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Long Agonist or Short Antagonist Protocol in Women with Intact Endometrioma(s) Undergoing ICSI: Retrospective Analysis

ICSI Yapılan Endometrioması Olan Kadınlarda Long Agonist veya Short Antagonist Protokol: Retrospektif Analiz

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ABSTRACT

Objective: Is to evaluate the efficacy of different ovarian stimulation (OS) protocols in patients with intact endometrioma(s) undergoing ICSI. **Material and Methods:** Retrospective chart review was performed. A total of 717 women were detected to have endometriosis of which 165 women with intact endometrioma(s) were included in the final analysis. A total of 60 women were detected in long agonist (AG) and 105 in short antagonist protocol (ANT). Sub-group analysis was performed to document OS outcomes of poor responders fulfilling the Bologna criteria. **Results:** Significantly shorter cycle duration and lower gonadotropin consumption was observed with ANT protocol compared to AG ($p<0.001$). The OS outcomes in terms of implantation, ongoing pregnancy (OP) and live birth rate per started cycle (LBR) were comparable in both groups. Overall LBR was 22,4%. Both protocols revealed similar but poor reproductive outcomes in terms of ongoing pregnancy (11.1%) and live birth rates (7.4%) in poor responders. **Conclusion:** AG or ANT protocols seemed to be equally effective in terms of oocyte yield and LBRs in women with intact endometrioma undergoing OS. Shorter duration and lower gonadotropin consumption may be attributed to the convenience of ANT protocol. In poor responders, reproductive outcomes are still not satisfactory with either protocol

Keywords: Agonist protocol; antagonist protocol; endometriomas

ÖZET

Amaç: ICSI uygulanan intakt endometrioma hastalarında farklı ovaryan stimülasyon protokollerinin etkinliğini değerlendirmektir. **Gereç ve Yöntemler:** Çalışma Retrospektif olarak yapıldı. Endometriosisi olan toplam 717 kadın çalışmaya dahil edildi. Bunlardan intak endometrioması olan 165 kadın nihayi analize dahil edildi. Uzun agonist protokol 60 kadına ve short antagonist protokolde toplam 105 kadına uygulandı. Alt grup analizi, Bologna kriterlerini yerine getiren poor responderlerin ovulasyon stimulasyon sonuçlarını dökümente etmek için gerçekleştirildi. **Bulgular:** Antagonist protokolde agoniste göre anlamlı derecede daha kısa siklus süresi ve düşük gonadotropin tüketimi gözlendi ($p<0,001$). Her iki grupta da, implantasyon, devam eden gebelik ve siklus başına canlı doğum oranı açısından ovulasyon stimulasyon sonuçları benzerdi. Canlı doğum oranı %22,4 idi. Her iki protokolde benzer sonuçlar ortaya çikardı.Ama poor responderlarda devam eden gebelik (%11,1), canlı doğum oranları (%7,4) açısından zayıf üreme sonuçları ortaya çıkmıştır. **Sonuç:** Agonist veya antagonist protokolleri, intak endometrioma olan kadınlarda oosit eldesi ve canlı doğum oranı açısından eşit derecede etkili görünmektedir. Kısa siklus süre ve daha düşük gonadotropin tüketimi, antagonist protokolünün kolaylığıdır. Poor responderlarda üreme sonuçları, her iki protokolde de tatmin edici değildir.

Anahtar Kelimeler: Agonist protokol; antagonist protokol; endometrioma

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Endometriosis is a serious health burden affecting 0.8-2% of women at a reproductive age.[1] The disease is closely associated with infertility as up to half of infertile women get diagnosed with endometriosis.[2,3] A staging system (American Society of Reproductive Medicine Endometriosis Classifiction) is currently being used to document the severity of the condition and to counsel patients as well.[4] Accumulating evidence suggests that advanced stage disease (III-IV) is associated with poorer reproductive outcomes when compared to earlier stages in women undergoing assisted reproductive technology (ART).[5,6] Advanced stage endometriosis may exist in several forms and is rather a heterogeneous group. Ovarian endometrioma is another clinical entitiy that is present in 20-40% of women with endometriosis.[7] Some authors have demonstrated poor ART outcomes in the presence of endometrioma; however others have failed to show any detrimental effect on outcomes.[8,9] In this view, infertile women with documented ovarian endometrioma require special attention.

Endometrioma can be identified by transvaginal sonography with high sensitivity and specificity without emerging diagnostic laparoscopy.[10,11] Resection of endometriomas prior to ART is controversial. According to a meta-analysis, no significant differences in pregnancy rates or in gonadotropin responses were reported between the surgical management and control groups prior to in-vitro fertilization (IVF).[12] In a more recent Cochrane Database review, lack of any benefit from either aspiration or cystectomy with regard to clinical pregnancy rates or the number of mature oocytes retrieved was reported when compared to expectant management.[13] Besides, accumulating evidence suggests that surgery has a detrimental impact on ovarian reserve in terms of serum anti-Mullerian hormone (AMH) levels and overall response to ovarian stimulation (OS).[14-16] Accordingly, increasing numbers of authors advocate against surgery prior to ART unless there is refractory pain, significant malignancy potential or inaccessibility to follicles during oocyte retrieval.

As a matter of fact, more and more infertile women with intact ovarian endometrioma are likely to enter an ART programme without having surgery. Hence,there is a need for studies evaluating the efficacy of different OS protocols particularly for this special population. Administration of GnRH agonists (GnRH-a) for a period of three to six months prior to ART has been shown to increase pregnancy odds.[17] However, this analysis was limited only to 3 studies without specifically examining those with intact endometrioma. The aim of our study is to evaluate the efficacy of different OS protocols in patients with intact endometrioma undergoing ICSI. The primary outcome was to report live birth rates and secondary outcomes were to compare OS characteristics and ongoing pregnancy rates per treatment cycle either in normal or poor responders.

MATERIAL AND METHODS

A chart review of a private assisted reproduction center was performed to detect eligible cases between January 2010 and August 2015 as retrospective. Complete data is comprised of the first ICSI cycle of each couple who have undergone OS. Informed consent was obtained from the participating patients. During the period, 717 subjects were detected to have endometriosis with or without endometrioma out of 4250 total admissions. Subjects diagnosed with endometriosis without intact endometrioma and/or who had at least one endometrioma surgery prior to a new OS cycle (N=498) were excluded. Out of the remaining 219 subjcets with endometrioma, 165 fulfilled the inclusion criteria, of which 60 underwent OS with agonist-protocol (AG, group I) and 105 with antagonist-protocol (ANT, group II). Both groups were compared in terms of pregnancy rates, live birth data and cancellation rates. Cycle cancellations were performed due to lack of ovarian response, fertilization failure or in the presence of no available embryos for transfer. Flowchart diagram is shown in Figure 1.

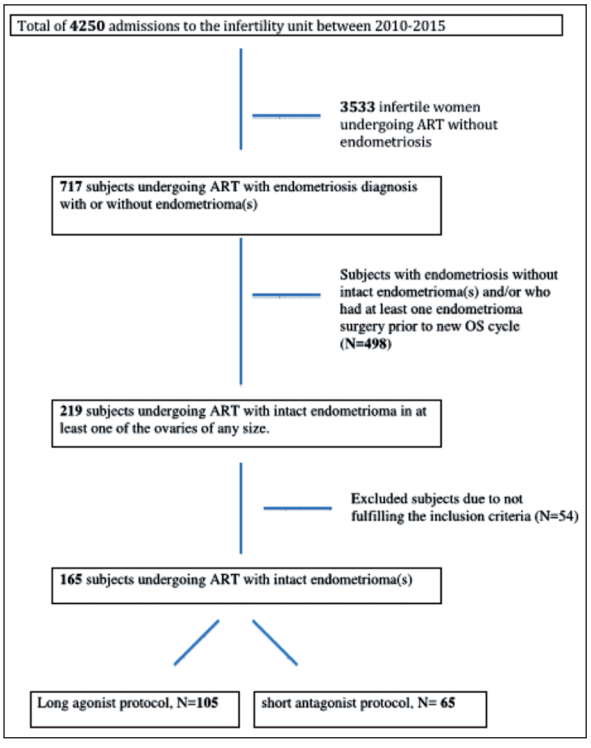

FIGURE 1: Flowchart diagram of the study design.

All included patients met the following inclusion criteria: subjects between the age of 18 and 42, with intact endometrioma of any size in at least one of the ovaries prior to ICSI cycle, with live birth data in the database, without prior ovarian surgery, with a body mass index between 18 and 34 kg/m^2, thyroid stimulating hormone (TSH) levels <4,5 IU/ml. In order to detect subjects with diminished ovarian reserve (DOR), the Bologna criteria was used as defined previously.[18] Exclusion criteria were: premature ovarian failure cases; subjects with documented Mullerian and/or uterine anomaly; GnRH-agonist down regulation longer than 1 month or oral contraceptive use prior to cycle; severe oligozoosperimia or azoospermia cases; Preimplantation genetic screening and frozen-thaw embryo transfer cycles; other ovarian cystic appearance rather than endometrioma during transvaginal sonography.

OVARIAN STIMULATION PROTOCOL

The study is comprised of one stimulation cycle of each subject in order to prevent possible crossover bias and of subjects to any OS protocol is made by physicians' discretion. Ovarian stimulation was carried out either with GnRH-antagonist (Cetrotide, Merck Serono) (0.25 mg/day) which was initiated when the leading folicle size >12 mm during follicular phase or with GnRH-agonist. In GnRH-agonist protocol ,Pituitary suppression was achieve by administration of triptorelin acetate (Decapeptyl®, Ferring, Germany) (1 mg/die, subcutaneously) in the midluteal phase of the cycle preceding the IVF procedure. When down-regulation was achieved (indicated by estradiol (E2) concentration <50 pg/ml and absence of follicles >10 mm diameter), recombinant human FSH (Gonal F®, Merck-Serono SA, Aubunne, Switzerland) (300 IU/die, subcutaneously) was administered. Starting from day 5, rhFSH was administered according to individual ovarian response and body mass index, as assessed by serum levels of E2 and sequential transvaginal ultrasonography; when the leading follicles reached a 18 mm diameter, recombinant human CG (Ovitrelle®, Merk-Serono SA, Bari, Italy) (500 µ g/subcutaneously) was injected for final oocyte maturation. Oocytes aspiration was performed 36 hours later.

Transvaginal ultrasound-guided oocyte retrieval and embryo transfer procedure was performed as described elsewhere.[14] Embryos on the 2nd and 3rd days were classified as cleavage stage embryos and were graded based on cell numbers and the degree of fragmentation.[15] Patients to whom embryos were transferred day 3. Clinical pregnancy was defined as the presence of a gestational sac with an embryonic pole and positive heart beat at 7 weeks of gestation and ongoing pregnancy was defined as the presence of an intrauterine sac with an embryonic pole demonstrating cardiac activity at 10 weeks of gestation.

STATISTICAL ANALYSIS

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by Kolmogorov Smirnov test. Data were

shown as mean± SD or number of cases and (%). Mean differences between groups were compared by Student's t test whereas Mann Whitney U test was applied for the comparison of median values. Nominal data was analyzed by Pearson's chi-square or Fisher's exact test, where applicable. A p value less than 0.05 was considered statistically significant.

RESULTS

The indication to ICSI was endometriosis-associated infertility in 52 (89,7%) women in AG and in 95 (90,5%) in ANT group (p=0,866). According to demographic characteristics, mean age, infertility duration, serum AMH levels, basal antral follicle count (AFC), basal FSH, E2, TSH and Ca-125 levels were similar among groups. Approximately 81% of subjects in AG and 82% in ANT group had unilateral endometrioma, whereas nearly 20% in both groups had bilateral endometrioma. The mean+SD diameter of ovarian endometrioma was 3.21±1.45 cm and 3.39±1.41 cm in ANT and AG groups, respectively (p=0.434). Semen parameters in terms of TPMS for both groups were comparable (p>0.05). Demographic characteristics of groups are shown in Table 1. Significantly higher cycle duration (11.1 vs 9.3 days) and higher gonadotropin use (3393 vs 2560 IU) was detected in AG group (p<0.001). Other parameters including endometrial thickness, peak serum E2, numbers of both retrieved and mature oocytes, numbers of 2PN and fertilization rates were all similar between the two groups. There wasno statistical difference in terms of implantation, ongoing pregnancy/started cycle and live birth rate/started cycle among groups. Cycle cancellations were also similar between groups. Cycle characteristics and pregnancy outcomes of groups are shown in Table 2.

A sub-group analysis was performed to detect subjects with normal ovarian reserve (normo-responder). A total of 138 subjects was detected of which 46 of them were in AG and 92 were in ANT group. Both groups revealed similar cycle characteristics and pregnancy outcomes that are shown in Table 2.

TABLE 1: Demographic data and cycle characteristics of study groups

	AG (N:60)	ANT (N:105)	p value
Age (years)	33.15±4.52	33.78±4.94	0.417
Duration of infertility (years)	4.94±3.72	4.83±3.47	0.852
Serum AMH (ng/ml)	1.90±0.55	2.13±0.98	0.104
Antral follicle count	4.03±1.19	4.20 ±1.47	0.430
TSH (mU/L)	1.98±1.32	2.01±1.04	0.921
CA-125 (mIU/ml)	31 (14 – 408)	30 (14 – 226)	0.769
Unilateral cyst	49/60 (81,6%)	85/105 (80,9%)	
Bilateral cyst	11/60 (18,3%)	20/105 (19%)	
Endometrioma size (cm)	3.21±1.45	3.39±1.41	0.434
TPMSC (x106)	34.5 (2 - 156)	31 (2 - 145)	0.826
Total gonadotropin dose (IU)	3393.33±1367.01	2560.67±1283.45	<0.001*
Peak serum estradiol (pg/ml)	1820.43±1190.55	1546.48±1166.26	0.152
Peak endometrial thickness (mm)	10.28±2.05	10.33±1.99	0.873
Duration of cycle (days)	11.12±2.44	9.37±3.62	<0.001*
No of retrieved oocytes	4.50±2.93	4.78±3.33	0.587
Mature oocytes	3.30±2.28	3.62±2.75	0.448
2 PN	2.53±1.86	2.89±2.26	0.308
Fertilization (%)	81.02±24.89	74.65±31.16	0.177

TABLE 2: Reproductive outcomes of study groups.

	AG (N:60)	ANT (N:105)	p value
Implantation rate (%)	16.35±29.48	17.11±33.40	0.883
Ongoing pregnancy rate (%)	16/60 (26.7)	25/105 (23.8)	0.683
Live birth rate (%)	14/60 (23.3)	23/105 (21.9)	0.832
Misscarriage (%)	2/60 (3.3)	2/105 (1.9)	1.000
Cancellation (%)	3/60 (5.0)	14/105 (13.6)	0.083

Values are given as mean±SD or median (min-max).
TPSMC: total progressive motile sperm count; TSH: thyroid stimulating hormone; AMH: Anti-Mullerian Hormone; 2PN: 2 pronuclei; *: statistically significant.

Further sub-group analysis was performed to detect subjects with DOR according to the Bologna criteria.Among all, 27 cases were detected to fulfill the Bologna criteria of which 14 of them were in AG and 13 were in ANT group. Cycle characteristics, ongoing pregnancy/cycle and live birth rate/cycle were similar among groups. All cycle cancellations were detected in ANT group. Outcomes are shown in Table 1.

DISCUSSION

This study revealed that both OS protocols yielded comparable pregnancy and live birth rates

per started cycle in patients with intact ovarian endometrioma undergoing ICSI. Significantly longer cycle duration and higher amounts of gonadotropin consumption were considered as major drawbacks of AG protocol. Additionally, very low pregnancy rates were detected in poor responders with an intact endometrioma in both OS protocols.

To date, several studies have evaluated the OS outcomes of endometriosis cases according to stage. Of those, very few have specifically examined women with intact endometriomaregardless of stage.[19] There are 3 studies available in the literature comparing OS outcomes of endometrioma cases with that of other infertility etiologies, as GnRH-a were the protocol in all. Yanushpolski et al. reported 13 retrieved oocytes and 62% fertilization rate with AG protocol in their cohort with intact endometrioma (>1 cm) regardless of size data.[8] Suzuki et al reported 4,4 retrieved oocytes and 77% fertilization rate with short AG protocol and Bongioanni et al reported 9.4 retrieved oocytes and 67% fertilization rate using AG protocol in cases with intact endometrioma £6 cm diameter.[20,21] To the best of our knowledge, there are 2 studies available comparing different OS protocols in endometriosis cases undergoing IVF/ICSI. Purata et al compared the efficacy of ANT protocols with that of AG in a large series including those with stage I-IV endometrioma without indicating endometrioma cases.[22] The study by Pabuccu et al is the only randomized controlled trial (RCT) comparing different OS protocols in cases with intact endometrioma regardless of size information.[19] Despite the higher number of oocytes (6.7 in ANT vs 8.2 in AG) that were retrieved with AG, both protocols yielded similar fertilization (73.5 vs 75.6) and CP (20.5 vs 24.2%) rates. In our data, retrieved number of oocytes (4.5 in AG vs 4.7 in ANT), fertilization rates (81% vs 74,6%) and clinical pregnancy outcomes (26.7% vs 23.8%) were found to be similar for both protocols where all parameters were in accordance with literature findings. Even though LBRs are quite comparable, significantly longer cycle duration and higher amounts of consumed gonadotropins that were noticed with AG protocol supports the convenience and applicability of ANT protocol.

There is evidence that women with advanced stage endometriosis (III-IV) had lower LBRs than those with minimal to mild endometriosis (I-II) or with no endometriosis.[23] However, Hamdan and coworkers reported similar LBRs in women with intact endometriomawhen compared to those without endometrioma or to those without endometriosis undergoing IVF/ICSI.[9] They examined 5 studies specifically evaluating intact endometrioma cases undergoing IVF/ICSI with different OS protocols, majorly using AG and including various endometrioma sizes either including those with >6 cm diameter. According to our results, overall LBR per started cycle is 22.4% and similar LBRs were reported in either protocol (AG: 23.3% and ANT: 21.9). It seems that, <30% LBR is somehow common with both OS protocols in those with intact endometrioma undergoing IVF/ICSI. Optimal OS protocol for such cases is yet to be determined.

The management of patients with DOR, especially those fulfilling the Bologna criteria remains one of the most significant challenges of ART. The pathophysiology behind ovaries responding poorly to OS is the presence of a reduced number of FSH-sensitive follicles. Hence, few oocytes at retrieval, reduced number of embryos available for transfer and poor pregnancy outcomes are the facts of poor responders.[24,25] Endometriosis has also been accused for contributing to DOR.[26] In this context, ovarian endometriomas have been questioned to influence ovarian response to OS and Hamdan et al reported relatively lower AFC in cases with intact endometrioma than those without it.[9] Moreover, the same group reported less retrieved oocytes in cases with intact endometrioma than those without endometriosis. The low number of oocytes retrieved and higher baseline levels of FSH in women with endometrioma than those without it indicate the possible detrimental effect of endometriotic cyst to ovarian reserve. According to

our results, both protocols yielded less than 2 retrieved oocytes, low implantation (<10%) and LBRs (<8%) in Bologna poor responders indicating that the impact of endometriomais likely to be more profound in those with DOR. In the literature, consistently low overall CPR and OPR per cycle (8.6% and 7.7%, respectively) were reported with different OS protocols in Bologna poor responders, however there is lack of data specifically investigating poor responders with endometriosis/endometrioma.[25]

Limitation of the current study is the retrospective nature and lack of power analysis. Additionally, we do not know exactly which ovary yielded more oocytes and responded better to OS in patients with unilateral endometrioma. Under these circumstances, it is hard to conclude which OS protocol is effective either in the ovary with endometrioma or in the contralateral ovary.

In conclusion, AG or ANT protocols seemed to be equally effective in terms of oocyte yield and LBRs, however shorter duration and lower gonadotropin consumption in ANT protocol may be attributed to the convenience of this protocol. Well-designed RCTs are needed specifically evaluating OS protocols in cases with intact endometrioma undergoing IVF/ICSI.

Conflict of Interest

No conflict of interest was declared by the authors.

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