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RESEARCH ARTICLE

ASSOCIATION BETWEEN ENDOMETRIOSIS AND HYPERPROLACTINEMIA IN INFERTILE WOMEN

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ABSTRACT

Background: The association of endometriosis with hyperprolactinemia is controversial. ***Objective:*** The present study aimed to determine the association of endometriosis with hyperprolactinemia in infertile women. ***Method:*** Women between age group 19-38 years who presented with chief complaint of infertility in the outpatient Department of Obstetric and Gynaecology at Sawai Maan Singh (SMS) Medical College and simultaneously underwent diagnostic laparoscopy were included in a cross sectional study. The presence of endometriosis was evaluated. To investigate the association of endometriosis with hyperprolactinemia, the patients whose infertility was not caused by endometriosis were included in the control group. Serum prolactin levels were measured in follicular phase in all females undergoing diagnostic laparoscopy for evaluation of infertility. The comparison of serum prolactin levels between the two groups was performed using unpaired t-test. ***Results:*** Prolactin levels were found to be significantly higher in the endometriosis group as compared to the control group (34.30±13.81 vs. 12.30±4.95 respectively). The results were statistically significant ($p< 0.001$). ***Conclusion:*** In the present study, hyperprolactinemia i.e. serum prolactin >20ng/ml was found to be associated with endometriosis. Hence, serum prolactin levels should be estimated in all patients who are suspected of endometriosis.

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INTRODUCTION

Endometriosis is the presence of endometrial glands and stroma outside the uterus[1], primarily the pelvic peritoneum, ovaries and rectovaginal septum. The prevalence of endometriosis in women experiencing pain, infertility, or both is as high as 35-50%.[2] Yet, endometriosis is under-diagnosed and associated with a 6.7 year mean latency from onset of symptoms to definitive diagnosis, which is due to requirement for surgical diagnosis.[3] The disease exhibits a broad spectrum of clinical signs and symptoms and is prone to progression and recurrence. The stigmata of endometriosis include dysmenorrhea, dyspareunia, chronic pelvic pain, irregular uterine bleeding and/or infertility. Lesions identified during laparoscopy are categorized as superficial peritoneal lesions, endometriomas or deep infiltrating nodules, with high degree of individual variability in lesion colour, size, and morphology. Histopathological analysis requires the presence of at least two features for the diagnosis of endometriosis, the features being endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin filled macrophages.[4] Several theories have arisen to account for the disparate observations regarding pathogenesis of endometriosis, and these can generally be categorizedas those proposing that implants originate from uterine endometrium and those proposing that implants arise from tissues other than the uterus.[5] Retrograde menstruation (Sampson's theory), metaplastic transformation (Meyer's theory), direct transplantation from endometrium or surgery, lymphatic or hematogenous spread distant to pelvis (Halban's theory) are some of the possible theories of histogenesis of endometriosis. Retrograde menstruation, in which uterine epithelial and stromal cells are disseminated and implanted into the peritoneal cavity via the fallopian tubes is the most accepted mechanism for the pathogenesis of endometriosis.[6]More recently, the in depth analysis of factors involved in this disease, including the role of immunogenetics, inflammation, angiogenesis, cytokine expression (leading to adhesion and fibrosis) and endocrine alterations such as steroid receptor expression have let to a better understanding of endometriosis than ever before. This disease is an interplay between intrinsic factors within the ectopic endothelium and permissive alterations within the host. Both these components forms a complex, interacting system greatly impacting the development of endometriosis. This starts with attachment of endometrial cells to mesothelial cells followed by invasion of endometrial cells into the mesothelium. Then angiogenesis occurs near nascent endometriosis implants and leads to proliferation of ectopic endometrial cells and finally recruitment of inflammatory cells that support persistence of the implants. The important mediator of local angiogenesis is Vascular Endothelial Growth Factor (VEGF). Human

peritoneal fluid from women with endometriosis show increased VEGF levels compared to normal women.[7-9] The gold standard for diagnosis of endometriosis remains laparoscopy followed by histopathology confirmation. Despite tremendous research in endometriosis there is no definite biological marker which can replace the need for this invasive diagnostic marker. As a result the disease is detected late and has a latency period of 6-7 years thereby increasing the overall burden of disease.[10]For the same reason we need to have a biological marker which can be easily assessed and at the same time have some prognostic value. Interestingly, prolactin is known to stimulate expression of VEGF receptor. Hence a correlation is assumed between serum prolactin levels and presence of endometriosis. Prolactin is a peptide hormone, encoded by the prolactin gene. Several isoforms of PRL exist in human circulation, including a 23kDa full length form and 16kDa isoform that is N-terminal fragment of full length form. Th intact human PRL molecule, with a molecular mass of 23kDa, has proangiogenic activity and reportedly stimulates endothelial cell proliferation[11], migration and tube formation.[12]

METHODS

This cross sectional study was conducted in the Department of Obstetrics and Gynecology, Gangori Hospital of SMS Medical College, Jaipur. All women of age group 19-38 years of age group attending the general outpatient gynecology clinic with chief complaint of infertility were admitted for diagnostic laparoscopy. Women with presence of the disease that cause hyperprolactinemia, with previous endocrine disorders like pituitary adenoma, thyroid disorder, polycystic ovarian syndrome and those using drugs that could affect prolactin such as tranquilizers, dopamine antagonist and antiemetic drugs were excluded. A written informed consent was taken from women who were participating in the study. Complete history and detailed examination were done. Investigations required for the pre anaesthetic check up and ultrasound pelvis with whole abdomen was done. Serum prolactin levels were measured in follicular phase in all females undergoing diagnostic laparoscopy for evaluation of infertility. The Calbiotech Inc(CBI) Prolactin ELISA kit was used for quantitative measurement of prolactin in human serum. Hyperprolactinemia was defined as serum prolactin levels more than 20ng/ml. Diagnostic laparoscopy was performed. Laparoscopically confirmed cases endometriosis subjects were considered as cases and the one without endometriosis on diagnostic laparoscopy were considered as controls. Unpaired t-test was used for analysing the data.

RESULTS

Two groups with 30 women in each group were included in this study. 30 laparoscopically confirmed endometriosis subjects constituted case group while 30 patients without endometriosis over diagnostic laparoscopy constituted control group. The maximum incidence of endometriosis (46.66%) was in the age group 23-26 years. The mean age of endometriosis was 26.36±3.96 years. Among the controls, the most common age group was 27-30 years to which 33.33% women belonged. 86.66% of women with endometriosis were of Hindu religion and 13.33% were Muslim. This result was statistically significant(p=0.0390). 76.66% of women with endometriosis were from urban area whereas 46.66% of women without endometriosis belonged to rural area. The result was again statistically significant as p = 0.0325. Majority i.e. 83.33% of women with endometriosis and 80% controls were literate. 50% of women with endometriosis belonged to upper class. The result was significant as p=0.0445. 17 cases i.e. 56.66% were working women whereas 8 in control group were working. The result was statistically significant (p=0.0352). 90% of women in the endometriosis group and 86.66% women in the control group had normal body mass index (BMI).

Table 1. Description of the study population (n=60)

Characteristics	Endometriosis(n=30)	Control(n=30)	p-value
Age(in yrs)	26.36±3.96	27.86±4.74	0.335
Religion			0.0390
Hindu	26(86.66%)	18(60%)	
muslim	4(13.33%)	12(40%)	
Residence			0.0325
Rural	7(23.33%)	16(53.33%)	
Urban	23(76.66%)	14(46.66%)	
Literacy			1.0
Literate	25(83.33%)	24(80%)	
Illiterate	5(16.66%)	6(20%)	
Socioeconomic status			0.0445
Lower	7(23.33%)	6(20%)	
Middle	8(26.66%)	27(56.66%)	
Upper	15(50%)	7(23.33%)	
Occupation			0.0352
Homemaker	13(43.33%)	22(73.33%)	
Working women	17(56.66%)	8(26.66%)	
Body Mass Index	20.785±1.5842	21.8167±3.4907	<0.001
Age of menarche			0.000049
<13yrs	20(66.66%)	4(13.33%)	
≥13yrs	10(33.34%)	26(86.66%)	
Cycle length	27.80±4.40	32.53±9.29	<0.001
Parity			0.534
Nulliparous	23(82.14%)	22(73.33%)	
Multiparous	5(17.86%)	8(26.66%)	
Symptoms			
Dysmenorrhoea	22(73.33%)	2	<0.0001
Dyspareunia	6(22.22%)	Nil	0.008
Menorrhagia	11(36.66%)	3	0.030

Table 2. Distribution of endometriosis women and control group according to serum prolactin level

Prolactin (ng/ml)	Endometriosis (n=30)	Control (n=30)
5-20	1	12
21-35	19	18
36-50	6	Nil
51-65	2	Nil
66-80	2	Nil
mean±SD	34.30±13.81	12.30±4.95

p-value <0.001

Mean BMI was significantly lower in endometriosis women as compared to controls (20.785±1.5842 kg/m^2 endometriosis vs 21.8167±3.4907kg/m^2 controls ; p <0.001). 66.66% women in endometriosis group had menarche after 13 years of age and 86.66% women in control group had menarche after 13 years of age. Significant association was found between the age of menarche and endometriosis (p=0.000049). Mean cycle length in endometriosis was 27.80±4.40 days whereas that in controls was 32.53±9.29 days. The difference was significant statistically (p<0.001). No significant difference with respect to parity was found. Dysmenorrhoea, dyspareunia and menorrhagia were more commonly found in the cases as compared to control group. Dysmenorrhoea was the most common associated symptom seen in 73.33% of women with endometriosis. The mean value of serum prolactin in endometriosis was 34.30±13.81 vs 12.30±4.95 in control group. Association of hyperprolactinemia with endometriosis was statistically significant (p<0.001). 29 out of 30 cases had serum prolactin level >20ng/ml.

DISCUSSION

In this study, we investigated association of serum prolactin levels with presence or absence of endometriosis in patients admitted for diagnostic laparoscopy. Both the groups were matched in the socio-demographic profile. The mean age of endometriosis was 26.36±3.96 years. In a similar study by Esmaeilzadesh et al (2015)[13], mean of endometrioticwomen was slightly more 30.80±5.03 years. According to Speroff, the mean age at the time of diagnosis of endometriosis ranges between 25 and 35 years.[14] 86.66% of women in our study were hindu. Various studies have given variable results on association of endometriosis with ethnicity but data in inconclusive. Hence, further studies are required to investigate these observations. Significant difference was found between occurence of endometriosis in women belonging to urban areas as compared to rural areas(p value =0.0325). This was in accordance with a study by Atef M. Darwish et al(2014)[15]in which significant association was seen between women living in urban area with the occurrence of endometriosis(p=0.001). However, VH Eisenberg et al(2017)[16] concluded a non significant trend towards residence in central urban areas and endometriosis. 50% women having endometriosis belonged to higher socioeconomic status. This result was in accordance to the study conducted by VH Eisenberg et al (2017)[16] where majority(49.8%)subjects belonged to high socioeconomic strata. Present study had 17 cases (56.66%) belonging to working class. This was inconsistent with the results obtained in a study by M. Darwish et al (2004)[15] where 32.9% of endometriosis patients were working women whereas 37.3% of controls were working class.

In our study the mean BMI was significantly lower in endometriosis women as compared to the control group (20.785±1.5842kg/m^2 vs. 21.8167±3.4907 kg/m^2, p <0.001). This result was consistent with the study done by Hediger ML et al(2005)[17] where a higher current BMI was statistically protective for endometriosis. In another study by VH Eisenberg et al (2017)[16], the mean BMI was 24.1±6.4 kg/m^2, with more than 50% of patients having a normal BMI.

In present study, 66.66% women in endometriosis group had menarche before 13 years and significant association was found (p=0.000049). In a study by Missmer SA et al(2004)[18] similar findings were observed among women with an earlier age at menarche. The mean cycle length in endometriosis group in this study was 27.80±4.40 days and hence endometriosis was associated with a short cycle length. Missmer SA et al(2004)[18] observed a more modest effect of cycle length. They observed that an average menstrual cycle length of 25 or fewer days was associated with a 30% increase in risk of endometriosis as compared to a cycle length of 26-31 days. All three symptoms, dysmenorrhoea, dyspareunia and menorrhagia were more commonly found in cases as compared to the control group. Ashrafi M et al (2016)[19] found similar results that both dyspareunia and dysmenorrhoea were associated with endometriosis. In our study presence of hyperprolactinemia was significantly associated with endometriosis (p<0.001). The mean value of serum prolactin in endometriosis group was 34.30±13.81ng/ml vs 12.30±4.95 ng/ml in control group. Similar results were obtained in a study by Esmaeilzadesh et al(2015)[13], where the mean prolactin level in the endometriosis group was 23.02±1.25 ng /ml while in the controls was 17.21±1.22 ng/ml. In another study by A.P. Lima, M.D. Moura et al (2006)[20] found that serum prolactin levels were significantly higher in infertile women with endometriosis (2.8.9±2.1 ng/ml) than in women without endometriosis (13.2±2.1 ng/ml).

Conclusion

Endometriosis is a common gynecological problem in women with reproductive age around the globe. In the present study, hyperprolactinemia i.e. serum prolactin >20ng/ml was found to be associated with endometriosis. Hence serum prolactin levels should be estimated in all patients who are suspected of endometriosis. This biological marker can help us in early diagnosis of endometriosis in women and pin down the actual burden of the disease. Further studies are however required to know whether symptoms of endometriosis improve by decreasing serum prolactin levels.

Conflict of interest: None declared.

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Key Points

- Association of endometriosis with hyperprolactinemia is controversial.
- Hyperprolactinemia i.e. Serum prolactin level > 20 ng/ml was found to be associated with endometriosis.
- Serum Prolactin levels should be estimated in all the patients suspected of endometriosis. This might help in reducing the burden of this disease.

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