DOI: 10.4274/anatoljmed.2024.36855
Anatol J Gen Med Res 2024;34(2):212-8

CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Identification of Corin and Procalcitonin in Endometrial Flushing Fluid Between Women with Polycystic Ovary Syndrome, Endometrioma, Unexplained Subfertility, and Fertile Healthy Women

Polikistik Over Sendromu, Endometrioma, Açıklanamayan Subfertilite ve Fertil Sağlıklı Kadınlarda Endometriyal Yıkama Sıvısında Corin ve Prokalsitonin Belirlenmesi

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Cite as: Şeyhanlı Z, Demir M, Oğuz Türkyılmaz F, Sağlam G, Yılmaz B, Kelekçi S, Aydoğmuş S. Identification of Corin and Procalcitonin in Endometrial Flushing Fluid Between Women with Polycystic Ovary Syndrome, Endometrioma, Unexplained Subfertility, and Fertile Healthy Women. Anatol J Gen Med Res. 2024;34(2):212-8

Abstract

Objective: Endometrial receptivity is a critical factor in achieving successful implantation; however, the precise molecular mechanisms underlying this process remain unclear. This study aimed to assess and compare the levels of corin and procalcitonin in the endometrial flushing fluid among women with unexplained infertility, polycystic ovary syndrome (PCOS), endometrioma, and fertile healthy women in relation to endometrial receptivity.

Methods: A study was undertaken on a cohort of women aged 20 to 40 from January 2013 to June 2015. The study cohort comprised 20 women diagnosed with unexplained subfertility, 20 women diagnosed with PCOS, and 20 women diagnosed with endometrioma. Additionally, a control group of 20 healthy fertile women was included. Corin and procalcitonin levels were assessed in endometrial flushing fluid from all patients during the implantation window, and compared between the different groups.

Results: Mean levels of corin (ng/mL) were 0.45, 0.54, 0.46, and 0.49 for PCOS, unexplained subfertility, endometrioma, and control groups, respectively (p=0.341). Mean levels of Procalcitonin (pg/mL) were 76.79, 112.21, 75.57, and 90.41 for PCOS, unexplained subfertility, endometrioma, and control groups (p=0.098). The corin and procalcitonin levels were seen to be lower in the PCOS and endometriosis groups in comparison to the control group. Nevertheless, this difference did not achieve statistical significance.

Conclusion: Understanding the molecular and biochemical aspects of endometrial receptivity can provide valuable insights for diagnosis and treatment. Further research is needed to elucidate the underlying mechanisms and establish the clinical relevance of corin and procalcitonin for endometrial receptivity.

Keywords: Corin, endometrial receptivity, procalcitonin, polycystic ovary syndrome, unexplained subfertility

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Received/Geliş tarihi: 20.02.2024
Accepted/Kabul tarihi: 04.07.2024

Öz

Amaç: Endometrial reseptivite, başarılı implantasyonun sağlanmasında kritik bir faktördür; ancak bu sürecin altında yatan kesin moleküler mekanizmaları belirsizliğini korumaktadır. Bu çalışma, açıklanamayan infertilitesi, polikistik over sendromu (PKOS), endometrioma ve fertil sağlıklı kadınlarda endometrial reseptivite ile ilişkili olarak endometrial yıkama sıvısındaki corin ve prokalsitonin düzeylerini değerlendirmeyi ve karşılaştırmayı amaçlamıştır.

Yöntem: Ocak 2013 ile Haziran 2015 tarihleri arasında 20-40 yaş arası kadınlardan oluşan bir kohorta çalışma yapıldı. Çalışma grubu açıklanamayan subfertilite tanısı alan 20 kadın, PKOS tanısı alan 20 kadın ve endometrioma tanısı alan 20 kadından oluşuyordu. Ayrıca 20 sağlıklı fertil kadından oluşan bir kontrol grubu da dahil edildi. İmplantasyon penceresi sırasında tüm hastaların endometrial yıkama sıvısında corin ve prokalsitonin seviyeleri değerlendirildi ve gruplar arasında karşılaştırıldı.

Bulgular: Corin düzeyleri (ng/mL) PKOS, açıklanamayan subfertilite, endometrioma ve kontrol gruplarında sırasıyla 0,45, 0,54, 0,46 ve 0,49 idi (p=0,341). PKOS, açıklanamayan subfertilite, endometrioma ve kontrol gruplarında ortalama prokalsitonin düzeyleri (pg/mL) 76,79, 112,21, 75,57 ve 90,41 olarak belirlendi (p=0,098). PKOS ve endometriozis gruplarında corin ve prokalsitonin düzeylerinin kontrol grubuna göre daha düşük olduğu görüldü. Ancak bu fark istatistiksel anlamlı düzeyde değildi.

Sonuç: Endometrial reseptivitenin, moleküler ve biyokimyasal yönlerini anlamak, tanı ve tedavi için değerli bilgiler sağlayabilir. Altta yatan mekanizmaları aydınlatmak ve corin ile prokalsitoninin endometrial reseptivite açısından klinik ilişkisini belirlemek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Croin, endometriyal reseptivite, prokalsitonin, polikistik over sendromu, açıklanamayan subfertilite

Introduction

Infertility is a complex and multifactorial condition affecting the reproductive system of a significant proportion of couples worldwide. According to data gathered worldwide from 1990 to 2021, the World Health Organization approximates that around 1 in 6 people has encountered infertility at least once in their lifetime[1]. The establishment of pregnancy relies on the successful implantation process, which involves a complicated sequence of interactions between different types of cells in the uterus and the blastocyst. Endometrial receptivity is the capacity of the uterine lining to receive and support an early-stage embryo, leading to a viable pregnancy. The synchronization of embryonic development and endometrial differentiation is crucial, thus establishing a distinct and temporary phase during which implantation can occur. This period is usually known as the "implantation window"[2]. Endometrial receptivity refers to the precise coordination of molecular, cellular, and structural changes in the endometrium to create an environment suitable for the implantation of an embryo. Endometrial receptivity is controlled by various variables, including hormone receptors, pro-inflammatory cytokines, and endometrial decidualization-related factors[3]. Understanding the molecular and biochemical aspects of reproductive health can provide valuable insights for diagnosis and treatment.

The uterine microenvironment and its primary constituent, the endometrial fluid, have a significant impact on reproductive success by affecting sperm motility within the uterus and fallopian tubes, as well as embryo development and implantation processes[4]. Understanding the biochemical differences in endometrial flushing fluid may contribute to the development of targeted diagnostic and therapeutic approaches for these conditions.

Corin is a transmembrane serine protease predominantly located in the heart. Its primary role is to convert the precursor peptide pro-atrial natriuretic peptide (ANP) into the active form of ANP. This conversion leads to the stimulation of natriuresis, diuresis, and vasodilation[5]. Corin has been identified in the pregnancy uterus, where it has a significant function in facilitating trophoblast invasion and spiral artery remodeling to provide sufficient uteroplacental perfusion[6]. Uterine artery perfusion in healthy women has been observed to enhance throughout the luteal phase, which aligns with the period of implantation[7]. Based on these studies, it appears that corin may be efficacious during the implantation period and in enhancing endometrial receptivity. Nevertheless, the role of corin as a biomarker in human endometrial receptivity throughout the implantation stage remains undetermined.

Procalcitonin is a 116-amino acid polypeptide that serves as the precursor to the calcitonin hormone. It is secreted by neuroendocrine C-cells in the thyroid gland and K-cells in the lung, as well as several cell types and organs, in reaction to pro-inflammatory stimulation[8]. It acts as a marker for sepsis and bacterial infection[9]. Although there have been studies examining procalcitonin levels in cervicovaginal secretions for preterm rupture of membranes[10,11], no research has been identified regarding the involvement of procalcitonin in endometrial receptivity.

This study aims to explore the levels of corin and procalcitonin in the endometrial flushing fluid of women with unexplained infertility, polycystic ovary syndrome (PCOS), endometrioma, and compare them to fertile healthy women during the implantation window.

Materials and Methods

Study Design

This cross-sectional controlled trial was performed in the infertility outpatient clinic of İzmir Katip Çelebi University, Atatürk Training and Research Hospital, Obstetrics and Gynecology Clinic from January 2013 to June 2015. The study design adhered to the ethical principles of the Helsinki Declaration and appropriate clinical practice, and received approval from the Local Ethical Committee (number: 2013-198).

Participants

All individuals involved in the study provided informed consent, including healthy controls and patients. The study involved 80 participants aged 20-40 years old, split into four groups. The first group comprised 20 patients diagnosed with PCOS based on the ESHRE Rotterdam 2003 criteria. The second group consisted of 20 individuals diagnosed with endometriosis using a clinical interview, physical examination, and transvaginal ultrasound using the Medison Sono Ace X8 from Seoul, South Korea. The third group comprised 20 individuals with unexplained subfertility who had undergone a basic infertility evaluation following the diagnostic criteria of the American College of Obstetricians and Gynecologists. The fourth group, serving as the control group, also consisted of 20 participants[12]. The control group comprised healthy women without any gynecologic problems. They were not utilizing an intrauterine device or hormonal contraception, and they were not consuming any prescription that could impact the endometrium.

Sample Collection

Patients who wished to voluntarily withdraw from the study, were pregnant, smoked, exhibited symptoms of pelvic infection, or had luteal phase serum progesterone levels less than 3 ng/dL were excluded from the research. After ovulation was confirmed by measuring blood progesterone levels during the implantation window, an endometrial fluid sample was obtained using a procedure similar to the saline infusion sonography method in both the study and control groups. A bivalve disposable speculum was introduced into the vagina, followed by the insertion of a menstrual-regulating cannula (4 mm in diameter) into the uterine cavity via the cervical canal. Using a syringe, 5 mL of sterile 0.154 mol/L sodium chloride saline solution was instilled into the uterine cavity. The contents of the uterus were aspirated rapidly. The endometrial fluid samples were collected in a standard microtest tube (Eppendorf, Hamburg, Germany) and the samples were then stored at a temperature of -80 °C. After obtaining endometrial fluid samples from every patient, the concentrations of corin and procalcitonin were determined using BioTek ELISA devices equipped with Eastbiopharm (Hangzhou Eastbiopharm Co. Ltd./China) ELISA kits [Human Procalcitonin (PCT) ELISA Kit and Human Corin (CRN) ELISA Kit]. During the whole collection of data procedure for all patients, the exact same kits were consistently employed for the same markers.

Statistical Analysis

A statistical analysis was conducted utilizing IBM SPSS Statistics 21.0 for Windows (SPSS Inc., Chicago, IL). In contrast with categorical variables, which are denoted by numbers (n) and percentages (%), numeric variables are represented by the median or mean. Shapiro-Wilks and Levene's tests were utilized to assess normality. Parametric MANOVA was not preferred over non-parametric analysis due to the skewed nature of the data. Comparisons of variables between groups were conducted using the Kruskal-Wallis H test. Pairwise comparisons were performed using Mann-Whitney U tests when the differences between groups were deemed statistically significant. Statistical significance was assigned to values less than 0.05.

Results

Table 1 contains the demographic information and serum progesterone levels of the subjects. Although there was no statistically significant distinction between the endometrioma group and the control group, there was a statistically significant distinction in terms of age only between the unexplained subfertility group and the endometrioma group in all other comparisons. The average ages of patients diagnosed with PCOS, unexplained subfertility, endometriosis, and the control group were 29.3, 28.15, 33.15, and 32.15, respectively. The PCOS group had the greatest body mass index (BMI) of 27.15 kg/m^2, whereas the endometrioma group had the lowest BMI of 23.35 kg/m^2. Furthermore, there was no statistically significant disparity in BMI when comparing the three groups with the control group, as well as when comparing any two groups. All

groups exhibited demographic similarity, with the exception of gravidity and parity. The serum progesterone levels (ng/mL) during the mid-luteal phase were similar across the unexplained subfertility (10.1), PCOS (10.06), and control groups (8.75). Nevertheless, the group with endometrioma exhibited notably reduced levels (5.85) (Table 1).

Table 2 presents the distribution of corin and procalcitonin levels in the endometrial flushing fluid across the three groups of gynecologic disorders, as well as the control group. Mean levels of corin (ng/mL) in endometrial flushing fluid were 0,45, 0,54, 0,46, and 0,49 for PCOS, unexplained subfertility, endometrioma, and control groups, respectively (Table 2). Nevertheless, there were no notable disparities that reached statistical significance (p=0.341). Mean levels of procalcitonin (pg/mL) in endometrial flushing fluid were 76,79, 112,21, 75,57, and 90,41 for PCOS, unexplained subfertility, endometrioma, and control groups, respectively. Procalcitonin levels were found to be lower in the PCOS and endometriosis groups compared to the control group; however, this distinction did not reach statistical significance (p=0.098). Furthermore, according to the data presented in Table 3, there was no statistically significant disparity observed in any of the pairwise comparisons when comparing corin levels between the paired groups. For procalcitonin level, this marker was notably lower in the PCOS (76,79) and endometrioma (75,57) patients relative to the unexplained subfertility in pairwise comparisons between all groups (p<0.05) (Table 3).

Discussion

We identified the presence of midluteal corin and procalcitonin expression in the endometrial flushing fluid of all the groups in this prospective and cross-sectional study. While the levels of corin and procalcitonin were found to be lower in the PCOS and endometrioma groups compared to the control group, the difference was not statistically significant.

Infertility is a significant clinical problem observed in patients with unexplained infertility, polycystic ovarian disease, and endometrioma. However, the underlying causes of infertility in these patients have not been fully understood. Nevertheless, the findings indicate that a crucial pathophysiological aspect is the compromised receptivity in the endometrium, which subsequently affects implantation. Various factors contribute to infertility, and understanding the molecular and biochemical aspects of reproductive health can provide valuable insights for diagnosis and treatment. Benign gynecological diseases such as endometriosis,

Table 1. Demographic, laboratory and clinical characteristics of the groups

	PCOS (n=20)	US (n=20)	End (n=20)	Control (n=20)	p-value*
Age (year)	29.3±5.36	28.15±4.56	33.15±6.65	32.15±5.18	**0.012**
BMI (kg/m^2)	27.15±5.55	23.37±3.97	23.35±4.09	24.93±3.67	0.057
Gravida (n)	0.55±0.6	0.5±1	1±1.21	3.75±1.77	**0.000**
Parite (n)	0.4±0.6	0.2±0.52	0.85±1.04	2.9±1.37	**0.000**
Progesteron (ng/mL)	10.06±4.5	10.1±5.25	5.85±3.06	8.75±3.67	**0.003**

Values 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 corin and procalcitonin levels among groups

	PCOS (n=20)	US (n=20)	End (n=20)	Control (n=20)	p-value*
Corin (ng/mL)	0.45±0.2	0.54±0.16	0.46±0.16	0.49±0.18	0.341
Procalcitonin (pg/mL)	76.79±44.94	112.21±58.39	75.57±30.55	90.41±44.63	0.098

Values are presented as mean ± standard deviation, *: Kruskal-Wallis test, BMI: Body mass ındex, PCOS: Polycystic ovary syndrome, US: Unexplained subfertility, End: Endometrioma

Table 3. The comparison of corin and procalcitonin levels between the two groups*

	PCOS vs. control	US vs. control	End vs. control	PCOS vs. US	PCOS vs. End	US vs. End
Corin (ng/mL)	0.534	0.297	0.626	0.133	0.797	0.104
Procalcitonin (pg/mL)	0.304	0.239	0.330	0.029	0.735	0.040

*: Mann-Whitney U test, PCOS: Polycystic ovary syndrome, US: Unexplained subfertility, End: Endometrioma

hydrosalpinx, and PCOS are linked to reduced fertility and altered endometrial receptivity functions[13]. A recent study has demonstrated that individuals with PCOS have changes in endometrial receptivity. This suggests that the presence of hyperandrogenism, as well as insulin resistance and obesity, may contribute to reduced embryo implantation and unfavorable pregnancy outcomes[14]. A study conducted in patients with PCOS revealed that insulin resistance had an impact on both endometrial function and the process of implantation[15]. Following a thorough assessment of infertility, the root cause of infertility remains unknown to around 15% of women[16]. Unexplained infertility may be attributed to disruptions in molecular and cellular indicators that play a role in endometrial receptivity[17]. In a comparable manner, in women affected by these illnesses, infertility may be attributed to issues concerning endometrial receptivity and its capacity to facilitate implantation. Hence, we selected these conditions that could potentially hinder endometrial receptivity while designing our study.

Corin, well known for its role in regulating blood pressure by the activating ANP[6,18,19], was shown to be expressed in the uterus of pregnant mice and humans, which is interesting[20]. Following these discoveries, investigations were initiated to explore the potential roles of corin within the pregnant uterus. Recently, it has been demonstrated that the expression of corin is increased in the uterus during pregnancy. In this context, corin and ANP play a role in enhancing trophoblast invasion and remodeling of spiral arteries[6,21]. Furthermore, in this study, given that corin seems to be exclusive to the secretory phase, its existence in endometrial glands and subsequent secretion into the uterine lumen suggest that corin produced by endometrial glands may contribute to endometrial receptivity and the interaction between blastocysts and the endometrium. Therefore, apart from its putative function in facilitating trophoblast invasion, it may also have a role in the initial phases of gestational implantation[21]. Pregnant mice that lack corin and ANP experience impaired remodeling of spiral arteries, resulting in gestational hypertension and proteinuria, which resemble the phenotype of preeclampsia[6,22,23]. Preeclamptic women have been found to exhibit decreased quantities of corin messenger RNA (mRNA) and protein, as well as harmful corin variations[6,24,25]. Recent transcriptome studies comparing mammalian species indicate that corin is expressed specifically in a group of cells within the endometrial stromal lineage. This expression may play a role in the development of profound placental invasion and significant modification of spiral arteries[26]. Progesterone therapy consistently elevated the expression of corin in ovariectomized mice[27]. Corin and ANP were observed to facilitate a series of molecular and cellular processes in uterine decidualization and spiral artery remodeling, as demonstrated by investigations involving mouse models and cultured human uterine cells[28]. Corin has been found to be present in the endometrium throughout the late secretory phase in non-pregnant individuals, as well as in the implantation sites of early human pregnancies. Additionally, its expression is increased through the process of *ex vivo* decidualization[21]. During the embryonic invasive phase, communication between the uterine stromal cells and trophoblasts may regulate the controlled breakdown of proteins and immune responses. This helps protect both the embryo and the mother from harm[29]. Specifically, the lack of successful trophoblastic invasion into the musculoelastic layer of the spiral arteries has been demonstrated to cause incomplete transformation of the blood vessels and consistently elevated resistance in the uterine arteries[30]. Furthermore, in these studies, given that corin seems to be exclusive to the secretory phase, its existence in endometrial glands and subsequent secretion into the uterine lumen suggest that corin produced by endometrial glands may contribute to endometrial receptivity and the interaction between blastocysts and the endometrium. Hence, apart from its putative function in facilitating trophoblast invasion, it might also play a role in the initial phases of gestational implantation. In our study based on this hypothesis, we detected the presence of corin in the endometrial flushing fluid during the implantation window period. We also found decreased corin levels in two groups with infertility that may cause endometrial receptivity disorders, such as PCOS and endometriosis. However, the lower levels in our collective were not statistically significant. These findings may serve as a starting point for future investigations aimed at elucidating the mechanism by which corin contributes to endometrial receptivity and infertility. Nevertheless, additional investigations on corin biology in implantation and early pregnancy may provide information on potential therapeutics aiming at enhancing implantation quality in early pregnancies. And it could potentially lessen the likelihood of pregnancy issues from poor implantation.

Procalcitonin is the precursor form of calcitonin, a hormone that is predominantly synthesized by the C-cells located in the thyroid gland and is generated by various cell types in response to pro-inflammatory triggers[31]. In addition to infectious diseases, we sought to determine their association

with endometrial receptivity in the context of fertility and reproductive health in the present study. We hypothesized that procalcitonin may play a role in the immune modulation and inflammation associated with the implantation process. Immune factors are crucial in establishing an environment that is favorable for embryo implantation, and procalcitonin may contribute to this immunomodulation. Calcitonin is intermittently secreted by the uterine epithelia throughout the implantation phase[32,33]. Embryo implantation rates in rats are substantially reduced when calcitonin expression is inhibited during the preimplantation phase; furthermore, exogenous calcitonin administration may stimulate implantation subsequent to embryo transfer[34]. Procalcitonin is the precursor form of calcitonin, has not been assessed in the literature as a marker of endometrial receptivity during the luteal phase. During the implantation window, we examined and demonstrated the presence of procalcitonin levels in the endometrial flushing fluid secreted into the uterine lumen. Additionally, procalcitonin levels were found to be lower in the PCOS and endometriosis groups compared to the control group; however, this distinction did not reach statistical significance.

Study Limitations

Recognizing the limits of our research, particularly the comparatively limited number of participants, is crucial. Further investigations involving larger cohorts of patients are crucial in order to enhance the dependability of these measures. Another limitation is the discrepancies in baseline demographic data among groups and the failure to utilize infertility as a criterion for classifying patients into distinct categories of benign gynecological conditions. Unfortunately, the existing constraints make it challenging to establish a clear connection between the levels of these indicators and endometrial receptivity, therefore hindering the acquisition of a conclusive outcome. However, we have not found any studies in the literature examining the relationship between corin and procalcitonin and endometrial receptivity, and conducting research on this subject is among the strengths of our study. Additionally, it is the initial study to demonstrate the existence of corin and procalcitonin in the fluid obtained from the endometrium at the specific time frame of implantation.

Conclusion

Implantation failure is a persistent issue in the field of reproductive medicine and is recognized as a significant factor contributing to infertility in women who are otherwise in good health. The discovery of biomarkers that indicate endometrial receptivity not only yields insights into the molecular processes that govern implantation, but also enables the development of novel therapeutic interventions aimed at enhancing endometrial receptivity. This, in turn, will help mitigate the financial burden and time constraints involved with the treatment of affected women. Although initial findings indicate a possible correlation, additional investigation is required to clarify the fundamental processes at play and establish the clinical significance of corin and procalcitonin in evaluating endometrial receptivity.

Ethics

Ethics Committee Approval: The study received ethical approval from the Local Ethics Committee of İzmir Katip Çelebi University, Atatürk Training and Research Hospital (number: 2013-198).

Informed Consent: Informed consent was obtained from patients who participated in this study.

Authorship Contributions

Surgical and Medical Practices: Z.Ş., S.A., Concept: Z.Ş., S.A., Design: S.A., Z.Ş., S.K., M.D., G.S., Data Collection or Processing: M.D., G.S., F.O.T., Analysis or Interpretation: Z.Ş., S.A., B.Y., F.O.T., Literature Search: Z.Ş., B.Y., M.D, Writing: Z.Ş., S.A., M.D.

Conflict of Interest: The authors affirm the absence of any conflicting interests.

Financial Disclosure: This study was funded by Scientific Research Projects Coordination Unit of the İzmir Katip Çelebi University.

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