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Evaluation of the Relation Between Ovarian Reserve and Cyst Dimension in Patients with Endometrioma

Endometriomalı Hastalarda Kist Çapı ile Over Rezervi Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objectives

Endometriosis is a gynecologic disease which has high prevalence among infertile population. It has increasing importance particularly for the patients with determined endometrioma cyst when there is an infertility problem during the surgery. In this study, we aimed to evaluate the ovarian reserve with basal hormone values and clomiphene citrate challenge test in patients with endometrioma, to compare results with control group and to determine a possible relationship between the cyst diameter and the ovarian reserve in condition of getting significant results.

Methods

Thirty-five patients who had diagnosis of endometrioma were included in the study. As the control group, 35 patients with borderline male infertility and similar demographic characteristics were selected from Infertility Clinic of the same hospital.

Results

There was no significant distinction between mean age values of groups. Mean cyst diameter was 33.65 ± 17.08 mm in the endometrioma group. No significant difference was determined between day 3 FSH, day 3 estradiol and day 10 FSH value after clomiphene citrate challenge test. There was also no significant distinction when the hormone values were categorized as normal and abnormal.

Conclusion

Although being statistically insignificant, due to the detection of a borderline significance in the 10th day FSH values after clomiphene citrate test and obtaining elevated hormone levels in the endometrioma group, we can conclude that it is probable to obtain siginificant results in a larger population.

Key Words: endometriosis, infertility, clomiphene citrate challenge test

ÖZET

Amaç

Endometriozis, infertil popülasyonda yüksek prevalansa sahip bir jinekolojik hastalıktır. Özellikle infertilite problemi olan hastalarda cerrahi esnasında endometrioma kisti karşımıza çıktığında daha da önem kazanmaktadır. Bu çalışmada, bazal hormon seviyeleri ve klomifen sitrat testi ile endometrioma hastalarının over rezervini değerlendirmeyi, sonuçları kontrol grubu ile karşılaştırmayı ve kist çapı ile over rezervi arasında muhtemel bir ilişkiyi anlamlılık derecesinde araştırmayı planladık.

Metod

Endometrioma tanısı alan 35 hasta çalışmaya dahil edildi. Benzer demografik özelliklere sahip ve sınırda erkek faktör infertilitesi olan 35 kontrol hastası aynı hastanenin İnfertilite Polikliniğinden seçildi.

Bulgular

Grupların yaş ortalamaları arasında anlamlı bir fark yoktu. Endometrioma grubunda kist ortalaması 33,65 ± 17,08 idi. Üçüncü gün FSH, estradiol ve klomifen sitrat sonrası 10.gün FSH değerlerinde anlamlı fark tespit edilmedi. Hormon değerleri normal ve anormal olarak sınıflandırıldığında da anlamlı fark tespit edilmedi.

Sonuç

İstatistiksel olarak anlamlılık tespit edilemese de; klomifen sitrat testi sonrasında 10. gün FSH değerinde sınırda bir anlamlılık tespit edilmesi ve kontrol grubuna nazaran endometrioma grubunda yüksek (anormal) hormon değerleri elde edilmesinden dolayı; büyük gruplarda daha anlamlı sonuçlar elde edilebileceği yorumu yapılabilir.

Anahtar Kelimeler: endometriozis, infertilite, klomifen sitrat testi

INTRODUCTION

Endometriosis has been one of the most confusing diseases since it was first described nearly a century ago. Pelvic pain and infertility are common problems and direct patients for medical help. Aim of treatment is make patients free of these endometriosis lesions by surgical resection or medical treatments. In this point, it is asked that how the treatment should be planned with considering patients fertility desire.

It is known that to a certain extent ovarian reserve (OR) is affected in the endometrioma cyst patients. Endometriosis is an important cause of secondary infertility. In the literature there are many studies investigating the relation between endometrioma and infertility. However there isn't any study correlating cyst dimension and the OR. It may be important to elucidate this relation and it can help in deciding for either conservative or surgical treatment.

We aimed to research OR of the endometrioma patients with clomiphene citrate challenge test prospectively and relation with the cyst diameter.

MATERIAL AND METHODS

A total of 35 women who were included had endometrioma cyst greater than 2 cm in diameter in the fertile period between 2006, October to 2007, April. Control group was consisting of 35 infertile women having "borderline male factor infertility" and similar demographic characteristics with the study group. Women who were pregnant, had an endocrine disorder, a contraindication for usage of clomiphene citrate, menstrual irregularities, ovarian cysts other than endometrioma and women with a body mass index greater than 30 were excluded.

Study protocol and ovarian reserve test

Patients from both groups was scheduled for blood hormone test at the third day of menstruation. Endometrioma diagnosis was made principally with trans-vaginal ultrasonography. Follicle stimulating hormone (FSH), luteinising hormone (LH) and estradiol blood levels were measured. All patients had at least one trans-vaginal ultrasonography examination in order to exclude ovarian cysts. OR was analysed via "clomiphene citrate challenge test" (CCCT) in both groups. All patients have been given 100 milligrams of clomiphene citrate tablets (Serophene®) orally from third to tenth day. After the last tablet had been taken at the tenth day of menstruation, blood tests for hormones were performed again. Hormone values were compared within and between groups. Accepted normal and abnormal values are given within the table below (Table 1).

Laboratory

Venous blood samples from patients on the third and tenth days were analyzed with chemiluminance method in the immunoanalyser (Roche Elecsys 2010, Mannheim, Germany). Analytic sensitivities (AS) and intra- and inter-assay variation coefficients (VC) are as follows: FSH (AS: 0.10 mIU/ml, intra-assay VC: %1.90, inter-assay VC: %2.11), LH (AS: 0.10 mIU/ml, intra-assay VC: %1.60, inter-assay VC: %2.11), Estradiol (AS: 15 pg/ml, intra-assay VC: %2.50, inter-assay VC: %3.23).

The diagnosis of endometrioma cyst was made with transvaginal ultrasonography (General Electric Logic 7) and cyst dimension was estimated from the mean of the two biggest dimensions

Statistical analysis

In comparisons of parametric and non-parametric independent variables, t-test and Mann-Whitney U test was used respectively. Nominal variables were tested with chi-square and Fisher's exact test. Results in numeric variables were presented mean $^{238}_{93}$ SD (standard deviation) (minimum-maximum).

All data are collected prospectively and statistics are done with SPSS for Windows 16.0 (SPSS Inc. USA) program. In all statistical analyses $p < 0.05$ was considered as significant.

Endometrioma group was further analyzed with division of the group according to the accepted hypothetic cyst dimensions as cut-off point and compared higher and smaller dimensions. Also hormone values of both groups were classified as normal and abnormal according to the accepted normal levels and comparisons of the categorical data also were done.

A written informed consent was obtained from all patients. The study was approved by the local ethic committee.

Table 1. Accepted normal and abnormal hormone values

Test	*Normal*	*Abnormal*
Third and tenth day FSH	<12 mIU/ml	≥12 mIU/ml
Third day estradiol	<80 pg/ml	≥80 pg/ml

Abbreviations: FSH: Follicle stimulating hormone

Table 2. Third and tenth day hormone values of endometrioma and control group.

		Endometrioma group	*Min-Max*	*Control group*	*Min-Max*	*p*
Third Day	Estradiol	75.05 ± 62.69	11-267	52.63 ± 46.77	12-288	NS
	FSH	10.44 ± 9.98	3-54	8.53 ± 5.74	3-32	NS
	LH	7.35 ± 4.83	2-22	5.66 ± 3.04	2-15	NS
Tenth Day	Estradiol	446.48 ± 378.53	18-1561	456.97 ± 277.55	37-1336	NS
	FSH	10.08 ± 7.97	3-40	8.59 ± 8.23	2-36	**0.048**
	LH	9.45 ± 4.52	3-22	14.06 ± 14.52	1-78	NS

Abbreviations: FSH: Follicle stimulating hormone, LH: Luteinising hormone, NS: Not significant

RESULTS

There was no significant difference between mean ages of two groups. Among hormone analyses only borderline significance was detected in 10th day FSH values of the both groups (Table 2). Mean cyst dimension in the endometrioma group was 33.65 ± 17.08 mm. Normal and abnormal hormone values were compared with chi-square test between groups. Also endometrioma group was divided into two; normal and abnormal hormone values and compared with cyst dimensions. These analyses also could not reveal a significant relation.

In order to elucidate relation of the endometrioma cyst dimension and the ovarian reserve, endometrioma group is re-categorized according to the defined cut-off point of cyst dimension. Afterwards comparisons of hormone values were again performed in these groups. We chose 4 cut-off points for cyst dimension as; 25 mm, 30 mm, 35 mm and 40 mm. Between re-categorized groups according to the cut-off cyst dimensions (smaller than cut-off and greater than cut-off) also could not show significance with regard to hormone levels.

DISCUSSION

Infertility and Endometriosis

It is a debate whether endometriosis is related with infertility or not. American Fertility Society classification stated that in moderate and severe endometriosis if ovaries are involved and adhesions extending towards ovaries can diminish tubo-ovarian motility and oocyte capture and effect infertility (1). However in the minimal endometriosis group this remains uncertain. There is 80% minimal or moderate and 20 % severe endometriosis prevalence in the fertile women. (2-4)

In the women having early onset and moderate endometriosis it is reported that endocrine disorders (5), anovulation (6), corpus luteum deficiency (7), hyperprolactinemia (8), luteinized unruptured follicle syndrome (9) and spontaneous abortion (10) incidences are increased.

Ovarian reserve tests

A number of tests and techniques are used to elucidate the reduction of OR. Because OR rapidly decreases by age, it is thought that age of women can be used as the indication of OR especially over 36. However, because it is concluded that the fertility prognosis is poor in correlation with OR independent from age, age and OR should be considered together (11). FSH values on the third day of menstruation are also important. If the value of FSH is greater than 12 IU/L, especially above 20 IU/L it is poor prognosis sign of estradiol values, number of aspirated follicle number and pregnancy in the in vitro fertilization techniques (12). Due to variability of threshold values between different laboratories, it is advised to have own levels (13). Basal estradiol and FSH measurements together are reported to be useful to evaluate OR (14). clomiphene citrate challenge test (CCCT) is performed within 5-9th days of menstruation with per-oral 100 milligrams tablets and collecting FSH levels or sum of two levels at 3rd and 10th days. According to this test, secondary to the follicle development, inhibin and/or estradiol are increased

and FSH levels are depressed to the normal values in the patients with normal ovarian reserve. Scott and colleagues proved that abnormal CCCT group of infertile women have poor pregnancy rates independent of age (15). Except of these there are some other techniques as inhibin B level, ovary volume, antral follicle measurements.

It is not clear that in which case surgery should be done if the infertility and endometriosis co-exists. There are also limited prospective studies in the literature. There are some handicaps of this area to investigate. In the point of benefit to the patient from surgery and improvement of infertility, experience of surgeon and technical opportunities are effective. There is also not any gold standard surgical technique for the endometriosis. In the last decade endometriosis cases are increased, this is associated with the incomplete removal of the cyst wall by former surgeons. Still there are many ways of removal of endometriosis foci; medical treatment, drainage of cyst with laser, ultrasonic energy or electrocautery. The choice of drainage is related with high recurrence rates (16). On the contrary, it is proved that whole cyst wall excision patients have more favorable pregnancy results. Wood and colleagues followed 52 patients having endometriosis surgery and detected 9,6 % recurrence and 50 % pregnancy rate in one year(17). In a study Marcoux and friends compared 341 infertile patients having mild endometriosis in a multi-center prospective and randomized study. They have performed ablative surgery to the first group and diagnostic laparoscopy to the other. They found that the outcome of the former group was better (18). Besides this study there is another study claiming no relation of prognosis with the surgery (19). In order to clarify this point there is need for big, randomized and prospective studies.

Nowadays it is accepted that any surgery to the ovaries is worsens ovarian reserve via removing some follicles, damage with electric current and foreign body reaction to the suture materials. Hsin-Yi Ho and colleagues compared ovarian reserve of infertile patients. They found surgical removal of endometrioma diminished the ovarian reserve compared to the healthy one (20).

From this aspect some questions arise;

− Endometrioma of which patient should be surgically removed in infertile patients?

− In which case medical treatment should be the way?

− To give a decision which test should be performed?

In this study we used CCCT for evaluation of ovarian reserve. We aimed to find a threshold level above which diameter of the endometrioma cyst we should give a surgery decision. Some authors have studied relation of basal estradiol and FSH levels and assisted reproductive techniques and found them to be good predictor of success (12, 21).

CCCT is a provocative test and first described in 1987 by Navot and friends (22). They showed significantly increased pregnancy rates in the patients having normal reserve. In various studies sum of the 3rd and 10th day FSH values are used. Kahraman and friends have proved CCCT to be a better predictor of pregnancy than basal FSH. They found significant difference of canceled cycle number, transferred embryo number and picked oocyte number between groups having normal and abnormal results (23). In our study there was no difference between groups with the 3rd day FSH, estradiol and 10th day FSH levels.

Buyalos and friends claimed that the addition of basal estradiol assessment to basal FSH and chronological age improved the ability to identify women with poor ovarian reserve (14). Similarly, we also divided women into normal and abnormal hormone groups and compared statistically. There was no significant difference between groups. However, despite of the absence of a statistical relationship there was borderline relation between 10th day FSH levels of two groups in our study. So it is possible to have significant results in a larger study group. By this way we can get more district criteria for the desicion of surgery concerning fertility.

There was no significant relationship between our groups with basal estradiol, FSH, and CCCT. Despite this there were higher values in the endometrioma group which reflects diminished ovarian reserve and especially 10th day FSH levels. Greater study groups can give us more valuable borders in cyst dimension.

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