

The treatment of moderate and severe forms of endometriosis in infertile patients using operative laparoscopy

Mladenko Vasiljevic
 Vladimir Rajkovic
 Lidiya Tasic

ABSTRACT

Objective: To assess the efficacy of the laparoscopic treatment of moderate and severe forms of endometriosis in infertile patients.

Design: Prospective study.

Setting: University Clinic of Gynaecology and Obstetrics.

Patient: 118 patients with variable degrees of endometriosis were subjected to either surgical or conservative treatment.

Methods: Surgical techniques included electrocoagulation of endometrial foci, enucleation of endometriomas, ovarian biopsy and endocoagulation, salpingostomy and salpingoophorolysis. Medical treatment included Danazol and an GnRH analogue Zoladex.

Results: Complete regression of endometriosis was found in 54.9% patients receiving combined (laparoscopic and medicamentous) treatment and in 30.77% patients receiving medical treatment only. The total incidence of successful pregnancies was 22.22%, 23.26%, and 37.50% in groups of patients receiving combined, medicamentous and controlled ovarian hyperstimulation/intrauterine insemination treatment, respectively.

Conclusions: Using combined treatment of severe forms of endometriosis, the fertility rates can be achieved which are similar to rates obtained in treating the mild forms of endometriosis with conservative therapy only.

Key words: endometriosis, laparoscopy, controlled ovarian hyperstimulation, danazol, zoladex

INTRODUCTION

Endometriosis is defined histologically by the presence outside the uterus of ectopic endometriotic glands together with stroma (Jansen and Russel, 1986; Martin et al., 1989). On the basis of the initial publications (Sampson, 1927), for a great many years the only lesions considered to be endometriotic lesions were the endometriomas, typical blackish or blueish lesions and pelvic adhesions. The progress made over more recent years has helped us understand certain aspects of endometriosis. To begin with, it is now definitely acknowledged that peritoneal endometriosis can appear in atypical forms: small white vesicles, red

vesicles, brown lesions, flame-like lesions, polypoid lesions etc. (Jansen and Russel, 1986; Stripling et al., 1988; Moen and Halvorsen, 1992). Secondly, it has been demonstrated that microscopic endometriotic lesions can be observed when the peritoneum appears normal to laparoscopy (Nisolle et al., 1990; Redwine and Yocom, 1990). Thirdly and finally, it has been shown that certain endometriotic lesions can penetrate the retroperitoneal space (Cornillie et al., 1990; Koninckx et al., 1991).

This disease develops in the generative phase of the woman, presenting in the form of endometrial glands in areas other than uterus, usually associated with the infertility and presence of pelvic pains. Endometriosis can be diagnosed in 30–40% of cases by means of laparoscopy of the infertile women and in 2.5% of the fertile women (Acosta et al., 1995). Due to the age of the patient and the extent of spread treatments could either be medical or surgical (Abroa et al., 2000; Berquist, 1995). Correction of the anatomical changes

Correspondence:
 Assoc. Prof. Dr Mladenko Vasiljevic
 Clinic of Gynaecology and Obstetrics "Narodni Front"
 University of Belgrade
 Belgrade 11000
 Yugoslavia

in patients suffering from endometriosis contributes to the increase in fertility.

Currently, the therapy for endometriosis-related infertility remains controversial. Treatment approaches include expectant management, medical intervention, major conservative surgery, and operative laparoscopy. Many surgical modalities have been used in the treatment of endometriosis with the goal of eradicating all visible endometriotic implants. (Olive and Haney, 1986). Conservative resection of endometriosis has been the procedure of choice, although more recently laparoscopic surgery to debulk the endometriotic lesions, lyse tubo-ovarian adhesions, and restore normal anatomy has been a more common procedure. Operative endoscopic techniques, including thermocoagulation and laser ablation, have been utilized to treat endometriosis.

Although the medical treatment can be efficient for the painful symptoms, the benefit is most often transitory and it is very likely that the pain will return when the treatment is discontinued (Waller and Shaw, 1993). Hence surgery remains the priority treatment of most cases of endometriosis.

The aim of this study was to evaluate efficacy of the laparoscopic treatment of infertility in patients suffering from the moderate and severe forms of endometriosis and compare it with efficacy of medication in patients suffering from minimal or mild form of endometriosis.

METHODS

The investigation comprises the prospective study performed in the Gynaecological – Obstetrical Clinic ‘Narodni Front’ of the Belgrade University School of Medicine. There were 118 patients suffering from endometriosis included in the study. The diagnosis of endometriosis was posed on the basis of Laparoscopy and histo-pathological examination of the tissue sample obtained by biopsy. The degree of severity of endometriosis was assessed according to the revised American Fertility Society Classification of endometriosis made in 1985.

All the observed patients were divided into three groups.

The first group was composed of 39 women with I and II stage of endometriosis, and they were subjected to the procedure of medicamentous treatment. Another 22 patients were treated with Danazol tablets, containing 600mg a day, during the three months period. Twenty nine patients were treated with GnRH analogue i.e. Zoladex ampoules containing 3.6 mg of active substance-one injection every 28 days, during the three months period.

The second group consisted of 51 patients with III and IV stage of the endometriosis in whom the endoscopic treatment was performed and followed by the medication during the period of 3 to 6 months. The endocoagulation procedure was performed by means of the bipolar electrical stream, while the enucleation of the endometriomas were performed by using the scissors.

The third group included the patients belonging to the I and II stage of endometriosis in whom the controlled ovarian hyperstimulation and intrauterine insemination with the husband’s sperm was performed (COH/IUI).

Following treatment all these patients were followed-up for at least one year. The success of treatment and percentage of successful pregnancies was analysed in all the patients. The results were assessed statistically by determining exact probability using the two-tailed Fisher’s exact test. The results obtained were compared with the findings of other authors.

RESULTS

The median age of patients was 29.6 years (interval between 23 and 35 years). There were 73 (61.86%) of patients suffering from the primary and 45 (38.14%) of patients suffering from secondary infertility. The average duration of infertility was 3.9 years. There were also 34 patients suffering from the I stage endometriosis, 33 patients from II stage, 29 from III stage and 22 patients suffering from the IV stage of endometriosis. One of the findings on the ovary or tubes as the possible cause of infertility was discovered in 41 women. The laparoscopic findings have been presented in Table 1.

In the group of patients presenting with stages I and II of endometriosis, 39 cases had conservative treatment, while the ovarian hyperstimulation and intrauterine insemination was done in 28 patients. In the group of patients belonging to the stages III and IV of endometriosis, the endoscopic treatment was associated with the medical therapy. The endoscopic treatment included 33 patients in whom the electro-coagulation of endometriotic foci were performed and 18 patients in whom the endometrioma enucleation and electrocoagulation were performed. After the enucleation of the endometriotic foci in order to improve fertility, there were 11 salpingostomatas, 7 multifollicular biopsies and endocoagulations of the ovaries and 23 salpingoophorolyses were performed in these group of patients. The endoscopic treatment of infertile patients suffering from endometriosis have been illustrated in Table 2.

During the course of the secondary laparoscopy in patients belonging to stages III and IV of endometriosis,

the complete evacuation of the endometriosis was found in 54.90% of patients while the renewal growth of residual endometriotic implants was discovered in 45.1% of patients. In the group of patients belonging to the I and II stage of endometriosis, treated with hormonal therapy the complete regression of endometriotic implants was discovered in 30.77% and the recurrence in 69.23% of patients. These differences are statistically significant, $p<0.05$. The endoscopic treatment contributes to the removal of endometrial implants significantly. These results are presented on Table 3.

The total incidence of successful pregnancies in patients with I degree of endometriosis treated with hormones was 23.81%. The pregnancy was successful in 25% of patients treated with Danazol and in 22.22% treated with Zoladex. In the group of patients belonging to the IIInd stage of endometriosis and treated with hormonal therapy, the successful pregnancy rate was 18.18%, it was 14.38% in women treated with Danazol and in 20% of cases treated with Zoladex.

Analysis of patients belonging to the IIIrd stage of endometriosis treated by means of laparoscopy followed by the hormone therapy, revealed that pregnancy was successful in 81% of women in whom electro-coagulation of endometriotic foci were performed and in 25% subjected to the endometrial enucleation.

In the group of patients belonging to stage IV of endometriosis the general pregnancy rate after treatment was obtained in 22.73% of cases. The pregnancy was successful in 25% of patients in whom electrocoagulation was performed and in 20% of patients undergoing endometrial enucleationand electrocoagulation. These results have been presented in Table 4.

Analysis of women belonging to the second group of patients suffering from endometriosis stage III and IV revealed a total pregnancy rate of 23.53%. On the other hand, in the first group of patients, suffering from endometriosis stage I and II treated with hormones, the pregnancy rate was 23.25%.

In the third group of patients suffering from endometriosis stage I and II in whom the controlled ovarian stimulation was applied in combination with the intrauterine insemination (IUI), the total pregnancy rates was 37.5%.

By observing the various groups of patients, it is evident that the highest pregnancy rate was achieved in the group of patients undergoing controlled ovarian hyperstimulation and intrauterine insemination. On the other hand, there are statistically significant differences in terms of pregnancy success rate between the third and second group, as well as between the third and the first group of observed patients ($p<0.05$). Besides this, there is no statistical difference between the first and the second group of patients in terms of pregnancy rate ($p>0.05$).

TABLE 1
Laparoscopic findings in infertile women with endometriosis

Endometriosis	N of women	%	Accompanying findings	N of women	%
I stage	34	28.81	Distal occlusions of tubes	11	9.32
II stage	33	27.97	Polycystic ovaries	7	5.93
III stage	29	24.58	Periadnexal adhesions	23	19.49
IV stage	22	18.64	Total	41	34.74
Total	118	100.00			

TABLE 2
Endoscopic treatment of endometriosis in infertile patients

Endoscopic operations of endometriosis	N	%	Endoscopic operations of sterility	N	%
Electrocoagulation of endometriotic foci	33	27.97	Salpyngoneostomy	11	9.32
Enucleation of endometriomas	18	15.25	Multiple biopsy of ovaries and endocoagulation	7	5.93
Celioscopy + Medicamentous treatment	67	56.78	Salpingoophorolysis	23	19.49
Total	118	100.00	Total	41	34.74

TABLE 3
Results of treatment of endometriosis

Method of treatment	N of patients	Complete enucleation of endometriosis N %		Recurrent growth of endometrial implants N %	
Stages I and II, Hormonal therapy	39	12	30.97	27	69.23
Stages III and IV, Laparoscopic operations and hormonal treatment	51	28	54.90	23	45.10
Total	90	40	44.44	50	55.56

TABLE 4
Pregnancy after treatment of endometriosis

Patients	Treatment of Endometriosis	Stage I N %	Stage II N %	Stage III N %	Stage IV N %	Total
GROUP I	Danazol	3/12 25.0	1/7 14.28			4/19 21.05
	Zoladex	2/9 22.2	4/15 26.67			6/24 25.0
GROUP II	Electrocoagulation + hormonal therapy			5/21 23.81	3/12 25.0	8/33 24.24
	Enucleation + Electrocoagulation + hormonal therapy			2/8 25.0	2/10 20.0	4/18 22.22
GROUP III	COH/IUI	5/13 38.46	4/11 36.36			9/24 37.5
Total		10/34	9/33	7/29	5/22	31/118

DISCUSSION

There are various strategies concerning the treatment methods of infertility in patients suffering from endometriosis. The operative method is indicated in cases with the presence of the mechanical factor of infertility. In our group of patients suffering from endometriosis, the median age was 26.6 years. In this group of patients there were 61.86% women suffering from primary and 38.14% suffering from secondary infertility. In 67 patients there were minimal or mild form of endometriosis present without any alterations in the internal genital organs. The conservative medical treatment was introduced in 43 cases and the controlled ovarian stimulation in 24 women in the group having a total of 67 cases.

Hormonal therapy can decrease activity and retard development of endometriosis or in other words, bring about temporary regression of endometriotic implants, but not remove them completely. The contemporary drugs of choice GnRH agonists are very expensive (Rock et al., 1993).

Endoscopic operations were performed in 51 patients suffering from endometriosis stages III and IV, out of which electrocoagulation in 33 patients, and enucleation of endometrioma along with electrocoagulation in 18 patients. Besides this, there were other alterations in the reproductive tract that could contribute to the aetiology of infertility. Severe endometriosis in 41 patients belonging to the III and IV stage of the disease were subjected to endoscopic operations for infertility.

During the course of secondary laparoscopy, the complete regression of endometriosis was found in 54.90% of patients belonging to the III and IV stage of the disease, and in 30.77% of cases in the patients suffering from I and II stage of endometriosis.

Introduction of endoscopic treatment in such cases enables the precise destruction of lesions with minimal bleeding and formation of adhesions. The total incidence of successful pregnancy in patients suffering from endometriosis was 26.27% in our group of patients. Incidence of successful pregnancy in the

group of patients suffering from stage I and II endometriosis treated with hormones was 23.25%, while Nalbanski et al. (1995) reported 27.27% pregnancy success rate for the same category of patients. Incidence of successful pregnancy in patients suffering from minimal and mild stages of endometriosis following the laparoscopic ablation was 28% (Marcoux et al., 1997), 24% (Parazzini et al., 1999), and 57.1% following the electrocoagulation (Tulandi et al., 1998). In our patients belonging to the endometriosis stage I and II subjected to the controlled ovarian hyperstimulation and intrauterine insemination, the successful pregnancy rate was 37.5%. The other authors have reported a higher incidence of successful pregnancy if the ovulation induction after the laparoscopic treatment was performed (Karaback et al., 1999).

Application of hormonal therapy in women suffering from milder forms of endometriosis did not seem to increase incidence of successful pregnancies. The controlled ovarian hyperstimulation and intrauterine insemination have demonstrated the best results in the treatment of infertility for these patients.

In patients belonging to stage III and IV of endometriosis in whom endoscopic operations were performed, successful pregnancy was obtained in

23.53% of cases. The reported incidence of pregnancy following the laparoscopic operative treatment of the severe stage of endometriosis was 45% (Sutton et al., 1997), 53% (Milingos et al., 1998), 44% (Bussaca et al., 1999). Application of the laparoscopic surgical treatment in such patients brought about the regression of endometriosis in 54.9% and development of pregnancy in 23.53% of cases. The method of choice in the treatment of such patients is laparoscopic treatment along with the hormonal therapy after this operative procedure. In case that there is no successful pregnancy six to twelve months after the laparoscopic treatment it may be advisable to institute some of methods of the assisted reproduction including COH/IUI, and IVF-ET procedures.

CONCLUSION

Patients suffering from stages III and IV of endometriosis should be treated with surgical/laparoscopic removal of endometriotic foci, followed by medical treatment. In cases of pregnancy failure for more than 12 months following the laparoscopic surgical procedure, the assisted reproduction methods could be adopted. In patients suffering from mild forms of endometriosis however controlled ovarian hyperstimulation with intrauterine insemination is a more viable method when compared with drug therapy of this condition.

REFERENCES

1. Abrao MS, Ikeda F, Podgaec S, Pereira PP. Microlaparoscopy for an intact ectopic pregnancy and endometriosis with the use of a diode laser: case report. *Hum Reprod* 2000; 15(6): 1369–71.
2. Acosta AA. Medical treatment of endometriosis. In: Hedon B, Bringer J, Mares P, eds. Proceedings of the 15th World Congress on Fertility and Sterility, Montpellier, France, Prthenon Publishing Group, 1995; 63–70.
3. American Fertility Society. Revised American Fertility Society Classification of endometriosis. *Fertil Steril* 1985; 43: 351–2.
4. Berqvist A. Hormonal regulation of endometriosis and the rationales and effects of gonadotrophin-releasing hormone agonist treatment: a review. *Hum Reprod* 1995; 10: 446–52.
5. Busacca M, Bianchi S, Agnoli B, Candiani M, Calia C, De Marinis S, Vignali M. Follow-up of laparoscopic treatment of stage III–IV endometriosis. *J Am Assoc Gynecol Laparosc* 1999; 6(1): 55–8.
6. Cornillie FJ, Oosterlynck D, Lauwereyns JM, Koninckx PR. Deeply infiltrating endometriosis: histological and clinical significance. *Fertil Steril* 1990; 53: 978–983.
7. Jansen RPS, Russel P. Non-pigmented endometriosis: clinical, laparoscopic and pathologic definition. *Am J Obstet Gynecol* 1986; 155: 1154–1158.
8. Karabacak O, Kambic R, Gursoy R, Ozeren S. Does ovulation induction affect the pregnancy rate after laparoscopic treatment of endometriosis? *Int J Fertil Womens Med* 1999; 44(1):38–42.
9. Koninckx PR, Meuleman C, Demeyere S et al. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. *Fertil Steril* 1991; 55: 759–765.
10. Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. *N Engl J Med* 1997; 337(4): 217–22.
11. Martin DC, Hubert GD, Vander Zwaag R, El-Zeky F. Laparoscopic appearances of peritoneal endometriosis. *Fertil Steril* 1989; 51: 63–67.
12. Milingos S, Kallipolitis G, Loutradis D, Liapi A, Drakakis P, Antsaklis A, Michalas S. Factors affecting postoperative pregnancy rate after endoscopic management of large endometriomata. *Int J Gynaecol Obstet* 1998; 63(2): 129–37.

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13. Moen MH, Halvorsen TB. Histologic confirmation of endometriosis in different peritoneal lesions. *Acta Obstet Gynecol Scand* 1992; 71: 337–342.
 14. Nalbanski B, Punevska M. The treatment of endometriosis in women with sterility. A prospective study over a 2-year period. *Akush Ginekol* 1995; 34(1): 18–20.
 15. Nisolle M, Paindaveine B, Bourdon A et al. Histologic study of peritoneal endometriosis in infertile women. *Fertil Steril* 1990; 53: 984–988.
 16. Olive DL, Haney AF. Endometriosis – associated infertility: a critical review of therapeutic approaches. *Obstet Gynecol Sur* 1986; 41: 538.
 17. Parazzini F. Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. *Hum Reprod* 1999; 14(5): 1332–4.
 18. Redwine DB, Yocum LB. A serial section study of visually normal pelvic peritoneum in patients with endometriosis. *Fertil Steril* 1990; 54: 648–651.
 19. Sampson JA. Peritoneal endometriosis due to the premenstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 1927; 14: 422–469.
 20. Stripling MC, Martin DC, Chatman DL et al. Subtle appearances of endometriosis. *Fertil Steril* 1988; 49: 427–431.
 21. Sutton CJ, Ewen SP, Jacobs SA, Whitelaw NL. Laser laparoscopic surgery in the treatment of ovarian endometriomas. *J Am Assoc Gynecol Laparosc* 1997; 4(3): 319–23.
 22. Tulandi T, al-Took S. Reproductive outcome after treatment of mild endometriosis with laparoscopic excision and electrocoagulation. *Fertil Steril* 1998; 69(2): 229–31.
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