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Serum kisspeptin levels in deep-infiltrating, ovarian, and superficial endometriosis

A prospective observational study

Mesut Önal, MD[a,*], Pervin Karlı, MD[b], Ayşe Zehra Özdemir, MD[a], Adem Kocaman, PhD[c], Yunus Katırcı, MD[a], Gülnur Çoban, MD[a], Gülen Kübra Nakışlı, MD[a], Yeşim Civil, MD[c], Bahattin Avcı, MD[d]

Abstract

The diagnosis of endometriosis may delay for many years due to non-deterministic symptoms and avoiding surgical interventions. Kisspeptins are hormones that interact with endometrial tissue to limit invasions during placentation and various cancers and are suggested to be also associated with endometriosis. This study evaluated if serum kisspeptin levels are associated with the invasion depth in endometriosis. Forty patients between 18 and 45 years of age and admitted to a tertiary-care Obstetrics and Gynecology Department between 2020 and 2021 with a diagnosis of endometriosis, and 40 patients without endometrioma were included in the study. Demographic, obstetric, clinical, and biochemical characteristics were evaluated in patients with superficial (SE) and deep infiltrating (DIE) endometriosis and healthy controls. Twenty patients (50%) had SE, 14 (35%) had DIE, and 22 (55%) had endometrioma in the patient group. Fertility rates were higher among controls, but similar between patients with SE and DIE. CA125 levels were significantly higher in the DIE group. SE and DIE groups had similar kisspeptin values, significantly higher than controls. CA125 and kisspeptin levels were not correlated in study groups. Serum kisspeptin levels were significantly different between endometriosis patients and healthy controls. However, kisspeptin levels were unable to differentiate endometriosis severity. Our results suggest that kisspeptins might play a role in the pathogenesis of endometriosis, which needs further assessment in more comprehensive studies.

Abbreviations: DIE = deep infiltrating endometriosis, MMP = matrix metalloproteinases, SE = superficial endometriosis.

Keywords: deep infiltrating, endometrioma, endometriosis, kisspeptin, pathogenesis, superficial

1. Introduction

Endometriosis is a benign condition characterized by the ectopic localization of the endometrial glandular and stromal structures out of the uterine cavity, with a prevalence of 10-15% among women at reproductive ages.[1–5] However, specific populations have significantly higher prevalence, such as 40% in adolescents with genital system abnormalities, 50% in infertile women, and 70% in patients with pelvic pain.[6–11] Although the exact path of progression is still unknown, several mechanisms are suggested to develop ectopic implants, including Mullerian residuals, lymphatic or vascular invasion, and coelomic metaplasia.[1] But, the most widely accepted is Sampson's retrograde menstruation theory, which suggests the endometrial cell backflow in fallopian tubes and implantation to the peritoneal cavity.[12] Pelvic endometriosis lesions are classified as superficial-peritoneal, ovarian (endometrioma), or deep infiltrating based on the localization and invasion depth.[13–16]

Matrix metalloproteinases (MMP) 2 and 9 facilitate cell migration and invasion by degrading the extracellular matrix and may play a role in the pathogenesis of endometriosis.[17–27] Although endometriosis is a benign disorder, it also has characteristics similar to malignities like adhesion, invasion, and localization on ectopic tissues.[28–30] Kisspeptins are peptides encoded by the KISS1 gene localized on 1q32 that was first described as a metastasis suppressor gene in human malign melanoma cell cultures, thus also called *metastin*.[31–34] Kisspeptins are also known as neuropeptide hormones of the RF-amid family that interact with MMP in endometrial tissue to form focal adhesions to limit the tissue, limit trophoblast invasion during placentation, and suppress metastasis in various cancers (malign melanoma, choriocarcinoma, and bladder, gastric, esophagus, pancreas, endometrium cancers).[21,32,33,35–40] Kisspeptins also regulate the hypothalamic-hypophysial-gonadal axis and acknowledge as neuropeptides that are effective during puberty and have reproductive roles.[41–44] Endometriosis changes kisspeptin and magnesium metabolism. Local role of kisspeptin signaling in the

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[a] Department of Gynecology and Obstetrics, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey, [b] Department of Gynecology and Obstetrics, Medical Park Hospital, Samsun, Turkey, [c] Department of Histology and Embryology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey, [d] Department of Biochemistry, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey.

** Correspondence: Mesut Önal, Department of Gynecology and Obstetrics, Ondokuz Mayıs University, Samsun 55200, Turkey (e-mail: mesut.onal@omu.edu.tr).*

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control of follicular dynamics and ovulation has been identified in accelerated ovarian aging in endometriosis. Magnesium and kisspeptin are successfully used as dietary supplements for treatment of endometriosis. Endometriosis changes kisspeptin and magnesium metabolism.[45,46] Local role of kisspeptin signaling in the control of follicular dynamics and ovulation has been identified in accelerated ovarian aging in endometriosis. Magnesium and kisspeptin are successfully used as dietary supplements for treatment of endometriosis.[45]

The diagnosis of endometriosis is generally delayed about 7 to 12 years due to inconclusive symptoms and risks associated with surgical diagnosis.[47–49] Nonsurgical diagnosis of endometriosis may include a combination of clinical and radiological assessments that might be supported by microRNA markers.[50–54] Currently, there is no pathognomonic laboratory test for endometriosis. Although the serum Ca125 levels increase in endometriosis (>35 U/mL), it has no role in primary diagnosis and does not inform about the invasion depth. Given the probable association of kisspeptin with the pathogenesis of endometriosis, this study hypothesized and evaluated whether it might also be associated with the invasion depth in endometriosis.

2. Materials and methods

This prospective observational study was conducted at the Ondokuz Mayis University Faculty of Medicine between 2020 and 2021 and approved by the local ethics committee of Ondokuz Mayıs University with the approval number of 2021/66. As a result of power analysis, forty women aged 18 to 45 years and diagnosed with endometrioma formed the patient group. Forty women in the same age range without endometrioma and any symptoms were included in the control group. Patients who had undergone endometrial cyst surgery or had a history of cancer were not included in the study. In the control group, patients underwent diagnostic L/S for infertility, and the presence or absence of endometriosis was confirmed surgically in all participants.

All participants provided informed consent at recruitment before collecting blood samples to analyze serum Ca125 and kisspeptin levels. Ca125 and kisspeptin levels were analyzed biochemically by Elisa method. In addition, the demographic, obstetric, clinical, and biochemical characteristics were evaluated in patients with superficial endometriosis (SE) and deep infiltrating endometriosis (DIE) and healthy controls.

2.1. Statistical analyses

Descriptive statistics were presented using frequency and percent for categorical data, median, interquartile range (25th–75th percentiles— inter-quartile range), and minimum and maximum values for non-normally distributed continuous variables. Comparisons between independent groups were performed using the Chi-square test for categorical variables and the Kruskal–Wallis non-parametric analysis of variances test for continuous variables. Post hoc pairwise comparisons for interpreting statistically significant results in overall comparisons were made using the Mann–Whitney *U* test. All statistical analyses were considered significant at a type-I error level of 5% ($P < .05$), and post hoc pairwise comparisons were evaluated using Bonferroni correction. SPSS 25 (IBM Inc., Armonk, NY) was used for statistical analyses.

3. Results

Twenty patients (50%) had SE, 14 (35%) had DIE, and 22 (55%) had endometrioma in the patient group. Median ages ($P = .12$) and body-mass indexes ($P = .64$) were similar. Obstetric characteristics revealed that the fertility rates were significantly different between groups ($P = .002$), but the gravida was similar ($P = .11$). The proportion of fertile patients was significantly higher among controls but similar between patients with SE and DIE. Clinical characteristics regarding dysmenorrhea ($P = .29$), dyspareunia ($P = .067$), and chronic pelvic pain ($P = .29$) were similar, but CA125 ($P < .001$) and kisspeptin ($P < .001$) levels were significantly different between groups. Accordingly, CA125 levels were significantly higher in the DIE group but similar between SE and control groups. For kisspeptin levels, SE and DIE groups had similar values, significantly higher than controls. Demographic, obstetric, and clinical characteristics and laboratory analyses are summarized in Table 1.

Correlations between CA125 and kisspeptin levels were presented in scatterplot graphs in Figure 1. Analyses revealed that CA125 and kisspeptin levels were not correlated in SE ($R = 0.27$; $P = .25$), DIE ($R = –0.11$; $P = .71$), and control ($R = 0.056$; $P = .73$) groups.

4. Discussion

The pathophysiology of endometriosis is still not known precisely despite rigorous research, and the treatment is symptomatic rather than curative.[55] Although Sampson's retrograde menstruation theory is widely accepted, other factors like genetic susceptibility, environmental factors, and changes in immune and endocrine functions are suggested to play a role in the pathogenesis.[30,56]

The eutopic endometrium of women with and without endometriosis are histologically similar but different at the cellular and molecular levels, including abnormal expression of tissue

Table 1

Basal demographic and clinical characteristics of patients.

	Superficial endometriosis (n = 20)	Deepinfiltrating endometriosis (n = 14)	Control (n = 40)	*P*
Age (yr), median [IQR]	32.5 [29.5–37.5]	36 [28–39]	29.5 [23–34.5]	.12
BMI (kg/m^2), median [IQR]	23.7 [22–28.5]	22.4 [21.3–28.8]	25.4 [21.6–29.7]	.64
Fertility, n (%)				.002
Virgin	6 (30)	3 (21.4)	–	
Infertile	6 (30)	7 (50)	11 (31.4)	
Fertile	8 (40)	4 (28.6)	24 (68.6)	
Gravida, median [min–max]	0 [0–5]	0 [0–6]	1 [0–6]	.11
Dysmenorrhea, n (%)	12 (60)	8 (57.1)	14 (40)	.29
Dyspareunia, n (%)	1 (5)	4 (28.6)	11 (31.4)	.067
Chronic pelvic pain, n (%)	11 (55)	8 (57.1)	13 (37.1)	.29
CA125, median [IQR]	40.3 [20.2–56.5]	227.1 [102.7–580]	59.3 [20.2–84.1]	<.001
Kisspeptin, median [IQR]	134.4 [108.9–525.8]	159.2 [91.2–188.2]	62.5 [39.9–96.1]	<.001

IQR = inter-quartile range.

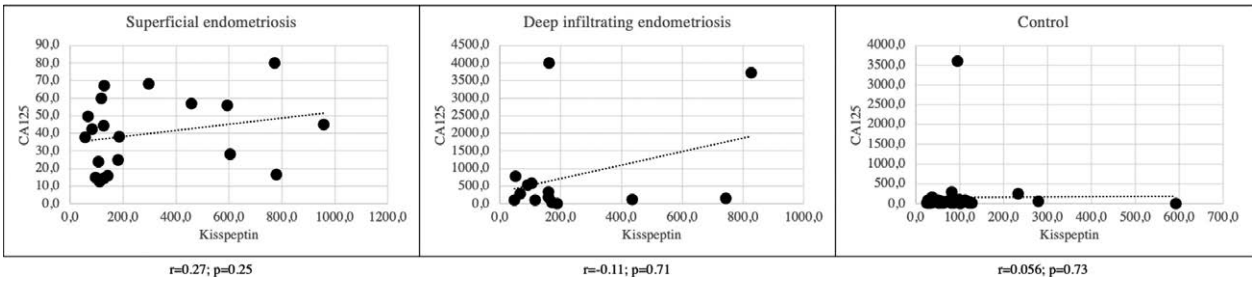

Figure 1. Correlations between CA125 and kisspeptin levels in study groups.

MMPs, several cytokines, growth factors, steroid receptors, 17-β-hydroxysteroid dehydrogenase deficiency, resistance to the protective effect of progesterone, and decreased apoptosis.[57] Moreover, an association between endometriosis and clear cell and endometrioid ovarian cancers was also shown by previous epidemiological studies.[29] Nevertheless, there is no pathognomic laboratory finding for endometriosis.

Several urinary and endometrial biomarkers are evaluated for noninvasive diagnosis of endometriosis, but none are found to have clinical utility.[58–62] The CA125 is the most studied marker and has shown to be correlated with endometriosis (>35 U/mL), but its sensitivity is low in mild endometriosis (sensitivity 28%, specificity 90%), and functions better in the diagnosis of grade 3 to 4 endometriosis, thus not routinely assessed for the primary diagnosis.[1,13,61,63–66] Some other biomarkers studied were CA19-9 which has shown to be correlated with the endometriosis severity,[67–69] serum placental protein 14 (PP14–glycodelin-A), interleukin-6, and tumor necrosis factor-α, which have limited diagnostic accuracy.[1,70–72] In addition, serum hepatocyte growth factor and CA19-9 expressions were correlated with patient age, prognosis, number of nodules, and infiltration depth and were found to be higher in grade III-IV patients than in grade I-II cases.[73] Another biomarker associated with ovarian endometriosis and enlargement of ovarian cysts is an estrogen-related receptor-α, which is suggested to be used to monitor the disease progression non-invasively.[74] Studies are ongoing to identify potential biomarkers to evaluate and monitor the disease progression.[75–79]

Endometriosis shares many features of cancer, particularly migration and invasion; on the contrary, kisspeptins have antimetastatic characteristics in various cancer types.[33,80] In addition, the KISS1R mRNA levels were previously found to be statistically significantly higher in the cumulus cells of endometriosis patients compared to healthy oocyte donors. Thus, KISS1R expression was suggested as a potential factor that might have a role in endometriosis and associated infertility and can be used as a biomarker for diagnosing endometriosis.[81]

Previous studies also revealed that kisspeptin expression varies in the glandular or stromal endometrial components in endometriosis.[80,82,83] The kisspeptin levels were lower in the eutopic endometrial glandular epithelium but similar in the stromal endometrium of women with endometriosis when compared to women without endometriosis.[80] Another study also reported that KISS1 expression was similar in stromal components from endometriosis lesions, eutopic endometrium, and healthy controls, but the expression was significantly lower in eutopic glandular endometrium than in ectopic lesions.[84] Since KISS1 is known to suppress metastasis, low levels in eutopic endometrium may permit migration to ectopic localization, suggesting a potential role of KISS1 in endometriosis, which also supports Sampson's theory.

A previous study reported that the expression of kisspeptin was significantly lower in DIE than in SE, which may explain that lower kisspeptin expression might be associated with invasion depth given the antimetastatic feature of the kisspeptin.[80] Another study showed that peripheral blood kisspeptin levels were significantly higher, but endometrial KISS1/KISS1R expressions were lower in endometriosis patients than in controls. In addition, the KISS1 expression and receptor KISS1R were significantly increased in endometrioid heterotopic regions on the pelvic peritoneum compared to normal peritoneal fragments. Also, the KISS1R receptor expression fields in the endometrioid heterotopic areas were significantly larger than the eutopic endometrium of endometriosis patients and the endometrium of the women in the control group.[85]Contrary to these findings, another study reported that KISS1 expression was not observed in any of the eutopic and ectopic endometrium samples from endometriosis patients, and almost none of the endometrial tissues of the control group,[86] which were then presumed to be associated with the methods as well as the limited number of the samples analyzed.[84]

The tissue studies evaluating the kisspeptin and its receptor levels in deep, superficial, and ovarian endometriosis patients reported that deep lesions had lower levels of KISS1, thus, suggesting that kisspeptin might contribute to implant invasiveness.[83] When compared to SE, lower KISS1 levels were found in both glandular and stromal endometrium in deep and ovarian endometriosis, whereas lower KISS1R levels were observed in the glandular component of ovarian endometriosis. Additionally, comparisons of KISS1 and KISS1R between eutopic endometrium of endometriosis patients and normal endometrium of control patients revealed that endometriosis patients had decreased levels, which are concordant with previous studies.[83,84]

This study found that the serum kisspeptin levels were significantly different between endometriosis patients and healthy controls. The increased levels among endometriosis patients were in accordance with the serum findings of Aylamazyan et al.[85] Nevertheless, our primary aim, determining the endometriosis severity using serum kisspeptin levels, seems not possible based on these results. Although endometriosis patients and the control group differ regarding kisspeptin levels, superficial and deep endometriosis patients were not significantly different.

To the best of our knowledge, there is no study on the kisspeptin and CA125 association in endometriosis in the literature. Our study is the first that reported on this association, but no further assessments are available due to the lack of simultaneous evaluation of tissue kisspeptin expression. Previous studies reported that serum levels of CA125 were associated with endometriosis severity, but our results were contrary. This might be partly associated with the patient characteristics, but we considered that kisspeptin and CA125 levels were not superior to each other in determining endometriosis severity.

The body mass index is strongly negatively correlated with the severity of endometriosis.[87,88] We have not evaluated the influence of BMI on Serum Kisspeptin Levels and we acknowledge this as a limitation of the study.

Kisspeptins are thought to have a role in the pathogenesis of endometriosis. Nevertheless, further studies are needed for utilizing KISS1 as a marker for a neater understanding of the

pathogenesis of the endometriosis, potentially targeted therapies, and identifying early and minimal invasive disease.

Author contributions

Conceptualization: Mesut Önal, Yunus Katırcı, Gülnur Çoban.
Data curation: Mesut Önal, Yunus Katırcı, Gülnur Çoban.
Funding acquisition: Pervin Karlı.
Methodology: Adem Kocaman, Pervin Karlı, Bahattin Avcı.
Project administration: Adem Kocaman, Gülen Kübra Nakışlı.
Resources: Adem Kocaman.
Supervision: Yeşim Civil.
Validation: Yeşim Civil, Ayşe Zehra Özdemir.
Visualization: Gülen Kübra Nakışlı.
Writing – original draft: Mesut Önal, Ayşe Zehra Özdemir.
Writing – review & editing: Mesut Önal, Adem Kocaman.

References

[1] Hoffman BLSJO, Schaffer JI, Halvorson LM, et al. Endometriosis. Williams Gynecology. Second Edition; 2015:281–303.
[2] Mehedintu C, Plotogea MN, Ionescu S, et al. Endometriosis still a challenge. J Med Life. 2014;7:349–57.
[3] Adamson GD, Kennedy S, Hummelshoj L. Creating solutions in endometriosis: global collaboration through the World Endometriosis Research Foundation. J Endometriosis. 2018;2:3–6.
[4] Soliman AM, Surrey E, Bonafede M, et al. Real-world evaluation of direct and indirect economic burden among endometriosis patients in the United States. Adv Ther. 2018;35:408–23.
[5] Shafrir AL, Farland LV, Shah DK, et al. Risk for and consequences of endometriosis: a critical epidemiologic review. Best Pract Res Clin Obstet Gynaecol. 2018;51:1–15.
[6] Dovey S, Sanfilippo J. Endometriosis and the adolescent. Clin Obstet Gynecol. 2010;53:420–8.
[7] Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am. 1997;24:235–58.
[8] Chatman DL, Ward AB. Endometriosis in adolescents. J Reprod Med. 1982;27:156–60.
[9] Goldstein DP, deCholnoky C, Emans SJ, et al. Laparoscopy in the diagnosis and management of pelvic pain in adolescents. J Reprod Med. 1980;24:251–6.
[10] Reese KA, Reddy S, Rock JA. Endometriosis in an adolescent population: the emory experience. J Pediatr Adolesc Gynecol. 1996;9:125–8.
[11] Laufer MR, Goitein L, Bush M, et al. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. J Pediatr Adolesc Gynecol. 1997;10:199–202.
[12] Sampson J. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol. 1927;14:422–69.
[13] Vercellini P, Vigano P, Somigliana E, et al. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10:261–75.
[14] Clement PB. The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. Adv Anat Pathol. 2007;14:241–60.
[15] Brosens IA, Puttemans PJ, Deprest J. The endoscopic localization of endometrial implants in the ovarian chocolate cyst. Fertil Steril. 1994;61:1034–8.
[16] De Cicco C, Corona R, Schonman R, et al. Bowel resection for deep endometriosis: a systematic review. BJOG. 2011;118:285–91.
[17] Rodgers WH, Matrisian LM, Giudice LC, et al. Patterns of matrix metalloproteinase expression in cycling endometrium imply differential functions and regulation by steroid hormones. J Clin Invest. 1994;94:946–53.
[18] Ye H, He Y, Wang J, et al. Effect of matrix metalloproteinase promoter polymorphisms on endometriosis and adenomyosis risk: evidence from a meta-analysis. J Genet. 2016;95:611–9.
[19] Yang H, Liu J, Fan Y, et al. Associations between various possible promoter polymorphisms of MMPs genes and endometriosis risk: a meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2016;205:174–88.
[20] Liu H, Wang J, Wang H, et al. Correlation between matrix metalloproteinase-9 and endometriosis. Int J Clin Exp Pathol. 2015;8:13399–404.
[21] Qiao C, Wang CH, Shang T, et al. [Clinical significance of KiSS-1 and matrix metalloproteinase-9 expression in trophoblasts of women with preeclampsia and their relation to perinatal outcome of neonates]. Zhonghua Fu Chan Ke Za Zhi. 2005;40:585–90.
[22] Wolber EM, Kressin P, Meyhofer-Malik A, et al. Differential induction of matrix metalloproteinase 1 and 2 in ectopic endometrium. Reprod Biomed Online. 2003;6:238–43.
[23] Uzan C, Cortez A, Dufournet C, et al. Eutopic endometrium and peritoneal, ovarian and bowel endometriotic tissues express a different profile of matrix metalloproteinases-2, -3 and -11, and of tissue inhibitor metalloproteinases-1 and -2. Virchows Arch. 2004;445:603–9.
[24] Szamatowicz J, Laudanski P, Tomaszewska I. Matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1: a possible role in the pathogenesis of endometriosis. Hum Reprod. 2002;17:284–8.
[25] Mizumoto H, Saito T, Ashihara K, et al. Expression of matrix metalloproteinases in ovarian endometriomas: immunohistochemical study and enzyme immunoassay. Life Sci. 2002;71:259–73.
[26] Chung HW, Lee JY, Moon HS, et al. Matrix metalloproteinase-2, membranous type 1 matrix metalloproteinase, and tissue inhibitor of metalloproteinase-2 expression in ectopic and eutopic endometrium. Fertil Steril. 2002;78:787–95.
[27] Pitsos M, Kanakas N. The role of matrix metalloproteinases in the pathogenesis of endometriosis. Reprod Sci. 2009;16:717–26.
[28] Starzinski-Powitz A, Handrow-Metzmacher H, Kotzian S. The putative role of cell adhesion molecules in endometriosis: can we learn from tumour metastasis? Mol Med Today. 1999;5:304–9.
[29] Zafrakas M, Grimbizis G, Timologou A, et al. Endometriosis and ovarian cancer risk: a systematic review of epidemiological studies. Front Surg. 2014;1:14.
[30] Zafrakas M, Tarlatzis BC, Streichert T, et al. Genome-wide microarray gene expression, array-CGH analysis, and telomerase activity in advanced ovarian endometriosis: a high degree of differentiation rather than malignant potential. Int J Mol Med. 2008;21:335–44.
[31] Lee DK, Nguyen T, O'Neill GP, et al. Discovery of a receptor related to the galanin receptors. FEBS Lett. 1999;446:103–7.
[32] Lee JH, Miele ME, Hicks DJ, et al. KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. J Natl Cancer Inst. 1996;88:1731–7.
[33] Kotani M, Detheux M, Vandenbogaerde A, et al. The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. J Biol Chem. 2001;276:34631–6.
[34] West A, Vojta PJ, Welch DR, Weissman BE. Chromosome localization and genomic structure of the KiSS-1 metastasis suppressor gene (KISS1). Genomics. 1998;54:145–8.
[35] Bilban M, Ghaffari-Tabrizi N, Hintermann E, et al. Kisspeptin-10, a KiSS-1/metastin-derived decapeptide, is a physiological invasion inhibitor of primary human trophoblasts. J Cell Sci. 2004;117:1319–28.
[36] Francis VA, Abera AB, Matjila M, et al. Kisspeptin regulation of genes involved in cell invasion and angiogenesis in first trimester human trophoblast cells. PLoS One. 2014;9:e99680.
[37] Qiao C, Cheng DL, Zhang SL, et al. [The role of KiSS-1 and matrix metalloproteinase-9 in regulation of invasion of trophoblasts]. Zhonghua Yi Xue Za Zhi. 2005;85:839–42.
[38] Ohtaki T, Shintani Y, Honda S, et al. Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. Nature. 2001;411:613–7.
[39] Makri A, Pissimissis N, Lembessis P, et al. The kisspeptin (KiSS-1)/GPR54 system in cancer biology. Cancer Treat Rev. 2008;34:682–92.
[40] Sanchez-Carbayo M, Capodieci P, Cordon-Cardo C. Tumor suppressor role of KiSS-1 in bladder cancer: loss of KiSS-1 expression is associated with bladder cancer progression and clinical outcome. Am J Pathol. 2003;162:609–17.
[41] Navarro VM, Fernandez-Fernandez R, Castellano JM, et al. Advanced vaginal opening and precocious activation of the reproductive axis by KiSS-1 peptide, the endogenous ligand of GPR54. J Physiol. 2004;561:379–86.
[42] Shahab M, Mastronardi C, Seminara SB, et al. Increased hypothalamic GPR54 signaling: a potential mechanism for initiation of puberty in primates. Proc Natl Acad Sci USA. 2005;102:2129–34.
[43] Gottsch ML, Cunningham MJ, Smith JT, et al. A role for kisspeptins in the regulation of gonadotropin secretion in the mouse. Endocrinology. 2004;145:4073–7.
[44] Rometo AM, Krajewski SJ, Voytko ML, et al. Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of postmenopausal women and ovariectomized monkeys. J Clin Endocrinol Metab. 2007;92:2744–50.
[45] Yalcin Bahat P, Ayhan I, Ureyen Ozdemir E, et al. Dietary supplements for treatment of endometriosis: a review. Acta Biomed. 2022;93:e2022159.

[46] Garalejic E, Bojovic-Jovic D, Damjanovic A, et al. Hamilton anxiety scale (HAMA) in infertile women with endometriosis and its correlation with magnesium levels in peritoneal fluid. Psychiatr Danub. 2010;22:64–7.
[47] Hadfield R, Mardon H, Barlow D, et al. Delay in the diagnosis of endometriosis: a survey of women from the USA and the UK. Hum Reprod. 1996;11:878–80.
[48] Husby GK, Haugen RS, Moen MH. Diagnostic delay in women with pain and endometriosis. Acta Obstet Gynecol Scand. 2003;82:649–53.
[49] Staal AH, van der Zanden M, Nap AW. Diagnostic delay of endometriosis in the Netherlands. Gynecol Obstet Invest. 2016;81:321–4.
[50] Eskenazi B, Warner M, Bonsignore L, et al. Validation study of nonsurgical diagnosis of endometriosis. Fertil Steril. 2001;76:929–35.
[51] Barcellos MB, Lasmar B, Lasmar R. Agreement between the preoperative findings and the operative diagnosis in patients with deep endometriosis. Arch Gynecol Obstet. 2016;293:845–50.
[52] Vercellini P, Bracco B, Mosconi P, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril. 2016;105:734–743.e3.
[53] Papari E, Noruzinia M, Kashani L, et al. Identification of candidate microRNA markers of endometriosis with the use of next-generation sequencing and quantitative real-time polymerase chain reaction. Fertil Steril. 2020;113:1232–41.
[54] Coutinho LM, Ferreira MC, Rocha ALL, et al. New biomarkers in endometriosis. Adv Clin Chem. 2019;89:59–77.
[55] Kaur KK. Current controversies and future directions for endometriosis therapy. EC Gynaecol. 2017:9–13.
[56] John AS. Heterotopic or misplaced endometrial tissue. Am J Obstet Gynecol. 1925;10:649–64.
[57] Ulukus M, Cakmak H, Arici A. The role of endometrium in endometriosis. J Soc Gynecol Investig. 2006;13:467–76.
[58] Gupta D, Hull ML, Fraser I, et al. Endometrial biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;4:CD012165.
[59] Liu E, Nisenblat V, Farquhar C, et al. Urinary biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2015;12:CD012019.
[60] Nisenblat V, Prentice L, Bossuyt PM, et al. Combination of the non-invasive tests for the diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;7:CD012281.
[61] Schenken RS. Endometriosis: pathogenesis, clinical features, and diagnosis 2021. Available at: https://www.uptodate.com/contents/endometriosis-pathogenesis-clinical-features-and-diagnosis?source=history_widget#H3930914865. [Access date July 15, 2021].
[62] Cho S, Choi YS, Yim SY, et al. Urinary vitamin D-binding protein is elevated in patients with endometriosis. Hum Reprod. 2012;27:515–22.
[63] Mol BW, Bayram N, Lijmer JG, et al. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. Fertil Steril. 1998;70:1101–8.
[64] Jager W, Diedrich K, Wildt L. Elevated levels of CA-125 in serum of patients suffering from ovarian hyperstimulation syndrome. Fertil Steril. 1987;48:675–8.
[65] Hornstein MD, Harlow BL, Thomas PP, et al. Use of a new CA 125 assay in the diagnosis of endometriosis. Hum Reprod. 1995;10:932–4.
[66] Cheng YM, Wang ST, Chou CY. Serum CA-125 in preoperative patients at high risk for endometriosis. Obstet Gynecol. 2002;99:375–80.
[67] Harada T, Kubota T, Aso T. Usefulness of CA19-9 versus CA125 for the diagnosis of endometriosis. Fertil Steril. 2002;78:733–9.
[68] Fiala L, Bob P, Raboch J. Oncological markers CA-125, CA 19-9 and endometriosis. Medicine (Baltim). 2018;97:e13759.
[69] Rokhgireh S, Mehdizadeh Kashi A, Chaichian S, et al. The diagnostic accuracy of combined enolase/Cr, CA125, and CA19-9 in the detection of endometriosis. Biomed Res Int. 2020;2020:5208279.
[70] Bedaiwy MA, Falcone T. Laboratory testing for endometriosis. Clin Chim Acta. 2004;340:41–56.
[71] Bedaiwy MA, Falcone T, Sharma RK, et al. Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial. Hum Reprod. 2002;17:426–31.
[72] Fan YY, Chen HY, Chen W, et al. Expression of inflammatory cytokines in serum and peritoneal fluid from patients with different stages of endometriosis. Gynecol Endocrinol. 2018;34:507–12.
[73] Zhang X, Nie D, Zhang L, et al. Study on diagnostic values and pathological conditions of serum HGF and CA199 in endometriosis. Am J Transl Res. 2021;13:2849–57.
[74] Liu C, Chen Y, Chen M, et al. A novel non-invasive molecular biomarker in ovarian endometriosis: estrogen-related receptor alpha. Arch Gynecol Obstet. 2020;302:405–14.
[75] Guralp O, Kaya B, Tuten N, et al. Non-invasive diagnosis of endometriosis and moderate-severe endometriosis with serum CA125, endocan, YKL-40, and copeptin quadruple panel. J Obstet Gynaecol. 2021;41:927–32.
[76] Tian Z, Chang XH, Zhao Y, et al. Current biomarkers for the detection of endometriosis. Chin Med J (Engl). 2020;133:2346–52.
[77] Guralp O, Acikgoz S, Tuten N, et al. Evaluation of serum endocan levels in endometriosis: a case-control study. Clin Ter. 2020;171:e517–22.
[78] Bilibio JP, Souza CA, Rodini GP, et al. Serum prolactin and CA-125 levels as biomarkers of peritoneal endometriosis. Gynecol Obstet Invest. 2014;78:45–52.
[79] Yu H, Li B, Li T, et al. Combination of noninvasive methods in diagnosis of infertile women with minimal or mild endometriosis, a retrospective study in China. Medicine (Baltim). 2019;98:e16695.
[80] Abdelkareem AO, Ait-Allah AS, Rasheed SM, et al. Differential expression of Kisspeptin in patients with and without endometriosis. Fertil Steril. 2016;106:e274.
[81] Blasco V, Pinto FM, Fernandez-Atucha A, et al. Female infertility is associated with an altered expression of the neurokinin B/neurokinin B receptor and kisspeptin/kisspeptin receptor systems in ovarian granulosa and cumulus cells. Fertil Steril. 2020;114:869–78.
[82] Bedaiwy MA, Allaire C, Alfaraj S. Long-term medical management of endometriosis with dienogest and with a gonadotropin-releasing hormone agonist and add-back hormone therapy. Fertil Steril. 2017;107:537–48.
[83] Abdelkareem AO, Alotaibi FT, AlKusayer GM, et al. Immunoreactivity of Kisspeptin and Kisspeptin receptor in eutopic and ectopic endometrial tissue of women with and without endometriosis. Reprod Sci. 2020;27:1731–41.
[84] Timologou A, Zafrakas M, Grimbizis G, et al. Immunohistochemical expression pattern of metastasis suppressors KAI1 and KISS1 in endometriosis and normal endometrium. Eur J Obstet Gynecol Reprod Biol. 2016;199:110–5.
[85] Aylamazyan EY, Ganbarli NF, Tkachenko NN, et al. The role of metastin in pathogenesis of genital endometriosis. J Obstetr Women's Dis. 2017;66:16–24.
[86] Makri A, Msaouel P, Petraki C, et al. KISS1/KISS1R expression in eutopic and ectopic endometrium of women suffering from endometriosis. In Vivo. 2012;26:119–27.
[87] Garalejic E, Arsic B, Radakovic J, et al. A preliminary evaluation of influence of body mass index on in vitro fertilization outcome in non-obese endometriosis patients. BMC Womens Health. 2017;17:112.
[88] Shah DK, Correia KF, Vitonis AF, et al. Body size and endometriosis: results from 20 years of follow-up within the Nurses' Health Study II prospective cohort. Hum Reprod. 2013;28:1783–92.