STUDY OF ENDOMETRIOSIS RELATED INFERTILITY, A COMPARATIVE STUDY

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Abstract- It seems that endometriosis plays an important role in female factor infertility but a clear causal relationship has yet to be established. This case-control study was conducted to determine and compare the frequency and severity of endometriosis in 100 infertile women and 120 fertile multi-para women as control group. Descriptive statistics, Student *t* test and Chi square test were used in analyzing data. Endometriosis was diagnosed in 38% of infertile versus 11.6% in fertile women (P=0.002). The mean age of women with endometriosis was 27.9±6.1 years; maximum prevalence of endometriosis was observed at 26 years of age. The mean duration of infertility was 4.3±1.9 years in women with endometriosis and 4.6±1.2 years in women without endometriosis. The prevalence of endometriosis in study population was comparatively higher than what has been reported in studies from other countries. There was a significant relation between endometriosis and infertility. Diagnostic time interval had no relation with infertility and severity of endometriosis. Age-related factors did not have any effect on fertility in women with endometriosis. Our study demonstrates a meaningful relation between endometriosis and infertility. Endometriosis may have a higher prevalence in Iranian population.
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Key words: Endometriosis, laparoscopy, infertility, severity of endometriosis

INTRODUCTION

Endometriosis is the presence of endometrial tissue outside the uterine cavity, most commonly surrounding the ovaries and fallopian tubes (1). Since its first description in the modern literature about 70-80 years ago by Sampson (2), endometriosis has been the focus of interest for gynecologists and reproductive endocrinologists.

The most widely accepted etiological theory of endometriosis is retrograde flow of menstrual flow through the fallopian tubes and deposition of viable endometrial tissue, with subsequent implantation on the peritoneal surface. Increasingly, the etiology of endometriosis is studied at the immunological and genetic levels (1).

Endometriosis plays an important role in female factor infertility. Several studies have shown this role, though with confusing results in some cases (3), and several hypotheses have been put forward to support these findings (4). In spite of high prevalence of endometriosis in infertile females, the exact prevalence of endometriosis has remained unknown. However, prevalence rates of 20% to 90% have been reported in women with pelvic pain and infertility (5).

Considering the lack of sufficient data on the exact prevalence of endometriosis in our population, we tried to determine the prevalence of endometriosis in fertile and infertile women and performed an analytic comparison between the two groups. Besides, we determined the age range, maximum age of prevalence, severity of endometriosis, the duration of infertility until diagnosis (diagnostic delay) and a possible relation between these variables and infertility.

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MATERIALS AND METHODS

This case-control study was performed to determine and compare the prevalence of endometriosis in infertile women and multi-parous female control group. One hundred patients with chief complaint of infertility, admitted in infertility clinics of Mashhad University of Medical Sciences, who were in the age range of 25 to 40 years and had no history of systemic disease, were included in this study. Laparoscopy was performed for etiologic diagnosis of infertility. We used goal-directed sampling method to choose samples among infertile female patients who were admitted at clinics.

The control group consisted of 120 fertile females in the age range of 25-40 years, who were matched with patients on the basis of age and underwent investigation for endometriosis while we were performing bipolar laparoscopy for tubal legation. On inclusion of cases in control group, special attention was paid to lack of history of prior infertility in samples to prevent a false increase in observed prevalence of endometriosis.

Laparoscopy remains to be the investigation of choice in cases of endometriosis associated infertility and allows the possibility of surgical ablation at diagnosis (6) and was our main diagnostic tool in this study. We used an Olympus laparoscope and investigated ovaries, broad ligament surfaces, anterior pouch, utero-sacral ligaments and col-de-sac at laparoscopy, both in the case and control groups, to prevent bias in the procedure of investigation.

We used Revised American Fertility Society (RAFS) (7) classification by American Society for Reproductive Medicine (ASRM) in 1996 for classification of severity of endometriosis in this study. This system classifies the severity of endometriosis into 4 stages, depending on the location, extent, presence of adhesion and obstruction, morphology and biologic activity of lesions (8, 9). The new ASRM classification of endometriosis is the best method to clearly document the extent and location of the disease (10, 11).

For analyzing data, we used frequency distribution tables and graphs and calculated distribution parameters of the variables. We used analytic statistical methods and Chi square test to determine the relationship between infertility and endometriosis in case and control groups. We also used independent *t* test to compare age distribution of fertile and infertile groups. To determine the relationship between severity of endometriosis and infertility duration with age, the Pearson correlation coefficient was used. The level of significance in the statistical methods has been P=0.05 at 95% confidence interval. Considering the natural distribution of variables, parametrical statistics were used in our calculations. The results of the statistical tests were re-evaluated with SPSS (Statistical Package for Social Sciences) software and illustrated with Microsoft Excel 2000.

The ethical issues considered in this study include keeping the security of patients' medical records, explaining the aims of study and laparoscopy procedure to attending patients and performing the non-invasive infertility diagnostic work-up before laparoscopy in all the women enrolled in the study.

RESULTS

Mean of ages had no significant difference in two groups of women. Endometriosis was proved to be present in 38% of infertile women, in comparison to 11.6% in fertile women.

As table 1 shows, there was a significant relation between endometriosis diagnosis with laparoscopy and infertility (Chi square=9.7, df=1, P=.002, odds ratio = 4.49). Primary infertility was 2.47 times more common than secondary infertility in our cases (Chi square = 0.01, df= l, P= .911).

Approximately 71% of cases with endometriosis had primary and 28.9% had secondary infertility. The mean age of women with endometriosis in our study was 27.9±6.1 years versus 30.1±4.6 years in women without it. Independent *t* test showed a significant difference between the ages of presentation in the two groups (t= 2.4, df= 105, P= 0.018).The mean of ages was 27.5±4.5 years in infertile women with endometriosis versus 26.8±0.5 years in infertile women without endometriosis.

Table 1. Clinical signs and symptoms in fertile and infertile women*

Variable†	Fertile	Infertile
Dysmenorrhea	38(31.7)	55(55)
Dyspareunia	4(3)	12(12)
Chronic pelvic pain	4(3)	28(28)
Douglas nodularity	-	11(11)
Endometriosis Diagnosis	14(11.6)	38(38)

* Data are presented as number (percent).
† There were significant differences between all variables in two groups.

No significant difference was observed among the ages of infertile women with and without endometriosis, based on the result of *t* test (*t*=0.6, df=98, *P*=0.544). The average age in fertile women without endometriosis was 34.3±4.3 years, which was higher than that of infertile women with endometriosis (27.1±4.9 years). Independent *t* test showed a significant difference between the two. (*t*=8.9, df=148, *P*< 0.0001). As figure 1 shows maximum prevalence of endometriosis in this study occurred in the age-range of 26-30 years, which was 36.4%. The youngest infertile patient in our study was 19 years old while the oldest was 39 years of age and the median age of our samples was 26.1 years. The mean duration of infertility was 4.3 ±1.9 years in patients with endometriosis and 4.6±1.2 years in patients without it. There was no meaningful difference between the duration of infertility until laparoscopy in infertile women, with and without endometriosis (*t*=0.3, df =20, *P*=0.782); though, the duration of infertility in women with endometriosis was slightly shorter than those without it (4.3 against 4.6 years).

As seen in figure 2, one-way analysis of variance test showed no meaningful difference between the duration of infertility in women with different level of endometriosis severity (f=1.6, df=3.13, *P*=0.237). Also, using Pearson coefficient of correlation test, there was no significant linear relation between the duration of infertility and the severity of endometriosis (r= -0.3, *P*=0.17).

The rate of clinical signs in two groups of fertile and infertile women is demonstrated in table 1. There was a significant positive correlation between the severity of endometriosis and dysmenorrhea (r=.49, *P*= 0.027).

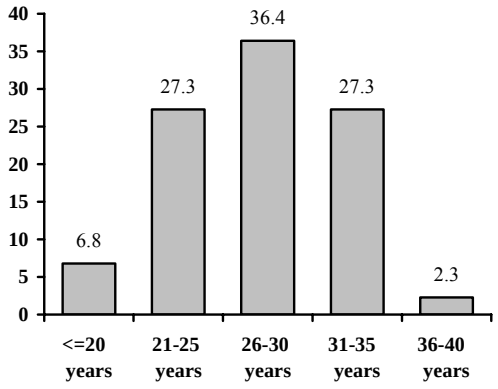

Fig. 1. Prevalence of endometriosis in different age ranges

Douglas nodularity was diagnosed in 22% of cases with endometriosis and in none of the fertile women.

Endometriosis was the most common etiology of infertility in our samples, contributing to 40% of cases. Table 2 demonstrates severity of endometriosis in women who suffered from endometriosis in fertile and infertile women. Laparoscopic findings showed that the tubal and peritoneal replacement of endometriosis were the most common etiologies of infertility in our samples, contributing to 40% of cases.

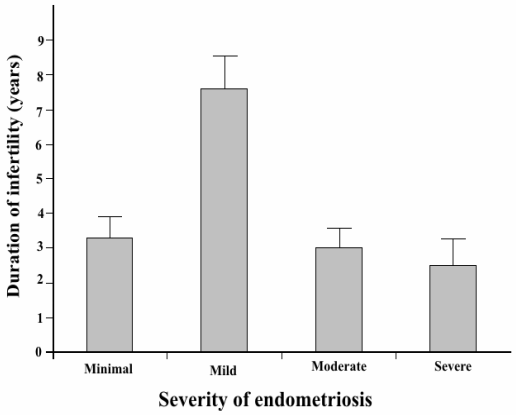

Fig. 2. Comparison of average duration of infertility in correlation with the severity of endometriosis in infertile women (One-way ANOVA, F=1.6, df=3.13, *P*=0.237). the height of each bar represent the mean of duration and error bars represent standard deviations.

Table 2. Severity of endometriosis in fertile and infertile women (n=52)*

Severity of endometriosis	Fertile	Infertile
Minimal (stage 1)	7(50.0)	3(7.9)
Mild (stage 2)	5(35.7)	9(23.7)
Moderate (stage 3)	2(14.3)	15(39.5)
Sever (stage 4)	-	11(28.9)
Total	14(26.9)	38(73.1)

* Data are presented as number (percent).

DISCUSSION

The goal of this study was to investigate the relation between infertility and endometriosis and determine the socio-demographic features of endometriosis. Several studies have been performed to determine the prevalence of endometriosis and its relation to infertility. The prevalence of endometriosis in our study was 38% in the infertile group and 11.6% in fertile control group. Other studies that have been performed in other regions of the world have revealed relatively lower prevalence rates, both in the fertile and infertile populations. Topalski *et al.* reported a prevalence rate of 26% in infertile versus 5% in fertile female population in Yugoslavia (12). In another study performed in Norway, the prevalence of endometriosis in total population was 2.0% (13). However, other studies have suggested an endometriosis prevalence of 0.5% to 5% in fertile and 25% to 40% in infertile women (1). It seems that the prevalence of endometriosis in our study is relatively higher or at least in the upper limit of what has been reported in other studies.

In accordance with other studies (3, 4, 14), our study demonstrates a meaningful relation between endometriosis and infertility. In an upsurge of studies in late 1990s on determining the relation between endometriosis and infertility, it was shown that there is a meaningful relation between endometriosis and infertility. Endometriosis is shown to be one of the 7 major reasons for infertility, responsible for 2.6% to 4.7% of cases of infertility (15). In cases with a negative reproductive work-up to the point of laparoscopy, endometriosis plays a more prominent role. In one study 43% of such patients had endometriosis (16). In our study, primary infertility was 2.47 times more common than secondary infertility in patients with endometriosis. In another study too, it has been shown that endometriosis occurs three times more often in the group of patients with primary sterility than in patients with secondary sterility (11). In our study the ratio of endometriosis in infertile women with secondary infertility to women with primary infertility was higher than mentioned study.

Although endometriosis is associated with infertility, a clear causal relationship has yet to be established unless adhesive disease is found (17).

The reasons for the occurrence of endometriosis and its consequences (pain, sterility, adhesions) are numerous and involve the endometrium, the immune system (macrophages, natural killer cells), the peritoneum and fallopian tubes. The failure of process of clearing the peritoneal cavity from endometrium fragments can result in local inflammation with hyperactivation of macrophages, secreting a variety of different compounds. Some of these compounds may bring about metaplasia of the peritoneum or the development of Mullerian residues, culminating in endometriosis (18). Whereas moderate or severe endometriosis causes infertility on the basis of mechanical disruption of ovulation or efficient gamete transport, the influence of minimal or mild disease on fertility has remained controversial (19,20). In the absence of objectively confirmed mechanisms, endometriosis may simply be a co-factor in infertility (21). Recent literature has, in fact, questioned whether endometriosis is truly a disease (22-24).

To some extent, these controversies may simply reflect our frustration and lack of consensus on this disorder. This view is further supported by the lack of evidence of a benefit of medical treatment of endometriosis and its associated infertility (21). The conclusion that subtle peritoneal lesions are not part of this disease (25) is probably premature and ignores important aspects of the biochemistry of endometriosis and its subtle impact on infertility. Indeed, the collective literature on endometriosis, infertility, and treatment has not always been helpful and confuses as often as it enlightens. In a randomized clinical trial to evaluate the effect of endometriosis on fertility, Parazzini treated 51 women with resection/ablation of endometriosis and

followed 45 women expectantly in this group. The pregnancy rate was 24% in the resection/ablation group and 29% in the no treatment group by one-year follow up (26).

On the other hand, several lines of evidence indicate that endometriosis, even in its mildest forms, contributes to infertility (27). Lessey found that concentration of integrins was less in the endometrial biopsies done in patients with endometriosis compared to patients without endometriosis (28). Treating patients with endometriosis certainly will improve the condition of the endometrium and its receptivity to the embryo for implantation. Alteration of all these factors by medical or surgical treatment may be responsible for the increased pregnancy rate that is documented in some studies. Recently, a large meta-analysis study of 22 published articles on endometriosis and its effect on in-vitro fertilization outcome revealed that the pregnancy rate is affected by endometriosis; the authors found that the fertilization rate was higher in women with severe endometriosis compared to women with tubal factor, and compared to mild endometriosis (29). It is difficult to explain these results; however, the authors suggest that various results may by due to endometriosis being present in an active or inactive form. The average duration of infertility in infertile women with endometriosis in our study was slightly less compared to women without endometriosis (4.3 against 4.6 years). This is slightly longer than what has been reported in other studies; a median duration of infertility of 2-4 years was reported in a study from Yugoslavia (12). The reason behind this difference may be the associated symptoms of endometriosis that brings the patient to the physician at an earlier time. In our study, no meaningful relation was observed between the duration of infertility based on severity of endometriosis. Also, there was no meaningful linear relation between duration of infertility and endometriosis severity, but there was a significant positive correlation between the severity of endometriosis and dysmenorrhea in our study. However, recently Muzii *et al.* found no correlation between the ASRM classification of endometriosis and associated dysmenorrhea (11)

The average age of women with endometriosis was less than those without it in this study. In fact, this significant difference was due to selection of multiparous women as our control group that included women of 26 to 40 years of age, with naturally a higher age than infertile nulliparous women. No significant difference was observed between average age of infertile women with and without endometriosis. It is well known that variables like age do not have any influence on endometriosis prevalence. The highest prevalence of endometriosis in our study was observed in the age range of 26 to 30 years and the lowest prevalence in age-range of 36 to 40 years. This significant decrease in the prevalence of the disease relates to the relatively scant number of samples in this age range. Since most of the infertile women visit their physician in a lower age-range, only 18 of our samples were in the age-range of 31 to 35, while we had 34 samples in 26-30 years age group and 36 cases in 21-25 years age group. The youngest infertile patient in our study was 19 years old while the oldest was 39 years of age and the median age of our samples was 26.1 years.

It should be remembered that potential threats to validity of substantial magnitude exist in both clinic- and population-based epidemiological studies of endometriosis. In clinic-based studies, control subjects (infertility clinic patients, women delivering infants, or women undergoing tubal ligation) often are not representative of the population from which the cases arose, and bias can be considerable for behavioral and hormone-related exposures. In population-based studies, substantial case under ascertainment may exist, and diagnosed cases may be a biased sample of all potential cases in the population. Although neither the ideal design nor the ideal case and control groups are likely to be achievable in epidemiological studies of endometriosis, more careful subject-selection strategies may improve the validity of studies that are obliged to depart from the ideal (30).

Overall, this study proposes that endometriosis, as compared with results of studies from other parts of world, may have a higher prevalence in Iranian population. The relation between endometriosis and infertility was observed clearly in this study. We did not find any significant or meaningful relation

between diagnostic time lag, existence of endometriosis, infertility and severity of endometriosis. Also, age-related specificity did not have any effect on fertility in women with endometriosis. Further studies on groups from other parts of country are needed to delineate these results in advance.

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