

The dilemma of endometriosis: is consensus possible with an enigma?

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Many will agree that the use of laparoscopy to diagnose and potentially treat endometriosis in patients who suffer from infertility has been superseded by IVF and sometimes oocyte donation, especially in older patients. The findings of our study add another dimension to management of endometriosis in the setting of infertility and emphasize the importance of keeping laparoscopy in the infertility management equation. (*Fertil Steril*® 2005;84:1587-8. ©2005 by American Society for Reproductive Medicine.)

Key Words: IVF, endometriosis, laparoscopy

Because endometriosis is a common disease entity among infertile patients with a prevalence of up to 50% (1, 2), one could argue that without laparoscopy clinical work-ups can not completely rule out all of the causes of infertility. The decision to perform laparoscopy on patients with infertility is very complex owing to a number of factors, such as maternal age, semen parameters, tubal patency, pelvic symptoms, insurance coverage, surgical risks, and availability of surgical expertise. Presently, many clinicians would advocate proceeding to IVF in patients with "unexplained" infertility without laparoscopic evaluation. However, the etiology of infertility cannot be totally unexplained unless the presence of endometriosis as a cause has been ruled out. In women with undiagnosed endometriosis, fertility treatments not only may be less effective but also may contribute to progression of disease (3, 4).

One of the advantages of laparoscopic evaluation of infertile patients is that the surgical findings could change the handling of their clinical cases. A study done by Tanahat et al. showed that laparoscopic evaluation of patients undergoing infertility treatment resulted in surgical treatment of endometriosis rather than further assisted reproductive techniques in 25% of their patients (5). In addition, in infertile couples, laparoscopy reveals abnormal findings in 21%–68% of cases with a normal hysterosalpingogram (HSG) (6). The additional value of laparoscopy over a normal HSG depends not only on the prevalence of disclosed pathology but also on the contribution of the diagnostic laparoscopy with regard to the decision of which treatment should be applied. Although time is of the essence in many clinical cases, the installation of laparoscopic treatment into the management of infertility early on could alleviate the need to continually expose patients to fertility medicines by altering

the treatment strategy. This approach may also improve the results of assisted reproductive treatment.

Several epidemiologic and molecular investigations have supported a link between endometriosis and ovarian cancer (7–13) and endometriosis has been found in significantly higher frequency in women undergoing surgery for endometrioid and clear-cell subtypes of ovarian cancers (14, 15). According to the literature, the incidence of malignant transformation is approximately 1% in patients with endometriosis (16–19). Without laparoscopic evaluation, the diagnosis of these serious pathologies may be delayed. Obviously when discussing the pros and cons of endoscopic surgery with infertility patients, the possible detection of neoplasms at the time of surgery should be addressed. In addition, the long-term effect of hormonal fertility treatments on female cancers is currently unknown. Although direct causal link between ovarian stimulation and cancer has not been established, until the relationship between ovulation induction and ovarian cancer risk is defined more accurately, a high index of vigilance is indicated. This is especially true in women with endometriosis.

Given the complexity of this matter, and the lack of prospective randomized trials to provide further clarification, a consensus on this subject in our field is far from being reached; the outcome of our retrospective study has raised some issues that deserve further discussion. We reported the outcome of patients with unexplained infertility, who have failed at least 1 cycle of IVF and who subsequently underwent either laparoscopy, additional IVF cycles, controlled ovarian hyperstimulation with intrauterine insemination, or no treatment.

Our study (20) was meant to offer an alternative to repeated IVF attempts or oocyte donation in women who had failed IVF. We acknowledge that patients need an individualized approach to infertility treatment and that every woman may not need to undergo a laparoscopic evaluation in order to achieve pregnancy. However, in patients who have not

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been able to achieve success by other methods, laparoscopy is a reasonable option. Our findings suggest that thorough laparoscopic treatment of endometriosis can be quite effective at improving pregnancy rates. In our study, 22 out of 29 patients (76%) achieved pregnancy after laparoscopic treatment of endometriosis. We concur that our study suffers from the handicaps of retrospective trials, and owing to the confounding factors elaborated by Drs. Penzias, Diamond, Adamson, and Hershlag, this study is limited in its ability to generalize the effect of laparoscopic treatment of endometriosis in all infertile patients. Further prospective randomized trials need to be performed to clarify this issue. However, this report should encourage practitioners to offer a thorough laparoscopic evaluation and treatment of endometriosis to patients who have failed IVF. After all, even some of the most advanced cases of endometriosis might result in pregnancy following surgical intervention (21).

Deepening the understanding of the mechanisms involved in infertility associated with endometriosis will allow further improvement of the outcome of infertility treatments and better care for endometriosis patients. Although it is still early to state the last words on this topic, we believe that laparoscopic diagnosis and treatment of endometriosis is a rational approach to increasing the probability of conception either spontaneously or with assisted reproductive treatment, especially in patients with multiple IVF failures.

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REFERENCES

1. Missmer SA, Cramer DW. The epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 2003;30:1-19.
2. The Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility. *Fertil Steril* 2004;81:1441-6.
3. Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a metaanalysis. *Hum Reprod* 1997;12:1865-72.
4. Barnhart K, Dunsmorr-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002;77:1148-55.
5. Tanahatue SJ, Hompes PG, Lambalk CB. Investigation of the infertile couple: should diagnostic laparoscopy be performed in the infertility work up program in patients undergoing intrauterine insemination? *Hum Reprod* 2003;18(1):8-11.
6. Kalir T, Nezhat FR. Endometriosis and clues to the pathogenesis of ovarian cancer. *CME J Gynecol Oncol* 2003;8:52-6.
7. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 1997;176:572-9.
8. Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, Westhoff CL. Ovarian cancer risk associated with varying causes of infertility. *Fertil Steril* 2004;82:405-14.
9. Jian X, Hitchcock A, Bryan E, Watsob R, Englefield P, Thomas E, et al. Microsatellite analysis of endometriosis reveals loss of heterozygosity a candidate ovarian tumor suppressor gene loci. *Cancer Res* 1996;56:3534-9.
10. Saio N, Tsunoda M, Nishida M, Morishiu Y, Takimoto Y, Kuho T, et al. Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor gene *PTEN* in benign endometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. *Cancer Res* 2000;60:7052-6.
11. Sato N, Nishida M, Noguchi M. An approach to early genetic alterations in precancerous cells. *Hum Cell* 2000;13:103-8.
12. Han AC, Hovenden S, Rosenblum NO, Salazar H. Adenocarcinoma arising in extragonadal endometriosis. An immunohistochemical study. *Cancer* 1998;83:1163-9.
13. Nezhat F, Cohen C, Rahman J, Gretz H, Cole P, Kalir T. Comparative immunohistochemical studies of bel-2 and p53 proteins in benign and malignant ovarian endometriotic cysts. *Cancer* 2002;94:2935-40.
14. Lavy Y, Lev-Sagie A, Holtzer H, Revel A, Hurwitz A. Should laparoscopy be a mandatory component of the infertility evaluation in infertile women with normal hysterosalpingogram or suspected unilateral distal tubal pathology? *Eur J Obstet Gynecol Reprod Biol* 2004;10:11464-8.
15. Nishida M, Watanabe K, Sato N, Ichikawa Y. Transformation of ovarian endometriosis. *Gynecol Obstet Invest* 2000;50:18-25.
16. Tagashira Y, Shimada M, Kigawa J, Iba T, Terakawa N. Ovarian endometrioid adenocarcinoma arising from endometriosis in a young woman. *Gynecol Oncol* 2003;91:643-7.
17. Kelly MG, Pejovic T, Nezhat F. What is the relationship between endometriosis and epithelial ovarian cancer? *CME J Gynecol Oncol* 2003;8:41-7.
18. Osias J, Nezhat FR, Nezhat CH, Nezhat C. Malignant transformation of extragenital endometriosis. *CME J Gynecol Oncol* 2003;8:48-51.
19. Ness RB. Ovarian Cancer, inflammation and endometriosis. *CME J Gynecol Oncol* 2003;8:33-40.
20. Littman E, Giudice L, Berker B, Milki A, Nezhat C. Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. *Fertil Steril* 2005;84:1574-8.
21. Mohr C, Nezhat FR, Nezhat CH, Siedman DS, Nezhat C. Fertility considerations in patients with bowel endometriosis. *J Laparoendosc Surg* 2005;9:16-24.