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The Assessment of the Relationship Between Endometrial Polyps and Basal Serum Estradiol Levels in Infertility Patients

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ÖZET

İnfertilite Hastalarında Endometrial Polip ile Serum Bazal Estradiol Seviyeleri Arasındaki İlişkinin Değerlendirilmesi

Dolaşımdaki hormon düzeyleri ile polip oluşumu arasındaki ilişkiye dair veriler yetersizdir. Bu çalışmada, infertilite popülasyonunda endometrial polip oluşumu ile dolaşımdaki bazal estradiol düzeyleri arasında bir ilişki olup olmadığını değerlendirmeyi amaçladık. Dahil edilme kriterleri şöyleydi; yaş ≥23 ve <40, BMI ≥18 ve <31 kg/m2, FSH <15 mIU/ml. Çalışma grubu, histeroskopide polip tespit edilen ve tanısı patoloji tarafından doğrulanan hastalardan seçildi (n=114). Çalışma grubu takiben 2 altgruba ayrıldı; polibi ≤10 mm olanlar (Grup 1, n=71) ve >10 mm olanlar (Grup 2, n=43). Polip grubundaki hastaların yaş ve BMI'e göre katmanlandırılmasını takiben histeroskopide polibi olmayanlardan bu yaş ve BMI'lara uygun özellik ve sayıda hasta seçilerek kontrol grubu oluşturuldu (n=114). Gruplar demografik ve klinik özellikler açısından birbirleriyle karşılaştırıldı. Polip ve kontrol gruplarındaki hastalar arasında, karşılaştırılan parametrelerden hiçbirisi anlamlı farklılık göstermedi. Serum bazal estradiol düzeyleri, istatistiksel olarak anlamlı olmasa da, Grup 2'de Grup 1'e göre daha yüksekti (sırasıyla 49.8±25.8 ve 59.8±29.0; p=0.058). Sonuç olarak, infertilite popülasyonunda polibi olan ve olmayan kadınlar arasında bazal serum estradiol düzeyleri farklılık göstermemektedir ve polip boyutlarındaki artışın serum estradiol düzeyleri ile ilişkisi yoktur.

Anahtar Kelimeler: *Endometrial polip; infertilite; histeroskopi, serum estradiol.*

SUMMARY

Data regarding the relationship between circulating hormone levels and polyp formation is lacking. In the present, we aimed to assess whether any relationship exists between the endometrial polyp formation and basal circulating estradiol levels in infertility population. Inclusion criteria were as follows; age ≥23 and <40, BMI ≥18 and <31 kg/m2, FSH <15 mIU/ml. Study group (n=114) was selected among patients who were detected to have polyps at the hysteroscopy, followed by a pathologic confirmation. Study group was further subdivided into two; those with polyps ≤10 mm (Group 1, n=71) and those with polyps >10 mm in-diameter (Group 2, n=43). Following the stratification of the patients in the polyp group according to age and BMI, a control group was constituted from those who had no polyp and who was the appropriate for the age and BMI groups (n=114). Groups were compared in terms of demographic and clinical characteristics. No parameters compared significantly differed between polyp and control groups. Serum estradiol levels were higher in Group 2 than in Group 1, even if statistically non-significant (49.8±25.8 versus 59.8±29.0, respectively; p=0.058). In conclusion, basal serum estradiol levels do not differ between women with and without endometrial polyp, in infertility population and the increase in polyp dimensions has no association with serum estradiol levels.

Key words: *Endometrial polyp; infertility; hysteroscopy; serum estradiol.*

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Introduction

Implantation is a result of a complex interaction between the hormonally primed endometrium and the conceptus (1). Structural abnormalities such as endometrial polyps, uterine fibroids, Mullerian abnormalities and intrauterine adhesions may interfere with this relationship and contribute to implantation failure and infertility. Endometrial polyps are the commonest form of intrauterine pathologies, being reported with prevalances varying between 7.8% and 34.9%, depending on the population studied (2-4). The mechanism by which endometrial polyps compromise the implantation is not clear. Although the high prevalence of endometrial polyps in infertile women suggests a causative relationship between the presence of endometrial polyps and infertility, a direct causal relationship between endometrial polyps and infertility have only been corroborated in a very limited number of studies (5).

Endometrial polyps are encountered rarely among women under the age of 20 years. The incidence appears to rise with the increasing age and peaks in the fifth decade of life, followed by a gradual decline after the menopause (6,7). Other risk factors for the development of endometrial polyps include hypertension, obesity, tamoxifen or hormone replacement therapy (HRT) use (8,9). Moreover, etiology of endometrial polyps still remains unrevealed. Many theories exist regarding the underlying pathophysiological mechanisms of endometrial polyps, however estrogen stimulation theory leads in all (10). The phenomenons that polyps are rarely diagnosed before menarche, the incidence peak in the 5th decade of life and that there is an association between tamoxifen use, endometriosis and endometrial polyps suggest that estrogen stimulation of the endometrium plays a crucial role in the genesis of endometrial polyps (11-13). Further, it has been known that estrogen and progesterone receptors are present in endometrial polyps in both pre- and post-menopausal women (14,15). Although many clinical and experimental studies indicate a hormonal background in the development of the endometrial polyps, data regarding the relationship between circulating hormone levels and endometrial polyp formation is lacking. We hypothesized that those with more intense estrogenic stimulation should have had higher levels of basal estradiol (E2) and, in case the significance of such a relationship could be shown, it would be useful for gynecology practice, specifically assisted reproduction applications, to determine from which cut-off value of E2 the polyp formation accelerates. The primary outcome of the present study was to define whether serum E2 levels differ between those with and without polyps and between those with polyps ≤10 mm and >10 mm. Secondary outcomes were to detect whether polyp

size differ as the E2 levels increases and beyond which level of E2 the genesis of polyps significantly accelerates.

In the present, we aimed to assess, following the adjustment for the established risk factors such as age and body mass index (BMI), whether any relationship exists between the endometrial polyp formation or dimensions and basal circulating E2 levels in an infertile patient population.

Material and Methods

The present was a retrospective case-control analysis of patients who admitted to the Assisted Reproduction Department and Gynecologic Endocrinology of Zeynep Kamil Training and Education Hospital in the period between June 2012 and August 2013 and who underwent hysteroscopy as a part of infertility work-up. Patients either with ≥2 in vitro fertilization (IVF) failures despite normal transvaginal sonography (TVS) and hysterosalpingography (HSG) results or those with any suspected intrauterine lesions at the TVS and/or HSG, were scheduled for hysteroscopy. All hysteroscopic procedures were performed under general anesthesia in a period varying between 20 to 30 minutes, in the follicular phase of the menstrual cycle.

Among patients who underwent hysteroscopic assessment, those aged between 23 and 40, with a BMI between 18 and 31 kg/m^2 and with follicle stimulating hormone (FSH) levels below 15 mIU/ml were included in the study. Patients who were detected to have endometrial polyps at the hysteroscopy and whose diagnoses were confirmed by the pathologic examination were selected to constitute a Study (Polyp) Group, which was further subdivided into two, as; those with endometrial polyps ≤10 mm (Group 1) and those with endometrial polyps >10 mm in-diameter (Group 2). In order to minimize the effects of the pre-identified risk factors, which are considered to play role in the etiopathogenesis of endometrial polyps, such as age and obesity, patients in the Polyp Group were stratified according to the age, as 23-29, 30-34 and 35-40 and BMI, as 18-24 and 25-30. Subsequently, for each member of Polyp Group, patients at the same age and BMI layers were selected by lot among those who revealed a normal hysteroscopic view without intrauterine lesions and they were assigned to the Control Group. Patients in the groups were compared in terms of age, BMI, infertility period, serum levels of FSH and E2, antral follicle count (AFC), primary/secondary infertility distribution, and rate of unexplained infertility.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows software version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were given as mean, standard deviation and percentage. Statistical analysis was performed using student's t test for continuous variables and chi-square test for categorical variables, considering p value < 0.05 to be significant. Pearson's correlation coefficient was used for regression analysis.

Results

A total of 228 patients, including 114 in each groups, were enrolled in the study. Of the 114 endometrial polyp patients, 71 were included in Group 1, whereas 43 were included in Group 2. Mean ages and BMIs were 33 years and 24 kg/m^2, respectively, in both groups.

Demographic and clinical characteristics of the patients enrolled in both Polyp and Control Groups are presented in Table I. There are no differences between the two groups in terms of demographic and clinical characteristics. Although E2 levels were higher in the Study Group as compared with the Control Group, the difference was not statistically significant (53.7 ± 27.4 versus 51.5 ± 32.5, respectively; p=0.582).

Table I. Basic demographic and clinical characteristics of the Polyp and Control Groups.

	Polyp Group (n=114)	Control Group (n=114)	p
Age (year)	33.4 ± 4.0	33.3 ± 4.2	0.760*
BMI (kg/m^2)	24.3 ± 2.9	23.7 ± 2.9	0.107*
Infertility period (year)	5.0 ± 3.6	5.2 ± 3.7	0.745*
FSH (mIU/ml)	7.7 ± 2.3	8.0 ± 2.1	0.276*
E2 (pg/ml)	53.7 ± 27.4	51.5 ± 32.5	0.582*
Antral Follicle Count	10.0 ± 4.8	10.7 ± 3.9	0.275*
Prim/sec infertility	108/6	106/8	0.783**
Rate of unexplained infertility	47,3%	50,8%	0.691**

**Chi-square test, **Unpaired student's t-test. Prim/sec; primary/secondary.*

Comparison of the demographic and clinical characteristics of the Groups 1 and 2 are presented in Table II. Accordingly, mean age was higher in Group 2 than in Group 1, however the difference was statistically not significant although it was close to the significance border (p=0.056). Similarly, serum basal E2 levels were higher in Group 2 than in Group 1, although the difference was statistically non-significant (49.8 ± 25.8 versus 59.8 ± 29.0, respectively; p=0.058). Furthermore, there existed no significant difference regarding BMI, infertility period, serum levels of basal FSH, AFC, primary/secondary infertility distribution, and rate of unexplained infertility.

Table II. Basic demographic and clinic characteristics of Groups 1 and 2.

	Grup 1 (n=71)	Grup 2 (n=43)	p
Age (year)	32.9 ± 4.1	34.3 ± 3.6	0.056*
BMI (kg/m^2)	24.3 ± 3.0	24.3 ± 3.2	0.905*
Infertility period (year)	5.3 ± 4.1	4.5 ± 2.5	0.242*
FSH (mIU/ml)	7.4 ± 2.3	7.8 ± 2.5	0.387*
E2 (pg/ml)	49.8 ± 25.8	59.8 ± 29.0	0.058*
Antral follicle count	9.7 ± 5.1	10.6 ± 4.4	0.372*
Prim/sec infertility	68/3	40/3	0.673**
Rate of unexplained infertility	42.2%	55.8%	0.275**

**Chi-square test, **Unpaired student's t-test. Prim/sec; primary/secondary. s*

The results of linear regression analysis, which performed to assess whether there were any relationship between polyp size and basal serum E2 levels, revealed a weak correlation between these two parameters (correlation coefficient, r=0.077, p=0.416).

Discussion

The present study results indicated that, regarding serum E2 levels, there is no difference between patients with and without endometrial polyps, who are in similar age and BMI ranges. Even if statistically insignificant, there existed difference between the patients with polyp ≤10 mm and >10 mm in terms of E2 levels. Hence, we could not define a threshold beyond which the frequency of polyp formation increased. Additionally, our results revealed a weak correlation between the serum basal E2 levels and polyp development.

Endometrial polyps are common symptoms in subfertile women. Despite this, evidence for their effect on fecundity or pregnancy outcome is very scarce. Although the contribution of endometrial polyps to infertility or miscarriages has not been precisely determined, it has been reported that hysteroscopic polypectomy prior to commencing intrauterine insemination improved the chance of conceiving (5,16) and the improved rates could be attributed to the normalization of endometrial implantation factors (17).

Established risk factors for women with endometrial polyps are advanced age, obesity, late menopause, use of Tamoxifen or estrogen-containing HRT (7,18). In order to exclude the possible effects of age and BMI on the development of endometrial polyp and to solely focus on the effects of E2 on polyps, following the stratification of the patients in the Polyp Group based on the age and BMI, Control Group was selected among those who were similar age and BMI ranges with the patients in these layers of Polyp Group and whose hysteroscopic evaluation revealed a normal intrauterine cavity view. Besides, further division of the patients in the Polyp Group into two subgroups based on the polyp dimensions revealed that those having polyp diameter exceeding 10 mm had a more advanced mean of age without statistical significance.

Several molecular mechanisms have been proposed to play a role in the development of endometrial polyps, including several gene mutations and overexpression of endometrial aromatase or hormone receptors (19-23). In both pre and postmenopausal women, endometrial polyps lose their apoptotic regulation and overexpress estrogen and progesterone receptors (ER and PR), thus avoiding the usual control mechanisms (10,24,25). Experimental studies at the cell receptor level also promote the role of estrogens in the formation of endometrial polyps. It was postulated that in the glandular epithelium of endometrial polyps, the immunohistochemical expression of the ER and PR is higher than that in the adjacent endometrium. However, in the stromal component of the endometrial polyps, only ER expression, but not PR expression, is higher than in the adjacent endometrium (15). These results suggest that polyps are relatively insensitive to cyclic hormonal changes and polyp's stroma do not undergo decidualisation, and subsequent menstrual shedding (24,25). HRT with or without progestogen and tamoxifen therapy has been associated with the development of endometrial polyps or stimulation of the preexisting polyps presumably mediated through agonistic estrogenic effects (18,26). Oguz et al. has indicated that HRTs containing a progestogen with high antiestrogenic activity may play an important preventive role in the development of endometrial polyps (27). The partial agonist activity of tamoxifen in postmenopausal women may thus produce a hormonal milieu of low levels of unopposed estrogen similar to that in perimenopausal women (28,29). Obesity characterized by increased peripheral aromatization of androgens to estrogens in adipose tissue seems to be associated with estrogenic state that may trigger the development of polyp in the endometrial tissue (27). All the aforementioned study consequences seem to support the estrogens to be the triggering factor in the formation of polyps. Nevertheless, we did not encounter, in the literature, any studies investigating the relationship between the serum basal estrogen levels and the polyp development. Our study results indicated that there appears no difference in E2 levels between patients with and without endometrial polyps, who are in similar age and BMI ranges. Additionally, E2 levels were higher in patients with polyp >10 mm than ≤10 mm and, although statistically not significant.

The present study brings a different perspective to the relationship between polyp and estrogenic milieu, which has been demonstrated by many previous studies and meta-analyses. Previous literature data poses the hypothesis that women with more prominent estrogenic stimulation, such as obesity, late menopause, use of HRTs or Tamoxifen, are more prone to develop endometrial polyp (18, 26-29) and this consideration was the basic rationale of our study. As we previously mentioned, we hypothesized that women with more vigorous estrogenic stimulation should have possessed higher levels of basal E2. However, our results indicated that basal serum E2 levels do not differ between women with and without endometrial polyp, in infertility population and the increase in polyp dimensions has no association with E2 levels. It is surprising that basal serum E2 levels are not enhanced in an estrogen-dependent pathology, even after adjustments for certain risk factors and this result has not been confirmed by any previous published reports.

Strength of the present study is the presence of a control group consisting patients of similar age and BMI with polyp group. Thus, the effects of identified two risk factors on the parameters examined have partially been restricted. One of the limitations of this study is that it was conducted through an infertility population and consequently, the result obtained may only be accurate for infertile patients, not be appropriate to generalize to the whole population. Second weakness of the study is the inclusion of the patients who experienced ≥2 previous IVF failures, which constituted one of the indications for hysteroscopy. It is known that those with ≥2 IVF failures have already been exposed to high doses of exogenous steroid hormones, including estrogens and progesterone, in the natural course of controlled ovarian hyperstimulation regimens that they previously experienced. Thus, these patients are at greater risk of developing endometrial polyps than control patients.

Based on the results of the present study, we suggest that basal serum estradiol levels do not differ between women with and without endometrial polyp, in infertility population and the increase in polyp size has no association with serum estradiol levels. However, the present is a pioneering study on this subject and more comprehensive randomized controlled trials will help clarify the relationship between serum E2 levels and polyp formation.

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