Clinical Profile and Correlation between Endometriosis in Infertile Women in Tertiary Health Care of India

Sukanya Sakhare, Atul Padmawar, Sushma Gore
Shri Vasantrao Naik Government College, Yavatmal, Maharashtra, India

Abstract: Background: Patients with endometriosis mainly complain of pelvic pain, dysmenorrhea, and dyspareunia. Approximate prevalence of endometriosis is 6-8%. A combination of surgical treatment and either preoperative or postoperative medical therapy has been suggested for endometriosis. Clinical impression of low incidence in Indian women may have been due to limited medical and diagnostic facilities available. So, we planned this study to evaluate the prevalence and clinical profile of endometriosis in Indian infertile women. Material and Methods: The present cross sectional, prospective and observational study was conducted on 50 women of ages 18-40 years, with history of primary or secondary infertility and whose husband semen analysis was normal, attending the Obstetrics and gynecology department during the period of February 2021 to January 2022, at tertiary health center, were included. All the suspected cases of endometriosis were undergone to laparoscopic examination. Diagnosed Endometriosis was scored and classified in stage-I, stage-II, stage-III and stage IV according to revised American Fertility Society Classification. Appropriate software and test applied to find the statistically significant difference. P value <0.05 was considered as statistically significant. Results: Majority (50.98%) of the patients had age range 21-26 years. Mean age of the patients were 24.35 ± 4.02. Highest (52.94%) number of patients had BMI 18.5-22.9 followed by BMI 23-24.9 present in 29.41% patients. Majority (70.59%) of the patients had primary infertility. Majority (37.25%) of the patients had mild (stage-II) disease and 29.41% patients had moderate (stage-III). Patients in stage-II disease, 7 patients (36.84%) had pelvic pain and in stage-III out of 15 patients, 5 patients (33.33%) had pelvic pain. In stage-II disease, 09 patients (47.38%) had heavy menses and in stage-III, 8 patients (53.33%) had heavy menses. Patients in stage-II disease, 09 patients (47.38%) had dyspareunia and in stage-III, 09 patients (60%) had dyspareunia. Patients in stage-III disease, 06 patients (40%) had adnexal mass and in stage-II, 04 patients (21.05%) had adnexal mass. Mean estradiol, prolactin, cortisol CA-125 and T3, T4 and TSH levels were highest in stage IV and mean FSH and LH levels were highest in stage I. Conclusion: Prevalence of endometriosis in infertile women was 33.33%. The common clinical features are dysmenorrhea, irregular and heavy menses, dyspareunia, pelvic pain and tenderness. As the severity of the disease increases the hormonal derangement also increases. High level of estradiol was present in patients with stage-III and IV disease.

Keywords: endometriosis, prevalence, clinical profile, adnexal mass, dyspareunia

1. Introduction

Endometriosis is defined as the presence of endometrial like tissue (glands and stroma) outside the uterus, which induces a chronic inflammatory reaction, scar tissue, and adhesions that may distort a woman’s pelvic anatomy. Endometriosis is primarily found in young women, but its occurrence is not related to ethnic or social group distinctions. Patients with endometriosis mainly complain of pelvic pain, dysmenorrhea, and dyspareunia. The severity of endometriosis symptoms and the probability of its diagnosis increase with age the incidence peaks in women in their 40s.

Recent data indicate that the approximate prevalence of endometriosis is 6-8%. In normal couples, fecundity is in the range of 0.15 to 0.20 per month and decreases with age. Several mechanisms have been proposed to explain the association between endometriosis and infertility. These mechanisms include distorted pelvic anatomy, endocrine and ovulatory abnormalities, altered peritoneal function, and altered hormonal and cell-mediated functions in the endometrium. Major pelvic adhesions or peritubal adhesions that disturb the tubo-ovarian coordination and tube patency can impair oocyte release from the ovary, inhibit ovum pickup, or impede ovum transport. A complex network of humoral and cellular immunity factors modulates the growth and inflammatory behaviour of ectopic endometrial implants and affects embryo implantation.

The reference standard for diagnosing endometriosis is laparoscopy, along with histological verification by biopsy of suspected lesions. As laparoscopy is invasive and costly procedure, the true prevalence of endometriosis in women of reproductive age remains uncertain. The American Society for Reproductive Medicine, ASRM) classification has been the most used for the severity assessment of endometriosis. It was first published in 1979 and revised twice afterwards. Unfortunately, it has remained unclear whether the ASRM classification has any prognostic significance regarding prediction of a woman’s fertility potential. A more recent classification system is the Endometriosis Fertility Index (EFI). This classification system is based on the point scores from the ASRM system combined with additional anamnestic, and post-surgical information. The EFI gives a score from zero to 10 points, and the score predicts results well from subsequent non-IVF treatments. After 3 years, those with a point score of 0-3 had only 10% probability of becoming pregnant, whereas those with the highest score of 9-10 points had an approximately 75% success rate.

The treatment for endometriosis is essentially chosen by each individual woman, depending on symptoms, age, and fertility. A combination of surgical treatment and either preoperative or postoperative medical therapy has been suggested for endometriosis. Surgical treatment followed by medical treatment may prolong the pain-free (or reduced-pain) interval compared to surgery alone. Effective, evidence-based treatments of endometriosis-associated infertility include conservative surgical therapy and assisted reproductive technologies. The treatment options of choice, include surgery or in vitro fertilization and embryo transfer (IVF-ET). The surgical removal of endometriotic implants in...
minimal-mild severity endometriosis was shown to improve fertility in two randomized controlled studies.\textsuperscript{10,11}

The true prevalence of endometriosis is difficult to establish since endoscopy or laparotomy is required for a definitive diagnosis and the disease may exist in patients who are asymptomatic. It is generally believed; the disease is relatively less common in Indian and Asian women.\textsuperscript{12} But study of Mishra et al demonstrated a very high prevalence of endometriosis 48.33%.\textsuperscript{13} Therefore, we feel that the clinical impression of low incidence in Indian women may have been due to limited medical and diagnostic facilities available. So, we planned this study to evaluate the prevalence and clinical profile of endometriosis in Indian infertile women.

**Objectives**
1) To assess the prevalence of endometriosis in infertile women attending the tertiary health care center.
2) To assess the clinical profile and characteristics of endometriosis in infertile women.

**2. Material and Methods**

The present cross sectional, prospective and observational study was conducted on 50 women of ages 18-40 years, with history of primary or secondary infertility and whose husband semen analysis was normal, attending the Obstetrics and gynecology department during the period of February 2021 to January 2022, at tertiary health center. were included. Patients with polycystic ovarian syndrome, pelvic inflammatory disease, Adhesion due to previous surgery or due to infectious disease were excluded.

**2.1 Methodology**

This study was conducted in compliance with the protocol, the Institutional Ethical Committee (IEC), and informed consent regulations. A pre-designed case record form (CRF) was used to collect demographic details like name, age, address along with data about physical examination and clinical history. Findings done with respect to presence of abdominal/adnexal masses, mobility of uterus and presence of adnexal tenderness.

All the suspected cases of endometriosis were undergone to laparoscopic examination. The presence of classical powder burn, blue/ black implant, vesicular hemorrhagic lesions, nodular, discolorated lesions, chocolate ovarian cyst, sub ovarian or peritoneal adhesions were taken as evidence of endometriosis. Diagnosed Endometriosis was scored and classified in stage-I, stage-II, stage-III and stage IV according to revised American Fertility Society Classification.

**Data Entry and Statistical Analysis**

Data was recorded in pre structure case record form. From this CRF, data enter in MS Excel and appropriate software and test applied to find the statistical significant difference. P value <0.05 was considered as statistical significant. For the comparison of qualitative data, Chi-square or Fishers exact test was used. For the comparison of quantitative data, repeated measure ANOVA was used. The confidence limit for significance was fixed at 95% level with p value <0.05.

**Table 1:** Revised ASRM classification for endometriosis

![Table 1: Revised ASRM classification for endometriosis](image)
Under aseptic precaution blood was collected and sent for the routine blood investigation and hormone estimation (Estradiol, FSH, LH, T4, T3, TSH, Cortisol and CA-125) and their finding was recorded in CRF.

3. Observations and Results

| Table 1: Distribution of patients according baseline characteristics |
|-----------------|-----------------|-------|
| Patients’ characteristics | Number | Percentage |
| Age Groups (years) | | |
| 18-20 | 10 | 19.6 |
| 21-23 | 13 | 25.49 |
| 24-26 | 13 | 25.49 |
| ≥30 | 6 | 11.76 |
| BMI of Patients (Kg/m2) | | |
| <18.5 (Underweight) | 5 | 9.8 |
| 18.5-22.9 (Normal) | 27 | 52.94 |
| 23-24.9 (Overweight) | 15 | 29.41 |
| 25-29.9 (Pre-obese) | 4 | 7.84 |

In the present study majority (50.98%) of the patients had age range 21-26 years. 19.6% patients had age range 18-20 years and 17.64% patients had age range 27-29 years. Mean age of the patients were 24.35 ± 4.02. Highest (52.94%) number of patients had BMI 18.5-22.9 followed by BMI 23-24.9 present in 29.41% patients.

Graph 1: Type of Infertility

Majority (70.59%) of the patients had primary infertility and 29.41% patients had secondary infertility.

Patient distribution according to severity of Endometriosis:

Majority (37.25%) of the patients had mild (stage-II) disease and 29.41% patients had moderate (stage-III). 21.6% patients had minimal (stage-I) disease and 11.76% patients had severe (stage-IV) disease.

Graph 2: Severity of Endometriosis among patients
Table 2: Distribution of patients according to menstrual complaints:

<table>
<thead>
<tr>
<th>Menstrual Symptoms and Signs</th>
<th>Severity/stage of Endometriosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage-I (n=11)</td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td></td>
</tr>
<tr>
<td>9 (9.09%)</td>
<td>2 (18.18%)</td>
</tr>
<tr>
<td>Irregular menstrual cycle</td>
<td>6 (54.54%)</td>
</tr>
<tr>
<td>Heavy menses</td>
<td>4 (36.36%)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>4 (36.36%)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>3 (27.27%)</td>
</tr>
<tr>
<td>Tenderness</td>
<td>1 (9.09%)</td>
</tr>
<tr>
<td>Adnexal mass</td>
<td>1 (9.09%)</td>
</tr>
<tr>
<td>Mobility of uterus</td>
<td>1 (9.09%)</td>
</tr>
</tbody>
</table>

Out of 19 patients in stage-II disease, 7 patients (36.84%) had pelvic pain and in stage-III out of 15 patients, 5 patients (33.33%) had pelvic pain. Out of 6 patients in stage IV, 50% patients had pelvic pain. Out of 19 patients in stage-II disease, 11 patients (57.89%) had irregular menses and in stage-III out of 15 patients, 9 patients (60%) had irregular menses. Out of 6 patients in stage IV, 50% patients and out of 10 patients in stage-1, 54.54% had irregular menses.

Out of 19 patients in stage-II disease, 09 patients (47.38%) had heavy menses and in stage-III out of 15 patients, 8 patients (53.33%) had heavy menses. Out of 6 patients in stage IV, 50% patients and out of 10 patients in stage-1, 36.36% had heavy menses. Out of 19 patients in stage-II disease, 11 patients (57.8%) had dysmenorrhea and in stage-III out of 15 patients, 11 patients (73.33%) had dysmenorrhea. Out of 6 patients in stage IV, 66.66% patients and out of 10 patients in stage-1, 36.36%.

Out of 19 patients in stage-II disease, 09 patients (47.38%) had dysmenorrhea and in stage-III out of 15 patients, 09 patients (60%) had dyspareunia. Out of 6 patients in stage IV, 66.66% patients and out of 10 patients in stage-1, 27.27% had dyspareunia. Out of 15 patients in stage-III disease, 06 patients (40%) had tenderness and in stage-II out of 19 patients, 04 patients (21.05%) had tenderness. Out of 6 patients in stage IV, 50% patients and out of 10 patients in stage-1, 9.09% had tenderness.

Out of 15 patients in stage-III disease, 06 patients (40%) had adnexal mass and in stage-II out of 19 patients, 04 patients (21.05%) had adnexal mass. Out of 6 patients in stage IV, 50% patients and out of 10 patients in stage-1, 9.09% had adnexal mass. Out of 15 patients in stage-III disease, 06 patients (40%) had uterine mobility and in stage-II out of 19 patients, 04 patients (21.05%) had uterine mobility. Out of 6 patients in stage IV, 50% patients and out of 10 patients in stage-1, 9.09% had uterine mobility.

Table 3: Hormones levels of the patients with Endometriosis

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Stage-I (n=11)</th>
<th>Stage-II (n=19)</th>
<th>Stage-III (n=15)</th>
<th>Stage-IV (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pg/mL)</td>
<td>261.2 ± 36.07</td>
<td>327.21± 36.59</td>
<td>449.66 ± 56.98</td>
<td>530.28 ± 53.05</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>17.16 ± 1.19</td>
<td>14.14 ± 1.57</td>
<td>12.88 ± 2.23</td>
<td>9.75 ± 1.90</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>8.57 ± 0.52</td>
<td>7.01 ± 1.31</td>
<td>6.70 ± 0.80</td>
<td>4.92 ± 1.64</td>
</tr>
<tr>
<td>Prolactin (μg/L)</td>
<td>15.18 ± 3.02</td>
<td>19.26 ± 2.19</td>
<td>24.22 ± 1.91</td>
<td>28.04 ± 1.98</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>13.71 ± 0.65</td>
<td>15.01 ± 0.44</td>
<td>18.07 ± 0.68</td>
<td>21.55 ± 0.93</td>
</tr>
<tr>
<td>CA-125 (U/mL)</td>
<td>28.74 ± 2.15</td>
<td>38.21 ± 2.76</td>
<td>49.77 ± 4.04</td>
<td>63.67 ± 5.26</td>
</tr>
<tr>
<td>T4 (pmol/L)</td>
<td>6.62 ± 1.00</td>
<td>6.97 ± 0.75</td>
<td>7.03 ± 0.99</td>
<td>7.01 ± 0.68</td>
</tr>
<tr>
<td>T3 (ng/dL)</td>
<td>119.16 ± 18.17</td>
<td>125.62 ± 13.67</td>
<td>126.6 ± 17.87</td>
<td>126.26 ± 12.3</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>2.23 ± 0.64</td>
<td>2.75 ± 0.64</td>
<td>3.01 ± 0.63</td>
<td>3.23 ± 0.50</td>
</tr>
</tbody>
</table>

Mean estradiol levels in stage I, II, III and IV were 261.2, 327.21, 449.66 and 530.28. Mean FSH levels in stage I, II, III and IV were 17.16, 14.14, 12.88 and 9.75. Mean LH levels in stage I, II, III and IV were 8.57, 7.01, 6.70 and 4.92. Mean prolactin levels in stage I, II, III and IV were 15.18, 19.26, 24.22 and 28.04. Mean cortisol levels in stage I, II, III and IV were 13.71, 15.01, 18.07 and 21.55. Mean CA-125 levels in stage I, II, III and IV were 28.74, 38.21, 49.77 and 63.67. Mean T4 levels in stage I, II, III and IV were 6.62, 6.97, 7.03 and 7.01. Mean T3 levels in stage I, II, III and IV were 119.16, 125.62, 126.6 and 121.26. Mean TSH levels in stage I, II, III and IV were 2.23, 2.75, 3.01 and 3.23.

4. Discussion

Presence of endometrial like tissue (glands and stroma) outside the uterus is known as endometriosis. It induces a chronic inflammatory reaction, scar tissue, and adhesions that may distort a woman’s pelvic anatomy.\(^1\) The endometrial tissue is found most frequently in the pelvis, where it can be limited to the superficial peritoneum or infiltrate deeply into bladder, ureters and intestines. Endometriosis occurs in 6 to 10% of the general female population and in women with pain, infertility, or both, the frequency is 35-50%.\(^2\) About 25 to 50% of infertile women have endometriosis, and 30 to 50% of women with endometriosis are infertile.

Patients with endometriosis mainly complain of pelvic pain, dysmenorrhea, and dyspareunia.\(^3\) The associated symptoms can impact the patient’s general physical, mental, and social well-being. The symptoms of endometriosis do not always correlate with its laparoscopic appearance.\(^5\) The severity of endometriosis symptoms and the probability of its diagnosis increase with age.\(^6\) Several mechanisms have been proposed to explain the association between endometriosis and infertility. These mechanisms include disturbed pelvic...
anatomy, endocrine and ovulatory abnormalities, altered peritoneal function, and altered hormonal and cell-mediated functions in the endometrium.

The reference standard for diagnosing endometriosis is laparoscopy, along with histological verification by biopsy of suspected lesions. As laparoscopy is invasive and costly procedure, the true prevalence of endometriosis in women of reproductive age remains uncertain. The revised ASRM classification is a scoring system based on localization and size of implants, and extent of adhesions. A point score defines four classes: minimal, mild, moderate, and severe endometriosis. Unfortunately, it has remained unclear whether the ASRM classification has any prognostic significance regarding prediction of a woman’s fertility potential.

The clinical management of an infertile couple should consider the age of the female, duration of infertility, male factor, duration of medical attention, pelvic pain, stage of endometriosis, and family history. Effective, evidence-based treatments of endometriosis-associated infertility include conservative surgical therapy and assisted reproductive technologies. The treatment options of choice include surgery or in vitro fertilization and embryo transfer (IVF-ET). It is generally believed the disease is relatively less common in Indian and Asian women. But study of Mishra et al demonstrated a very high prevalence of endometriosis 48.33%. So the objectives of this study was to assess the prevalence of endometriosis and clinical profile and characteristics of endometriosis in infertile women.

Prevalence of the Endometriosis
In the present study we screened 170 infertile women in the department of gynecology during the period of February 2021 to January 2022, at tertiary health center. Three eligible infertile women included in the study out of which 51 women diagnosed with endometriosis by laparoscopy. Therefore, the prevalence of endometriosis in infertile women comes out 33.33%. Mohan R et al performed a retrospective study they found that incidence of endometriosis among infertile patients who have undergone laparoscopy was 195/569 (34.2%). In the study of Mishra V et al the frequency of endometriosis among women with infertility subjected to diagnostic hysterolaparoscopy was found to be 48.38%. Smorgick et al reported a 47% prevalence of endometriosis among adolescent girls with chronic pelvic pain undergoing laparoscopy. According to Tsuzi et al worldwide endometriosis has been found up to 63%.

In the study of Ashish et al all subjects were of Indian ethnicity from Eastern Uttar Pradesh and Bihar, the two states of northern Indian population. The point prevalence of endometriosis disease (n=221) in population had a mean age of 32.10±8.08 years. Shaista Z et al performed a prospective study on patients of reproductive age with history of infertility and sub-fertility with normal semen analysis of husband. They found that the frequency of endometriosis in women with infertility and sub-fertility was 10 (20%). In a study of Meuleman C et al the prevalence of endometriosis was 47% (104/221). These including stage I (39%, 41/104), stage II (24%, 25/104), stage III (14%, 15/104), and stage IV (23%, 23/104) endometriosis.

So, the prevalence of endometriosis in present study similar to study of Mohan R et al. The prevalence in other studies are higher as compared to our study because the true incidence of endometriosis is difficult to establish as laparotomy is required for a definitive diagnosis and the disease may still exist in patients who are asymptomatic.

Demographic Details
In the present study majority (50.98%) of the patients had age range 21-26 years. Mean age of the patients were 24.35 ± 4.02. Highest (52.94%) number of patients had BMI 18.5-22.9 followed by BMI 23-24.9 present in 29.41% patients. Majority (70.59%) of the patients had primary infertility and 29.41% patients had secondary infertility. In the study of Mohan R et al age group at which highest incidence observed is between 26-30 years (37%). Between the ages of 21 to 25 years incidence of endometriosis was 18%, 21-30 years which is the optimum age for reproduction the incidence was 55 %. Primary infertility was seen in 84.5% subjects. In the study of Mishra V et al the mean age of patients was 29± 4.3 years.135 patients (75.0%) had primary infertility and 45 patients (25.0%) had secondary infertility. In the study of Bhatt et al majority of the patients were in the age group of 40 to 49 years (40%), followed by 30 to 39 years (30%), and 20 to 29 years (17%).

The observations in present study are in accordance with previously done studies which indicate that patients are commonly diagnosed or present in third and fourth decade of life. In the present study 37.25% of the patients had mild (stage-II) disease and 29.41% patients had moderate disease (stage-III). 21.6% patients had minimal (stage-I) disease and 11.76% patients had severe (stage-IV) disease.

In the study of Mishra V et al most (87%) of the cases had STAGE I & II endometriosis. Most of these patients were asymptomatic. Patients with STAGE III & IV in 6.1% of cases each. In a study of Meuleman C et al patients had stage I (39%, 41/104), stage II (24%, 25/104), stage III (14%, 15/104), and stage IV (23%, 23/104) endometriosis. The findings of our study is similar to other descriptive studies also.

Clinical Presentation
In present study 36.84% patients in stage-II disease, 33.33% patients in stage-III and 50% patients in stage IV had pelvic pain.57.89% patients in stage-II disease, 60% patients in stage-III and 50% patients in stage IV had irregular menses.73.33% patients in stage-III disease, 57.38% patients in stage-II, 66.66% patients in stage IV and 36.36% in stage I had dysmenorrhea. Adnexal mass and tenderness present in 40% patients in stage-III disease, 21.05% patients in stage-II, 50% patients in stage IV and 9.09% in stage I. In the study of Mishra et al apart from infertility, the commonest complaints were dysmenorrhea (42.22%) followed by menstrual irregularity (17.77%), menorrhagia (12.22%), dyspareunia (9.4%) and chronic pelvic pain (4.41%). Significant association of symptoms and signs like dyspareunia, chronic pelvic pain, restricted uterine mobility and adnexal tenderness with staging of disease was noted.

Volume 12 Issue 4, April 2023
www.ijsr.net
Licensed Under Creative Commons Attribution CC BY
In the study of Bhatt et al, the presence of chronic pelvic pain was the most common complaint, which was witnessed in 50% of cases, followed by dysmenorrhea (30%) and menorrhagia (14%). Other complaints included mass per abdomen, infertility, irregular cycles, polynorrhagia, dysfunctional uterine bleeding (DUB) and bleeding per vagina. In the studies done by Amaral et al and Satyanarayana et al, most patients were presenting with menstrual abnormalities and chronic pelvic pain. So, the clinical features in present study are in accordance with the previous studies.

In the present study mean estradiol levels shows that as the disease advances the level of estradiol also increases. Mean FSH levels (IU/L) in stage I, II, III and IV were 17.16, 14.14, 12.88 and 9.75. Mean LH levels (IU/L) in stage I, II, III and IV were 8.57, 7.01, 6.70 and 4.92. In the present study mean prolactin levels (μg/L) in stage I, II, III and IV were 15.18, 19.26, 24.22 and 28.04. Mean cortisol levels (μg/dL) in stage I, II, III and IV were 13.71, 15.01, 18.07 and 21.55. Mean CA 125 levels (μg/dL) in stage I, II, III and IV were 6.62, 6.97, 7.03 and 7.01. Mean T3 levels (ng/dL) in stage I, II, III and IV were 119.16, 125.62, 126.6 and 121.26. Mean TSH levels (mIU/L) in stage I, II, III and IV were 2.23, 2.75, 3.01 and 3.23.

In the study of Ashish et al, prolactin, Triiodothyronine (T3), CA-125, fasting and post prandial sugar, Estradiol and cortisol were significantly associated with the staging of endometriosis. The levels of prolactin, T3, T4, estradiol and cortisol hormones, and the tumour marker, CA-125 was found significantly higher with the progression of the disease from stage-I to stage-IV. These findings are also similar to present study. In present study also as the severity of the disease increases the hormonal derangement also increases. High level of estradiol was present in patients with stage-IV disease.

5. Conclusion

Out of 153 eligible infertile women, 51 diagnosed with endometriosis by laparoscopy. Therefore, the prevalence of endometriosis in infertile women comes out 33.33%. The common clinical features are dysmenorrhea, irregular and heavy menses, dyspareunia, pelvic pain and tenderness. As the severity of the disease increases the hormonal derangement also increases. High level of estradiol was present in patients with stage-III and IV disease.

References


