Original Research Article

Incidence of Endometriosis in Symptomatic and Asymptomatic Cases of Primary Infertility in Tanta University Hospital

Abstract

Background: Endometriosis is the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction. Some women with endometriosis experience painful symptoms and/or infertility, others have no symptoms at all. The aim of this study was to detect the incidence of endometriosis among symptomatic and asymptomatic cases of primary infertility in Tanta University Hospital over one year.

Methods: This prospective observational study was conducted on 50 females aged between 20 and 35 years old, with unexplained infertility, symptoms of endometriosis and infertility for 1 or more years. Patients were divided into two equal groups: group (1): cases with unexplained infertility for 1 year or more and group (2): cases with symptoms of primary infertility and endometriosis for 1 year or more. Patients were subjected to the following: meticulous history taking (personal, obstetric and menstrual history, history of present illness, past history 'medical and surgical'), thorough clinical examination, routine laboratory investigations, imaging techniques (ultrasound and HSG) and laparoscopy for diagnosis of possible presence of endometriosis.

Results: Endometrioma size was significantly higher in group 2 compared to group 1 (P value = 0.020). Stage 1 of endometriosis was significantly lower in group 2 compared to group 1 and Stage 2, 3 and 4 of endometriosis were significantly higher in group 2 compared to group 1 (P value = 0.04). Dysmenorrhea of endometriosis after treatment were significantly higher in group 2 compared to group 1(P value <0.001). Chronic pelvic pain was significantly higher in group 1 compared to group 2 (P value <0.001).

UNDER PEER REVIEW

Conclusions: The presence of dysmenorrhea, dyspareunia, pelvic pain, infertility, and clinical signs of cul-de-sac tenderness raise the suspicion of endometriosis in infertility patients.

Keywords: Endometriosis, Symptomatic Primary Infertility, Asymptomatic Primary Infertility.

UNDER PEER REVIEW

Introduction:

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction. While some women with endometriosis experience painful symptoms and/or infertility, others have no symptoms at all [1].

Infertility is the failure to conceive (regardless of cause) after 1 year of unprotected intercourse. This condition affects approximately 10-15% of reproductive-aged [1].

The definite pathogenesis of endometriosis is still unknown but there are several leading theories, including retrograde menstruation, altered immunity, coelomic metaplasia, and metastatic spread. Newer research is also proposing stem cell and genetic origins of the disease [2].

Endometriosis is classified into one of four stages (I-minimal, II-mild, III-moderate, and IV-severe) based upon the exact location, extent, and depth of the endometriosis implants as well as the presence and severity of scar *tissue* and the presence and size of endometrial implants in the ovaries. Most cases of endometriosis are classified as minimal or mild, which means there are superficial implants and mild scarring. Moderate and severe endometriosis typically result in cysts and more severe scarring. The stage of endometriosis is not related to degree of symtoms awomn experiences [2].

Endometriosis is said to be responsible for one third of infertility cases, however up to 70% of women with mild to moderate endometriosis are still capable of conceiving [3].

Endometriosis can lead to infertility by adhesions among ovaries, uterus and fallopian tubes impede the transfer of the egg to the fallopian tube, ovarian implants prevent release of the ova, decrease in the number and quality of healthy eggs and hyperestrogenemia [3].

Symptoms of endometriosis are pain, which can be: pelvic pain, severe menstrual cramps [4], low backache 1 or 2 days before the start of the menstrual period (or earlier), pain during sexual

UNDER PEER REVIEW

intercourse (dyspareunia), rectal pain (dyschezia), pain during bowel movements, infertility may be the only sign that you have endometriosis and abnormal bleeding [4].

Finding pelvic tenderness, a fixed retroverted uterus, tender utero-sacral ligaments or enlarged ovaries on examination is suggestive of endometriosis. The diagnosis is more certain if deeply infiltrating nodules are found on the utero-sacral ligaments or in the pouch of Douglas, and/or visible lesions are seen in the vagina or on the cervix [5].

The aim of this study was to detect the incidence of endometriosis among symptomatic and asymptomatic cases of primary infertility in Tanta University Hospital over one year.

Patients and Methods

This prospective observational study was conducted on 50 females aged between 20 and 35 years old, with unexplained infertility for 1 or more years and symptoms of endometriosis and infertility for 1 or more years.

Written informed consent was obtained from all participants after full explanation of the technique and potential side effects following the guidelines of the ethical committee.

Exclusion criteria were female more than 35 or less than 20 years old, female with infertility less than 1-year, male factor of infertility, cases of secondary infertility, cases with irregular sexual life, ovulatory causes of infertility, cases with congenital anomalies and hostile cervical mucous.

Patients were divided into two equal groups: group (1): cases with unexplained infertility for 1 year or more and group (2): cases with symptoms of primary infertility and endometriosis for 1 year or more.

All patients were subjected to: meticulous history taking [personal history, obstetric history, menstrual history, history of present illness, past history 'medical and surgical'], thorough clinical examination, [vitals, appearance, regional, abdominal, gynaecological], routine investigation [complete blood picture, coagulation profile, fasting blood glucose, liver

UNDER PEER REVIEW

enzymes, urea and creatinine, FSH, LH, AMH, PRL, TSH, Ca125, semen analysis, post coital test], imaging techniques [ultrasound and HSG], laparoscopy for diagnosis of possible presence of endometriosis, sample was taken from suspicious lesion [vesicles, endometriosis patches, chocolet cyst], then treated by fulguration electrocautery, or excision, and histopathology of any suspicious lesion taken by laproscope.

Statistical analysis

Statistical package for social sciences (IBM-SPSS), version 24 (IBM-Corporation, Chicago, USA; August 2017) was used for statistical data analysis. Data was expressed as mean, standard deviation (SD), number and percentage. Mean and standard deviation were used as descriptive value for quantitative data. Student t test was used to compare the means between two groups, and one-way analysis of variance (ANOVA) test was used to compare means of more than two groups; with LSD post HOC test to calculate the individual p values between each two groups. Mann-Whitney and Kruskal-Wallis tests were used instead of student t test and ANOVA for non-parametric data to compare medians rather than means between two or more groups; respectively. Pearson Chi square test was used to compare percentages of qualitative variables, and Fisher's exact test was used instead for non-parametric data. Pearson correlation test was used to compare two quantitative variables. For all these tests, the level of significance (P-value) significance $P < 0.05$.

Results:

There was no significant difference between both groups regarding age, age of menarche, BMI, duration of infertility, cycle length and history. **Error! Not a valid bookmark self-reference.**

UNDER PEER REVIEW

Table 1: Comparison between the two studied groups according to age, age of menarche, BMI, duration of infertility, cycle length, previous oral contraception use, family history of endometriosis, previous gynecological surgery and menstrual disturbances

		Group 1 (n = 25)	Group 2 (n = 25)	T test	P value
Age		26.88±4.456	25.57±5.43	0.063	0.950
Age of menarche		13.61±0.986	12.72±0.922	0.893	0.376
BMI		27.40±0.912	26.77±0.957	0.756	0.453
Duration of infertility (years)		2.96±1.25	2.88±1.37	0.155	0.877
Cycle length (21-35 days)		26.52±5.08	27.28±4.17	0.751	0.456
Previous oral contraception use		14 (56%)	15 (60%)	0.082	0.774
Family history of endometriosis		8 (32%)	10 (40%)	0.347	0.556
Previous gynecological surgery		6 (24%)	8 (32%)	0.397	0.529
Menstrual disturbances	Amenorrhoea	5 (20%)	5 (20%)	1.451	0.683
	Amenorrhoea, pain	3 (12%)	1 (4%)		
	Oligomenorrhoea	11 (44%)	14 (56%)		
	Oligomenorrhoea, hirsutism	6 (24%)	5 (20%)		

Data are presented as mean ± SD or frequency (%), BMI: Body mass index.

Table 2 shows that there was no significant difference between both groups regarding laboratory investigations and pathological examination.

Table 2: Comparison between the two studied groups according to laboratory investigations and pathological examination

	Group 1 (n = 25)	Group 2 (n = 25)	P value
AMH	2.056±0.6378	2.008±0.5480	0.793
LH (mIU/ml)	9.896±2.2369	8.836±2.3088	0.926
FSH (mIU/ml)	4.8912±1.262	4.122±1.112	0.789
PRL (ng/ml)	4.512±1.1421	4.112±1.001	0.971
TSH (mIU/ml)	3.93±0.430	4.05±0.358	0.831
FT3 (pg/ml)	3.124±0.652	2.99±0.696	0.512
FT4 (ng/dl)	1.382±0.72119	1.538±0.760	0.788
Serum testosterone (ng/ml)	28.22±4.7633	27.056±4.7194	0.390
Fasting serum insulin (ulU/ml)	19.036±2.0031	18.556±2.4614	0.453
Fasting sugar (mg/dl)	98.280±9.7447	96.760±10.3653	0.596
CA125	46.040±4.9622	47.400±5.6726	0.793
Lesion of endometriosis	7 (70%)	13 (65%)	0.606
Lesion of other pathology	3 (30%)	7 (35%)	0.844
Simple cyst	1 (33.3%)	4 (57.1%)	
Hemorragic cyst	2 (66.6%)	2 (28.5%)	
Benign tumor	0 (0%)	1 (14.2%)	

AMH: Anti-Mullerian hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, PRL: prolactin, TSH: thyroid stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, CA125: cancer antigen 125

UNDER PEER REVIEW

Regarding pelvic pain symptoms, no symptoms and chronic pelvic pain were significantly higher in group 1 compared to group 2 and dysmenorrhea and dysmenorrhe, Dyspareunia pain were significantly lower in group 1 compared to group 2 (P value <0.001). Regarding TVU, cysts and endometriotic lesion were significantly lower in group 1 compared to group 2 and normal finding was significantly higher in group 1 compared to group 2 (P value <0.001). Regarding HSG, adhesions was significantly lower in group 1 compared to group 2 and normal was significantly higher in group 1 compared to group 2 (P value <0.001). Table 3

Table 3: Comparison between the two studied groups according to pelvic pain symptoms, TVU and HSG

		Group		Chi square	P value
		1	2		
Pelvic pain symptoms	No symptoms	8 (32.0%)	0 (0.0%)	50.000	**<0.001***
	Chronic pelvic pain	8 (32.0%)	7 (28.0%)		
	Chronic pelvic pain, Dysmenorrhea	5 (20.0%)	5 (20.0%)		
	Dysmenorrhea	1 (4.0%)	6 (24.0%)		
	Dysmenorrhe, Dyspareunia	3 (12.0%)	7 (28.0%)		
TVU	Cysts	2 (8.0%)	7 (28.0%)	14.561	<**0.001***
	Endometriotic lesion	2 (8.0%)	8 (32.0%)		
	Normal finding	21 (84.0%)	10 (40.0%)		
HSG	Adhesions	2 (8.0%)	14 (56.0%)	13.235	<**0.001***
	Normal	23 (92.0%)	11 (44.0%)		

*: significant as P value ≤0.05, TVU: transvaginal ultrasound, HSG: hysterosalpingography

Endometrioma size was significantly higher in group 2 compared to group 1 (P value = 0.020). Stage 1 of endometriosis was significantly lower in group 2 compared to group 1 and Stage 2, 3 and 4 of endometriosis were significantly higher in group 2 compared to group 1 (P value = 0.04). Absence of deeply infiltrating endometriosis was significantly lower in

UNDER PEER REVIEW

group 2 compared to group 1 and presence of deeply infiltrating endometriosis was significantly higher in group 2 compared to group 1 (P value = 0.024). Total number of DIE lesions was significantly lower in group 2 compared to group 1 (P value = 0.037). Laparoscopically confirmed endometriosis, peritoneal superficial endometriosis, ovarian endometrioma isolated and anatomical distribution of DIE were insignificantly different between both groups. Table 4

Table 4: Comparison between the two studied groups according to endometriosis and DIE

		Group 1 (n = 25)	Group 2 (n = 25)	Chi square test	P value
Laparoscopically confirmed endometriosis	**No**	18 (72.0%)	12 (48.0%)	0.725	0.395
	Yes	7 (28.0%)	13 (52.0%)		
Endometrioma size (cm)		**(n =7)**	**(n = 13)**	1.624	**0.020***
Mean ± SD.		1.34 ± 0.66	3.43 ± 0.56		
Stages of endometriosis (rARM) classification)		**(n = 7)**	**(n = 13)**		
	1	5 (71.4%)	3 (23.1%)	27.600	**0.04***
	2	1 (14.3%)	2 (15.4%)		
	3	1 (14.3%)	5 (38.5%)		
	4	0 (0.0%)	3 (23.1%)		
Peritoneal superficial endometriosis	**No**	23 (92.0%)	20 (80.0%)	1.495	0.209
	Yes	2 (8.0%)	5 (20.0%)		
Ovarian endometrioma isolated	**No**	22 (88.0%)	19 (76.0%)	1.220	0.463
	Yes	3 (12.0%)	6 (24.0%)		
Deeply infiltrating endometriosis (DIE)		**(n =25)**	**(n =25)**		
	No	22 (88.0%)	15 (60.0%)	5.094	**0.024***
	Yes	3 (12.0%)	10 (40.0%)		
Total number of DIE lesions		**(n = 3)**	**(n = 10)**	2.402	**0.037***
Mean ± SD.		3.00 ± 0.707	2.20 ± 0.92		
Anatomical distribution of DIE		**(n = 3)**	**(n = 10)**		
	Uterosacral ligament	1 (33.3%)	2 (20.0%)	0.956	0.695
	Intestine, USL	2 (66.7%)	5 (50.0%)		
	Vagina,	0 (0%)	3 (30.0%)		

UNDER PEER REVIEW

	Bladder				

*: significant as P value ≤0.05, DIE: deeply infiltrating endometriosis, USL: Uterosacral ligament

Regarding dysmenorrhea of endometriosis after treatment, no dysmonrrhea was significantly lower in group 2 compared to group 1 and little improvement less than 50%, moderate improvement of symptoms 50-60%, significant improvement of symptoms 70-80% and complete improvement of symptoms 90-100% were significantly higher in group 2 compared to group 1(P value <0.001). Pregnancy rate was insignificantly different between both groups. Table 5

Table 5: Comparison between the two studied groups according to dysmenorrhea in endometriosis among 3 months after laparoscopy and Pregnancy rate after laparoscopy

		Group 1 (n = 25)	**Group 2 (n = 25)**	**Chi square**	**P value**
Dysmenorrhea of endometriosis after treatment		**(n =18)**	**(n = 13)**		
	No dysmonrrhea	18 (100.0)	0 (0.0)	22.496	**<0.001***
	Little improvement less than 50%	0 (0.0)	3 (23.1)		
	Moderate improvement of symptoms 50-60%	0 (0.0)	2 (15.4)		
	Significant improvement of symptoms 70-80%	0 (0.0)	3 (23.1)		
	Complete improvement of symptoms 90-100%	0 (0.0)	5 (38.5)		
Pregnancy rate	**No**	15 (60.0)	17 (68.0)	0.347	0.556
	Yes	10 (40.0)	8 (32.0)		

*: significant as P value ≤0.05

Discussion

Endometriosis is a gynecological enigma since it is difficult to diagnose and treat. Endometriosis is a benign disease in which endometrial-like tissue persists outside the uterine

UNDER PEER REVIEW

cavity. Pelvic structures are most commonly affected, but endometriosis can involve extrauterine organs as distant as the lung [6].

Furthermore Moghadam et al. found that the prevalence of infertility on all couples in Canada-2011 was 11.5% - 15.7% [7].

A meta-analysis study in Iran was conducted on 13 Iranian studies during 2003-2011 by Bentley et al. which reported the overall infertility prevalence 13.2% [8].

In our study, we found that among cases of unexplained infertility in group (1), 28 % had endometriosis and among cases of primary infertility in group (2), 52% had endometriosis (P= 0.395, chi = 0.725).

Similar to our results a retrospective study conducted among 372 cases by Mao et al, which demonstrates a very high incidence of endometriosis 48.33% [9].

In the opposite to our study, study of Khadawardi et al, found that 10.7% of cases had endometriosis which lower than our percentage [10].

In Egypt, another study by Kulkarni et al, conducted among 100 patients attending Menoufia University Hospital and subjected to diagnostic laparoscopy reported that 33% of them had endometriosis [11]. Another study by Gad et al, conducted among 1285 women reported; the estimated point prevalence of endometriosis was 4.0% [12].

There was high significant difference between both groups regarding pelvic pain symptoms. Most prevalent symptoms for endometriosis in this study were had chronic pelvic pain (32% in group 1 and 28% in group 2), dysmenorrhea (20% in both groups), dysmenorrhea together with dyspareunia (12% in group 1 and 28% in group 2). However, 32% of cases in group (1) experienced no symptoms and only 0 % of group (2).

In line with our results, Minko et al. concluded that twenty-five percent of women experienced no symptoms while chronic pelvic pain, dysmenorrhea and dyspareunia were the most prevalent symptoms recorded in their study [13].

UNDER PEER REVIEW

In the present study, there was high significant difference between groups regarding TVU.As we found in group (1), 8% of cases had cysts ,8% had endometriotic lesions and 84 % show normal finding. In group (2), 28% of cases had cysts, 32% had endometriotic lesions and 40% show normal finding.

In Egypt, a prospective study done in Obstetrics and Gynecology Department, Faculty of Medicine, Alexandria University in 2016 to evaluate the role of HSG in the prediction of endometriosis among 86 females with primary infertility who undergo HSG 3 months before laparoscopy and the result is 36 cases (41.99%) show positive finding for endometriosis as adhesion and 50 cases (58.1%) show normal finding.

Furthermore, there was low significant difference between groups regarding laparoscopically confirmed endometriosis, peritoneal superficial endometriosis, and ovarian endometrioma isolated but high significant difference between them regarding endometrioma size, stages of endometriosis (rARM) classification.

In current study, there was significant difference between both groups regarding pregnancy rate. The pregnancy rate in our study was 40% in first group and 32% in second group who had endometriosis. In accordance with, the pregnancy rate in study of Kulkarni et al, was 36.36% and the fertility rate is (36.36%) comparatively lesser than other studies. The probable reason could be the higher prevalence of moderate to severe disease in infertile patients (75.75%) and many patients with severe disease were unwilling to undergo ART due to financial constraints [11].

In a study by Sahu L et al, the fertility rate was 46% [15].

The recent advances in operative laparoscopy have changed the view in the management of endometriosis with infertility. The laparoscopic treatment involves the identifying and removal of lesions by cauterization, fulguration or laser evaporation for minimal to mild

UNDER PEER REVIEW

disease, adhesiolysis, excision of deep lesions, cystectomy, drainage and coagulation for endometriomas of ovary (moderate to severe disease) [11].

Conclusions

The Presence of dysmenorrhea, dyspareunia, pelvic pain, infertility, and clinical signs of cul-de-sac tenderness raise the suspicion of endometriosis in infertility patients. Laparoscopy remains the gold standard for diagnosis. As we found in our study that 28% of cases of unexplained infertility and 52% of cases of primary infertility had endometriosis.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

UNDER PEER REVIEW

References:

1. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. 2005;20:2698-704.

2. van der Zanden M, Nap AWJRbo. Knowledge of, and treatment strategies for, endometriosis among general practitioners. 2016;32:527-31.

3. Goud PT, Goud AP, Joshi N, Puscheck E, Diamond MP, Abu-Soud HMJF, et al. Dynamics of nitric oxide, altered follicular microenvironment, and oocyte quality in women with endometriosis. 2014;102:151-9. e5.

4. Giudice LCJNEJoM. Endometriosis. 2010;362:2389-98.

5. Koninckx PR, Meuleman C, Oosterlynck D, Cornillie FJJF, sterility. Diagnosis of deep endometriosis by clinical examination during menstruation and plasma CA-125 concentration. 1996;65:280-7.

6. Azizad-Pinto P, Clarke D. Thoracic endometriosis syndrome: case report and review of the literature. Perm J. 2014;18:61-5.

7. Moghadam AD, Delpisheh A, Sayehmiri K. The trend of infertility in Iran, an original review and meta-analysis. Nurs Pract Today. 2014;1:46-52.

8. Bentley GR, Mascie-Taylor CN. Infertility in the modern world: Present and future prospects: Cambridge University Press; 2000.

9. Mao AJ, Anastasi JK. Diagnosis and management of endometriosis: the role of the advanced practice nurse in primary care. J Am Acad Nurse Pract. 2010;22:109-16.

10. Khadawardi K. Endometriosis as a Cause of Primary Infertility in Western Regions of Saudi Arabia. Open J Obstet Gynecol. 2020;10:333-40.

11. Kulkarni C. Study of endometriosis in women of reproductive age, laparoscopic management and its outcome. Int J Reprod Contracept Obstet Gynecol. 2016;5:515.

12. Gad MS, Abdel-Gayed AM, Dawoud RM, Amer AF. Prevalence of endometriosis in unexplained infertility and chronic pelvic pain in women attending Menoufia University Hospital. Menoufia Med J. 2017;30:356.

13. Minko SE, Mvondo MA, Romeo G, Bonsou F, Tetsatsi ACM, Watcho P. Prevalence of Diagnosed Endometriosis Among Infertile Women in Yaounde, Cameroon: A Cross-Sectional Survey. Int J Reprod Med Gynecol. 2020;6:36-40.

UNDER PEER REVIEW

14. Kuohung W, Jones GL, Vitonis AF, Cramer DW, Kennedy SH, Thomas D, et al. Characteristics of patients with endometriosis in the United States and the United Kingdom. Fertil Steril. 2002;78:767-72.

15. Sahu L, Tempe A. Laparoscopic management of endometriosis in infertile women and outcome. Int J Reprod Contracept Obstet Gynecol. 2013;2:177-81.

UNDER PEER REVIEW