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Association of Serum Prolactin with Endometriosis

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Abstract

Background: *Endometriosis is a disease where tissue similar to the lining of the uterus grows outside the uterus, causing pain and/or infertility. The variable and broad symptoms of endometriosis make it difficult for healthcare workers to diagnose the disease in a timely manner, and many individuals suffering from it have limited awareness of the condition. Therefore, this study was conducted to determine the association of serum prolactin with endometriosis.*

Methods: *This was a case-control study among purposively selected women matched for age attending the outpatient department of Obstetrics and Gynaecology, Institute of Child and Mother Health, Matuail, Dhaka from January 2021 to December 2021. A total of 64 women between 15-49 years of age were included in this study and equally divided into two groups: 32 laparoscopically diagnosed endometriosis patients (cases) and 32 age-matched healthy women without endometriosis (controls).*

Results: *The distribution of infertile women was found significantly higher in endometriosis cases (40.6%) compared to that of the healthy controls (12.5%), p-value 0.011. The overall PRL level was found significantly higher among the endometriosis cases 20.24±9.09 ng/mL compared to the controls 11.72±5.95 ($p<0.001$). Considering PRL level of 20.0 as a cut-off value, odd's ratio calculation showed endometriosis was 6.94 times more likely in women with elevated PRL level of ≥20 ng/mL than those with < 20 ng/mL (OR=6.94; 95% CI=2.12-22.65, p-value=0.001).*

Conclusion: *Raised serum prolactin level was found associated with endometriosis.*

Keywords: *Endometriosis, PRL, Hyperprolactinemia, Infertility, Biomarker, Laparoscopy.*

1. INTRODUCTION

Endometriosis is one of the common gynecologic disorders that is classically defined by the presence of endometrial glands and stroma outside the uterine lining [1]. It triggers a persistent inflammatory response that can lead to the development of scar tissue, such as adhesions and fibrosis, in the pelvic region and other areas of the body.

Several lesion types have been described; superficial endometriosis found mainly on the pelvic peritoneum, cystic ovarian endometriosis

(endometrioma) found in the ovaries, deep endometriosis found in the recto-vaginal septum, bladder and bowel, and in rare cases, endometriosis has also been found outside the pelvis [2].

The true incidence or prevalence of endometriosis is difficult to establish due to the heterogeneity of the condition with significant variability in terms of presentation and progression [3]. The disease affects 10–15% of women of reproductive age, and has substantial impacts on the quality of life [4]. The Global Burden of Disease study suggests endometriosis was associated with 405 disability-adjusted life years (DALYs) per 1,000 women in 1990, increasing to 545 per 1,000 in 2010, representing a 35% increase over that 20 year period [5]. Endometriosis occurs in 6-10% of US women in the general population and approximately 4 per 1000 women are hospitalized with this condition each year [6]. The annual costs of endometriosis treatment in Europe range from €0.8 billion to €12.5 billion depending on the country and are comparable to other chronic diseases such as diabetes [5]. Roughly 26 million in India have endometriosis [7]. According to the Endometriosis Adenomyosis Society of Bangladesh (EASB), there are about 12 lac patients with endometriosis [8].

Endometriosis chiefly affects adult women, regardless of race or ethnicity or whether or not they have had children, and in less common cases, individuals may have had endometriosis symptoms before they even reach menarche [9]. Symptoms associated with endometriosis can vary widely from patient to patient. Some women experience no symptoms. Others experience numerous painful and several other symptoms that can lower the quality of life of women affected. The most common symptoms include dysmenorrhea, dyspareunia, chronic pelvic pain which is defined as more than 6 months of non-cyclic pain, abnormal uterine bleeding, and reduced fertility. Less common symptoms include chronic fatigue, painful bowel movements, painful urination, or pain in areas other than the pelvis, such as back, legs or shoulders. There are also numerous psychological symptoms, such as depression, that can be associated with endometriosis due to the heavy emotional burden of the disease [10].

According to American Society of Reproductive Medicine (ASRM), endometriosis can be categorized into four stages: stage I (minimal), stage II (mild), stage III (moderate), and stage IV (severe). More advanced stages may be deeply invasive and present as endometrioma. Nearly a third (32%) of the patients with endometriosis have moderate to severe disease, while 58% have minimal or mild endometriosis [11]. Hence, a variety of endometriosis risk factors have been reported including abnormal or heavy bleeding, cyclic gastrointestinal/urinary symptoms, dyschezia, dysmenorrhea, dyspareunia, dysuria, and pelvic pain. Increasing age, alcohol use, early menarche, family history of endometriosis, infertility, intercourse during menses, low body weight, prolonged menstrual flow, and short cycle interval are also alleged risk factors. Endometriosis has been negatively associated with exercise and smoking. Recently, red hair, blue or green eyes, and freckles have been reported to increase the odds of diagnosis [12].

2. Objective

The objective of this study was to determine the relationship of serum prolactin level with endometriosis.

3. Methodology & Materials

This hospital-based case-control study was conducted in the Department of Obstetrics and Gynecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, from January 2021 to December 2021. A total of 64 women aged 15–49 years were purposively selected and equally divided into two groups: 32 laparoscopically diagnosed endometriosis patients (cases) and 32 age-matched healthy women without endometriosis (controls). Women with thyroid disorders, polycystic ovarian syndrome, pituitary tumors, systemic diseases, epilepsy, or those taking medications affecting prolactin or hormonal therapy within the last six months were excluded. Data were collected using a pretested semi-structured questionnaire covering socio-demographic, clinical, and anthropometric variables. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) and categorized according to WHO guidelines. After obtaining written informed consent, 5 mL of venous blood was drawn aseptically from the antecubital vein 3–4 hours after awakening following an overnight fast. The serum was separated and analyzed for prolactin concentration using enzyme-linked fluorescent immunoassay (ELFA) technology on the VIDAS® analyzer. A serum prolactin level of ≥20.08 ng/mL was considered hyperprolactinemia. All procedures were performed following biosafety protocols and using personal protective equipment. Data

were analyzed using SPSS version 27.0. Descriptive statistics such as frequency, percentage, mean, and standard deviation were calculated. Differences in mean prolactin levels between the two groups were assessed using an independent sample t-test, and associations between serum prolactin and endometriosis were determined using the chi-square test. Odds ratios (OR) with 95% confidence intervals (CI) were estimated to measure the strength of association, and a p-value ≤0.05 was considered statistically significant.

Ethical clearance for the study was obtained from the Institutional Review Board of ICMH, Dhaka, and written informed consent was taken from all participants, ensuring confidentiality and the right to withdraw at any stage.

4. RESULTS

This case-control study was carried out to assess the association of serum prolactin status with endometriosis. Total 64 patients of 15-49 years of age attending the outpatient of Department of Obstetrics and Gynaecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka fulfilling the selection criteria were enrolled for this study.

Among them, 32 diagnosed women with endometriosis were included as the cases, and other 32 healthy women without endometriosis were included as the controls.

They were evaluated for their serum prolactin levels. Findings of the study are presented by tables.

Table 1. *Categorization of the respondents according to their socio-demographic characteristics by group (cases = 32, controls = 32)*

Sociodemographic characteristics	Case n (%)	Control n (%)	*P*-value
Age (in years)			
15 - 20 years	7 (21.9)	7 (21.9)	0.191[a]
21 – 30 years	5 (15.6)	11 (34.4)	
> 30 years	20 (62.5)	14 (43.8)	
Mean ± SD	32.09 ± 9.67	28.69 ± 7.73	0.125[b]
Marital status			
Unmarried	5 (15.6)	7 (21.9)	0.809[c]
Married	25 (78.1)	24 (75.0)	
Widow/separated	2 (6.3)	1 (3.1)	
Educational qualification			
Illiterate	11 (34.4)	9 (28.1)	0.857[a]
Up to JSC	15 (46.9)	16 (50.0)	
SSC and above	6 (18.8)	7 (21.9)	
Occupation			
Student	5 (15.6)	2 (6.2)	0.571[c]
Housewife	23 (71.9)	26 (81.3)	
Self-employed/service holder	4 (12.5)	4 (12.5)	
Socio-economic status			
Lower class	12 (37.5)	11 (34.4)	0.380[a]
Lower middle class	17 (53.1)	14 (43.8)	
Upper middle class	3 (9.4)	7 (21.9)	

[a] *Chi-square test was done to measure the level of significance.*

[b] *Unpaired t-test was done to measure the level of significance*

[c] *Fisher's Exact test was done to measure the level of significance.*

The figure within parentheses indicates in percentage.

Case: Women with endometriosis

Control: Women without endometriosis

Table 1 illustrates the mean (±SD) age of the cases was slight higher than the control group of respondents, but the difference was statistically not significant (p=0.125).

The distribution of the respondents according to educational qualification, occupation, and socioeconomic status between the case and control groups were statistically not significant (p>0.05).

Table 2. *Categorization of the respondents according to their menstrual characteristics by group (cases = 32, controls = 32)*

Menstrual characteristics	Case *n* (%)	Control *n* (%)	*P*-value
Age at menarche (in years)			
Mean ± SD	12.59 ± 0.665	12.50 ± 0.672	0.561[b]
Menstrual cycle length (in days)			
< 28 days	25 (78.1)	18 (56.3)	0.062[a]
≥ 28 days	7 (21.9)	14 (43.8)	
Menstrual phase length (in days)			
< 4 days	0 (0.0)	1 (3.1)	0.148[c]
4-6 days	25 (78.1)	29 (90.6)	
> 6 days	7 (21.9)	2 (6.3)	
Menstrual flow			
Light	3 (9.4)	4 (12.5)	0.660[c]
Normal/average	17 (53.1)	20 (62.5)	
Heavy	12 (37.5)	8 (25.0)	

[a] *Chi-square test was done to measure the level of significance.*

[b] *Unpaired t-test was done to measure the level of significance*

[c] *Fisher's Exact test was done to measure the level of significance.*

The figure within parentheses indicates in percentage.

Case: Women with endometriosis

Control: Women without endometriosis

According to Table 2 there was no statistically significant difference in the distribution of the respondents according to menstrual characteristics (p>0.05).

Table 3. *Distribution of the endometriosis patients according to their presence of symptoms (case = 32)*

Presenting complaints (symptoms)	Frequency (*n*)	Percentage (%)
Dysmenorrhea	23	71.88
Chronic pelvic pain	15	46.87
Deep dyspareunia	12	37.50
Premenstrual spotting	4	12.50

Table 3 shows, among the endometriosis cases dysmenorrhea was present in 71.88%, and chronic pelvic pain in 46.87%. Deep dyspareunia and premenstrual spotting were complained by 37.5%, and 12.5% of patients, respectively.

Table 4. *Categorization of the respondents according to the history of infertility by group (cases = 32, controls = 32)*

Characteristics	Case *n* (%)	Control *n* (%)	*P*-value
H/O- infertility			
Yes	13 (40.6)	4 (12.5)	0.011[a]
No	19 (59.4)	28 (87.5)	

[a] *Chi-square test was done to measure the level of significance.*

The figure within parentheses indicates in percentage.

Case: Women with endometriosis

Control: Women without endometriosis

There was a statistically significant difference in the distribution of the respondents according to their infertility history (p=0.011) (Table 4).

Table 5. *Categorization of the respondents according to the use of oral contraceptives by group (cases = 32, controls = 32)*

Characteristics	Case *n* (%)	Control *n* (%)	*P*-value
H/O- taking OCP (≥5 years)			
Yes	4 (12.5)	1 (3.1)	0.355[c]
No	28 (87.5)	32 (100.0)	

[c] *Fisher's Exact test was done to measure the level of significance.*

The figure within parentheses indicates in percentage.

Case: Women with endometriosis

Control: Women without endometriosis

There was no statistically significant difference in the distribution of the respondents according to the use of oral contraceptives for 5 years and more (p>0.05) (Table 5).

Table 6. *Categorization of the respondents according to the body mass index by group (cases = 32, controls = 32)*

Characteristics	Case *n* (%)	Control *n* (%)	*P*-value
BMI			
Underweight (<18.5)	3 (9.4)	1 (3.1)	0.325[c]
Normal (18.5-24.9)	16 (50.0)	22 (68.8)	
Overweight (25.0-29.9)	13 (40.6)	9 (28.1)	
Mean ± SD	24.05 ± 2.61	24.11 ± 1.93	0.909[b]

[b] *Unpaired t-test was done to measure the level of significance*

[c] *Fisher's Exact test was done to measure the level of significance.*

The figure within parentheses indicates in percentage.

Case: Women with endometriosis

Control: Women without endometriosis

Table 6 illustrates, the categorization of respondents according to body mass index. Between the cases and control group there was no statistically significant difference both in respect of distribution and mean (±SD), p-value > 0.05.

Table 7. *Distribution of mean (±SD) serum prolactin level by group (cases = 32, controls = 32)*

Serum prolactin level (ng/mL)	Case Mean ± SD	Control Mean ± SD	*P*-value
Mean ± SD	20.24 ± 9.09	11.72 ± 5.95	<0.001[b]

[b] *Unpaired t-test was done to measure the level of significance*

Case: Women with endometriosis

Control: Women without endometriosis

Patients with endometriosis had significantly higher level (20.24±9.09 ng/mL) of serum prolactin compared to control group (11.72±5.95 ng/mL) (Table 7).

Table 8. *Odds ratios (OR) and 95% confidence intervals (CI) for endometriosis according to serum prolactin levels in women (case = 32, control = 32)*

Serum prolactin level (ng/mL)	Case *n* (%)	Control *n* (%)	p-value	Odds Ratio	95% CI (lower-upper)
≥ 20	18 (56.3)	5 (15.6)	0.001[a]	6.94	2.12 – 22.65
< 20	14 (43.8)	27 (84.4)			

[a]*Chi-square test was done to measure the level of significance.*

The figure within parenthesis indicates in percentage.

Case: Women with endometriosis

Control: Women without endometriosis

The respondents with serum prolactin level ≥ 20 ng/mL had 6.94 times more chance to develop endometriosis compared to those of the participants with prolactin level <20 ng/mL (p=0.001; OR=6.94; 95% CI=2.12-22.64) (Table 8).

5. Discussion

This case-control study was carried out with the aim to evaluate any association of serum prolactin with endometriosis. A total of 64 women matched for age (15-49 years), attending outpatient Department of Obstetrics and Gynecology, Institute of Maternal and Child Health (ICMH), Dhaka, Bangladesh was included in this study. Among them, 32 diagnosed cases of endometriosis were considered as cases and the rest 32 (without endometriosis) were considered as controls.

In this present study, above three-fifths (62.5%) of the cases were > 30 years of age, in comparison to controls 43.8% above 30 years of age.

The mean (±SD) age of the cases were found also higher (32.09±9.67 years) compared to that in control women (28.69±7.73 years), which was found statistically not significant (p>0.05). Treloar et al., also had demonstrated that the mean age of the moderate-to-severe cases were

36.4±7.1 years and among the controls were 36.3±7.6 which was statistically not significant (p=0.61) [13].

In this study majority of the participants in both cases and controls groups were married (cases: 78.1% vs. controls: 75.0%) and 46.9% cases and half (50.0%) of the control group of respondents had completed Junior School Certificate (JSC) which was dissimilar with a study that reported, the majority of the patients of both case-control groups have completed college education and this dissimilarity might be due to geographical variation and small sample size [14]. Above half (53.1%) of the endometriosis case belonged from lower-middle-class families in comparison to 43.8% of the control group participants. Only 9.4% of the cases and 21.9% respondents in the control groups were from upper-middle-class families. All these findings in the study were found statistically non-significant. Bano et al., in their study demonstrated that the majority of the patients belonged to the lower middle class of socioeconomic status (23 cases = 38.3%) which is followed by patients belonging to the upper-middle-class (22 cases = 36.7%) [15]. These findings were in accordance to the current study.

Positive history of infertility was higher in cases (40.6%) compared to that in control (12.5%) group which was statistically significant (p=0.01). In a similar study De Ziegler et al. reported, endometriosis and infertility are associated clinically which supports the finding of present study [16].

Among cases (12.5%) and among controls only (3.1%) had positive history of taking OCP for ≥5 years, which was not statistically significant (p=0.355). A study observed OCP might have a protective effect against endometriosis [17]. This dissimilarity was probably due to small sample size and different selection criteria of the present study.

In regards of clinical presentations of endometriosis in this study majority had dysmenorrhea (71.88%), followed by chronic pelvic pain in 46.87%, deep dyspareunia in 37.5%, and premenstrual spotting in 12.5% of patients. Similar findings were observed in a study conducted by Esmaeilzadeh et al [14].

Regarding patients' mean body mass index, the present study observed no statistical significant difference between case and control groups (p>0.05), and mean BMI was almost similar both in case (24.05±2.61 kg/m2) and controls (24.11±1.93 kg/m2) groups. A study on BMI in China, also concluded that no association between BMI and the incidence of endometriosis, but there was a significant increase in the incidence of endometriosis in obese women, compared with women with normal weight [18].

In the present study, the mean (±SD) serum Prolactin level in patients with endometriosis was higher 20.24±9.09 ng/mL compared to that in patients without endometriosis 11.72±5.95 ng/mL which was statistically highly significant (p≤0.001). In a study Mirabi et al., observed that prolactin level was higher in woman with endometriosis when compared to women without endometriosis. Prolactin levels act as a probable prognostic biomarker to detect endometriosis stage which supports the findings of present study [11].

In this study majority among cases (56.3%) had serum prolactin level ≥ 20.08 ng/ml compared to that in control group (15.6%). Patients with serum prolactin level ≥ 20.08 ng/ml had 6.94 times more chance to develop endometriosis compared to that in patients with serum prolactin level <20.08 ng/ml which was statistically significant (p-0.001; OR=6.94; 95% CI=2.12-22.64). Almost similar finding was observed in a study conducted by Mirabi et al who demonstrated that, with a serum prolactin level ≥ 20.08 ng/ml had more chance to develop endometriosis [11].

In current study, all the findings had given rise to concerns about higher serum prolactin level status among the women with endometriosis. So, screening for serum prolactin level might be considered as a part of routine check-up for woman.

6. Limitations Of The Study

This study had several limitations. It was conducted in a single tertiary care hospital with a relatively small sample size and a short study duration, which may limit the external validity of the findings. The sampling was purposive rather than random, potentially introducing selection bias.

Moreover, there is no established consensus on the cut-off value for serum prolactin levels in patients with endometriosis, which may affect the interpretation of results. Additionally, only one neurohormonal marker—serum prolactin—was evaluated, without consideration of other related

hormonal or inflammatory parameters. Therefore, the findings of this study should be interpreted with caution and cannot be generalized to the broader population.

7. Recommendations

In light of the findings and discussion of the present study, the following recommendations are proposed: Future studies should be conducted on a larger scale across multiple centers and over an extended duration to enhance the validity and generalizability of the results. Random sampling techniques should be employed to minimize selection bias and ensure a more representative sample. Additionally, longitudinal follow-up studies are recommended to evaluate whether elevated serum prolactin levels observed in endometriosis patients have a contributory role in reproductive dysfunction and infertility.

8. Conclusion

The study concluded that raised serum prolactin (PRL) level is significantly associated with endometriosis. Infertility is a common presentation of the women with endometriosis. Therefore, this study concludes that high level of serum prolactin can be considered as a risk factor for the development of endometriosis.

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Conflicts of interest

There are no conflicts of interest.

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