

1 **IVF sikluslarında GnRH agonist tedavisi sonrası oluşan over kistleri oosit kalitesini**
2 **düşürür**

3 **ÖZET**

4 **Amaç : Bu çalışmada, in vitro fertilizasyon sikluslarında GnRH agonist**
5 **uygulaması sonrası oluşan over kistlerinin, tedavi sonuçlarına etkisi araştırılmaya**
6 **çalışılmıştır.**

7 **Yöntem ve gereç : Toplam 931 siklus içinden over kisti olan 78 hasta retrospektif**
8 **olarak tarandı. Bu hastalar gonadotropin stimülasyonu öncesi kisti aspire edilenler**
9 **(Grup 1 ; n=46) ve kisti aspire edilmeyenler (Grup 2 ; n=32) olarak iki gruba ayrıldı.**
10 **Demografik ve hormonal sonuçlar, metafaz II oosit oranı, fertilizasyon hızı, iyi kalite**
11 **embiryo oranı, implantasyon ve klinik gebelik hızları karşılaştırıldı.**

12 **Sonuç : Metafaz II oosit oranı, fertilizasyon hızı ve grade I embiryo oranı kisti olan**
13 **ve olmayan hastalar arasında anlamlı olarak fazla bulundu ($p<0.0001$, $p<0.0001$, $p <$**
14 **0.05). Kist aspirasyonu yapılan grupta, metafaz II oosit oranı, fertilizasyon hızı, grade I**
15 **embiryo oranı ve kist çapında anlamlı farklılık tespit edildi ($p< 0.01$; $p<0.05$; $p<0.05$;**
16 **$p<0.05$). Tüm gruplarda implantasyon ve klinik gebelik hızları arasında bir fark**
17 **bulunamadı.**

18 **Tartışma : GnRH-a uygulaması sonrası oluşan over kistleri, IVF sikluslarında oosit**
19 **kalitesini düşürür. Bu kistlerin gonadotropin stimülasyonu öncesinde aspire edilmesi,**
20 **IVF başarısına bir katkı sağlamaz.**

21 **ANAHTAR SÖZCÜKLER**

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23 **Over kisti; IVF, GnRH agonisti**

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25 **Ovarian cyst formation following gonadotropin-releasing hormone-agonist**

26 **administration decreases the oocyte quality in IVF cycles**

27 **ABSTRACT**

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29 **Aim:** The gonadotropin-releasing hormone-agonist (GnRH-a) treatment during in
30 vitro fertilization (IVF) sometimes causes a functional ovarian cyst during the
31 administration period before gonadotropin stimulation, as an undesired event. The aim
32 of this study was to analyze the effect of these cysts on the IVF outcomes.

33 **Materials-Methods :** Out of 981 IVF cycles, 78 with ovarian cysts were
34 retrospectively analyzed with respect to the demographic characteristics, hormonal
35 outcomes, and fertilization, implantation and clinical pregnancy rates.

36 **Results :** The metaphase II oocyte ratio, fertilization rate and the percentage of high
37 quality embryos (grade 1) were significantly higher in the cyst-negative group
38 ($p<0.0001$; $p<0.0001$; $p\leq 0.05$). These same three parameters were also significantly
39 higher in the cyst-aspirated group ($p<0.01$; $p<0.05$; $p<0.05$). Cyst diameters of the
40 aspiration group were significantly higher ($p<0.05$). No statistically significant
41 differences in implantation and clinical pregnancy rates were determined between the
42 groups.

43 **Conclusion :** An ovarian cyst formation during the GnRH-a suppression period
44 negatively affects oocyte quality. Cyst aspiration before gonadotropin stimulation does
45 not improve the IVF outcome.

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47 **Key words:** Ovarian cyst; in vitro fertilization (IVF); gonadotropin-releasing hormone
48 agonist.

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50 **INTRODUCTION**

51 Gonadotropin-releasing hormone-agonist (GnRH-a) treatment is one of the main
52 pathways in the long agonist protocol of in vitro fertilization (IVF) treatments. In
53 addition to the many advantages of GnRH-a, it sometimes causes a functional ovarian

54 cyst during the administration period as an undesired event. Such ovarian cysts are still
55 being discussed in terms of their proper management and their impact on the IVF
56 outcome. Mechanical pressure on the ovarian tissue that reduces the area for growing
57 follicles and the decreased blood circulation in and around the follicles are physical
58 explanations for their negative impacts (1-4). Another likely problem concerning these
59 ovarian cysts may be endocrinological in nature. Such cysts may impair folliculogenesis
60 in such a way as to decrease the pre-ovulatory follicle numbers and their quality (2,3). In
61 addition to the studies showing the negative effect of the cysts that appear during
62 GnRH-a administration, other studies have concluded that the functional cysts are
63 ineffective on the IVF outcome (5-11).

64 In this study, we aimed to analyze the ovarian cysts in IVF patients, which were
65 found at the end of the GnRH-a administration period, with respect to their effects on
66 the cycle outcome.

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68 MATERIALS METHODS

69 Nine hundred and thirty-one patients completed the IVF and intracytoplasmic
70 sperm injection (ICSI) programs between March 2008 and January 2010 in Zekai Tahir
71 Burak Women's Education and Research Hospital, Infertility Research and Treatment
72 Center. Among the 931 patients, 78 with ovarian cysts ≥ 10 mm in diameter (3) at the end
73 of the GnRH-a suppressive period of the proceeding IVF cycle comprised the study
74 group. Of these 78 patients with ovarian cysts, 46 continued the cycle without cyst
75 aspiration, while the remaining 32 patients with ovarian cysts underwent transvaginal
76 ovarian cyst aspiration (gonadotropin stimulation was administered the day after
77 aspiration in these patients). Patients with aspirated and non-aspirated ovarian cysts

78 were compared with a control group of 163 patients who had no ovarian cysts at any
79 time in their cycle.

80 The IVF treatment consisted of the long agonist protocol, in which leuprolide
81 acetate (Lucrin, Abbott, Germany) was used in the mid-luteal phase of the preceding
82 cycle for pituitary downregulation. Controlled ovarian hyperstimulation was started on
83 the 2nd or 3rd cycle days with human-derived follicle-stimulating hormone (FSH)
84 (Menogon, Ferring Pharmaceuticals, Germany) or recombinant FSH (Puregon, NV
85 Organon, The Netherlands or Gonal-F, Merck Serono, Germany). Gonadotropin
86 administration was continued until the appearance of at least three follicles ≥ 16 mm on
87 serial ultrasound examinations. Endometrial thickness was measured in the fundal
88 longitudinal axis transvaginally. Ovulation was triggered with 0.25 μg recombinant
89 human chorionic gonadotropin (hCG) (Ovitrelle, Merck Serono, Germany).
90 Transvaginal-guided oocyte retrieval was done under general anesthesia 36 hours after
91 the hCG injection. The morphological grading of the oocytes was done according to
92 oocyte-cumulus complex, and embryo transfer was done between the 2nd to 5th days.

93 This study was approved by the Local Ethical Committee of Zekai Tahir Burak
94 Women's Education and Research Hospital.

95 Statistical Analysis:

96 Statistical analysis was carried out using the Statistical Package for the Social
97 Sciences software (SPSS, version 11.0). All variables were tested for normal distribution
98 with Kolmogorov-Smirnov test, histogram, and P-P plots. Variables were compared
99 with independent samples t-test or Mann-Whitney U test. All categorical variables were
100 compared with Pearson chi-square and Fisher's exact tests. A p value < 0.05 was
101 considered as indicating the level of statistical significance.

102 RESULTS

103 **The demographic data of the women with basal ovarian cysts in the proceeding**
104 **IVF cycle and the control group of women without ovarian cyst are presented in Table I.**
105 **The causes of infertility were categorized as unexplained, male and tubal factors.**
106 **Unexplained infertility was the most common factor among the women with ovarian cyst**
107 **(52.6%) and in the control group (58.3%).**

108 **Basal hormonal profile and outcomes of the patients with ovarian cysts and of the**
109 **control group are summarized in Table II. There were no statistically significant**
110 **differences in Day 3 FSH, luteinizing hormone (LH) and E2 levels, the duration of**
111 **stimulation, and the amount of total gonadotropin used (IU) between the patients with**
112 **and without ovarian cysts. Of the 78 patients with ovarian cysts, 32 (41%) underwent**
113 **cyst aspiration procedure. Cyst diameters in the aspirated and the non-aspirated groups**
114 **ranged between 1850 mm (mean \pm SD: 29.0 \pm 8.6) and 10-30 mm (mean \pm SD: 18 \pm 5.1),**
115 **respectively, and the difference was statistically significant (p=0.0001). E2 levels on the**
116 **day of hCG administration were significantly higher in women with ovarian cyst**
117 **(p<0.05). The metaphase II (MII) oocyte number was significantly lower in patients with**
118 **ovarian cysts (p<0.05). Percentages of MII oocytes, fertilization rate and the percentage**
119 **of high quality (Grade 1) embryo transfers were significantly higher in the cyst-negative**
120 **group (p<0.05; p<0.0001; p<0.0001, respectively). MII oocyte ratios and the fertilization**
121 **rate were significantly correlated between the two groups (p<0.01; p<0.05).**

122 **The cycle characteristics and the outcomes of the patients with and without cyst**
123 **aspiration are presented in Table III. The differences in MII oocyte ratio (p<0.01),**
124 **fertilization rate (p<0.05), Grade 1 embryo percentage (p<0.05), and cyst diameters**
125 **(p<0.05) were statistically significant between the two groups.**

126 **DISCUSSION**

127 **The appearance of a functional ovarian cyst during the GnRH-a suppression**
128 **period of the IVF cycle is a controversial issue. The incidence varies between 5.5% and**
129 **53% in different studies (1,4,5,8,12). In a recent study performed by Qublan et al. (4),**
130 **the rate was reported as 9.3% in a large population of IVF patients, which was**
131 **consistent with our results, at 8.3%.**

132 **The mechanism of the cyst formation is not clearly understood. The impressive**
133 **transient flare-up effect of GnRH-a on immature antral follicles with LH surge**
134 **inhibition has been the most frequent explanation (5-8). The presence of ovarian cyst in**
135 **IVF cycles has been studied frequently in terms of its effect on the clinical outcomes.**
136 **Segal et al. (3) pointed out the mechanical effect of the cysts inside the ovary. They**
137 **suggested that the decreased area in the ovary may impair folliculogenesis and**
138 **angiogenesis, which was the cause of the poor IVF outcomes. Thatcher et al. (13)**
139 **stressed the importance of the ovarian cyst found in the follicular phase, which had a**
140 **more negative effect on the success of ovarian stimulation. Biljan et al. (10) explained the**
141 **passive diffusion of E2 from the cyst content into the circulation, which increased the**
142 **basal E2 levels and decreased the basal FSH to false-negative low levels. Our study**
143 **supported the risk of lower embryo quality in the cyst-positive cycles. IVF patients with**
144 **cyst occurrence during the GnRH-a administration period had a lower Grade 1 embryo**
145 **percentage. The higher E2 levels on the hCG administration day in the cyst-positive**
146 **patients in our study may be explained as in Biljan's study (10), i.e. passive perfusion of**
147 **E2 from the cyst mass into the circulation may increase the final E2 level at the end of**
148 **the stimulation period with an ineffective impact on implantation and the clinical**
149 **pregnancy rates. Keltz et al. (12) reported that ovarian cysts in IVF cycles were seen**
150 **more in older patients with higher basal FSH levels and lower pregnancy rates. Qublan**
151 **et al. (4) had also supported the poor IVF outcomes among patients with ovarian cysts.**

152 In his study, cycle cancellation rate, the number and quality of the embryos,
153 implantation, and the clinical pregnancy rates were negatively affected. Other studies
154 showed that the pre-stimulation cyst was ineffective (5,7,11,14). Levi et al. (15) showed
155 similar IVF results between the cyst-positive and the cyst-negative groups. Kumbak et
156 al. (16) concluded that the pre-stimulation ovarian cyst was not related with poorer
157 pregnancy outcomes and was not an indication to cancel the cycle. Our study also
158 showed similar pregnancy rates between the cyst-positive and cyst-negative groups, but
159 the higher MII oocyte ratio and fertilization rate in the cyst-free patients highlighted
160 that cyst existence in fact has a negative impact on IVF treatments. The better quality of
161 transferred embryos followed the healthier retrieved oocytes in cyst-negative patients.
162 The imbalanced intraovarian environment of cyst-positive ovaries with the physical
163 pressure, disturbed hormonal status or ineffective oxygenation may explain the poorer
164 oocyte results.

165 Once an ovarian cyst is diagnosed in an IVF patient, the decision regarding
166 intervention is problematic. It is still controversial as to whether or not to aspirate the
167 cyst (3-6,8,10,-13). The results of many studies were consistent in recommending
168 conservative, non-invasive, non-aspirated treatment of these cysts. Our results showed a
169 significantly higher cyst diameter in the aspirated group. This study was retrospective,
170 and it was ascertained that the larger cysts caused more stress for the physicians leading
171 to their decision to aspirate. We found that the negative effect of an ovarian cyst on
172 oocytes was more pronounced with a larger cyst with a worse MII oocyte ratio and
173 lower fertilization rate. The favorable fertilization rate in the non-aspirated group may
174 be due to the existence of a smaller cyst with less ovarian damage or the absence of any
175 direct disturbing impact of the aspiration procedure on the ovaries. Cyst aspiration with
176 the intraovarian instrumentation may cause bleeding, impair the perifollicular

177 circulation, or increase the inflammatory chemicals. These probable explanations
178 suggest that aspiration of such cysts should be avoided before stimulation. As the
179 pregnancy rates of the aspirated and non-aspirated groups were not statistically
180 different, it is once again shown in this analysis that aspiration of an ovarian cyst before
181 gonadotropin administration has no positive impact on the IVF outcome. Further, the
182 aspiration procedure itself may cause psychological stress for the patient, and the risks
183 of anesthesia may also be problematic; thus, intervention with aspiration does not
184 appear to be mandatory.

185 In summary, the results of our study support the findings of previous studies in
186 which cyst appearance during the GnRH-a administration period was harmful for the
187 ovary. The impressive negative effects were on fertilization, but not on the overall
188 implantation and pregnancy rates. Once a cyst is observed, we do recommend the
189 continuation of the IVF treatment without cyst aspiration in order to prevent the likely
190 ovarian damage.

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Table 1. Demographic characteristics of IVF patients with and without ovarian cysts.

	Patients with Ovarian cysts (n=78)	Patients without Ovarian cysts (n=163)
Age(years)	31.2 ± 4.5	30.6 ± 4.6
Infertility duration(years)	8.1 ± 4.3	8.6 ± 4.5
Causes of infertility		
Unexplained	41/78 (52.6 %)	95/163 (58.3 %)
Male factor	30/78 (38.5 %)	62/163 (38 %)
Tubal factor	7/78 (9 %)	6/163 (3.7 %)

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Values are expressed as mean ± SD.

289 **Table 2. Patient characteristics and the IVF outcomes of the cycles with and without**
 290 **ovarian cysts.**

	Patients with ovarian cyst (n=78)	Patients without ovarian cyst (n=163)	P value
Basal E2 levels(pg/ml)	45.8 ± 22.4	42.7 ± 40	NS
D3 FSH(mIU/ml)	6.8 ± 2.0	6.9 ± 1.9	NS
D3 LH(mIU/ml)	5.5 ± 3.1	5.6 ± 3.0	NS
Total gonadotropin used(IU)	2506.8 ± 1378.2	2506.8 ± 1378.2	NS
Stimulation duration(days)	10.7 ± 2.2	10.5 ± 1.8	NS
HCG E2	2222.1 ± 1006.1	1996.1 ± 1113.8*	0.05
HCG endometrium	10.3 ± 1.9	10.2 ± 1.9	NS
No. of follicles≥16mm	6.0 ± 3.0	5.1 ± 3.1	NS
No. of oocytes retrieved	8.0 ± 5.0	8.9 ± 6.0	NS
MII oocyte ratio	427/630 (67.7 %)	1110/1440 (77 %)	0.0001
Fertilization rate	308/630 (48.8 %)	1128/1440 (78.3 %)	0.0001
No. of embryos transfered	2.4 ± 0.7	2.3 ± 0.8	NS
Grades I embryo ratio	139/308 (45.1 %)	640/1128 (56.8 %)	0.05
Implantation rate	25/87 (29.5 %)	64/181 (35.6 %)	NS
Pregnancy rate	21/87 (24.3 %)	53/181 (29.4 %)	NS

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Values are expressed as mean ± SD. NS: Not significant

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Table 3. Cycle characteristics and IVF outcomes of patients with cyst aspiration and non-aspiration

	Cyst aspirated group (n=32)	Cyst non-aspirated group (n=46)	P value
MII oocyte ratio	179/284 (63.0 %)	248/346 (71.6 %)	0.01
Fertilization rate	122/284 (42.9 %)	186/346 (53.7 %)	0.05
No. of embryos transferred(n)	2.3 ± 0.8	2.6 ± 0.6	NS
Grades I embryo ratio	49/122 (40.8 %)	95/186 (51.5 %)	0.05
Cyst diameter(mm)	29.9 ± 8.6	18.2 ± 5.1	0.05
Implantation rate	10/38 (28.1 %)	14/49 (30.4 %)	NS
Pregnancy rate	6/38 (17.3 %)	7/49 (15.6 %)	NS

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Values are expressed as mean ± SD. NS: Not significant.