahtar Kelimeler: Zayıf over yanıtı, azalmış over rezervi, büyük antral folikül

Introduction

Diminished ovarian reserve (DOR) is defined as a reduction in the quantity of the ovarian follicular reserve, which occurs in 31% of ART cycles[1]. Patients with DOR are generally considered challenging because they exhibit poor ovarian response (POR), which accounts for 9-24% of patients undergoing ovarian stimulation for in vitro fertilization (IVF) treatment[2,3]. POR leads to fewer retrieved oocytes and fewer embryos to be transferred, which lowers pregnancy and live birth rates (LBR)[4].

Patient-oriented strategies encompassing individualized oocyte number (POSEIDON) classification, which was established in 2016, is used to classify and treat patients with POR. The "low prognosis patient" is defined in this categorization and is divided into four subgroups according to (i) age, (ii) ovarian reserve markers [antral follicle count (AFC) and/or anti-mullerian hormone (AMH)], and (iii) the results of prior ovarian stimulation. Groups 1 and 2 are designated for women under the age of 35 and women over the age of 35 who have sufficient ovarian reserve parameters (AFC >5, AMH >1.2 ng/mL). Groups 3 and 4 are designated for women under the age of 35 and 35 years or older who have inadequate ovarian reserve parameters (AFC <5, AMH <1.2 ng/mL), respectively[5]. POSEIDON groups 3 and 4 are called "expected POR," constituting 10% and 55% of the IVF cycle, respectively[6].

The management of patients with POR remains a challenge for clinicians. The number of retrieved oocytes considerably influences clinical outcomes concerning cumulative LBR. The increasing number of retrieved oocytes, the higher cumulative LBR[7,8]. However, the IVF cycle for patients with POR often results in a follicular developmental arrest, premature ovulation, and cancellation of oocyte retrieval[9,10]. Additionally, these women have a high risk of not having any high-quality embryos available for transfer; they often undergo multiple ovarian stimulation cycles, which causes physical, emotional, and financial costs[6].

There is no standard treatment for POR concerning protocol and drugs. Ovarian stimulation is suggested to be started when the serum estradiol level is <50 pg/mL, the endometrial lining is <5 mm, and no dominant follicle >10 mm exists during the early follicular phase, typically on day 2nd or 3rd of the following menses[11]. When an antral follicle >15 mm exists, it can be diagnosed as a retantional ovarian follicle or physiological ovarian cyst. Controlled ovarian stimulation was postponed. Whether or not to stimulate has been a conundrum.

This study facilitates decision- making when an antral follicle >15 mm is detected at the start of the menstrual cycle.

Materials and Methods

Patient Selection

Between January 2020 and February 2021, the IVF Center at Acıbadem University Maslak Hospital in İstanbul, Turkey, conducted this retrospective cohort study. The POSEIDON groups 3 and 4 criteria were met by patients who had IVF cycles and were recruited in the study. Group 3 consisted of women <35 years of age, AFC <5, and AMH <1.2 ng/mL. Group 4 consisted of women ≥35 years of age, AFC <5, and AMH <1.2 ng/mL. Age requirements for inclusion were 25-45 years old, and at least one leading follicle must have a diameter of 15-24 mm on the 2nd-4th days of the menstrual cycle. Women with body mass indices greater than 30 kg/m^2 and partners who had severe male factor infertility were excluded (e.g., aspermia, azoospermia). Each patient's complete medical history was analyzed, including their age, the age of their partners, any prior treatments, and the duration of their infertility. The primary outcome measures were the total number of oocytes, mature oocytes, and embryos.

Controlled Ovarian Stimulation

Gonadotrophin stimulation was initiated at 300 IU recombinant follicle-stimulating hormone (FSH) (randomized Gonal F randomly; Merck, or Fostimon; IBSA) with one falcon of Gonadotropin hormone-releasing hormone (GnRH) antagonist if TV-USG revealed a follicle >15 mm on the 2nd-4th days of the menstrual cycle (0.25-mg cetrorelix; Cetrotide; Merck Serono). Serum estradiol (E2) and progesterone levels were checked at each examination. Whenever the diameter of the leading follicle at the beginning of the cycle was 18 mm, final oocyte maturation was triggered by the administration of 250 mcg recombinant human choriogonadotropin alfa (rHCG, Ovitrelle; Serono).

If TV-USG revealed a follicle with a diameter between 18 and 24 mm on the 2nd-4th days of the menstrual cycle, final oocyte maturation was triggered by the administration of 250 mcg rHCG (Ovitrelle; Serono) with one dose of GnRH antagonist (0.25-mg cetrorelix; Cetrotide; Merck Serono). After 36 h following hCG injection, oocyte pick-up (OPU) was performed under sedation anesthesia using a 35 cm 17-G double lumen needle. Four hours after retrieval, oocyte denudation and ICSI were conducted. The cell quantity and morphological quality of embryos were evaluated using the İstanbul consensus workshop criteria[12]. Good-quality embryos were frozen at the cleavage stage for embryo banking.

Statistical Analysis

SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables were expressed using the median, mean, and standard deviation (minimum-maximum). Categorical variables were reported as numbers and percentages (%). Through using Kolmogorov-Smirnov test, the distribution of the data was examined. The two groups were compared using the Student's t-test. Statistical significance was defined as $p<0.05$.

Results

Eighty-three women were retrospectively enrolled. The mean age of the females was 40.1±4.8 (26-45), and the mean partners' age was 42.1±7.8 (26-65). Table 1 lists the baseline characteristics of the included cycles: Age, length of infertility, basal FSH levels, AMH, and the number of antral follicles. Fifty-one (61.4%) women underwent an OPU procedure 36 h after the first ultrasonographic examination on 2nd-4th days of the menstrual cycle. Gonadotrophin stimulation was initiated in 32 (38.6%) patients. Gonadotropin duration was one day in 20 (24.1%) patients, two days for 10 (11%), and three days for 2 (2.4%) patients subsequently. The mean follicular diameter of the largest follicle (mm) at the start of the cycle was 18.7±2.5 (15-24). The mean follicular diameter of the largest follicle (mm) on hCG day was 19.6±2.0 (17-24). Table 2 summarizes the clinical and IVF outcome characteristics for women. Oocyte retrieval was successfully performed in 82 women, while one woman was unable to be retrieval due to premature ovulation. At least one oocyte was found in 49 patients with oocyte retrieval (59.75%). One oocyte was obtained in 42 patients, and two oocytes were obtained in seven patients. No mature oocytes were obtained in 13 of the 49 patients (26.5%). Fertilized 2pn embryos were obtained in 18 of 33 patients (54.5%). Among the fertilized embryos, 12 were of good quality, six were moderate quality, and two were poor quality. Eighteen patients opted for embryo pooling in the cleavage stage, but unfortunately, one embryo was arrested in the 2pn stage. Two patients underwent frozen embryo transfer, and a patient experienced a clinical pregnancy as a result. When we compared the baseline characteristics of the women in whom at least one oocyte was obtained or not, the analysis revealed that the partner's age was significantly higher in at least one oocyte-obtained group (p=0.03). The peak serum E2 level was significantly higher in at least one oocyte-obtained group (p=0.05) (Table 3). The flow chart of this study is detailed in Figure 1.

Table 1. Baseline characteristics and cycle parameters of the women

	Mean ± Standard deviation (min-max)
Age (years)	40.1±4.8 (26-45)
Partner's age (years)	42.1±7.8 (26-65)
Infertility duration (months)	50.8±52.6 (5-240)
Number of previous IVF attempts (n)	2.64±3.23 (0-15)
Number of AFC (n)	1.4±1.2 (0-4)
Mean follicular diameter of the largest follicle (mm) at the start of the cycle	18.7±2.5 (15-24)
Mean follicular diameter of the largest follicle (mm) on hCG day	19.6±2.0 (17-24)
FSH (mIU/mL)	33.6±24.8 (7.3-123)
AMH (ng/mL)	0.16±0.21 (0-0.9)

IVF: In vitro fertilization, AFC: Antral follicle count, AMH: Anti-Mullerian hormone, FSH: Follicle stimulating hormone, hCG: Human chorionic gonadotrophin. Data were expressed as mean ± standard deviation

Discussion

In this study, we investigated whether the cycle should be started immediately or postponed to the next cycle in case of a large antral follicle at the start of the menstrual cycle with at least an antral follicle >15 mm in women diagnosed with POR. A total of 82 women underwent an OPU procedure. At least one oocyte was obtained in 49 (59.75%) of the 82 patients. Among them, 18/33 (54.5%) had at least fertilized cleavage stage embryos.

In the previous studies in the 1950s-1970s, the traditional theory of human folliculogenesis stated two phases[13-15]. The first two weeks of the menstrual cycle are termed the "follicular phase," that a single cohort of antral follicles grows. The last two weeks of the cycle are termed the "luteal phase," when the corpus luteum grows in the absence of a follicle. Inhibin B suppresses FSH secretion during the follicular phase, whereas by regressing the corpus luteum, inhibin A secretion decrease, and FSH inhibition escape during the luteal-follicular transition[16]. When ovarian reserve diminishes, granulosa cells show a gradual decline in inhibin B secretion, with a consequent rise in FSH levels that stimulate earlier follicular development during

Table 2. Clinical and IVF outcome parameters of women

	Mean ± Standard deviation (min-max)
Days of stimulation (in women who underwent ovarian stimulation, n=32)	1.4±0.6 (1-3)
Total gonadotrophin dose (IU) (in women who underwent controlled ovarian hyperstimulation; n=32)	512±408 (150-1800)
E2 level (pg/mL) on hCG day	177±141 (5-468)
Number of retrieved oocytes (n=49)	1.1±0.4 (1-3)
Number of mature oocytes (n=36)	0.8±0.6 (0-2)
Number of 2 pronuclei embryos (n=21)	0.6±0.6 (0-2)
Number of cleavage stage embryos (n=20)	0.58±0.6 (0-2)

hCG: Human chorionic gonadotrophin, IVF: In vitro fertilization, E2: Estradiol. Data were expressed as mean ± standard deviation

the luteal-follicular transition period. As a result, accelerated follicular growth can be pictured[17,18]. Klein et al.[19] reported that the older patients over >40-45 years of age in the control cycles demonstrated an elevated day 3 FSH and a shortened follicular phase compared with the younger patients aged 20-25 years.

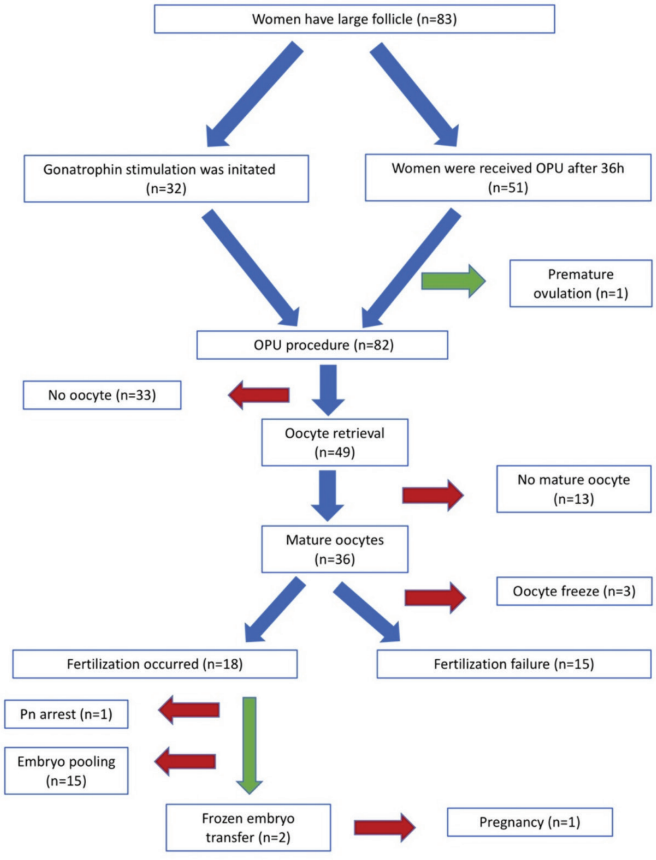

Figure 1. Flow chart of the study

OPU: Oocyte pick-up

In our study, the mean patient's age was 40.1±4.8 (26-45), the mean AFC was 1.4±1.2 (0-4), both advanced female age and DOR resulted in accelerated follicular growth. These women were also likely to have large antral follicles due to advanced follicular maturation in the very early days of the follicular phase. Turan et al.[20] reported the IVF conception of seven patients with DOR following a very short ovarian stimulation of incidentally discovered large antral follicles in the early follicular phase. Six embryos were obtained after eight oocytes from seven patients were removed, and two live births and a 50% ongoing pregnancy rate per transfer were the results[20].

In this study, oocytes were obtained in 59.75% of the patients, who was an undeniably high rate. The number of oocytes retrieved during controlled ovarian stimulation has a considerable impact on the cumulative LBR each cycle initiated[3]. The number of oocytes retrieved had a substantial relationship with LBR; the predicted LBR for one oocyte recovered at ages 18-34, 35-37, 38-39, and 40 years and older was 8%, 7%, 5%, and 1%, respectively[21]. According to the national summary report of patients with DOR in 2020, the chance of live birth with intended egg retrieval and first embryo transfer was 2.6% at more than 42 years of age, 13.6% between 38 and 40 years of age; 22.8% at <35 years[22]. In another study, Polyzos et al.[23] analyzed 14.469 patients and reported that cumulative LBRs steadily increased with the number of oocytes, which was categorized according to age (<36, 36-39, >40 years), revealed the same pattern, showing a steady increase in cumulative LBR with the number of oocytes, but cumulative LBRs decreased with increasing age for a given number of oocytes. In other

Table 3. Participant characteristics and cycle parameters of two groups

	No oocyte Mean ± Standard deviation (min-max)	At least one oocyte retrieved Mean ± Standard deviation (min-max)	p
Age (years)	39.71±5.1 (26-45)	40.61±4.3 (29-45)	0.39
Partner's age (years)	40.4±6.45 (25-57)	44.15±8.8 (29-65)	0.03
Infertility duration (months)	50.2±50.7 (5-240)	51.5±55.4 (6-240)	0.73
Number of previous IVF attempts (n)	2.62±3.4 (0-15)	2.66±2.9 (0-12)	0.96
Number of AFC (n)	1.4±1.1 (0-4)	1.4±1.1 (0-4)	0.84
Mean follicular diameter of the largest follicle (mm) at the start of the cycle	18.25±2.3 (15-23.3)	19.2±2.7 (15.3-24)	0.97
Mean follicular diameter of the largest follicle (mm) on hCG day	19.3±1.65 (17.2-23.4)	19.96±2.25 (17-24)	0.14
FSH (mIU/mL)	34.2±23 (7.3-115)	32.95±27.2 (7.8-123)	0.84
AMH (ng/mL)	0.16±0.21 (0-0.9)	0.17±0.2 (0-0.8)	0.74
E2 level (pg/mL) on hCG day	126.3±114.15	251.1±146.9	0.05

IVF: In vitro fertilization, AFC: Antral follicle count, AMH: Anti-Müllerian hormone, FSH: Follicle stimulating Hormone, E2: Estradiol, hCG: Human chorionic gonadotrophin. Data were expressed as mean ± standard deviation

words, one retrieved oocyte provides 1-8% live birth chances, so every additionally retrieved oocyte has a significant impact on the LBR. As our study proved, each follicle that develops in patients with POR is important and contributes to the LBR.

There are a limited number of studies on this subject in the literature. This study is unique, with a high number of cases. Clinicians encounter this situation frequently, but generally, oral contraceptive drugs are prescribed or postponed in stimulation protocols that may cause emotional stress and costs to the anxious infertile couple. When an antral follicle diameter more than 15 mm is detected at the start of the menstrual cycle in patients with POR, clinicians may recommend an OPU procedure. Additionally, it is a cost-effective treatment because of its short stimulation duration.

Study Limitations

The limitation of this study is that only two patients underwent frozen embryo transfer because of embryo pooling continuing. Also, thin endometrium development is not appropriate for receiving fresh embryo transfer.

Conclusion

Clinical management and treating patients with POR is still challenging. Patients should be followed cautiously because each oocyte considerably affects the LBR. Our study could be guided when the emergence of big antral follicles at the beginning of the menstrual cycle should not be misdiagnosed as a physiological ovarian cyst and should be given a chance.

Ethics

Ethics Committee Approval: This study was approved by the local ethics committee with an approval number 2021/05 (Acıbadem University Clinical Research Ethics Committee, date: 13.03.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.Y.K., A.Y., Z.E.U.K., Concept: Ş.Y.K., Y.Ç., B.T., Design: Ş.Y.K., Y.Ç., B.T., Data Collection or Processing: Ş.Y.K., Z.E.U.K., Ö.K., Analysis or Interpretation: Ş.Y.K., A.Y., Y.Ç., Literature Search: Ş.Y.K., A.Y., Writing: Ş.Y.K., Z.E.U.K., Y.Ç.

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