Migraine among women with endometriosis: a hospital-based case-control study in Bangladesh

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BACKGROUND: Endometriosis is a disease among women of reproductive age, which causes several health problems, such as dysmenorrhea, dyspareunia, and subfertility. In addition, it increases psychological stress and often results in marital disharmony. Similarly, migraine is more frequent among this group of women. Several studies have shown an association between endometriosis and migraine among groups of populations completely different from Bangladesh.

OBJECTIVE: This study aimed to identify the association between endometriosis and migraine among the Bangladeshi population.

STUDY DESIGN: This nonrandomized case-control study was conducted with cases of endometriosis and controls without endometriosis who were confirmed by laparoscopy or laparotomy. Among the study participants, cases of migraine in 1 group of respondents who were already diagnosed as patients of migraine were identified, and the others with complaints of headaches were further confirmed by a medicine specialist. Patients were recruited from the Department of Obstetrics and Gynecology at the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders General Hospital and Ibrahim Medical College. The study was approved by the ethical review committee of the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders General Hospital. Multivariate logistic regression was used to identify the association between endometriosis and migraine using odds ratios and 95% confidence intervals.

RESULTS: Of 1496 patients who underwent laparoscopy or laparotomy during the study period, the frequency of endometriosis was found to be 12.7%. A total of 190 patients with confirmed endometriosis cases and an equal number of controls without endometriosis were enrolled, maintaining the age distribution of the controls similar to that of the cases. Compared with controls, the distribution of age, body mass index, education, and marital status of the patients with endometriosis were similar. The average ages of respondents were 30.6 years in both the case and control groups. Regarding occupation, cases included more students than controls (12% vs 0%, respectively). The odds of suffering from dysmenorrhea and dyspareunia among the cases were 3.3 (95% confidence interval, 2.66–4.15; $P<.001$) and 9.5 (95% confidence interval, 5.3–17.9; $P<.001$) times higher than that of controls, respectively. In addition, the odds of menstrual irregularity was 60% lower among the cases than among controls (odds ratio, 0.4; 95% confidence interval, 0.24–0.64; $P<.001$). No significant difference was observed in having primary subfertility and secondary subfertility among the 2 groups of respondents. Univariate regression analysis showed that patients with endometriosis have 6.13 times higher odds (95% confidence interval, 2.50–18.40; $P<.001$) of having a migraine and 2.00 times higher odds (95% confidence interval, 1.2–3.2; $P=.01$) of having a headache than controls. Furthermore, the age- and body mass index–adjusted multivariate model showed that patients with endometriosis have 5.4 times higher odds of having migraine than patients without endometriosis (95% confidence interval, 2.11–16.4; $P<.001$). In addition, the higher the age of reproductive-age women, the higher the odds of having migraine. A 1-year increase in age increases the odds of having migraine by 23% (odds ratio, 1.23; 95% confidence interval, 1.13–1.16; $P<.001$).

CONCLUSION: Our results support the association between endometriosis and migraine among the Bangladeshi population, which is similar to relevant studies conducted in other geographic locations. The groups of physicians who treat patients suffering from the 2 diseases, endometriosis and migraine, should keep this interrelationship in mind to ensure a better quality of life for the patient.

Key words: Bangladesh, dysmenorrhea, dyspareunia, endometriosis, migraine

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Why was this study conducted?

Endometriosis and migraine are both chronic diseases that affect reproductive-age women. This hospital-based case-control study was conducted to understand the association between endometriosis and migraine among the Bangladeshi population.

Key findings

Patients with endometriosis were more likely to suffer from migraine than patients without endometriosis. Furthermore, with advancing age, the likelihood of experiencing migraines tended to rise among women of reproductive age. Dysmenorrhea and dyspareunia were significantly higher among the women with endometriosis.

What does this add to what is known?

The frequency of endometriosis was 12.7% among the women of reproductive age who underwent laparoscopy or laparotomy during the study period. A strong association between endometriosis and migraine was observed in this study among the participants. The physicians who treat patients with endometriosis and migraine should keep this interrelationship in mind to ensure a better quality of life for the patient.

Introduction

Endometriosis is a benign gynecologic disorder among women of reproductive age, characterized by the existence of viable and functioning extrauterine endometrial tissue. During menstruation, endometrial tissue located outside the uterus bleeds cyclically, leading to tissue reactions in the surrounding areas resulting in fibrosis and extensive adhesions.[1,2] Patients with endometriosis usually present with complaints of pelvic pain, dysmenorrhea, dyspareunia, and subfertility.[2]

It is difficult to predict the precise prevalence of endometriosis, and invasive procedures, such as laparotomy or laparoscopy, are required for confirmatory diagnosis. Current research indicates that endometriosis affects 6% to 10% of women in their reproductive years.[3] In addition, 50% to 60% of women and teenage girls who had complaints of pelvic pain and 50% of women with subfertility were found to have endometriosis.[3] Endometriosis with dyspareunia, pelvic pain, subfertility, and persistent poor health conditions eventually result in psychological stress and discomfort for both male and female partners and marital disharmony.[4,5] Simultaneously, the disease adds a huge economic burden with substantial costs for its confirmatory diagnosis and management of complications.[6]

Migraine, a chronic neurologic disorder, predominantly occurs in women of reproductive age.[7] Patients with migraine generally present with recurrent and moderate to severe headaches, which are often connected with several autonomic nervous system symptoms, such as nausea, vomiting, photophobia, and phonophobia.[8] Although migraine and endometriosis involve different organs of women's bodies, they share many common features in epidemiology, pathogenesis, and physical or psychiatric comorbidities.[9–13] Nyholt et al[14] recommended that there might be similar genetic influences that affect the comorbid relationship between the 2 diseases. In support of the genetic correlation between the 2 distant morbidities, relevant research showed early menarche as a leading common risk factor for endometriosis and migraine.[14–16] Another population-based study conducted by Yang et al[7] identified a 1.7 times higher migraine in women with endometriosis than in those without the disease. In addition, several other studies found higher rates of migraine among women with endometriosis,[17–19] although research conducted by Karp et al[20] in 2011 showed no association between 2 painful disorders of reproductive-age women.

In addition, endometriosis is a common health problem among women of reproductive age in Bangladesh, similar to other geographic locations. According to the Endometriosis and Adenomyosis Society of Bangladesh, there are 1.2 million patients with endometriosis in Bangladesh.[21] In addition, a study conducted among university students identified that 29% of their female respondents had migraine.[22] To date, no study has been conducted in Bangladesh and neighboring South Asian countries to understand the association between these 2 common diseases, endometriosis and migraine, for which women are suffering at their prime age. With this background, this study was conducted to identify the association of endometriosis with migraine among the Bangladeshi female population of reproductive age.

Materials and Methods

Study site and design

The Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital and Ibrahim Medical College is a 650-bed multidisciplinary tertiary care facility that treats approximately 3000 patients per day in the outpatient department. The Department of Obstetrics and Gynecology has 4 units to serve patients with reproductive health-related complications. This nonrandomized case-control study was conducted under unit 2 over 30 months from October 2016 to March 2019. Interviews of the respondents were conducted using a semistructured questionnaire, and perioperative findings were entered in a datasheet attached to the interview questionnaire.

Ethical considerations

The study was approved by the ethical review committee of the Diabetic

Association of Bangladesh (reference number: BADAS-ERC/EC/13/0073). Written informed consent was taken from each of the respondents with a prior explanation of the aim and purpose of the research. Confidentiality and anonymity were assured and maintained. The respondents remained entirely free to withdraw their participation at any stage or at any time during the interview and clinical examination.

Sample size

A study conducted in Taiwan showed that patients with endometriosis were more likely to suffer from migraine headaches than controls, with an odds ratio (OR) of 1.7, and that the age-adjusted prevalence of migraine was mentioned to be 8% among men and 26% among women.[7]

Here, we assumed to have the same level of OR and migraine prevalence among Bangladeshi women of reproductive age who have been suffering from endometriosis and migraine. Using the following formula to calculate the sample size, a sample size of 440 (220 per group) would allow us to detect the OR within 25% of the true value, which is believed to be approximately 1.7 with a 95% confidence interval (CI).

$$n = \frac{Z_{\alpha}^{2}\left(\frac{1}{P_1(1-P_1)} + \frac{1}{P_2(1-P_2)}\right)}{[Log(1-\epsilon)]^{2}}$$

Where $Z_{\alpha} = 1.96$, OR = 1.7, $P_2 = 0.26$ (26%), $\epsilon = 0.25(25\%)$, $P_1 = 0.37(37\%)$, and Log $(1-\varepsilon) = -0.288$.

P_1 was calculated from the following formula:

$$P_1 = \frac{OR \times P_2}{1 + P_2(OR - 1)}$$

It has been observed that unit 2 of the Department of Obstetrics and Gynecology at BIRDEM General Hospital receives a monthly average of 9 potential patients with endometriosis, ranging from 8 to 13. With a planned data collection period of 30 months, the study could enroll a max of 390 participants. During this period, the study may enroll up to 195 participants per arm during the data collection period, which will provide a deviation of 1% in precision from our assumed precision of ϵ. However, the study was able to enroll 190 eligible and evaluable participants per group by the study timeline.

Selection of cases and control

Cases were women with endometriosis, and controls were the women without endometriosis. Both cases and controls were enrolled from the pool of patients undergoing laparoscopy or laparotomy because of different reproductive health-related complaints on Sunday and Wednesday, the scheduled days of routine operation for unit 2. For enrollment of cases and controls in the study, the following inclusion and exclusion criteria were used:

- Inclusion criteria: All female patients, aged between 18 and 49 years, who underwent laparoscopy or laparotomy (routine operative cases) under unit 2 of the Department of Obstetrics and Gynecology at BIRDEM General Hospital.
- Exclusion criteria: The study did not include women below the age of 18 years who were undergoing laparoscopy or laparotomy, as they were not eligible to give consent. In addition, patients with medical disorders, such as a known case of heart disease, psychological disorder, hyperprolactinemia, history of recent head injury, history of recent operation at the head-neck region (tonsillectomy, mastoidectomy, thyroidectomy, etc.), and known case of reproductive tract (cervix, uterus, fallopian tube, and ovary) cancers, and patients who required emergency laparoscopy or laparotomy (ectopic, rupture ectopic, twisted ovarian cyst, etc.) were excluded from the study.

We requested all eligible patients, according to the inclusion and exclusion criteria, who were diagnosed with endometriosis through laparoscopy or laparotomy to participate in the study. After receiving informed written consent, they were enrolled as cases in the study. An equal number of patients without endometriosis of similar ages who underwent the same procedures were asked to participate in the study as controls, and informed written consents were taken accordingly. The procedure for selecting cases and controls is shown in the Figure.

Identification of migraine

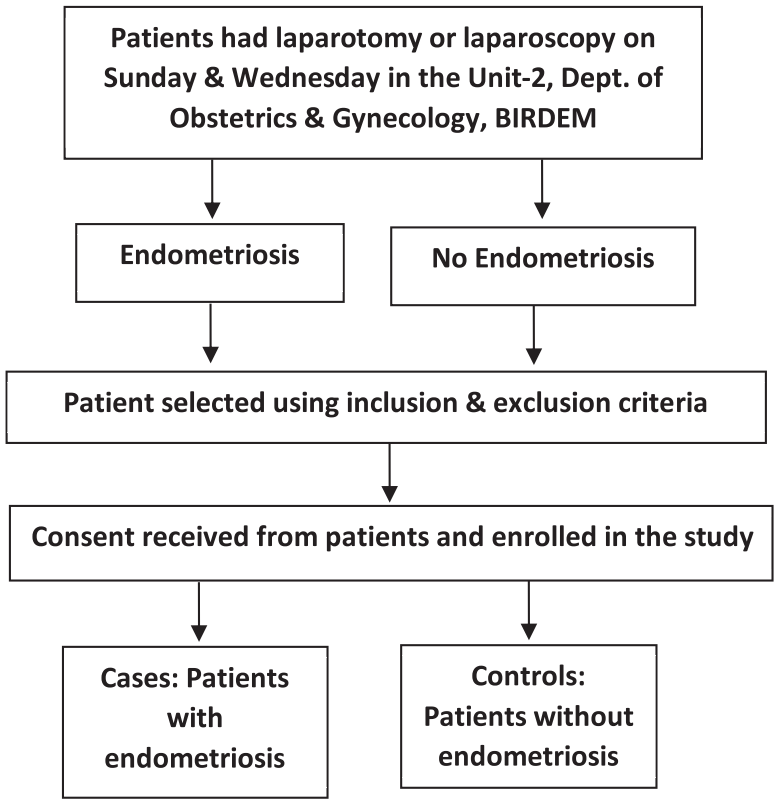
The evaluation of migraine was performed in both cases and controls on the 15th postoperative day during the follow-up visit. There were 2 groups of patients. One group was already diagnosed with a case of migraine by medicine or neuromedicine specialists and was receiving treatment. The other group was the respondents who had a history of 2 or more episodes of headache during the past 3 months before laparotomy or laparoscopy. This group had in-depth interviews using a structured questionnaire prepared for the diagnosis of migraine by the Committee for Headache Education of American Headache Society in tabulated form to differentiate migraine from tension headache.[8] Next, they were referred to a medicine specialist for a confirmatory diagnosis of migraine.

Bias control

The study was planned to be randomized; however, because of the study setup and infrastructure, the randomization was compromised. We confronted selection bias in our study. We had 2 predefined enrollment dates; Sunday and Wednesday for unit 2 of the Department of Obstetrics and Gynecology at BIRDEM General Hospital. On those days, the patients who visited the unit and were confirmed as endometriosis cases were primarily selected and offered to participate in the study. With this enrollment plan, we ensured that laparoscopy- or laparotomy-confirmed endometriosis cases who visited the BIRDEM General Hospital were equally likely to get selected in our study.

We have limited information on possible sources of confounding and other sources of bias regarding the association between endometriosis and migraine from the published literature. We

FIGURE
Flow diagram of the case and control selection process



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followed the standard case-control study patient selection procedure and strictly evaluated the inclusion-exclusion criteria so that cases and controls are comparable. Except for the age variable, we do not have enough data to identify a demographic or clinical variable as a confounder for the association between endometriosis and migraine. To limit the confounding bias because of age, we tried to keep the age distribution of the controls similar to that of cases enrolled in the study. In addition, we evaluated the effect of different demographic and clinical variables to be associated with endometriosis and migraine.

Statistical analysis

The data were entered, processed, and validated using IBM SPSS Statistics for Windows (version 25; IBM, Armonk, NY). We performed an exploratory data analysis for demographics and clinical characteristics using descriptive statistics. For descriptive statistics, we reported mean and standard deviation and median and interquartile range for continuous variables and number and percentage for categorical variables. In addition, we performed z tests to test whether the difference in proportions between different groups of patients with endometriosis in our study was due to chance.

We performed univariate analysis for the associations between endometriosis and migraine with the possible independent factors, such as headache, tension headache, age, and body mass index (BMI), individually using univariate logistic regression and reported the ORs, P values, and 95% CIs. In the multiple logistic regression model, we used migraine as the dependent variable and endometriosis, age, and BMI as independent variables. We have included age and BMI in the multiple logistic regression model as covariates to adjust for those possible confounding biases because of age and BMI. In all statistical tests, a P value of $<.05$ was considered significant. Statistical analysis was performed using R (version 4.2.2; R Core Team, Vienna, Austria)[23] and IBM SPSS (IBM, Armonk, NY).

Results

A total of 1496 patients of reproductive age (15−49 years) underwent laparoscopy or laparotomy at unit 2 of the Department of Obstetrics and Gynecology to seek treatment of different gynecologic problems. Among them, 190 patients (12.7%) were found to have endometriosis, and all patients gave consent to take part in the study, of which 168 were identified through laparoscopy and 22 were identified during laparotomy. Another 190 controls of similar age were selected from the same patient pool who were confirmed negative for endometriosis.

Sociodemographic characteristics of the respondents

In terms of demographic characteristics, patients in the case and control groups were comparable. The distributions of age at visit, BMI, education, occupation, and marital status of the patients with endometriosis were similar to that of patients in the control group with a few exceptions. In the occupation category, cases included more students than controls (12% vs 0%, respectively). The average age of respondents in cases with endometriosis and the control group was 30.6 years, with the ranges of 19 to 42 years for cases and 20 to 42 years for controls. The respondents were mostly housewives representing 64.7% (123) of the cases and 73.2% (139) of the control group. Only 22.6% (43) of the cases and 26.8% (51) of the controls were gainfully employed. The respondents who were engaged in income-generating activities were teachers, physicians, nurses, nongovernmental organization workers, and other service holders. Regarding marital status, 154 patients (81.1%) were married in the case group, whereas 185 patients (97.4%) were married in the control group. The socioeconomic conditions of all responders were nearly similar and represented the

TABLE 1
Sociodemographic and basic health characteristics of the respondents

Characteristics	Cases with endometriosis (n=190)	Controls (n=190)
Age (y)		
Mean (SD)	30.7 (6.04)	30.7 (4.25)
Median (IQR)	32.0 (19.0−42.0)	30.0 (20.0−42.0)
BMI		
Mean (SD)	22.9 (3.32)	23.2 (3.46)
Median (IQR)	23.0 (17.8−31.4)	23.0 (17.2−32.3)
Years of education		
Mean (SD)	13.0 (2.94)	13.2 (2.88)
Median (IQR)	14.0 (5.00−20.0)	14.0 (5.00−18.0)
Occupation		
Housewife	123 (64.7)	139 (73.2)
Employed	43 (22.6)	51 (26.8)
Students	24 (12.6)	0 (0)
Marital status		
Married	154 (81.1)	185 (97.4)
Unmarried	36 (18.9)	5 (2.6)

BMI, body mass index; *IQR*, interquartile range; *SD*, standard deviation.

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middle-class or upper middle−class group; hence, no stratum of socioeconomic status was performed during analysis. The characteristics of the cases and controls are summarized in Table 1.

Associated concurrent reproductive health complaints of the respondents

The other common reproductive health concerns stated by the respondents, in both case and control groups, were dysmenorrhea, dyspareunia, menstrual irregularities, subfertility, spontaneous abortion, and lower abdominal pain.

Dysmenorrhea was reported by 82 patients (43.1%) with endometriosis and only 10 patients (5.3%) without endometriosis. The odds of suffering from dysmenorrhea among patients in the case group was 3.3 times higher than that of patients in the control group (95% CI, 2.66−4.15; $P<.001$).

The history of dyspareunia was investigated only among the married respondents, as premarital sex is culturally unacceptable and embarrassing to the respondents. Dyspareunia was experienced by 73 patients (47.4%) who were married in the case group and only 16 patients (8.6%) who were married in the control group. The odds of developing dyspareunia among patients with endometriosis was 9.5 times higher than that of controls (95% CI, 5.3−17.9; $P<.001$).

The odds of menstrual irregularity was 60% lower among the case group than among the control group (OR, 0.4; 95% CI, 0.24−0.64; $P<.001$), wherein 64 respondents (33.7%) in the control group and 32 respondents (16.8%) in the case group had menstrual cycle irregularity.

Primary subfertility (when a person has never achieved pregnancy) was reported by 108 respondents (56.8%) in the case group and 118 respondents (62.1%) in the control group, whereas secondary subfertility (when a person has achieved at least one pregnancy) was reported by 20 respondents (21.1%) in the case group and 23 respondents (24.2%) in the control group. However, no significant difference was observed in having primary subfertility and secondary subfertility among the 2 groups of respondents. The reproductive health reports are shown in Table 2.

Association of migraine with endometriosis

Of note, 53 patients with endometriosis reported headaches, of which 27 (14.2%) were confirmed to have migraine. Among these cases with both endometriosis and headache, 19 patients were previously identified as cases of migraine by neurologists or medicine specialists, whereas 8 cases of migraine were identified during the study. Among patients in the control group, 32 (18.9%) reported headache, and only 5 (2.6%) were found to have migraine. Among the 5 mentioned migraine patients in the control group, 2 patients were identified as cases of migraine during the study, while 3 patients had previously consulted a medical specialist and were diagnosed with migraine. All previously identified patients with migraine reported taking prescribed medications.

Independently, patients with endometriosis have 6.13 times higher odds (95% CI, 2.5−18.4; $P<.001$) of having migraine and 2.00 times higher odds (95% CI, 1.2−3.2; $P=.01$) of having headache than controls. In contrast, from the multivariate model, for any age or BMI, patients with endometriosis have 5.4 times higher odds of having migraine than controls (95% CI, 2.11−16.4; $P<.001$) (Table 3). In addition, the likelihood of experiencing migraines increases with the age of women in their reproductive years. A 1-year increase in age increases the odds of having a migraine by 23% (OR, 1.23; 95% CI, 1.13−1.16; $P\leq.001$). Migraine or endometriosis was not associated with BMI.

Comment

Principal findings

The frequency of endometriosis was found to be 12.7% among reproductive-age women who had laparoscopy or laparotomy for different gynecologic disorders. The sociodemographic characteristics of both the case and control groups were similar to the Bangladeshi population in general. As expected,

TABLE 2
Reproductive health complaints of patients in the case and control groups

Characteristics	Cases with endometriosis (n=190)	Controls (n=190)	OR (*P* value)
Dysmenorrhea			
Present	82 (43.1)	10 (5.3)	3.3 (<.001)
Absent	108 (56.8)	180 (94.7)	
Dyspareunia			
Present	73 (47.4)	16 (8.6)	9.5 (<.001)
Absent	81 (52.6)	169 (91.4)	
Menstrual irregularity			
Present	32 (16.8)	64 (33.7)	0.4 (<.001)
Absent	158 (83.2)	126 (66.3)	
Subfertility			
Primary subfertility	108 (56.8)	118 (62.1)	0.95 (.840)
Secondary subfertility	40 (21.1)	46 (24.2)	
Not applicable	42 (22.1)	26 (13.7)	

OR, odds ratio.

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reproductive health problems, such as dyspareunia and dysmenorrhea, were significantly higher among the reproductive-age women with endometriosis (OR: 3.3 [95% CI, 2.66−4.15; *P*<.001] and 9.5 [95% CI, 5.3−17.9; *P*<.001], respectively). Age- and BMI-adjusted multivariate analysis showed that patients with endometriosis have 5.4 times higher odds of having migraine than controls. An increase in age increases the likelihood of having migraine by 23% (OR, 1.23; 95% CI, 1.13−1.16; *P*≤.001).

Results in the context of what is known

During the study period, among 1496 patients of reproductive age who underwent laparoscopy or laparotomy, 190 (12.7%) were found to have endometriosis. Using a 1-sample proportion test (*z* test), no significant difference was detected between the estimated frequency of endometriosis (6%−10% among the general population)[2,3,7] and the observed frequency of endometriosis (12.7%) (z score, 4.486; *P*>.05) in our study population. A hospital-based study among women with subfertility, in Pakistan, reported endometriosis rates to be 16.8%.[24] Hence, the estimated rates of endometriosis among the hospitalized patients and in the general population were comparable.

Although the data were collected from a tertiary care hospital in the capital of Bangladesh, where respondents were mostly from the middle-class and upper middle−class groups of society, the participants were mostly found to be housewives. Only 22.6% of patients with endometriosis and 26.8% of patients in the control group were gainfully employed. This scenario showed poor participation of females in income-generating activities in Bangladesh.[25]

Dysmenorrhea is one of the common complaints and an important cause of absence in school and other activities among young women. Research shows that 20% to 40% of reports of missed school are due to dysmenorrhea and that 40% of students report a negative effect on school performance and concentration because of dysmenorrhea.[26] Endometriosis being a common cause of secondary dysmenorrhea has a major negative effect on women's daily life and activities. According to the "*Textbook of Gynecology*" by D.C. Datta, approximately 70% of patients with endometriosis suffer from dysmenorrhea.[1] Here, we found that 82% of our study participants with endometriosis complained of dysmenorrhea. Although sexual intimacy is a fundamental aspect of a couple's life, painful coitus, such as deep dyspareunia, has a major negative effect on both partners, which may even result in marital disharmony. A study that tried to identify the effect of endometriosis-associated dyspareunia on women's lives found that 78% of their respondents avoided sex because of deep dyspareunia.[27] In another cross-sectional survey, Ferrero et al[28] identified that women with endometriosis experienced higher rates of deep dyspareunia than controls (60.6% vs 34.9%, respectively). Here, we also found that 46% of patients with endometriosis had deep dyspareunia, whereas only 8% of patients in the control group informed the same. Another study conducted by Fauconnier et al[29] showed that deep dyspareunia was associated with endometriotic lesions in the uterosacral ligaments.

Here, we found that migraine was significantly more prevalent in patients with endometriosis than in controls (14.2% vs 2.6%, respectively; 95% CI, 2.50−18.41; *P*<.001). The OR for migraine among patients with endometriosis and controls was 6.13 in univariate analysis, which indicates that the endometriotic respondents are 6 times more likely to suffer from migraine. Moreover, age- and BMI-adjusted multivariate analysis found that an OR of 5.35 signifies that the difference is not by chance and that there might be a strong association between endometriosis and migraine. The research conducted by Yang et al[7] also identified significantly higher rates of migraine among patients with endometriosis (*P*<.001). Migraine was significantly more frequent among women with endometriosis than among women in the control group, as documented in several other studies.[15−19,30−32] Moreover, a meta-analysis conducted by Jenabi and Khazaei[33] found migraine to

TABLE 3
Univariate and multivariate analyses to determine the association of endometriosis, headache, and migraine

Endometriosis (univariate analysis)				Migraine (multivariate analysis)			
Predictors	OR	95% CI	*P* value	Predictors	OR	95% CI	*P* value
Migraine	6.13	2.50–18.41	<.001	Endometriosis	5.35	2.11–16.40	.001
Headache	1.91	1.17–3.16	.010	Age	1.23	1.13–1.36	<.001
Tension headache	0.96	0.53–1.71	.882	BMI	0.93	0.82–1.05	.261
Age	1.00	0.96–1.04	.945				
BMI	0.98	0.92–1.04	.451				

BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio.

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be significantly associated with endometriosis.

Clinical implications

Both endometriosis and migraine are grim clinical problems that affect reproductive-age women and decrease their quality of life during the most productive age of their lives. These 2 conditions are treated by 2 different groups of physicians, namely, gynecologists and medicine specialists or neuromedicine specialists. Pain remains the main complaint in both groups. Thus, when treating patients with migraine or endometriosis, clinicians should bear in mind that the patients might have other linked comorbid conditions as well, for which he or she might need to seek help from colleagues of different specialties. Pain management issues remain pivotal in treating endometriosis and migraine to improve the quality of life. Furthermore, patients with endometriosis are many times treated with hormone therapies, which cause headaches, making it difficult to treat patients with endometriosis who have a comorbidity, such as migraine.[34,35] Hence, colleagues from the pain management team may also provide valuable assistance. Researchers have also found an association of several other autoimmune disorders, such as allergies, asthma, and fibromyalgia with endometriosis.[36] Considering these autoimmune phenomena among patients with endometriosis and concurrent comorbid migraine conditions, individual treatment regimens should be set by clinicians of various disciplines with a coordinated approach.

Research implications

Increasing numbers of observational epidemiologic studies on endometriosis and migraine have been performed, which constantly showed comorbidities in women of reproductive age, although the synergistic biological mechanisms for the co-occurrence are not yet clear. Moreover, diagnostic limitations because of unexplored biological markers along with ambiguous pathophysiology and lack of definitive medications to provide treatment have made the situation complicated for both disorders. In addition, further to the evidence pool of the traditional observational studies on endometriosis-migraine comorbid connection, it requires confirmation whether it is a true association or reflection of confounding effects and biases or false-positive results. Both disorders may also have a causal relationship or possess some shared genetic variants, susceptibility loci, genes, biological pathways, and unexplored mechanisms. However, to confer a correlation between endometriosis and migraine through a genome-wide association study, recent studies established a noncausal connection but determined genetically controlled similar biological mechanisms to reflect the co-occurrence of the 2 morbid conditions.[14] Being distant anatomically, common epidemiologic criteria of both illnesses explicitly affecting women than men with shared specific risk factors in women have increased the possibilities of extended research on the comorbidity of endometriosis with migraine. To elucidate the pathophysiology of endometriosis-migraine co-occurrence, attempts are also essential to understand the potential biological mechanisms involving increased circulating prostaglandins, nitric oxide synthesis dysregulation, and, most importantly, fluctuations of hormones that regulate shared risk factors for early menarche and menorrhagia. Concurrently, progress has been shown recently on the fundamental mechanisms of endometriosis and migraine. Various collaborative research outcomes on both disorders revealed interleukin 1 receptor binding, focal adhesion-PI3K-Akt-mTOR-signaling, mitogen-activated protein kinase signaling, and tumor necrosis factor-alpha signaling as the targeted genetically controlled biological pathways.[37] It is known that these immunologic pathways influence protein adhesion and phosphorylation and inflammatory and immune system dysfunction, followed by sex hormone dysregulation to stimulate pathophysiological expression of both disorders with severe pain.[38,39] Hence, further extensive research on these comorbid disorders to determine proper biomarkers for early diagnostics and remedies for controlling the inflammatory pathways in different geographic locations can be planned.

Strength and limitations

This study was conducted in Bangladesh where we tried to understand the association between medical disorders and endometriosis. The strengths of the current study include the diagnosis of endometriosis, which was performed by

direct laparoscopic observation and after laparotomy. The case and control groups were nearly similar concerning age, occupation, BMI, education, and marital status. Several previous studies that attempted to identify the association between medical disorders and endometriosis had smaller sample sizes. Here, 190 identified cases of endometriosis and an equal number of controls without the condition were enrolled.

In addition, we recognize that this study had several limitations. First, the diagnosis of migraine was performed by using questionnaires followed by consultation with a medicine specialist and current use of migraine medications as respondents revealed in their interview that there is no proof of any medical certificate available. Second, because of the limitation of funds, we were not able to do histopathologic confirmation of endometriosis. Hence, a small proportion of patients might have a diagnosis other than endometriosis. Third, the study participants were exclusively from middle- and upper middle−income families, limiting its generalizability to the full socioeconomic spectrum in Bangladesh, where endometriosis affects individuals across economic backgrounds.

Conclusion

Our research has provided significant insights into the association of endometriosis with migraine among the Bangladeshi population. When both endometriosis and migraine are comorbid conditions, the well-being of the patient must be reasonably impaired with considerably compromised quality of life, and their work performance should be significantly reduced. Although a complete remedy is impossible from the sufferings of the comorbid conditions of both disorders with available treatment regimes, pain and related symptoms can be reduced, and disabilities can be lessened with proper diagnosis and treatment. Thus, we recommend appropriate pain management treatment for women suffering from migraine and endometriosis. The 2 comorbid conditions, endometriosis and migraine, along with other immune system dysfunction disorders, such as allergies, asthma, and fibromyalgia, should be taken care of by a team of relevant clinicians. To understand the in-depth pathophysiology of the disease processes, the contributions of immunologists and molecular biologists are crucial. Hence, clinicians of relevant disciplines, immunologists, and molecular biologists require collaborative efforts with intensified queries for migraine in women with endometriosis. Further research with planned molecular, proteomics, and metabolomics studies should be conducted to determine potential therapeutic targets for alleviating autoimmune-mediated disorders related to endometriosis and migraine. ■

CRediT authorship contribution statement

Samina Sultana: Writing − review & editing, Writing − original draft, Validation, Supervision, Software, Project administration, Methodology, Formal analysis, Conceptualization. **Touhidul A. Chowdhury:** Writing − review & editing, Supervision, Methodology, Conceptualization. **Tanzeem S. Chowdhury:** Writing − review & editing, Supervision, Project administration, Data curation. **Nusrat Mahmud:** Writing − review & editing, Supervision, Project administration, Data curation. **Rebeka Sultana:** Writing − review & editing, Project administration, Data curation. **Naushaba T. Mahtab:** Writing − review & editing, Project administration, Data curation. **Yushuf Sharker:** Writing − review & editing, Validation, Methodology, Data curation. **Firoz Ahmed:** Writing − review & editing, Writing − original draft, Methodology, Formal analysis, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xagr.2024.100344.

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