J Minim Invasive Surg Sci. 2015 August; 4(3): e24236. DOI: 10.17795/minsurgery-24236

Published online 2015 August 1. **Research Article**

Clinical Predictive Factors for Diagnosis of Endometriosis in Iranian Infertile Population

Shahla Chaichian,[1,2] Abolfazl Mehdizadehkashi,[3,*] Zahra Najmi,[3] Alireza Mobasseri,[3] Atoosa Jahanloo,[4] Behnaz Mohabbatian,[3] Mahjabin Marashi,[3] and Mohadeseh Pishgahroudsari[5]

[1]Minimally Invasive Techniques Research Center in Women, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, IR Iran
[2]Pars Advanced and Minimally Invasive Manners Research Center, Pars Hospital, Tehran, IR Iran
[3]Endometriosis Research Center, Rasool-e-Akram Hospital, Iran University of Medical Sciences, Tehran, IR Iran
[4]Obstetrician and Gynecologist, Endometriosis Research Center, Rasool-e-Akram Hospital, Iran University of Medical Sciences. Tehran, IR Iran
[5]Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Abolfazl Mehdizadehkashi, Endometriosis Research Center, Rasool-e-Akram Hospital, Iran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2122602478, Fax: +98-2122600714, E-mail: amehdizadehkashi@yahoo.com

Received: September 30, 2014; **Revised:** July 1, 2015; **Accepted:** July 30, 2015

Background: Endometriosis changes the management of infertile women.
Objectives: Our aim was to evaluate some of the clinical predictive factors among an Iranian infertile population.
Patients and Methods: Infertile women, scheduled for diagnostic laparoscopy, were recruited into the study and their information including age, weight, height, educational level, marriage and breast-feeding duration, history of fertility, menstrual characteristics, dysmenorrhea, and dyspareunia were collected. Clinical characteristics were then compared with laparoscopic results.
Results: Of 441 infertile women, 82 (18.6%) had endometriosis. 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 = 0.002), older age at first pregnancy (OR = 1.21, P < 0.05), lower BMI (OR = 0.9, P = 0.001), 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. The risk of the endometriosis also decreased significantly with increased numbers of previous pregnancies. The OR for endometriosis in the presence of dysmenorrhea and dyspareunia were 1.80 (1.02 - 3.04) and 1.82 (1.01 - 3.29), respectively.
Conclusions: Lower BMI, longer duration of marriage, shorter menstrual cycles, dyspareunia, and dysmenorrhea are predictive factors for diagnosis of endometriosis in infertile population. These clinical factors should be considered prior to diagnostic laparoscopy for infertility.

Keywords: Endometriosis; Infertility; Diagnosis; Laparoscopy

1. Background

Endometriosis is the presence of endometrial glandular or stromal tissue outside the uterine cavity. It affects 5 - 15% of women in their child-bearing years (1). Many women are asymptomatic, though others experience variable degrees of chronic pelvic pain, dysmenorrhea, and dyspareunia (2).

Between 25 - 50% of infertile women are diagnosed with endometriosis (2), though the precise mechanisms are unclear. Infertile women with severe endometriosis have distorted pelvic anatomy at laparoscopy (3). Endometriosis also alters the pituitary-ovarian axis, causing delayed follicular growth, and affects endometrial receptivity and embryo development thorough complex molecular mechanisms (4).

Normal infertile patients could wait or be managed medically, while patients suffering from mild endometriosis might benefit from ovulation-induction, and intrauterine insemination, and moderate to severe cases may only respond to surgery or in-vitro fertilization (IVF) (5).

Although laparoscopy is the gold standard for diagnosis of endometriosis, this costly invasive procedure might cause severe complications, whereas the results are not always confirmatory (6).

2. Objectives

We aimed to evaluate some clinical characteristics of an infertile population and their association with laparoscopic findings for detecting their predictive value of endometriosis diagnosis.

3. Patients and Methods

This prospective study was performed from May 2008 to June 2012 at the department of Obstetrics and Gynecology of Rasool-e-Akram Hospital, Tehran, Iran. The protocol of the study was approved by the Ethical Committee

in the Center. The aim and protocol of the study was explained to all participants and written informed consent was obtained from them.

Infertility was defined as "no conception in the last 12 months, despite unprotected intercourse". The male factor causing infertility was ruled out in all participants. Infertile women with normal or abnormal hysterosalpingography (HSG), scheduled for a diagnostic laparoscopy, were included in the study, if they had not received any treatment in the last three months. The patients' data were analyzed, including age, weight, height, educational level, duration of marriage, duration of breast-feeding, history of fertility, menstrual characteristics, dysmenorrhea, and dyspareunia at their first clinical visit. Menstrual bleeding was categorized as irregular, if each cycle lasted longer than 35 days or the cycle length varied more than 10 days.

The diagnosis of endometriosis was based on direct visualization at laparoscopy or pathologic confirmation. Clinical characteristics were then compared with laparoscopic results for evaluating their predictive value.

Results were expressed as mean and standard deviation or frequency of the observation. ANOVA and chi square tests were used for comparison of variables between women with and without endometriosis. Odds ratio (OR) and 95% confidence interval (95% CI) of each clinical variable were calculated by performing univariable analysis. P-value less than 0.05 was considered statistically significant.

4. Results

A group of 441 infertile women were included in the study, among whom 82 were diagnosed with endometriosis, representing a prevalence of 18.6%. Major laparoscopic findings, other than endometriosis, included tubal abnormalities (including hydrosalpynx, isthmic nodosa, and tortuosity) in 83 cases (18.8%), tubal adhesions in 56 (12.7%), frozen pelvis in 12 (2.7%), and mullerian anomalies in 14 (3.2%) patients. Table 1 presents the general characteristics of women with and without endometriosis.

Table 1. Distribution of Selected Demographic, Menstrual, Reproductive and Clinical Characteristics of Women With and Without Endometriosis [a]

	No Endometriosis (n = 359)	Endometriosis (n = 82)	P Value	OR (CI 95%)
Age, y	29.02 ± 5.96	30.23 ± 6.22	0.10	1.03 (0.99 - 1.07)
Education				
High school	183 (51)	35 (42.7)	> 0.05	
Diploma	101 (28)	20 (24.4)		1.03 (0.57 - 1.89)
University	61 (17)	23 (28)		1.97 (1.08 - 3.59)
BMI, kg/m^2	27.75 ± 4.11	26.11 ± 3.74	0.001	0.90 (0.84 - 0.96)
Duration of Marriage, y	8.58 ± 7.17	13.62 ± 19.72	0.002	1.03 (1.01 - 1.06)
Duration of Infertility, y	5.77 ± 3.91	6.06 ± 5.35	0.57	1.02 (0.96-1.08)
Age at first pregnancy, y	23.76 ± 2.43	25.21 ± 4.24	< 0.05	1.21 (1.02 - 1.43)
Breast Feeding duration, mo	17.65 ± 9.66	12.50 ± 13.28	0.29	0.96 (0.90 - 1.03)
Previous Pregnancy			0.005	
None	197 (54.9)	63 (76.8)		
1	98 (27.3)	13 (15.8)		0.41 (0.22 - 0.79)
2	37 (10.3)	4 (4.9)		0.34 (0.12 - 0.95)
≥ 3	27 (7.5)	2 (2.5)		0.23 (0.54 - 1.0)
Previous Delivery				
Nulligravida	197 (54.9)	63 (76.8)	0.002	
Nuliparus	92 (25.6)	12 (14.6)		0.41 (0.21 - 0.79)
Parus	70 (19.5)	7 (8.6)		0.31 (0.14 - 0.71)
Intervals of Menses, day	36.65 ± 20.46	30.59 ± 13.57	< 0.05	0.98 (0.96 - 1.00)
Duration of Menstrual flow, day	6.09 ± 2.08	6.57 ± 1.67	0.20	1.13 (0.93 - 1.37)
Irregular Menstrual history	105 (29.2)	15 (18.3)	< 0.05	0.54 (0.30 - 0.99)
Dysmenorrhea	229 (63.8)	62 (75.6)	< 0.05	1.80 (1.02 - 3.04)
Dyspareunia	51 (14.2)	19 (23.2)	< 0.05	1.82 (1.01 - 3.29)

[a] Data are presented as No. (%) or mean ± SD.

Although women with endometriosis were slightly older with longer history of infertility than those without endometriosis, the difference was not statistically significant (P > 0.05). Women with endometriosis had longer duration of marriage, compared to those without endometriosis (13.62 ± 19.72 years vs. 8.58 ± 7.17 years, P = 0.002), and older age at their first pregnancy (25.21 ± 4.24 years vs. 23.76 ± 2.43 years, P = 0.002). The mean BMI of patents without endometriosis was higher than those with endometriosis (P < 0.05). There was no difference regarding educational level of two groups.

Sixty-three women (76.8%) with endometriosis and 197 (54.9%) without endometriosis were nulli-gravida (P = 0.002). The risk of endometriosis decreased significantly with increase in the number of previous pregnancies. The risk of endometriosis in parus women decreased, compared with nulliparous women (OR = 0.41 (0.21 - 0.79 95% CI)).

Women with endometriosis experienced shorter intervals of menses (30.59 ± 13.57 days vs. 36.65 ± 20.46 days, P < 0.05), and longer menstrual flow (6.57 ± 1.67 days vs. 6.09 ± 2.08 days, P = 0.2), compared to those without endometriosis.

Irregular menstrual history was reported in 15 women with endometriosis (18.3%), and 105 women without endometriosis (29.2%) (P < 0.05). Complaints of dyspareunia, and dysmenorrhea were more frequent among women with endometriosis (23.2, and 75.6% respectively), compared to those without endometriosis (P < 0.05). The OR for endometriosis in the presence of dysmenorrhea and dyspareunia were 1.80 (1.02 - 3.04) and 1.82 (1.01 - 3.29), respectively.

5. Discussion

The prevalence of endometriosis was 18.6% among infertile women who underwent laparoscopic evaluation, although higher frequencies of endometriosis are expected under laparoscopic evaluation. Other studies that have studied infertile women with diagnostic laparoscopy have reported different frequencies, which might be due to difference in race or patients' characteristics. Camilleri et al. (7) reported endometriosis in 74 Maltese women out of 437 cases (16.9%). Calhaz-Jorge et al. (8) reported its prevalence at 45% in Portuguese infertile women. Its prevalence was reported 16.8%, 34.5% and 47% among Pakistanian, Mexican, and Belgic infertile women, respectively (9-11).

Overall, there was no difference regarding age, duration of infertility, duration of breast-feeding, duration of menstrual flow, and educational level between infertile women with and without endometriosis in our study. Other factors, more related to menstrual and pregnancy variables were statistically different between two groups, indicating that these factors should be considered in diagnosis of infertility resulting from endometriosis.

Lower BMI was also associated with endometriosis in our infertile population. Similarly, Lafay Pillet et al. (12) have reported that patients with different types of endometriosis had significantly lower BMIs. Vitonis et al. (13) reported an inverse association between early adulthood body size and endometriosis, independent of adult BMI and menstrual cycle characteristics, indicating a more relevant exposure at the time of menarche. Even severe endometriosis is associated with significantly lower BMI, compared to mild cases (14). This might be explained by the fact that hyperestrogenism state may cause irregular menstrual cycles due to obesity, which is associated with lower risk of endometriosis (15, 16). Women with endometriosis might also have different dietary habits (17), as higher fat intake is associated with decreased risk of endometriosis (18).

Our results showed that endometriosis was associated with higher rate of dyspareunia and dysmenorrhea. Previous studies have also revealed the association between endometriosis and different pain symptoms, such as dysmenorrhea, dyspareunia, and chronic pelvic pain (19, 20). It has been shown that density of nociceptive nerve fibers are six-fold more than normal peritoneum in peritoneal endometriosis (21). Endometriosis, as a pelvic inflammatory process, is associated with increased numbers of activated macrophages, degranulating mast cells, within or near nerve fibers, and increased concentrations of interleukins (IL-1, IL-6, IL-8, and TNF-α) (22). These interleukins can stimulate different pain fibers, directly or indirectly, through the synthesis of prostaglandins (22).

Although age and duration of infertility was statistically same in two groups, the endometriosis group had significantly longer duration of marriage. Beside the association between infertility and endometriosis, which delays pregnancy, it has been shown that women suffering from endometriosis do not postpone pregnancy voluntarily, but they cannot conceive due to reproductive, sexual, and fertility-related factors (23).

Endometriosis had also a significant association with shorter menstrual intervals, but not with duration of menstrual flow. Theoretically, any factor increasing the probability of peritoneal cavity exposure to retrograde menstruation, increases the risk of subsequent endometriosis, but there is still a large controversy in this regard. One study showed that among various factors, including early menarche, duration of menstrual flow, and menstrual cycle length, only menstrual cycle length of less than 28 days was associated with increased risk of developing endometriosis (24). Another study, comparing infertile women with and without endometriosis, reported shorter cycle length, and heavier menstrual cycles as risk factors for subsequent endometriosis (25). It has been also shown that longer cycles (≥ 6 days per month) and heavier menstrual flows in women younger than 30 years old causes a 2.5-fold increase in the risk of developing endometriosis (26).

Although we tried to consider various clinical factors, future studies evaluating socio-economic and behavioral

factors are needed. Our study was also limited, as only the records of one center were evaluated.

Our study has shown that lower BMI, longer duration of marriage, dyspareunia, dysmenorrhea, and shorter menstrual cycles are associated with increased risk of endometriosis diagnosis at laparoscopy among infertile women. These factors should specifically be considered at the time of diagnostic laparoscopy for infertility.

Authors' Contributions

Study concept and design: Zahra Najmi, Shahla Chaichian, Abolfazl Mehdizadehkashi; acquisition of data: Alireza Mobasseri, Atoosa Jahanloo, Behnaz Mohabbatian, Mahjabin Mahjabin Marashi; analysis and interpretation of data: Mohadeseh Pishgahroudsari; drafting of the manuscript: Zahra Najmi, Shahla Chaichian, Abolfazl Mehdizadehkashi; critical revision of the manuscript for important intellectual content: Zahra Najmi, Shahla Chaichian, Abolfazl Mehdizadehkashi; statistical analysis: Mohadeseh Pishgahroudsari; administrative, technical, and material support: Zahra Najmi, Shahla Chaichian, Abolfazl Mehdizadehkashi; study supervision: Zahra Najmi, Chaichian, Abolfazl Mehdizadehkashi.

References

1. Vigano P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: epidemiology and aetiological factors. *Best Pract Res Clin Obstet Gynaecol.* 2004;**18**(2):177–200.
2. Bulletti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. *J Assist Reprod Genet.* 2010;**27**(8):441–7.
3. Dai Y, Leng JH, Lang JH, Li XY, Zhang JJ. Anatomical distribution of pelvic deep infiltrating endometriosis and its relationship with pain symptoms. *Chin Med J (Engl).* 2012;**125**(2):209–13.
4. Stilley JA, Birt JA, Sharpe-Timms KL. Cellular and molecular basis for endometriosis-associated infertility. *Cell Tissue Res.* 2012;**349**(3):849–62.
5. Senapati S, Barnhart K. Managing endometriosis-associated infertility. *Clin Obstet Gynecol.* 2011;**54**(4):720–6.
6. Richardson WS, Stefanidis D, Chang L, Earle DB, Fanelli RD. The role of diagnostic laparoscopy for chronic abdominal conditions: an evidence-based review. *Surg Endosc.* 2009;**23**(9):2073–7.
7. Camilleri L, Schembri A, Inglott AS. Prevalence, characteristics, and management of endometriosis in an infertile Maltese population. *Int J Gynaecol Obstet.* 2011;**115**(3):293–4.
8. Calhaz-Jorge C, Mol BW, Nunes J, Costa AP. Clinical predictive factors for endometriosis in a Portuguese infertile population. *Hum Reprod.* 2004;**19**(9):2126–31.
9. Khawaja UB, Khawaja AA, Gowani SA, Shoukat S, Ejaz S, Ali FN, et al. Frequency of endometriosis among infertile women and association of clinical signs and symptoms with the laparoscopic staging of endometriosis. *J Pak Med Assoc.* 2009;**59**(1):30–4.
10. Preciado Ruiz R, Torres Calleja J, Zuniga Montiel JA, Martinez Chequer JC, Manterola Alvarez D, Garcia Luna A. [Incidence of endometriosis in infertile women: clinical and laparoscopic characteristics]. *Ginecol Obstet Mex.* 2005;**73**(9):471–6.
11. Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, D'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. *Fertil Steril.* 2009;**92**(1):68–74.
12. Lafay Pillet MC, Schneider A, Borghese B, Santulli P, Souza C, Streuli I, et al. Deep infiltrating endometriosis is associated with markedly lower body mass index: a 476 case-control study. *Hum Reprod.* 2012;**27**(1):265–72.
13. Vitonis AF, Baer HJ, Hankinson SE, Laufer MR, Missmer SA. A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. *Hum Reprod.* 2010;**25**(5):1325–34.
14. Yi KW, Shin JH, Park MS, Kim T, Kim SH, Hur JY. Association of body mass index with severity of endometriosis in Korean women. *Int J Gynaecol Obstet.* 2009;**105**(1):39–42.
15. Parazzini F. Risk factors for pelvic endometriosis in women with pelvic pain or infertility. *Eur J Obstet Gynecol Reprod Biol.* 1999;**83**(2):195–9.
16. Parazzini F, Ferraroni M, Fedele L, Bocciolone L, Rubessa S, Riccardi A. Pelvic endometriosis: reproductive and menstrual risk factors at different stages in Lombardy, northern Italy. *J Epidemiol Community Health.* 1995;**49**(1):61–4.
17. Parazzini F, Chiaffarino F, Surace M, Chatenoud L, Cipriani S, Chiantera V, et al. Selected food intake and risk of endometriosis. *Hum Reprod.* 2004;**19**(8):1755–9.
18. Trabert B, Peters U, De Roos AJ, Scholes D, Holt VL. Diet and risk of endometriosis in a population-based case-control study. *Br J Nutr.* 2011;**105**(3):459–67.
19. Porpora MG, Koninckx PR, Piazze J, Natili M, Colagrande S, Cosmi EV. Correlation between endometriosis and pelvic pain. *J Am Assoc Gynecol Laparosc.* 1999;**6**(4):429–34.
20. Barlow DH, Glynn CJ. 7 Endometriosis and pelvic pain. *Baillieres Clin Obstet Gynaecol.* 1993;**7**(4):775–89.
21. Tokushige N, Markham R, Russell P, Fraser IS. Nerve fibres in peritoneal endometriosis. *Hum Reprod.* 2006;**21**(11):3001–7.
22. Howard FM. Endometriosis and mechanisms of pelvic pain. *J Minim Invasive Gynecol.* 2009;**16**(5):540–50.
23. Darrow SL, Selman S, Batt RE, Zielezny MA, Vena JE. Sexual activity, contraception, and reproductive factors in predicting endometriosis. *Am J Epidemiol.* 1994;**140**(6):500–9.
24. Arumugam K, Lim JM. Menstrual characteristics associated with endometriosis. *Br J Obstet Gynaecol.* 1997;**104**(8):948–50.
25. Matalliotakis IM, Cakmak H, Fragouli YG, Goumenou AG, Mahutte NG, Arici A. Epidemiological characteristics in women with and without endometriosis in the Yale series. *Arch Gynecol Obstet.* 2008;**277**(5):389–93.
26. Darrow SL, Vena JE, Batt RE, Zielezny MA, Michalek AM, Selman S. Menstrual cycle characteristics and the risk of endometriosis. *Epidemiology.* 1993;**4**(2):135–42.