

DOES THERAPY FOR MINIMAL/ MILD ENDOMETRIOSIS ENHANCE CONCEPTION?

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The infertile patient with endometriosis is a challenging and frequently frustrating clinical problem for the gynecologist. Endometriosis is a common and enigmatic disease in reproductive-aged women. Several theories have been proposed in an attempt to explain the pathogenesis of associated infertility. This has contributed to the diversity of therapeutic approaches currently used for endometriosis-associated infertility. Despite the many studies comparing the various therapies, the optimal treatment approach for enhancing fertility has not yet been determined. Most of the studies have been retrospective, contain significant selection bias, and are not well-designed. Moreover, the data on treatment comparisons according to stage of endometriosis are dependent on a classification system that has not been determined to be particularly reproducible or predictive for the outcome measure of infertility.

Nonetheless, decisions regarding treatment must be made. The first step is an assessment of the reproductive goals of the patient. Identification of the patient as a teenager contemplating future pregnancy, a woman attempting pregnancy, or a woman who has completed childbearing will influence the treatment course. In women who wish to maintain or restore fertility, the treatment objectives are to restore normal anatomy, remove or ablate endometrial implants, and prevent or delay recurrence of disease. For patients with minimal or mild endometriosis in whom no anatomic

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distortion exists, serious consideration must be given to the different therapies and their effectiveness. This article examines the issues involved in making rational decisions regarding the treatment of minimal/mild endometriosis in patients with infertility.

MECHANISM OF INFERTILITY

In the absence of anatomic distortion of the pelvis by endometriosis, the method of interference with fertility has not been determined. Various theories have been proposed to explain the possible reduction in fertility associated with endometriosis.^{28, 29} Some of these include altered folliculogenesis, ovulatory dysfunction, impaired fertilization, sperm phagocytosis, defective implantation, luteal-phase defects, inhibition of early embryo development, and immunologic alterations.* In women with endometriosis, chronic inflammatory changes in the peritoneal cavity have been observed as manifested by increased peritoneal fluid volume and increased number, concentration, and activity of macrophages.^{18, 27, 39, 46} The activated leukocytes in peritoneal fluid are thought to impair fertility by exerting direct cytotoxic effects or by releasing cytokines and proteolytic enzymes into the pelvic milieu.

A recent retrospective study in an in vitro fertilization (IVF) and oocyte donation program showed that patients with endometriosis had poorer outcomes in comparison with patients with tubal factor infertility.⁶⁰ In a comparison of oocyte recipients with endometriosis with other recipients, no difference was observed in the pregnancy and implantation rates when the oocytes were from donors without endometriosis. However, fertilized donor oocytes from patients with endometriosis (extensive disease inclusive of endometriomas) resulted in a lower implantation rate in comparison with fertilized oocytes from donors without endometriosis. This study suggests that alterations in the oocyte and the resulting embryo which reduce the implantation capacity may be a contributing factor to endometriosis-associated infertility.

EVALUATION OF TREATMENT OF ENDOMETRIOSIS

An association between minimal endometriosis and subfertility has been supported by numerous studies, but a relationship of causation has yet to be demonstrated. Current treatment approaches to endometriosis-associated infertility are based on the assumption that endometriosis causes a decrease in fertility. Endometriosis, however, may be only a linked marker for infertility. An underlying pathologic process associated with endometriosis may exist that could interfere with fertility. In the absence of mechanical distortion of the pelvis, we cannot assume that endometrial implants are directly responsible for a decline in the ability

* References 14, 17, 19, 23, 25, 36, 38, 50, 63, and 65

to conceive. Despite the lack of definitive data, the causation hypothesis is plausible and logical.

Ultimately, outcomes assessment produces the data most relevant to the patient. The effectiveness of a particular treatment in shortening the interval to conception or in increasing the monthly chance of conceiving is the question addressed by numerous clinical studies. Ideally, to determine the most effective treatment, a prospective randomized controlled clinical study must be performed. The majority of studies, however, are uncontrolled or retrospective, making them prone to selection bias. As a result, studies are more likely to conclude that a treatment is efficacious when in actuality it is not. The use of life-table analysis or fecundity rates to evaluate the effectiveness of a particular therapeutic approach also cannot correct for selection bias. Meta-analysis is useful because the data from several studies are pooled together. However, it does not correct for different lengths of follow-up among studies. Moreover, the subtleties of each study may be lost in the analysis.

Studies addressing stage-specific treatment comparisons are hindered by using a classification method that concentrates on the perceived extent of disease involvement rather than on how fertility is affected. Based on the American Society for Reproductive Medicine classification scheme, minimal and mild endometriosis can include deeply invasive nodular lesions that may have severe effects on fertility. Although such a classification system is necessary to compare the visual extent of disease in different studies, numerous studies have shown only a weak, if any, correlation with infertility.

Minimal and mild endometriosis can be difficult to diagnose because of its multiple and highly varied phenotypic presentation. The difference between minimal and mild endometriosis is determined by subjective clinical assessment in which the interobserver and intraobserver variation are unknown. Moreover, the threshold from minimal-to-mild disease is arbitrary, because both minimal and mild endometriosis do not cause anatomic distortion and are not associated with endometriomas or significant adhesions. Thus, minimal and mild endometriosis are considered as one group of entities.

TREATMENT OPTIONS

In managing the infertile patient with endometriosis, the extent of the disease and the reproductive goals must be considered to determine the best treatment option. Therapeutic approaches are selected that will best restore the anatomic, hormonal, or immunologic alterations in the pelvis for future reproductive events. This approach focuses attention on the treatment of implants rather than on subfertility directly. When anatomic distortion of the pelvis is present from moderate or severe endometriosis, surgery is usually considered the treatment of choice. If endometrial implants are present that are not causing anatomic distortion (e.g., minimal/mild endometriosis), the optimum treatment modality is

less clear. The various approaches to the management of minimal/mild endometriosis-associated infertility may be categorized into no treatment, medical treatment, surgical treatment, and combinations of medical and surgical treatments.

Medical Treatment

Medical treatment utilizes hormonally active medications, which include oral contraceptives, high-dose progestins, danazol (a derivative of 17-alpha-ethinyltestosterone), and gonadotropin-releasing hormone agonists (GnRHa). Administration of these medications disrupts the cyclical pattern of stimulation and bleeding and induces atrophy of endometrial implants. The ultimate goal is to decrease or prevent pain and the inflammatory response which may result in fibrosis and adhesion formation. Depending on the medication used, most patients experience side effects to some degree.³⁰ Treatment with GnRHa and danazol may be associated with higher costs in comparison with operative laparoscopy for the treatment of minimal or mild disease. A contraception period is required and is a consequence of medical therapy. For older patients with infertility, the loss of up to 6 months of time spent trying to conceive may decrease their chances for success.

Surgical Treatment

Surgical treatment may be accomplished by laparotomy or laparoscopy. The advent of advanced equipment and operative techniques has allowed surgeons to perform increasingly complex operations laparoscopically. For endometriosis, the most common surgical approach is via laparoscopy. However, the outcome is dependent on the skills of the surgeon. The advantages of laparoscopy are better visualization, less tissue trauma and exposure to foreign bodies, possibly less *de novo* adhesion formation, and a lower incidence of complications.^{8, 12} Moreover, recovery time is faster because of smaller, less painful incisions.⁴⁹ The disadvantages of laparoscopy in comparison with laparotomy are the inability to palpate structures directly, the lack of a three-dimensional perspective, and the greater possibility of operator fatigue. Laparotomy is usually reserved for the removal of large endometriomas, extensive enterolysis, bowel resection, or other cases deemed too complex for laparoscopic treatment^{35, 53} and is rarely indicated for minimal/mild endometriosis.

Medical and Surgical Treatment

Combination therapy consists of the preoperative and postoperative use of the aforementioned medications. Preoperative use of GnRHa has been suggested for controlling pelvic pain before delayed surgery or for

attempting to improve the pelvis before surgery.⁵⁹ Decreasing lesion size, blood flow, and inflammation preoperatively may improve the technical results of surgery.¹⁻⁵³ As is true with medical therapy alone, the side effects and the time spent on medications are drawbacks.

In the majority of women with endometriosis-associated infertility, the condition manifests as a relative decrease in fertility rather than as absolute infertility from tubal obstruction or adnexal involvement. A spectrum of disease severity occurs which is reflected in the pregnancy outcomes following treatment. Although it is difficult to make definitive conclusions regarding the efficacy of the various treatment options, knowledge of the data currently available will assist the clinician in making a more rational decision regarding treatment.

PREGNANCY OUTCOME

No Treatment

Expectant management following the diagnosis of minimal or mild endometriosis has been reported in numerous studies, with an average pregnancy rate of approximately 45%.^{*} The average monthly fecundity rate is 6.8%. The following sections examine the data on pregnancy outcome comparing medical and surgical treatment with expectant management.

Surgical Treatment

In general, within 1 to 2 years after surgical therapy for endometriosis, a pregnancy rate of approximately 65% can be expected. In a meta-analysis of studies comparing surgery with nonsurgical treatment of endometriosis-associated infertility, the superiority of the surgical approach was observed, with crude pregnancy rates estimated to be 38% higher than for the nonsurgical approach (95% confidence interval, 28% to 48% higher) (Fig. 1).³ Meta-analysis comparing laparoscopy and laparotomy separately with nonsurgical treatment also showed evidence favoring the surgical approach (Figs. 2 and 3).³ These meta-analyses, however, included studies of all stages of endometriosis. For minimal or mild endometriosis, similar pregnancy rate outcomes have been observed following expectant management and surgical treatment.^{2, 5, 43} Following surgical therapy for minimal or mild endometriosis, the average pregnancy rate in several studies was approximately 58%.^{2, 9, 24, 33, 48, 52, 56, 57} Although surgical treatment seems to be effective in treating endometriosis in comparison with expectant management, no obvious difference can be detected when the monthly fecundity rate is calculated.^{40, 44, 54, 58} Moreover, the variable length of follow-up is one of many reasons that may account for the

^{*} References 6, 7, 22, 31, 33, 45, 48, 51, 55, 57, 58, and 64

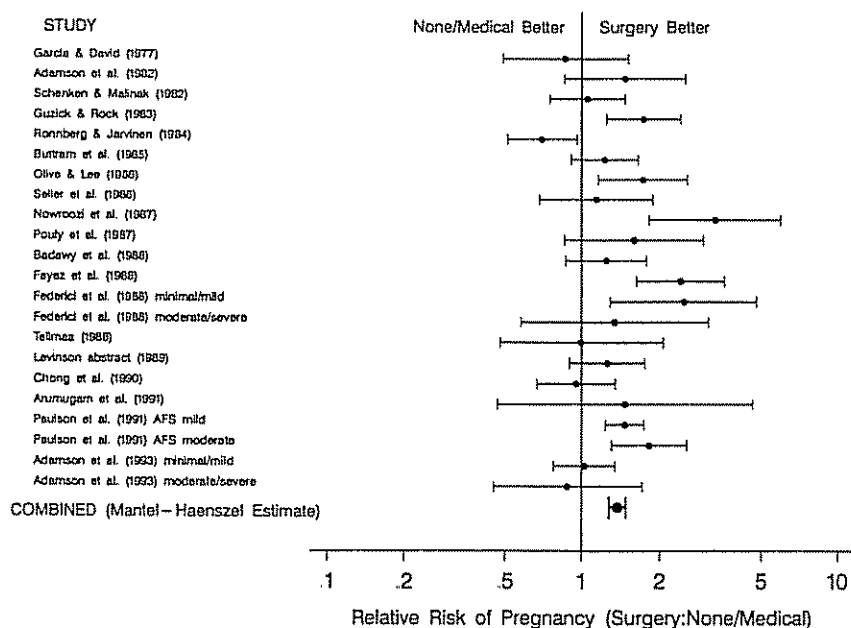


Figure 1. Meta-analysis of data comparing the surgical to the nonsurgical approach for managing endometriosis-associated infertility. The surgical approach is favored with crude pregnancy rates 38% higher than non-surgical treatment.

differences seen in the pregnancy rates. Thus, the efficacy of surgery for the treatment of minimal or mild endometriosis has been difficult to demonstrate.

In view of the difficulties in evaluating the data in the literature and the lack of rigorous clinical studies showing an improvement in infertility, conventional wisdom has been that surgical treatment does not confer an advantage over expectant management. Recently, however, data have emerged that support the surgical approach to infertile patients with minimal or mild endometriosis. In a multicenter, prospective, double-blinded, controlled, randomized study, surgical treatment by laparoscopy resulted in a significantly higher pregnancy rate after 9 months in comparison with expectant management (37.5% versus 22.5%, $P = 0.002$). This large well-designed study provides the first convincing evidence that surgical intervention may be beneficial in minimal or mild endometriosis-associated infertility.³⁷

In patients with minimal/mild endometriosis, laparoscopic treatment has frequently been used because of the ease with which treatment can be simultaneously accomplished during diagnostic laparoscopy. Studies do not indicate any detrimental effect on pregnancy outcome following surgery. However, the removal or ablation of endometriosis implants in patients with minimal or mild disease can potentially increase the risk for postsurgical adhesion formation. The decision to treat has been based on the location and nature of the lesions, on whether pain symptoms are

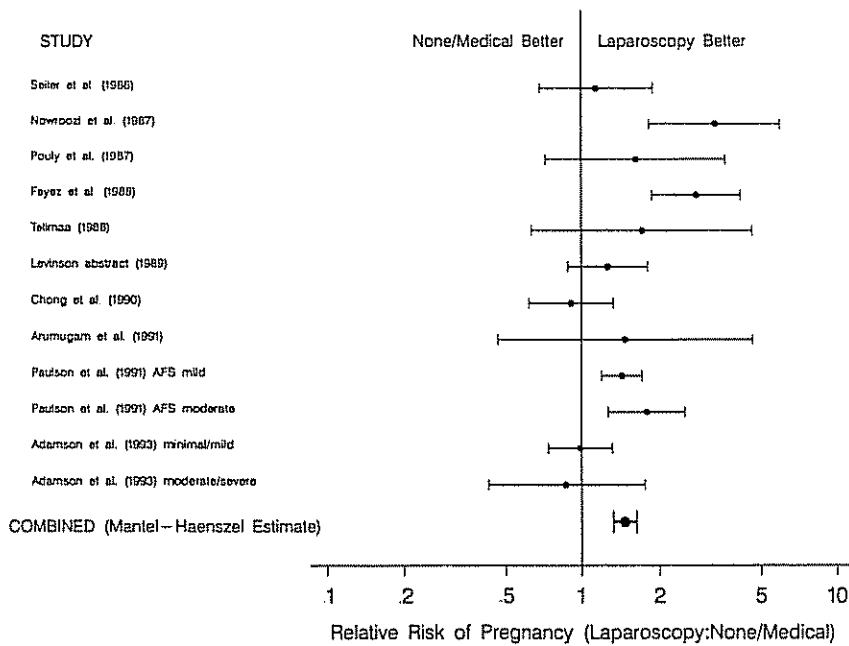


Figure 2. Meta-analysis of data comparing the laparoscopic approach to the nonsurgical approach for treating endometriosis-associated infertility. Laparoscopy is favored over expectant or medical management.

present and on the potential of the disease to become more advanced. The risk of de novo adhesion formation can be minimized if microsurgical principles are followed

Medical Treatment

Following the introduction of medical approaches to the treatment of endometriosis, studies were conducted to determine the efficacy of treating infertile patients with mild endometriosis. Although the initial studies reported pregnancies following treatment, suggesting a potential beneficial effect, the findings were difficult to interpret and were not useful due to the lack of control groups for comparison.⁴² Several later studies which were controlled did not demonstrate an improvement in endometriosis-associated infertility following the use of progestins,⁶ danazol,^{6, 10, 64} gestrinone,⁴⁸ and GnRH agonists.^{20, 53} The 3-year estimated cumulative life-table pregnancy rates for expectant management, laparoscopy, and laparotomy are higher than the rates following medical treatment (Table 1).⁵⁷ This observed difference is primarily a result of the time lost from the contraceptive period while taking medications. In a meta-analysis comparing medical therapy with expectant management, no significant difference in cycle pregnancy rates was observed (relative risk of 0.98;

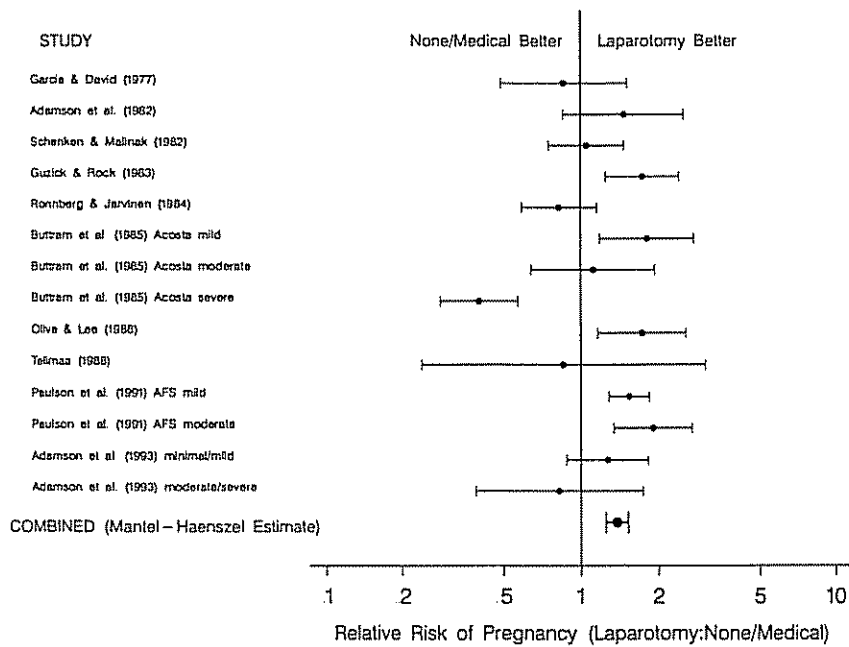


Figure 3. Meta-analysis of data comparing laparotomy to nonsurgical treatment for endometriosis-associated infertility. Laparotomy is favored over nonsurgical management.

95% confidence interval, 0.81 to 1.18) (Fig. 4).²² These data and the observations that lesions of endometriosis persist following medical treatment^{21, 41} provide strong support for the ineffectiveness of the medical approach to endometriosis-associated infertility.¹¹

Surgical and Medical Treatment

The combined data show that medical therapy after surgery is not better than laparoscopy or laparotomy alone (relative risk of 0.97; 95% confidence interval, 0.87 to 1.09) (Fig. 5).²² The homogeneity of studies in this comparison strengthens the conclusion that no difference exists. Without clear evidence of benefit from the postoperative use of medications, the cost and side effects argue against any role of medical therapy in the postoperative period. There are insufficient data to evaluate preoperative treatment.

ALTERNATIVE TREATMENTS

The surgical and medical approaches to treating minimal or mild endometriosis attempt to eliminate or greatly reduce implants to improve

Table 1. ESTIMATED CUMULATIVE LIFE-TABLE PREGNANCY RATES BY TREATMENT GROUP FOR MINIMAL/MILD ENDOMETRIOSIS

Treatment Group	Entire Patient Population				Endometriosis-Only Subset†			
	Number	1 Year (%)	2 Years (%)	3 Years (%)	Number Pregnant at 3 Years	1 Year (%)	2 Years (%)	3 Years (%)
No treatment	15	53.3 ± 12.9*	66.7 ± 12.2	66.7 ± 12.2	13	61.5 ± 13.5	69.2 ± 12.8	69.2 ± 12.8
Medical treatment	44	26.5 ± 7.2	53.0 ± 8.9	62.3 ± 9.3	32	25.6 ± 8.4	47.7 ± 10.2	55.2 ± 11.2
Laparoscopy	241	43.6 ± 3.5	59.6 ± 3.8	67.8 ± 4.1	134	45.5 ± 4.7	60.4 ± 5.1	70.3 ± 5.4
Laparotomy	46	55.7 ± 7.9	65.6 ± 7.9	74.3 ± 8.1	13	38.0 ± 15.1	50.4 ± 16.4	64.5 ± 16.8

* Values are estimates ± SE.

† Patients in the endometriosis-only subset have at least one normal adnexa, normal semen analysis, and normal ovulation.

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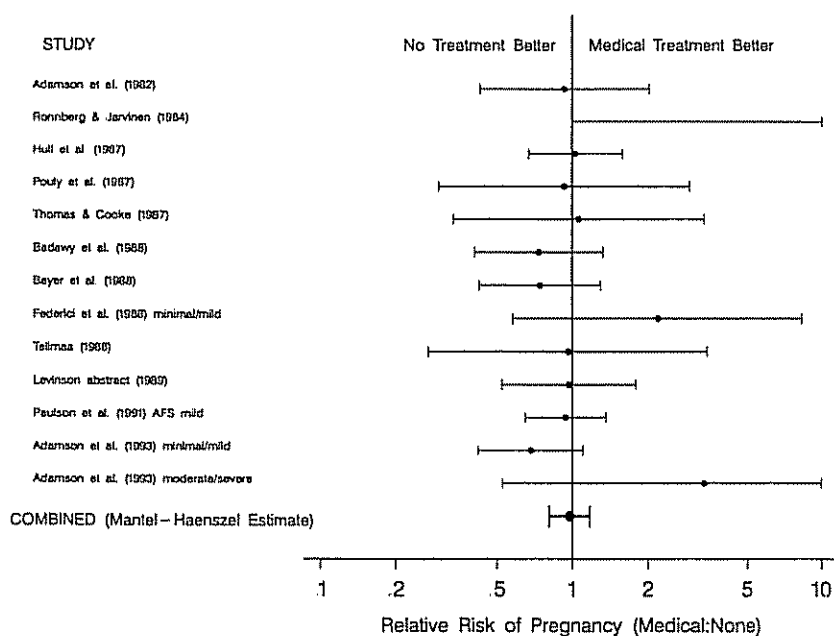


Figure 4. Meta-analysis of data comparing medical treatment of endometriosis to expectant management in infertility patients. The relative risk of pregnancy indicates no difference between these approaches (95% confidence interval 0.81 to 1.18).

pregnancy outcome. In the absence of anatomic distortion, treatments to improve fecundity without addressing endometriosis implants are a possible approach. Controlled ovarian hyperstimulation has been used successfully in patients with endometriosis to improve cycle fecundity.^{13, 16, 32, 34} This approach avoids the loss of time with medical treatment and the risk of adhesion formation from surgery. By inducing the development of multiple oocytes per cycle for release into the reproductive tract, potential defects which hinder the ability for a successful pregnancy may be overcome. Ovulation induction with intrauterine insemination can improve timing, correct subtle ovulatory dysfunction, overcome sperm transport problems, and increase the odds of overcoming a toxic pelvic milieu. This method carries the risk of multiple pregnancies and ovarian hyperstimulation syndrome which varies on an individual basis.

A more aggressive approach is use of the assisted reproductive technologies such as IVF, gamete intrafallopian transfer (GIFT), and zygote intrafallopian transfer (ZIFT). These technologies, in general, result in a higher monthly fecundity rate in comparison with controlled ovarian hyperstimulation alone.³⁴ The results for 1994 from the United States IVF Registry showed a 20.7% delivery rate per retrieval for IVF, a 28.4% delivery rate for GIFT, and a 29.1% rate for ZIFT.⁶¹ When outcome is

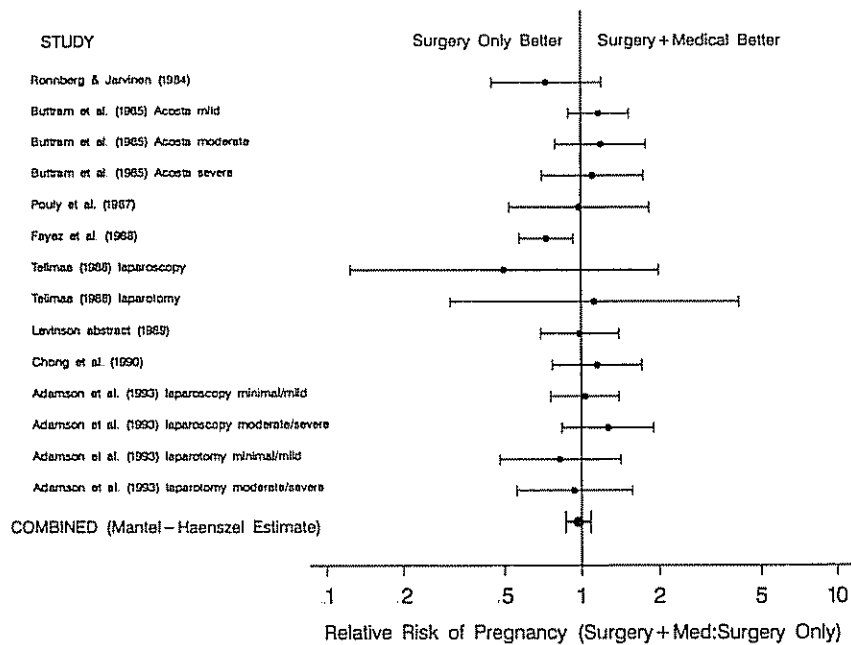


Figure 5. Meta-analysis of data comparing the addition of medical treatment (hormonal suppression) to no additional treatment following surgery for endometriosis. No difference was observed between these approaches, as shown by the combined estimate of the relative risk (95% confidence interval 0.87 to 1.09).

assessed according to diagnosis, patients with endometriosis treated by IVF seem to have lower implantation rates and at least a trend toward lower pregnancy rates in comparison with patients with tubal factor infertility in some studies^{4, 60} and no difference in pregnancy rates in others.^{15, 47} An assessment of the outcome of patients with endometriosis according to stage of disease did not reveal any significant difference.^{4, 15, 47} Thus, mild endometriosis does not seem to have a significant detrimental effect on the outcome of IVF. The manner in which IVF overcomes the suspected adverse impact of minimal or mild endometriosis on fertility is unknown in contrast to the anatomic distortion of severe endometriosis. With respect to GIFT, some studies report a decrease in the pregnancy rate if endometriosis is present,²⁶ whereas other studies suggest no decrease in the pregnancy rate.⁶² Because of the tremendous financial, emotional, physical, and time commitments involved with IVF, expectant management with or without controlled ovarian hyperstimulation with intrauterine insemination is frequently the approach initially utilized for mild endometriosis. In the older patient, however, a more aggressive approach with one of the

assisted reproductive technologies may be the best option in selected cases.

SUMMARY

Treatment of minimal/mild endometriosis, primarily by surgical means, has been a widely used adjunct in therapy for endometriosis-associated infertility. Unfortunately, current knowledge of the relationship between infertility and minimal/mild endometriosis is inconclusive. The development of a scoring system correlating endometriosis with the severity of reproductive dysfunction would be a significant contribution to infertility research. Given the lack of prospective, randomized, controlled studies, it has been difficult to make firm conclusions regarding the best treatment approach for patients with minimal/mild endometriosis and infertility. All of the evidence regarding medical treatment has shown that this approach to endometriosis-associated infertility is ineffective and should not be used. The recent data collected by Maheux and co-workers³⁷ in the Endocan study are the strongest evidence to date that higher pregnancy rates occur following surgical ablation, which generally is the treatment of choice for most patients.

Another reasonable option for treatment is clomiphene citrate or gonadotropin ovulation induction or one of the assisted reproductive technologies. These treatments may be employed as a primary option or following the failure of expectant management or surgery. As always, proper patient selection is a prerequisite for the successful outcome of any given treatment.

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