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ORIGINAL PAPER

# Kisspeptin Serum Levels in Patients with Endometriosis, New Research Pathways Regarding Female Infertility

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*ABSTRACT*

***Introduction:*** *Endometriosis is defined by the presence of endometrial tissue outside the uterus, therefore leading to a chronic inflammatory reaction, adhesions development, scar tissue and a distorted pelvic female anatomy, most of the times leading to female infertility. Kisspeptin represents a neuropeptide thought to have an essential role in the reproductive functions of both female and male patients. Recently, positive correlations with kisspeptins were noticed in patients diagnosed with endometriosis.*

***Materials and methods:*** *Our study was performed between January 2021-March 2022 in "Elena Doamna" Clinical Hospital of Obstetrics and Gynecology Iasi, Romania. It was a prospective case-control study and included two groups of patients. Both groups consisted in female patients aged between 18 and 45 years, with a body mass index (BMI) between 18,5-30 kg/m$^2$ and similar medical data. Patients in the study group had primary or secondary infertility and endometriosis, while the control group consisted of women with no reproductive issues who had healthy regular menstruations and at least one child. All patients agreed to participate in our study and signed the consent form. Clinical examination, pelvic ultrasound and hormonal dosages were performed. We tested the levels of LH, FSH, kisspeptin, estradiol, prolactin, testosterone, insulin and the glycemic levels in both groups during the follicular phase of their menstrual cycle.*

***Results:*** *We managed to enroll eight patients with endometriosis in the study group and an equal number of patients in the control group. There were significant differences between serum kisspeptin levels, but not also between other hormonal dosages. All patients in the study group had medical evidences of endometriomas but none of them had been subjected to laparoscopy.*

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***Conclusions:*** *When considering our study, we regarded the first attribution given to kisspeptin, the one of a metastasis suppressor, and concluded that the high serum values of kisspeptin in patients with endometriosis represented a compensatory-adaptive mechanism needed to constrain future spread of endometriomas in early stages of this pathology.*

**Keywords**: kisspeptin, endometriosis, infertility.

## INTRODUCTION

Endometriosis is characterized by the presence of endometrial-like tissue outside the uterus leading to a chronic inflammatory reaction, development of adhesions, scar tissue and a distorted pelvic female anatomy (1). It is considered a complex clinical syndrome caused by a chronic inflammatory process due to a high estrogen level. It is commonly encountered in reproductive-age women and the most common cause of chronic pelvic pain related to menstruation and ovulation timing. Due to its chronic inflammatory nature, it resembles other chronic inflammatory disorders associated with abdominal pelvic pain and it is most frequently misdiagnosed as an inflammatory bowel disease (2, 3). However, the main feature for this specific pathology is the dependence on estrogen as the key biologic driver of inflammation (4). Endometriosis has certain key features such as intense primary dysmenorrhea, repetitious episodes of ovulation leading to heavy periods associated with retrograde menstruation, pelvic endometriosis diagnosed by laparoscopy, all these representing progressive stages (5). Patients experience chronic pain continually or intermittently until the end of their reproductive life period. Pelvic endometriosis mainly includes peritoneal endometrial implants, ovarian endometriomas and rectovaginal nodules, all three forms being probably caused by the retrograde menstruation that follows ovulation (6).

Currently, the gold-standard in diagnosing endometriosis consists in laparoscopic exploration of the pelvic abdominal cavity but this technique does not take in consideration the possibility of microscopic inflammatory disease in the pelvic peritoneum or the eutopic endometrial tissue, both being possible causes for chronic pelvic pain that might respond to ovulation suppression (7, 8). Ovulation suppression seems to be the key for successful management in pelvic pain associated to endometriosis (9). The essential role of estrogen excess in endometriosis has been compared to the role of insulin deficiency in diabetes (10). Estradiol continuous secretion seems to be essential for the attachment of endometrial tissue to the peritoneum, survival of endometrial lesions and production of proinflammatory substances such as cytokines, metalloproteinases and growth factors, and the angiogenesis process (11). Blocking estradiol production either through menopause or pharmacologically causes regression of the disease and it is specific symptomatology (12). One of the main hormonal features of endometriosis is the progesterone resistance caused by a deficiency of progesterone receptors in the endometrial stromal cells (13). Genital endometriosis is characterized by a decrease of apoptosis, increased levels of proinflammatory cytokines and high proliferative activity and angiogenesis.

Kisspeptin (KISS1), a neuropeptide with essential implications in the regulation of the hypothalamic–pituitary–gonadal (HPG) axis, was first isolated from melanoma cell lines and had the potential of a metastasis suppressor gene. In 1999, G protein coupled receptor (KISS1R), part of the galanin receptor family, was discovered (14). The KISS1/KISS1R system is essential for an appropriate hormonal secretion during puberty and in establishing mammalian reproductive function and regulation of the HPG axis (15). It was shown that kisspeptin administration in immature rodents was able to lead to a precocious activation of the gonadotropic axis and premature puberty development (16). Studies using immunohistochemical and real time polymerase chain reaction (RT-PCR) analyses managed to bring scientific evidence of the presence of KISS1/KISS1R expression in the human ovaries, tubes and uterus, especially in the luminal and glandular epithelial cells from the endometrium. Infertility represents a social and public health

problem affecting 15-20% of couples of reproductive age. Most studied pathologies for infertility consist in the advanced female age for reproduction, tubal obstruction, endometriosis and polycystic ovary syndrome. In the past two decades, numerous studies have been conducted in order to connect the dysregulations of KISS1/KISS1R to infertility issued, premature ovarian failure and precocious or late onset of puberty; however, even nowadays results are not clear (17). When taking into consideration the suppressor potential of kisspeptin (firstly named metastin) and the proliferative potential of endometriosis, it is difficult not to suspect a correlation. ❑

## MATERIALS AND METHODS

Our study was performed between January 2021-March 2022 in "Elena Doamna" Clinical Hospital of Obstetrics and Gynecology, Iasi, Romania. It was a prospective case-control study which included two groups of patients. The study group comprised female patients aged between 18 and 45 years, with a BMI between 18,5-30 kg/m$^2$, who had primary or secondary infertility and endometriosis. The control group was composed of female patients aged between 18 and 45 years, with a BMI between 18,5-30 kg/m$^2$ and no reproductive issues, who had healthy regular menstruations and at least one child. All patients agreed to participate in our study and signed a consent form before being examined. Exclusion criteria consisted in patients who did not have the appropriate age or BMI, had either other endocrinology pathologies that might have influenced the results or psychiatric diseases, or had given birth 12 months prior to the beginning of the study. This study was performed in compliance with the ethical principles of the assigned institutional board and national committee.

All patients who signed the consent form and agreed to enter our study went through a detailed clinical examination. Medical history was noted in each patient's medical chart and recorded for the study as well. Patients had blood samples taken during the follicular phase of their cycle in order to identify the serum levels of luteinizing hormone (LH), foliculo-stimulating hormone (FSH), testosterone, prolactin, kisspeptin, estradiol, insulin and glycemic levels. All patients had a pelvic ultrasound performed during their follicular phase as well. Those from the study group had medical letters confirming the diagnosis of endometriosis based on clinical and paraclinical examinations, but none of them had either laparoscopic or histological confirmation.

The test protocol included obtaining five milliliters of blood once from all patients; blood samples were taken during one of their three days of menstruation. The serum was separated by centrifugation for 20 minutes at 3000 rpm. Further on, all samples were transferred to plain tubes and stored until the assay process. All parameters were measured by enzyme-linked immunosorbent assay (ELISA). ❑

## RESULTS

In our study, both cases and controls had general medical data. We managed to enroll eight patients with endometriosis for the study group and an equal number of patients for the control group. Significant differences were observed when comparing the serum kisspeptin levels, but no significant differences were observed for the other hormonal dosages. Patients in the control group were between 29 and 42 years old compared to the study group that had patients with ages between 24 and 45 years old. All patients in the control group had at least one child, regular and unpainful menstrual cycles. Patients in the study group had no children, declared chronic pelvic pain, dysmenorrhea and had imagistic and clinical evidences of endometriomas (Table 1). ❑

**TABLE 1.** Comparisons between control group and study group

| | Control group | Study group |
|---|---|---|
| Mean kisspeptin serum levels | 77.446 pg/mL | 112.250 pg/mL |
| Mean estradiol serum values | 69.180 pg/mL | 79.353 pg/mL |
| Mean LH serum values | 8.862 mUI/mL | 10.731 mUI/mL |
| Mean FSH serum values | 25.606 mUI/mL | 13.381 mUI/mL |
| Mean age | 33.5 years | 31.5 years |
| Mean number of children | 2 | 0 |
| Chronic pelvic pain | Absent | Present |
| Primary infertility | Absent | Present |
| Mean IMC | 26.6 kg/m$^2$ | 28.9 kg/m$^2$ |

## DISCUSSION

According to most studies in the recent years, it seems that the KISS1/KISS1R plays an essential role when it comes to reproductive functions. Normal regulation of the HHO axis due to a physiological secretion of kisspeptin is important for the normal puberty development, and a key point in the reproduction mechanisms such as the LH peak needed for ovulation, pregnancy and implantation. Several other studies have shown the opposite: significantly lower kisspeptin levels in patients with ovarian endometriomas when compared to healthy patients. Abdelkareem *et al* considered that the downregulation of KISS1 levels had a contribution to implant invasiveness (18). ❑

## CONCLUSIONS

When considering our study, we regarded the first attribution given to kisspeptin, the one of a metastasis suppressor, and concluded that the high serum values of kisspeptin in patients with endometriosis represented compensatory-adaptive mechanisms needed to constrain future spread of enometriomas in early stages of this pathology. The particularity of the present study consists in the recent correlations being created between patients with endometriosis and serum kisspeptin levels. Even though the number of patients included in this study is minor, it represents a new beginning in this direction and a possible hypothesis for future therapeutic novelties in the treatment of endometriosis. ❑

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