ORIGINAL RESEARCH

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Comparison of Endometrial Receptivity Markers Between Women with Polycystic Ovary Syndrome, Endometrioma and Unexplained Subfertility: A Cross-Sectional Study

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ABSTRACT Objective: Uterine receptivity and implantation are complex processes that require the coordinated expression of molecules by the zygote and uterus. Some molecules have been identified at different stages of the luteal phase as receptivity markers that play roles in implantation. This cross-sectional prospective study aimed to compare the levels of insulin-like growth factor binding protein 1 (IGFBP 1), osteopontin (OPN) and prostaglandin E2 (PGE2) in endometrial flushing liquid during the midluteal phase between patients diagnosed with polycystic ovary syndrome (PCOS), endometrioma and unexplained subfertility, and ovulatory women. **Material and Methods:** The study groups were formed by women with ovulatory PCOS (n=24), endometrioma (n=17) and unexplained subfertility (n=25). The control group consisted of fertile women (n=18). During the implantation window, endometrial flushing samples were taken and IGFBP1, OPN and PGE2 levels were analyzed and compared among the groups. **Results**: There were no significant differences in the levels of IGFBP1, PGE2 and OPN among groups. PGE2 levels were 367.7±96.3 ng/mL and 239.2±106.9 ng/mL in women with PCOS and in healthy women, respectively. This difference was statistically significant (p=0.002). The present results show that PGE2 might be an indicator of unfavorable endometrial receptivity and might be responsible for the low pregnancy rates in patients with PCOS. **Conclusion**: We hypothesized that PGE2 downregulation may facilitate decidualization and improve the pregnancy rate in ovulatory PCOS. So, this can guide us about future treatment in the management of patients.

Keywords: Endometrial receptivity; endometrioma; insulin-like growth factor binding protein 1; osteopontin; prostaglandin E2

A receptive uterine endometrium during the implantation window, a viable embryo and effective compatible dialogue between them are indispensable for accomplished embryo implantation. It is essential that the surface of the embryo is mature, the hormone-protein content of uterine fluid is concordant, as required, and the right signals are raised. Implantation is a complex process involving the attachment and penetration of the blastocyst to the endometrium through adhesion molecules, secreted enzymes, and extracellular-intercellular matrix components, following the placement of the embryo in the uterus.[1-3]

The period that the uterine endometrium is receptive to the embryo is called the window of implantation. The luminal and glandular epithelium as well as endometrial stroma undergo significant changes to reach the optimum state for implantation. Apart from morphological changes, in recent studies, several markers for endometrial receptivity which are expressed during the implantation window and crucial for implantation have also been noted.[3-7]

Insulin-like growth factor binding protein 1 (IGFBP-1) has a substantial effect in terms of implantation of the embryo. It is released from the ovarian stroma and is involved in decidual differentiation of the stroma and proliferation/differentiation of the endometrium.[8] Moreover, it has been proven that the

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increase in IGFBP-1 expression in endometrial stromal cells throughout decidualization may increase pregnancy rates in both spontaneous and assisted reproductive techniques.[9-11]

Osteopontin (OPN) is located in the endometrium of fertile women with normal menstrual cycles, with maximum release throughout the implantation window.[12,13] Hence, it has been claimed that OPN is an effective marker of endometrial implantation and, together with its receptor αvβ3 integrin, promotes embryonic adhesion to the uterine epithelium.[13-18] Also, Wang, et al. showed that the OPN level was significantly suppressed in the group that failed in vitro fertilization (IVF) cycles and so established that OPN plays a role in success of IVF techniques.[19]

Prostaglandins are lipid compounds that are also contained in the endometrium, of which the importance in female fertility has been emphasized in the evidence up to now. Among the prostaglandins, prostaglandin E2 (PGE2) is thought to have a significant role especially for decidualization and implantation of pregnancy. The levels of PGE2 in endometrial fluid have been implicated as a marker for endometrial receptivity.[20] In addition, elevated amounts of PGE2 were detected in polycystic ovarian cells compared to women with normal ovulation.[21,22]

The purpose of the present study was to investigate the concentrations of IGFBP-1, OPN and PGE2 in endometrial flushing fluids of patients with ovulatory polycystic ovarian syndrome (PCOS), endometrioma, unexplained subfertility and healthy fertile women.

MATERIAL AND METHODS

This cross-sectional controlled study was carried out between January and June 2013 in Subfertility Unit of the Department of Obstetrics and Gynecology, İzmir Katip Çelebi University, Atatürk Training and Research Hospital İzmir, Türkiye. The unit is a tertiary center that treats referral patients from the region. The study design was in accordance with the ethical standards of the Helsinki Declaration and good clinical practice, and was approved by the Institutional Review Board of İzmir Katip Çelebi University, School of Medicine, Atatürk Training and Research Hospital (date: 17.05.2012, no: 25). Detailed information was conveyed to all volunteers regarding the research and both verbal and written informed consent were taken.

A total of 112 patients ranging between the ages 20 to 40 who referred to the subfertility outpatient clinic were included in the study. Voluntary patients diagnosed with PCOS (n=38), endometrioma (n=19) and unexplained subfertility (n=27) constituted the study groups, while the control group consisted of fertile women (n=28). In these 4 groups, 14 patients with PCOS, 2 patients with endometrioma, 2 patients diagnosed with unexplained subfertility and 10 patients in the control group who were detected as having anovulation with blood progesterone levels on the 21st day of menstruation were excluded from the study. The control group comprised of healthy women with no gynecologic disorder, not using an intrauterine device or hormonal contraception, or not receiving any medication that may affect endometrium and who had the intellectual capacity to give written informed consent and to understand the information concerning the study. Exclusion criteria for the volunteers were having a pregnancy, smoking, pelvic infection, a serum progesterone level of <3 ng/dL in the luteal phase or endometrial pathology (submucosal myoma, endometrial polyp etc.) during the endometrial fluid sampling or a patient's reluctance to be included.

A total of 24 patients who showed ovulatory phenotype and were diagnosed with PCOS according to the ESHRE Rotterdam 2003 criteria; a total of 17 patients who were diagnosed with endometrioma by clinical history, physical examination and transvaginal ultrasonography (Medison Sono Ace X8 Seoul, South Korea); and a total of 25 patients diagnosed with unexplained subfertility after undergoing basic infertility evaluation which were performed according to American College of Obstetricians and Gynecologists diagnostic criteria were included. The control group consisted of a total of 18 healthy ovulatory, parous women who had no history of subfertility and who were using the barrier contraception method.

In the study and control groups, after confirmation of ovulation with the blood progesterone levels on the 21st day of menstruation, 0.154 mol/L sodium chloride was administered via a thin cannula (2 mL per administration into the uterine cavity, a total of 10 mL following fluid collection sampling performed 5 times in total) resembling the saline infusion sonography administration technique, 1 mL of uterine aspirate was transferred to a standard micro test tube (Eppendorf, Hamburg, Germany), was frozen at -20°C and finally stored at -80°C until biochemical analysis. After the endometrial fluid samples were accumulated from study and control groups, IGFBP-1, OPN and PGE2 levels were analyzed by using East biopharm branded (Hangzhou East biopharm Co., Ltd./China) Elisa kits (PGE2 LOT: 20130924, OPN LOT: 20130924, IGFBP-1 LOT: 20130924, PGE2 Cat. No: CK-E10702, OPN Cat. No: CK-E10857, IGFBP-1 Cat. No: CK-E10159) with the Biotec branded Elisa device. The patients were warned about not having sexual intercourse until the endometrial fluid is obtained in that menstrual cycle. Patients were kept under observation for half an hour after the endometrial fluid sampling.

The statistical analysis was performed using SPSS (version15.0, 2006; SPSS Inc., Chicago, IL, USA) program. Shapiro-Wilks and Levene tests were carried out to control the distribution of the data. Because of the fundamental hypothesis of parametric statistics was not met, use of non-parametric tests was considered appropriate instead of parametric MANOVA. Therefore, Kruskal-Wallis tests were conducted for 2 variables, 4 groups were tested in the same hypothesis and paired comparisons were performed via Mann-Whitney U tests as follow-up tests between the groups in the event of statistically significant differences. Data analysis was considered significant when p values were less than 0.05.

RESULTS

Twenty eight (25%) of 112 women included in the study were excluded from the study in both study and control groups due to anovulation. This cross-sectional, controlled study consisted of 24 patients with ovulatory PCOS, 25 patients with unexplained subfertility, 17 patients with ovulatory endometrioma and 18 healthy fertile ovulatory women out of 84 volunteers.

The demographic data and serum progesterone levels of the patients were shown in Table 1. While there was no statistically significant difference between the endometrioma and control groups, there was a statistically significant difference in terms of age only between unexplained subfertility and endometrioma groups in all other pairwise comparisons. The mean body mass index (BMI) was highest in the PCOS group (28.67) and lowest in the endometrioma group (24.11), while it was similar in the unexplained infertility (24.25) and control (25.16) groups. In addition, there was no statistically significant difference in terms of BMI when the 3 groups were compared with the control group and all 2-group comparisons. All groups were similar in terms of demographically, except for gravidity and parity. Statistically significant differences were detected between fertile group and each one of study groups as expected. The mean serum progesterone level at mid-luteal phase was highest in the unexplained subfertility group (10.38) and was similar in PCOS (9.98) and control groups (8.19), while it was statistically significantly lower in the endometrioma group (5.95) when compared to these other three groups.

TABLE 1: Evaluation of demographic and baseline data of the groups.

	PCOS (n=24)	US (n=25)	End (n=17)	Control (n=18)	p-value*
Age (year)	29.87±5.61	29.05±4.81	33.05±6.68	33.55±5.90	0.013
BMI (kg/m^2)	28.67±7.93	24.25±3.61	24.11±3.56	25.16±2.68	0.209
Gravida (n)	0.95± 1.04	0.48±0.96	1.02±1.28	3.66±2.08	0.000
Parite (n)	0.70±0.95	0.20±0.50	0.88±1.05	2.77±1.59	0.000
Progesteron (ng/mL)	9.98±4.61	10.38±5.51	5.95 ±3.32	8.19±3.92	0.006

Data are presented as mean±standard deviation, *Kruskal Wallis test, BMI: Body Mass Index; PCOS: Polycystic ovary syndrome; US: Unexplained subfertility; End: Endometrioma.

TABLE 2: The distribution of IGFBP-1, PGE2 and OPN value according to the group.

	PCOS (n=24)	US (n=25)	End (n=17)	Control (n=18)	p-value*
IGFBP-1, (ng/mL)	310.22±70.76	396.51±130.55	391.18±118.86	377.36±123.10	0.028
PGE2,(ng/mL)	367.75±96.37	292.68±123.42	259.16±117.80	239.25±106.97	0.003
OPN, (ng/mL)	12.09±7.72	13.03±9.61	16.67±6.27	10.04±4.74	0.029

Data are presented as mean±standard deviation; *Kruskal Wallis test; IGFBP-1: Insulin-like growth factor binding protein 1; PGE2: Prostoglandin E2; OPN: Osteopontin; PCOS: Polycystic ovary syndrome; US: Unexplained subfertility; End: Endometrioma.

TABLE 3: The comparison of IGFBP-1, PGE2 and OPN values between the 2 groups.

	PCOS vs control	US vs control	End. vs control	PCOS vs US	PCOS vs end	US vs end
IGFBP-1 (ng/mL)	0.349	1.000	1.000	0.055	0.152	1.000
PGE2 (ng/mL)	0.002	0.769	1.000	0.133	0.017	1.000
OPN (ng/mL)	1.000	1.000	0.068	1.000	0.356	0.794

*Mann-Whitney U test; IGFBP-1: Insulin-like growth factor binding protein 1; PGE2: Prostoglandin E2; OPN: Osteopontin; PCOS: Polycystic ovary syndrome; US: Unexplained subfertility; End: Endometrioma. Polycystic ovary syndrome; US: Unexplained subfertility; End: Endometrioma.

Mean levels of IGFBP-1 (ng/mL) of endometrial flushing fluid were 396.5, 310.2, 391.1 and 377.3 for the unexplained subfertility, PCOS, endometrioma and control groups, respectively (Table 2). In addition, as seen in Table 3, there was no statistically significant difference in all pairwise comparisons when IGFBP-1 levels were compared between paired groups. Mean PGE2 (ng/mL) levels in the endometrial fluid were similar for endometrioma (259.16), unexplained subfertility (292.6) and control groups (239.2). But, this marker was notably higher in the PCOS (367.7) patients relative to the endometrioma ($p<0.05$) and control groups ($p<0.001$). On the contrary, mean OPN levels (ng/mL) in endometrioma (16.67), ovulatory PCOS (12.09), unexplained subfertility (13.03) and control groups (10.04) were similar. No statistically significant difference was found in pairwise comparisons between all groups either.

DISCUSSION

This prospective study was conducted to evaluate the amounts of IGFBP-1, OPN and PGE2 in the uterine washing fluids of patients with ovulatory PCOS, endometrioma, unexplained subfertility and fertile women during implantation window. According to the findings of the present study, the levels of PGE2 were greater in ovulatory PCOS patients compared to the control group. Midluteal PGE2 expression was also found to be higher in patients with endometrioma and unexplained infertility group compared to the control group, but the difference was not statistically significant. It was determined that there was a similarity in IGFBP-1 and OPN values in both the patient and control groups.

The dysregulated expression of uterine receptivity markers in women with PCOS has been addressed in most of the available evidence. In our study, midluteal PGE2 amount was greater in the ovulatory PCOS group than in the control group. Even though ovulatory dysfunction in PCOS appears to be the main reason for subfertility, following the ovulation induction, the weak link between ovulation and pregnancy and low pregnancy rates despite providing ovulation are important indicators with regard to endometrial dysfunction. Recently, in PCOS as well as in other gynecological diseases which may influence fertility, endometrial receptivity studies concentrate on endometrial receptivity markers. Meaningful elevation of PGE2 levels has been noted in polycystic ovaries and this was parallel to our finding.[21,22] Furthermore, it has been pointed out that amount of PGE2 in the uterine endometrial fluid may be a potential endometrial receptivity marker.[20] Data ob-

tained in the present study showed similar findings. Increased PGE2 in PCOS is coupled with suppressed a propensity to apoptosis which plays a vital role with a delicate cell balance between proliferation and differentiation. It has been shown in both genital system cancers and the endometrial cells also.[23,24] It is known that cells overexpressing cyclooxygenase-2 have inability to increase proliferation and the ability to downregulate apoptotic processes. Besides the underlying of physiopathology that appears to be the resistance of endometrial cells to undergo programmed cell death, PGE2 may also contribute to endometrial dysfunction through its effects on cell proliferation, angiogenesis and immunosuppression by affecting the estrogen levels at the receptor level.

Although the distribution of IGFBP-1 in our PCOS patients with ovulatory phenotype was lower than in the control group, the difference was statistically insignificant. Low levels of IGFBP-1 have been found in PCOS and obesity, but the results of studies on this subject in the literature are contradictory. It has been mentioned that decreased amount of IGFBP-1 in PCOS patients may be related to BMI rather than ovarian hyperandrogenism.[25] Taking into account that the BMI of the ovulatory PCOS group was 28.6 kg/m^2 in our study, it may clarify the low IGFBP-1 levels although it is not statistically significant. In addition, considering the trend of the data in the current study, the low expression of IGFBP-1 may gain statistical significance by increasing the number of cases. OPN levels were reported to be similar in patients with the ovulatory PCOS phenotype compared to the controls; in a recent study.[26] Important reduction of OPN levels was observed in infertile women with isolated PCO. But, ovulatory dysfunction was the main factor for subfertility in this study. Of course, conflicting results affect the comparability of these data with our study.

In the current study, the amounts of 3 markers evaluated in the midluteal phase of patients with endometriosis were found to be similar to the normal control group. Genetic factors are known to be associated with the development and progression of endometriosis, but endometriosis-associated genes have not been described. IGFBPs are thought to have major effects in cell apoptosis, proliferation and pathophysiology of endometriosis. It has been stated that IGFBP-1 is not associated with endometriosis, but IGFBP-3 has a significant relationship with endometriosis.[27] αvβ3 integrin and its extracellular matrix ligand OPN are involved in the regulation of endometrial receptivity. While OPN expression was unaffected in patients with endometriosis, αvβ3 integrin expression was shown to be decreased. On the other hand, OPN binding to the surface epithelium is so limited when αvβ3 expression is missing. This information indicates that the endometrium of some women with endometriosis is dysfunctional and is responsible for decreased fertilization.[28] In the current study, making the diagnosis of the endometrioma group by history, physical examination and transvaginal sonography imaging may be the reason for partially inconsistent data. In addition, the relative increase in OPN and IGFBP-1 levels and the relative low expression of PGE2 may negatively affect embryo implantation in endometriosis by causing both apoptosis inhibition and immune compromise.

Diagnosis of unexplained subfertility made by exclusion in many guidelines, ovulation is diagnosed by excluding the male and tuboperitoneal factors. However, high prevalence of this diagnosis in all infertile couples and the perception that there is no treatment terminologically lead to serious perceptual problems. Nevertheless, many associated issues for infertility may go unnoticed with basic infertility research. Endometrial dysfunction in unexplained subfertility has been ignored until recently. In this study, the levels of all 3 markers in the midluteal phase in the unexplained subfertility group were found to be similar to the control group. In the literature, studies investigating endometrial dysfunction during the implantation window in patients with unexplained infertility are very limited. OPN and its receptor αvβ3 integrin, recently proposed as an important complex in embryo implantation, may be useful as endometrial receptivity markers in a variety of infertility states.[13] In the last 20 years, an extremely considerable rise was observed in genomic studies and an unpredictable amount of data was collected. A total of 1,453 gene pairs that have been identified are kept responsible for implantation and nearly 200 of them

have quite important functions. Whereas, this is not sufficient to explain the mechanism of implantation of a single marker expressed by each gene, because implantation has a complex physiopathology, and a decrease in a protein that a gene expresses is compensated by an increase in a protein that another gene expresses.[29]

The strengths of our study were that diseases scarcely included in the literature were selected, the number of subjects were sufficient, the biomarkers studied were diverse and the subgroups were included in the analysis. But, the limitations of the present study were that the diagnosis of endometrioma was made by imaging methods, the control group consisted of random advanced age fertile women due to sequential collection, and fewer biomarkers were included in the study due to the limitation in gene expression. Another limitation of this study was the lack of the power analysis. Therefore; although PGE2 levels were higher in patients with endometrioma as well as unexplained subfertility compared to the normal control group, the difference was not statistically significant.

CONCLUSION

Consequently, in the literature, endometriosis, unexplained subfertility and PCOS may be associated to a decreased fertility cycle and impaired endometrium receptivity. According to our results, PGE2 may be an indicator of poor endometrial receptivity, which may be responsible for low pregnancy rates in patients with ovulatory PCOS. A single marker is not satisfactory to explain the mechanism of implantation as well as many markers play role in endometrial receptivity. For this reason, there is a need for more comprehensive studies with a large number of markers in more different female infertility issues.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Emine Demir, Fulya Oğuz Türkyılmaz, Sefa Kelekçi;* ***Design:*** *Emine Demir, Fulya Oğuz Türkyılmaz, Sefa Kelekçi;* ***Control/Supervision:*** *Emine Demir, Fulya Oğuz Türkyılmaz, Mustafa Şengül, Sefa Kelekçi;* ***Data Collection and/or Processing:*** *Emine Demir, Fulya Oğuz Türkyılmaz, Sefa Kelekçi;* ***Analysis and/or Interpretation:****Emine Demir, Fulya Oğuz Türkyılmaz, Mustafa Şengül, Sefa Kelekçi;* ***Literature Review:*** *Emine Demir, Fulya Oğuz Türkyılmaz, Mustafa Şengül, Sefa Kelekçi;* ***Writing the Article:*** *Emine Demir, Fulya Oğuz Türkyılmaz, Mustafa Şengül, Sefa Kelekçi;* ***Critical Review:*** *Emine Demir, Fulya Oğuz Türkyılmaz, Sefa Kelekçi;* ***References and Fundings:*** *İzmir Katip Çelebi University;* ***Materials:*** *Emine Demir, Fulya Oğuz Türkyılmaz, Mustafa Şengül, Sefa Kelekçi.*

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