Endometriosis: The impact of surgery and ART.

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ENDOMETRIOSIS: THE IMPACT OF SURGERY AND ART

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INTRODUCTION

Studies have reported that a wide range (14%–67%) of infertile women who undergo laparoscopy have endometriosis [1-3].

A connection between endometriosis and infertility can be easily established when extensive scarring interferes with tubal motility or entirely blocks the tubes. With early-stage disease, when the lesions do not distort the pelvic anatomy the causal relationship is less clear[4].

Increased or decreased secretion of various cytokines that regulate the immunologic processes has been shown to occur among women with endometriosis. These changes may affect sperm, egg function, or embryo development. We need to better understand the effect these cytokines have on reproduction before treatment that modulates the immune response can be evaluated[5].

The efficacy of management of endometriosis-associated infertility is a source of ongoing controversy. For patients with endometriosis who are interested in fertility, medical therapy has a limited role[6]. The 2 treatment options of choice, in this case, include surgery or IVF.

In infertile women presenting with minimal or mild endometriosis (American Fertility Society (AFS) classification), laparoscopic *destruction* was proven to be the first line of therapy[7], although a recently published Italian study[8] demonstrated exactly the opposite. Taken together, a meta-analysis of these results shows destruction of lesions to be significantly beneficial, albeit less so than was estimated with the original Canadian study[9].

In cases of moderate-severe endometriosis, when endometriosis is extensive, leading to significant pelvic anatomic distortion, pregnancy is a rare event in untreated patient[4]. In this case, conservative surgery is often utilized in an attempt to normalize anatomy and enhance fertility. Uncontrolled trials show significant pregnancy rates with this intervention[10]. However no randomized trials have examined the issue to determine the relative benefit of surgery when compared with other therapies (such as assisted reproduction)[4].

Although most treatments for endometriosis are directed at the implants themselves, the symptoms

can be treated directly. Infertility associated with endometriosis has been treated empirically with assisted reproductive techniques. These include the induction of ovulation with clomiphene or gonadotropins, the induction of ovulation combined with intrauterine insemination, and more advanced techniques such as in vitro fertilization, gamete intrafallopian transfer, and zygote intrafallopian transfer.
The aim of this study is to obtain data about surgical treatment, integrated with ART, of infertile women with endometriosis.

MATERIALS AND METHODS

This was a retrospective study of infertile women with endometriosis who were submitted to a laparoscopy at Department of Obstetrics and Gynecology of Florence. All patients with endometriosis were included in this study.
Between March 1993 and December 2003, 440 women underwent a laparoscopy for endometriosis in our department. Indications for surgery were pelvic-pain for 164 women; infertility for 180; 96 patients were asymptomatic.
During laparoscopy endometriosis was classified on the basis of ASRM guidelines. When necessary electrocoagulation or resection of implants, adhesiolysis, cistectomy were performed. Histopatological confirmation of endometriosis was obtained.
Laparoscopy was diagnostic or corrective in I-II stages. Surgical treatment of all patients with III and IV stages of endometriosis was performed by complete removal of all endometrial implants and adhesiolysis of all pelvic organs involved.
Mean age of women was 32 years with a range 16-55. After laparoscopy 239 women received an i.m. injection of GnRH analogue depot (3.75 mg) every 4 weeks for a mean period of 4.1 months (range 18-1).
Our study group consisted of 106 infertile women, out of the 440 women submitted to laparoscopy, who were followed up for a very long period of time (from 1 to 11 years).
Clinical data of the patients are listed in Table 1.
Seventy-three patients were treated with GnRHa after laparoscopy (26 I-II stages; 47 III-IV stages), 23 did not receive any medical treatment after surgery (18 I-II stages; 15 III-IV stages). These women received GnRHa monthly over 1-6 cycles.
In the course of follow-up a questionnaire was administered by telephone to 106 infertile women. Patients were answered about outcome of infertility: duration of infertility and type of stimulation

Table 1 - ***Characteristics of 106 infertile women.***

	Infertile women with endometriosis
Number of cases	106
Mean age	34 (25-45)
Median age	32
Stages I-II	44
Stages III-IV	62

therapy after the treatment were asked. The pregnancy rate, whether spontaneous or under stimulation programs, the birth rate, the miscarriage rate and the rate of ectopic pregnancies were evaluated. Pregnancy was defined by a positive pregnancy test and confirmed by the presence of an intrauterine gestation sac by ultrasonography.

STATISTICAL METHODS AND ANALYSIS

Time to outcome may be affected by a number of factors. Analyses of these factors provide concomitant information that may improve the description and interpretation of the data.
The main outcome of interest was pregnancy rate at the end of treatment. To avoid a bias caused by unequal proportions of cases with minimal, mild, moderate and severe endometriosis analysis was done according to two strata: I-II stages, III-IV stages.
All analyses were performed by using Statistical Package for the Social Science (SPSS for windows, Microsoft, version 10.1). Significant correlation were given at values of $P<0.05$.

RESULTS

One hundred six infertile patients were followed up for a very long period of time (from 1 to 11 years). Average age at the time of surgery was 34 years (range 25-45). 97.2% women (103/106) were nulliparous, 2.8% (3/106) had one or more children.
At the time of surgery, endometriosis was found to be stages I-II in 41.5% (44/106) and stages III-IV in 58.5% (62/106).
In women with I-II stages of endometriosis (44) we have observed 19 (43.2%) spontaneous pregnancies. Sixty two patients with III-IV stages obtain 19 (30.6%) pregnancies. A greater percentage of spontaneous pregnancies was observed in patients with reduced severity of disease (43.2% vs 30.6%), but this difference does not gain any significance (P>0.05).
We have evaluated the effects of a post-operative regimen of GnRH analogue in infertile women who underwent laparoscopic conservative surgery for endometriosis.
Among patients with I-II stages 26 (26/44, 59.1%) were treated with GnRHa after laparoscopy. Eighteen women did not receive any treatment after laparoscopy (18/44, 40.9%). Among women who received post-laparoscopy GnRHa we have observed 11 spontaneous pregnancies (11/26, 42.3%). In no treatment group 8 spontaneous pregnancies occurred (8/18, 44.4%). Forty seven women with III-IV stages of endometriosis received GnRHa treatment after laparoscopy (47/62, 75.8%), while 15 were not treated (15/62, 24.2%). In the first group we observed 13 (13/47; 27.6%) spontaneous pregnancy the second one 6 (6/15; 40%). Table 2.
Administration of GnRHa therapy either single or combined with surgical treatment do not seems to increase the life table fertility rate in I-II group patients in comparison to no treatment; we obtain unexpected globally very good results in III-IV stages (40%) and a quite better trend in patient treated only by laparoscopy probably due to selection worst patients to GnRHa. These differences do not reach statistical significance (P>0.05).
Thirty six women with stages I-II underwent resection or ablation of visible endometriosis, 8 were submitted to a diagnostic laparoscopy only. Percentages of spontaneous pregnancies were higher in the first group (44.4% vs 37.5%) but no significance was reached (P<0.05).

Table 2 - **Pregnancy rates in treatment groups.**

	Post-laparoscopy		Spontaneous pregnancies
Stages I-II	*GnRHa*	26	11 (42.3%)
44	*No medical treatment*	18	8 (44.4%)
Stages III-IV	*GnRHa*	47	13 (27.6%)
62	*No medical treatment*	15	6 (40%)

Among 106 infertile patients were observed 60 (56.6%) pregnancies. Thirty eight (35.8%) pregnancies were spontaneous, whereas the remaining 22 (32%) pregnancies were achieved after stimulation with HMG/HCG, insemination, FIVET, ICSI. Since only 70 women have attempted ART after surgery, we can say that pregnancies after ART were 31.4% (22/70). Out of the 60 pregnancies, 12 resulted in a miscarriage (9 in spontaneous pregnancies and 3 after ART). An important observation is that 45,6% of pregnancies were observed in 6 months following treatments. Table 3.

The overall pregnancy rate among women submitted to surgery and ART was 56.5% (60/106) compared with 35.8% (38/106) in patients who had surgery only (Table). (P=0.004)

DISCUSSION

This study indicates that at up to 11 years follow-up there is a high significant percentage (56.6%) of infertile women with endometriosis who obtain pregnancy trough a surgical-ART integrated approach. These findings confirm the effectiveness of laparoscopic excision of endometriosis that is reported by others[7,11].

Our data show as severity disease influence fertility outcome (PR: I-II stages 43.2% *vs* III-IV stages 30.6%), thus this difference does not gain any significance (P>0.05).

Our results do not support the routine post-operative use of a 3 month course of GnRH analogue in infertile women with endometriosis. Previous studies agreed that post-operative medical treatment does not confer significant additional benefit in improving pregnancy rates[12-17]. It should be noted

Table 3 - **Pregnancy rates after laparoscopy**

	I-II STAGES		III-IV STAGES		ALL STAGES	
Num. women	44	41.5%	62	58.5%	106	100%
Spontaneous Pregnancies	19	43.2%	19	30.6%	**38**	**35.8%**
COH-ART Pregnancies	12	48%	10	23.3%	**22**	(22/70)31.4%
Tot. pregnancies	31	70.4%	29	46.8%	**60**	56.6%

that the immediate post-operative period is thought to be particularly favorable for conception; therefore, suppressing ovulation for some months after surgery has been claimed to be detrimental in infertile women[17,18].

We found that resection or ablation of minimal-mild endometriosis, as compared with diagnostic laparoscopy alone, increased the likelihood of pregnancy in infertile women. The issue of surgically treating early-stage endometriosis in the infertile woman has been examined in two randomized trials[7,8]. The first, a large multicenter trial conducted in Canada, demonstrated a clear advantage to operative laparoscopy in the patients[7]. A second, smaller study, performed in Italy, failed to demonstrate any difference between treating and not treating visible lesions[8]. The Canadian study and a subsequent Italian trial were included in a systematic review that concluded that the use of laparoscopic surgery in the treatment of minimal and mild endometriosis might improve success rates, but there were some methodologic problems with the studies[9].

No RCTs or meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances pregnancy rate[19]. Based upon three studies[10,20,21] there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis, but statistical significance was only reached in one study[21]. According to Adamson, a surgical approach, by normalizing pelvic anatomic distortion and by adhesiolysis enhances fertility[11].

The assisted reproductive technologies, in particular IVF, theoretically should maximize fertility rates by removing gametes and zygotes from the *hostile* peritoneal environment and bypassing abnormal pelvic anatomy associated with endometriosis[6]. Many innovations have been made in advanced reproductive technologies (ART) over the past several years. These procedures now yield pregnancy rates of over 20% per cycle, rates that compare favorably to many types of reproductive surgery. Therefore, ART now represents a viable alternative for many patients suffering from infertility. As these pregnancy rates continue to rise, gynecologists will have to choose between ART, reproductive surgery or an integrated approach for a larger number of patients.

In a meta-analysis of 22 studies from 1983 to 1997, Barnhart *et al.* concluded that, overall, endometriosis significantly reduces all markers of the reproductive process, which results in an IVF pregnancy-rate that is almost one-half that for women who undergo IVF for other indications[22]. However, analysis of large databases (e.g. SART and HFEA) indicates that there is no difference in outcome[23].

No randomized trials have examined the issue to determine the relative benefit of surgery when compared with other therapies (such as assisted reproduction) in infertile patients with endometriosis[4].

The endoscopist Donnez suggests that in case of ovarian endometrioma-associated infertility, surgery must be considered as *first-line* treatment, whatever the proposed techniques. The mean pregnancy rate of 50% reported in the literature following surgery is scientific proof that operative treatment should first be undertaken to give patients the best chance of conceiving naturally. IVF is only indicated as *second-line* treatment. Donnez *et al.*, after two IVF cycles, have obtained a pregnancy rate of approximately 61%. So today it may well be possible, by a combination of surgery and IVF, to offer the chance of pregnancy to ±80% of women with endometriosis-associated infertility[24].

Aboulghar, on the other hand, suggests that if the objective is essentially treatment of infertility, IVF without prior surgery would probably be a good option[25]. Patients with the diagnosis of

advanced endometriosis may be encouraged to be treated by IVF as first-line treatment before any attempt at surgical treatment[26].

According to our results, it seems that correct management of infertile women affected by endometriosis is a combination of surgery and IVF at proper time in women who did not obtain post-surgery pregnancy spontaneously. Such approach made us obtain a pregnancy rate of 56.5%. Appropriately designed clinical trials are essential for determining which is the correct management of infertile women with endometriosis.

REFERENCES

1) FORMAN RG, ROBINSON JN, MEHTA Z, BARLOW DH: *Patient history as a simple predictor of pelvic pathology in subfertile women*. Hum Reprod 1993;8:53–55
2) BALASCH J, CREUS M, FABREGUES F, et al.: *Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: a prospective study*. Hum Reprod 1996;11: 387–391
3) BUTTRAM VC Jr.: *Conservative surgery for endometriosis in the infertile female: a study of 206 patients with implications for both medical and surgical therapy*. Fertil Steril 1979;31:117–123
4) OLIVE DL, LINDHEIM SR, PRITTS EA: *Endometriosis and infertility: what do we do for each stage?* Curr Womens Health Rep 2003;3(5):389-94
5) Giudice LC, Kao LC: *Endometriosis*. Lancet 2004 ;364(9447):1789-99
6) SURREY ES, SCHOOLCRAFT WB: *Management of endometriosis-associated infertility*. Obset Gynecol Clin N Am 2003;30:193–208
7) MARCOUX S, MAHEUX R, BERUBE S: *Laparoscopic surgery in infertile women with minimal or mild endometriosis*. Canadian collaborative group on endometriosis. New England Journal of Medicine 1997;24:217–222
8) GRUPPO ITALIANO PER LO STUDIO DELL'ENDOMETRIOSIS: *Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial*. Human Reproduction 1999;14:32–34
9) JACOBSON TZ, BARLOW DH, KONINCKX PR, et al.: *Laparoscopic surgery for subfertility associated with endometriosis (Cochrane Review)*. In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.
10) ADAMSON GD, HURD SJ, PASTA DJ, RODRIGUEZ BD: *Laparoscopic endometriosis treatment: is it better?* Fertil Steril 1993;59:35-44
11) ADAMSON GD, BAKER VL: *Subfertility: causes, treatment and outcome*. Best Pract Res Clin Obstet Gynaecol 2003;17(2):169-85
12) TELIMAA S, APTER D, REINILA M, et al: *Placebo-controlled comparison of hormonal and biochemical effects of danazol and high-dose medroxyprogesterone acetate*. Eur J Obstet Gynecol Reprod Biol 36(1-2):97-105, 1990
13) PARAZZINI F, FEDELE L, BUSACCA M et al.: *Postsurgical medical treatment of advanced endometriosis: results of a randomized clinical trial*. Am J Obstet Gynecol 171:1205–1207, 1994
14) HORNSTEIN MD, HEMMINGS R, YUZPE AA, et al.: *Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis*. Fertil. Steril 68:860–864, 1997
15) BIANCHI S, BUSACCA M, AGNOLI B, et al.: *Effects of 3 month therapy with danazol after laparoscopic surgery for stage III/IV endometriosis: a randomized study*. Hum Reprod 14(5):1335-7, 1999
16) VERCELLINI P, CROSIGNANI PG, FADINI R et al.: *A gonadotrophin-releasing hormone agonist*

compared with expectant management after conservative surgery for symptomatic endometriosis. Br J Obstet Gynecol 106:672–677, 1999

17) BUSACCA M, SOMIGLIANA E, BIANCHI S, et al.: *Post-operative GnRH analogue treatment after conservative surgery for symptomatic endometriosis stage III-IV: a randomized controlled trial.* Hum Reprod 16(11):2399-402, 2001

18) BUTTRAM VC, REITER RC: *Treatment of endometriosis with danazol: report of a 6-years prospective study.* Fertil. Steril 43:353–360, 1985

19) ESHRE – European Society for Human Reproduction & Embryology: *Guideline for the Diagnosis and Treatment of Endometriosis.* www.eshre.com, 2004

20) GUZICK DS, SILLIMAN NP, ADAMSON GD, et al.: *Prediction of pregnancy in infertile women based on the American Society for Reproductive Medicine's revised classification of endometriosis.* Fertil Steril 1997;67:822-829

21) OSUGA Y, KOGA K, TSUTSUMI O, et al.: *Role of laparoscopy in the treatment of endometriosis-associated infertility.* Gynecol Obstet Invest 2002;53 Suppl 1: 33-39

22) BARNHART KT, DUNSMOOR-SU R, COUTIFARIS C: *Effect of endometriosis on in-vitro fertilisation.* Fertil Steril 2002;77:1148–1155

23) TEMPLETON A, MORRIS JK, PARSLOW W: *Factors that affect outcome of in-vitro fertilisation treatment.* Lancet 1996;348:1402-6

24) DONNEZ J, PIRARD C, SMETS M, et al.: *Surgical management of endometriosis.* Best Pract Res Clin Obstet Gynaecol 2004;18:329–348

25) ABOULGHAR MA, MANSOUR RT, SEROUR GI, et al.: *The outcome of in vitro fertilization in advanced endometriosis with previous surgery: a case-controlled study.* Am J Obstet Gynecol 2003;188(2):371-5

26) TRUMBULL KA, DMOWSKI WP: *Endometriosis and infertility: the role of IVF.* Middle East Fertil Soc J 1998;3:197-208