Risk Profiles Associated with Endometriosis among Infertile Women

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Abstract:

Background: Endometriosis is a common gynaecological disorder which is found in about 5% of women and in 30% of infertile women. Identification of risk factors and timely intervention is useful.

Methods: A case control study was conducted in the Dept. of obs & gynae of Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, from October 2015 to March 2016 on 50 infertile patients attending the Infertility unit of the institute with the objective to determine the risk factors of endometriosis. Twenty five women with endometriosis was taken as cases (group-I) and twenty five women without endometriosis was taken as controls (group-II).

Result: The mean age was 32.8±5.4 years in group I and 35.1±5.7 years in group II which is similar. Urban residents were 3.21 times (with 95% CI 0.87-12.71%) more likely to develop endometriosis than rural resident which was statistically significant (p<0.05).

Among the study population BMI of 72% patients in group I and 68% in group II were within 19-24 kg/m². The difference was not statistically significant (p>0.05). There was not statistically significant difference (p>0.05) between two groups in OCP use (84%vs80%).

Women with endometriosis had less physical activity than the women without endometriosis; the differences was statistically significant (p<0.05). Consumption of caffeine, red meat, vegetables and fruits has no effect on endometriosis. Women with pain during menstruation were 29.33 times (with 95% CI 5.17-100%) and women with heavy amount of blood flow were 5.09 times (with 95% CI 1.24-22.06%) more likely to be endometriosis, which was statistically significant (p<0.05). Other risk factors like- age, occupation, educational status, age at menarche and cycle length were not significantly (p>0.05) associated with endometriosis.

Conclusion: Urban residence and all types of physical activities d"1 hour per day were significantly higher in infertile women with endometriosis.

Keyword: Risk factors of endometriosis, physical activity and endometriosis, urban residence and endometriosis.

Introduction:

Endometriosis is a common gynecological disorder in which endometrial tissue (glandular epithelium and

stroma) is found outside the uterine cavity. It has been estimated to affect 2.5-3.3% of women of childbearing age. Clinical presentations of

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endometriosis varies from asymptomatic to symptoms including dysmenorrhea, dyspareunia, pelvic pain, abnormal menstrual bleeding (menorrhagia and/or metrorrhagia), subfertility and infertility.^{3,4}

Although the pathogenesis of endometriosis is still unknown, the most common etiology is believed to involve retrograde menstruation. Almost all women have some menstrual effluent that passes through the fallopian tubes during menstruation, but only a minority develops endometriosis due to the fact that those cells can be cleared by peritoneal macrophages.⁵

One of the most important complications of endometriosis is reduced fertility and infertility. Although endometriosis affects approximately 5% of the general population, its prevalence may be as high as 30% in infertile women.⁶

One of the challenging subjects in endometriosis is lack of non-invasive tests by which accurate diagnosis can be made.⁵ Endometriosis is always finally diagnosed by visualizing the lesions, cysts, implants, and nodules by laparoscopy. Nevertheless, there are accompanying symptoms that may be indicative such as pelvic pain, adnexal masses, and dyspareunia⁷ or some biochemical markers which are useful in detecting and monitoring endometriosis such as cancer antigen-125 (CA-125).⁸

In order to facilitate diagnosis of endometriosis by non-invasive methods, it is very important to know the risk factors which make women susceptible to endometriosis. By knowing the risk factors, women who may be at a high risk of developing endometriosis may be recognized earlier so that serious complications of endometriosis such as infertility can be prevented by diagnosis and treatment of women suffering from endometriosis in earlier stages (I and II).

Several studies have showed that age, race, body mass index (BMI), alcohol usage, and cigarette smoking were associated with the incidence of endometriosis in the USA⁹. They also stated that some of these associations may differ by infertility status at the time of laparoscopic diagnosis.⁹ Calhaz-Jorge *et al.*¹⁰ found that prevalence of endometriosis in subfertile women was related to race, BMI, irregular menstrual cycles, intensity of menstrual flow, dysmenorrhea, chronic pelvic pain, obstetrics history,

oral contraceptive pills (OCPs) use, and smoking habits. 10

Endometriosis is a disease with pain and infertility. For endometriosis there is no obvious cause or cure. The symptoms of endometriosis, although characteristic, are extremely variable and not related to the stage of the disease. Furthermore, a variety of factors, including general health, depression, anxiety, and psychosocial attitudes, environmental factors, seem to affect the perception of symptoms and the need for medical attention. 11-12 Treatment of infertile women with endometriosis is difficult and expensive. Identification of risk factors of this patients and treating them is an ideal approach to reduce disease progression. It will be significantly helpful for infertile women with endometriosis of our country with limited resource.

Methods:

A case control study was conducted at the Infertility unit of the Dept of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka during the period October 2015 to march 2016 among the infertile patients attending the Infertility unit of the Department.

Fifty infertile women with or without endometriosis were selected by inclusion & exclusion criteria by purposive sampling. Twenty five women with endometriosis was taken as cases (group-I) and twenty five women without endometriosis was taken as controls (group-II).

Inclusion criteria women of reproductive age group, women having history of infertility (primary or secondary), women either diagnosed as a case of endometriosis (by laparoscopy/ laparotomy/ sonographic evidence of having chocolate cyst) or not. Exclusion criteria was women beyond reproductive age group.

Data was collected in a structured data collection sheet after taking history from the patient requested physical examination and procedure performed and from hospital indoor documents i.e. patient chart and treatment record.

Statistical analysis was carried out by using the Statistical Package for Social Sciences version 16.0 for Windows. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Chi-

Square test was used to analyze the categorical variables, shown with cross tabulation. Student t-test was used for continuous variables. P values <0.05 was considered as statistically significant. Ethical permission was taken from the Institute. All patients were explained about their conditions. The study did not interfere with the patient management nor deal with moral or social issues. Informed written consent was obtained.

Results:

The mean age was found 32.8±5.4 years in group -I and 35.1±5.7 years in group-II. Which was similar (Table-I). So was the occupation and level of education of the women. Residents in urban area were 18(72%) in group I and 11(44%) in group II. This difference was statistically significant (p<0.05) between the two groups. Considering the body mass index of the study population, 72.0% patients in group I and 68.0% in group II were within BMI 19.0-24.0

kg/m². The difference was not statistically significant (p>0.05) between two groups. (Table-I)

In group I, 84% women used OCP and 80%in group II. The difference was not statistically significant (p>0.05) between two groups.

Combining hours of physical activity (walking, house hold work, exercise/swimming and climbing stairs) women with endometriosis had less physical activity than the women without endometriosis. The differences were statistically significant (p<0.05) between two groups (Table-III).

Women having total activity <4 hours per day were 4.75 times (with 95% CI 1.21-19.59%) more likely to develop endometriosis. Women who walk d"1 hour per day are 8.50 times (with 95% CI 2.00-38.95%) more likely to develop endometriosis. Those who do house hold work ≥1 hour per day are 3.78 times (with 95% CI 1.01-14.63%) more likely to develop endometriosis. Those who exercise/swimm d"1 hour per day are 13.50 times (with 95% CI 2.88-70.41%)

Table-IDistribution of the study population by particulars of the patients (n=50)

Particular of the patients	Group-	I (n=25)	Group-	P value	
	n	%	n	%	
Age (in years)					
<30	6	24.0	4	16.0	
30-35	10	40.0	7	28.0	
36-40	7	28.0	10	40.0	
>40	2	8.0	4	16.0	
Mean±SD	32.8	±5.4	35.1	±5.7	^a 0.150 ^{ns}
Range (min-max)	21	-42	20	-44	
Occupational status					
House wife	18	72.0	17	68.0	^b 0.758 ^{ns}
Working lady	7	28.0	8	32.0	
Residence					
Urban	18	72.0	11	44.0	^b 0.045 ^s
Rural	7	28.0	14	56.0	
Educational status					
SSC /O Level or below	5	20.0	11	44.0	
HSC/A level	11	44.0	10	40.0	^b 0.121 ^{ns}
Graduate&above	9	36.0	4	16.0	
BMI (kg/m ²)					
<19.0 (underweight)	2	8.0	3	12.0	
19.0-24.0 (normal)	18	72.0	17	68.0	^b 0.892 ^{ns}
>24.0 (Overweight)	5	20.0	5	20.0	

s= significant, ns= not significant

^aP value reached from unpaired t-test

^bP value reached from chi square test

Group I= Infertile women with endometriosis

Group II= Infertile women without endometriosis

more likely to develop endometriosis. Women who climb upstairs d"1 hour per day are 4.13 times (with 95% CI 0.82-23.19%) more likely to develop endometriosis (Table-III)

Regarding food habits of the study population, consumption of caffeine, red meat, vegetables and fruits, there were no significant (p>0.05) difference between two groups (Table-IV).

Patients experiences pain during menstruation were 29.33 times (with 95% CI 5.17-100%) more likely to diagnosed as endometriosis, which was statistically significant (p<0.05) between two groups.

Patients with heavy amount of blood flow were 5.09 times (with 95% CI 1.24-22.06%) more likely to be endometriotic, which was statistically significant (p<0.05) between two groups(Table-II)

Urban residents were 3.21 times (with 95% CI 0.87-12.71%) more likely to develop endometriosis, which was statistically significant (p<0.05) between two groups.

Other risk factors like- age, educational status, age at menarche and menstrual cycle length were not significantly (p>0.05) associated with endometriosis.

Table-IIDistribution of the study population by menstrual history (n=50)

Menstrual history	Group-	I (n=25)	Group-	Group-II (n=25)	
	n	%	n	%	
Age at menarche (years)					
≤11	6	24.0	4	16.0	
12	10	40.0	7	28.0	0.458 ^{ns}
13	5	20.0	10	40.0	
≥14	4	16.0	4	16.0	
Cycle length (in day)					
≤25	18	72.0	16	64.0	
26-31	6	24.0	7	28.0	0.768 ^{ns}
>31	1	4.0	2	8.0	
Cycle pattern					
Regular	20	80.0	23	92.0	0.209 ^{ns}
Irregular	5	20.0	2	8.0	
Amount of flow					
Light	5	20.0	6	24.0	
Moderate	6	24.0	14	56.0	0.022 ^s
Heavy	14	56.0	5	20.0	
Pain associated with menstrua	ition				
Yes	22	88.0	5	20.0	0.001 ^s
No	3	12.0	20	80.0	

s= significant, ns= not significant

P value reached from chi square test

Table-III Distribution of the study population by physical activity (n=50)

	Group	Group-I (n=25)		Group-II (n=25)		95% CI	P value
	n	%	n	%		(Lower-upper)	
Total activity							
<4 hours per day	19	76.0	10	40.0	4.75	1.21-19.59	0.010 ^s
≥4 hours per day	6	24.0	15	60.0			
Walking							
≤1 hour per day	20	80.0	8	32.0	8.50	2.00-38.95	0.001s
>1 hours per day	5	20.0	17	68.0			
House hold work							
≤1 hour per day	17	68.0	9	36.0	3.78	1.01-14.63	0.024 ^s
>1 hours per day	8	32.0	16	64.0			
Exercise/swimming							
≤1 hour per day	21	84.0	7	28.0	13.50	2.88-70.41	0.001s
>1 hours per day	4	16.0	18	72.0			
Climbing stairs							
≤1 hour per day	22	88.0	16	64.0	4.13	0.82-23.19	0.047 ^s
>1 hours per day	3	12.0	9	36.0			

OR=Odds ratio

CI-Confidence interval

s= significant P value reached from chi square test

Table-IV Distribution of the study population by food habits (n=50)

Food habits	Group-	-l (n=25)	Group-	P value	
	n	%	n	%	
Caffeine consumption					
≤1 time per week	10	40.0	9	36.0	
>1 times per week	5	20.0	3	12.0	0.624 ^{ns}
None	10	40.0	13	52.0	
Red meat consumption					
≤1 time per week	2	8.0	5	20.0	
>1 times per week	1	4.0	4	16.0	0.133 ^{ns}
None	22	88.0	16	64.0	
Vegetables consumption					
≤1 time per week	8	32.0	9	36.0	
>1 times per week	4	16.0	5	20.0	0.845 ^{ns}
None	13	52.0	11	44.0	
Fruits consumption					
≤1 time per week	4	16.0	8	32.0	
>1 times per week	2	8.0	5	20.0	0.122 ^{ns}
None	19	76.0	12	48.0	

ns= not significant

P value reached from chi square test

Discussion:

Chaichian et al.¹³ evaluated some of the clinical predictive factors among Iranian infertile population. Clinical characteristics were compared with laparoscopic results. No statistically significant difference was identified in the participants' age, educational level, duration of breast-feeding, duration of infertility, and menstrual flow. On the contrary, women with endometriosis had longer duration of marriage (OR = 1.03, P<0.05), older age at first pregnancy (OR = 1.21, P<0.05), lower BMI (OR = 0.9, P<0.05), shorter interval of menses (OR = 0.98, P<0.05), and history of irregular menstrual cycles (OR = 0.54, P<0.05), compared to those without endometriosis.

Yasui et al.¹⁴ examined risk profiles in imaging-diagnosed endometriosis with and without surgical confirmation in a large population of Japanese women. Two hundred and ten women had surgically confirmed endometriosis (Group A), 120 had imaging diagnosed endometriosis without a surgical procedure (Group B), and 264 had adenomyosis (Group C). A short menstrual cycle at 18–22 years of age and cigarette smoking at 30 years of age were associated with significantly increased risk of endometriosis (Group A plus Group B), while older age was associated with risk of adenomyosis (Group C).

Darwish et al.¹⁵ estimated the prevalence of typical and atypical (subtle) pelvic endometriosis as diagnosed by laparoscopy, and to define risk factors for this disease among Egyptian women. Laparoscopically, 469 patients (18.8%) were diagnosed to be endometriosis. Of those, typical and atypical endometriosis were diagnosed in 220 patients (8.8%) and 249 patients (9.98%) respectively. Concerning risk factors, only decreased patient's age (less than 30 years), low parity, and urban residence were significantly correlated with endometriosis.

Calhaz-Jorge et al. ¹⁰ evaluated the demographic and clinical characteristics in a cohort of Portuguese subfertile women in relation to the presence of endometriosis. Primary subfertility, regularity of menstrual cycles, dysmenorrhoea, chronic pelvic pain, obesity, ever use of oral contraceptives and smoking were the most important predictors of endometriosis.

Endometriosis is commonly found on the ovaries and is characterized by a range of symptoms and severity, including chronic pelvic pain and infertility. The role of modifiable exogenous factors such as exercise in the development of this disease is not well understood.

In this study mean age was 32.8±5.4 years (range 21-42 yrs) in cases and 35.1±5.7 years (range 20 - 44 yrs) in control. In the study of Chaichian et al. 13 the mean age was 30.23±6.22 years in endometriosis group and 29.02±5.96 years in control group. Similar age range also observed by Moini et al. 16; Dhillon and Holt. 4 On the other hand in the study by Darwish et al. 15 mean age was 26.8±5.3 years and 29.0±5.3 years in case and control respectively. Mean age of cases and controls are a little higher in our study than that of others.

Regarding occupational status, it was observed that, majority were housewives (72.0% in cases and 68.0% controls). Moini et al. 16 found that housewives was 40.7% and employee was 32.3% in their study patients, which is lower than our study.

In our study residents in urban area were 72.0% in cases and 44.0% in controls and In Darwish et al.¹⁵ study, urban residence was 71.1% in case and 45.3% in control. Which is comparable to the finding of current study. Increased prevalence of endometriosis in urban women may be explained by their medical awareness and educational level. Urban residence is associated with increasing problems of pollution. There is a possible link between endometriosis and one of the most harmful components of pollution, dioxin.¹⁷

It this study there was no significant difference in educational status of women with or without endometriosis which is consistent with the findings of study conducted by Darwish et al.¹⁵; An Italian group¹⁸; Berube et al.¹⁹ found no relation between education and presence of endometriosis. Chaichian et al.¹³ reported that there was no difference regarding educational level of two groups.

In this study 72.0% patients in group I and 68.0% in group II were within BMI 19.0-24.0 kg/m². The difference was not statistically significant (p>0.05) between two groups, a findings similar with that of Darwish et al. 16 study. Moini et al. 15 obtained that BMI had an inverse correlation with endometriosis as infertile obese women were at lower risk for

endometriosis (p < 0.05). Similar finding was also observed by Missmer et al.⁹; Calhaz-Jorge et al.¹⁰; Hediger et al.²⁰. In contrast, Hemmings et al.²¹ did not find any significant correlation between BMI and endometriosis similar to our study.

The exact relationship of oral contraceptive pills to the risk of endometriosis is controversial.²¹ In our study it was observed that more women (84.0%) used OCP in group I than group II (80.0%). The difference was not statistically significant (p>0.05). Darwish et al. 15 found oral contraceptive use of 5.9% in women with endometriosis and 7.9% in women without endometriosis. The difference was statistically significant (p<0.05) between two groups. In another study Dhillon and Holt4 found current oral contraceptive use was 5.2% patients in case group and 23.2% in control group. Previously oral contraceptive users were 81.9% in case group and 64.3% in control group. Total absence of oral contraceptive use was 13.0% in case group and 12.6% in control group, which are comparable with the current study.

Regarding the menstrual history it was observed in this study that more women with endometriosis had short menstrual cycle than women without endometriosis. The difference was not statistically significant (p>0.05) between two groups. Heavy amount of flow and pain associated with menstruation were significantly higher in women with endometriosis. Matalliotakis et al.5 showed that shorter cycle length and heavier menstrual cycles were associated with endometriosis. Also other groups of researchers such as Arumugam and Lim²². Cramer and Missmer²³ revealed that women with a menstrual cycle shorter than 27-28 days had higher risk of developing endometriosis. On the other hand, Calhaz-Jorge et al.¹⁰; Hemmings et al.²¹ Parazzini et al.²⁴ did not find any significant correlation between shorter menstrual cycle and endometriosis. In addition, Mamdouh et al.25 found that women with irregular cycles were three times more likely to develop endometriosis than women with regular cycles, which is inconsistent with our finding. In another study Chaichian et al. 13 found that irregular menstruation was 18.3% in endometriosis group and 29.2%% in non endometriosis group. The above findings closely differ from the findings of current study.

Dhillon and Holt⁴ found no association between "any physical activity" during the 2 years prior to the reference date and risk of endometrioma after controlling for age, number of live births, oral contraceptive use, and cigarette smoking. To evaluate the effects of physical activity in accordance with public health recommendations.²⁶ the authors focused on women who participated in high-intensity activity for at least 30 minutes per episode, three or more times per week, and 10 or more months per year. The risk of endometrioma was significantly lowered by 70.0% for consistent, high intensity exercisers in comparison to women reporting no highintensity activity during the 2 years prior to the reference date (OR = 0.30 with 95% CI: 0.12 - 0.74). A similar analysis focusing on the period between 12 and 21 years of age yielded a 35.0% reduced risk, although the association was non significant. One advantage of Dhillon and Holt4 study is that the intensity level of physical activity was based on the determination of metabolic equivalents for specific activities by using the recently updated Compendium of Physical Activities²⁷ and not on a study subject's interpretation of "vigorous" or "regular" exercise. The investigators were also able to evaluate the combined effects of duration, frequency, and intensity level of physical activity and consequently activity levels suggested in public health recommendations.²⁶ The inverse associations between physical activity and endometriotic disease in the present study are similar to those found in the two previous studies²⁸⁻²⁹ even though cases in Dhillon and Holt⁴ study were women with more severe disease and cases in previous studies had infertility- associated endometriosis, often a mild or moderate form of disease. In a crosssectional study in Norway,30 investigators compared women with and without a self reported diagnosis of endometriosis and did not find a reduced risk associated with "regular" exercise (OR = 0.7 with 95% CI: 0.3 - 1.5). In none of the two studies²⁹⁻³⁰ did the authors address whether the presence of preexisting disease may have influenced the levels of recent physical activity reported by endometriosis cases. Dhillon and Holt⁴ study was able to address this issue by obtaining exercise patterns during adolescence, a time when activity would unlikely be affected by undiagnosed disease.

In a case control study conducted by Parazzini et al.²⁴ in Northern Italy, there was significant reduction in risk emerged for higher in take of green vegetables

(OR = 0.3 for the highest tertile of intake) and fresh fruit (OR= 0.6), whereas an increased in risk was associated with high intake of beef and other red meet (OR = 2.0) and ham (OR = 1.8) Consumption of milk, liver, carrot, cheese, fish and whole grain foods as well as coffee and alcohol consumption were not significantly related with endometriosis. However, in our study it was observed that with regard to consumption of caffeine, red meat, vegetables and fruits there were no significant (p>0.5) difference between two groups.

The study population was selected from one hospital of Dhaka city, so that the results of the study may not reflect the exact picture of the country. Small sample size was also a limitation of this study. Therefore, in future further study may be under taken with large sample size.

Conclusion:

This study was undertaken to determine the risk factors of endometriosis in infertile women. Most of the infertile women were in 3rd decade and housewives. Use of oral contraceptive use have no relation with endometriosis. Urban residence, heavy amount of flow, pain associated with menstruation and all types of physical activities d"1 hour per day were significantly higher in infertile women with endometriosis. Regarding food habits like consumption of caffeine, red meat, vegetables and fruits, there were no significant (p>0.05) association with endometriosis.

Age, educational status, age at menarche and menstrual cycle length were not significantly (p>0.05) associated with endometriosis.

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