

# Pregnancy Rate in Endometriosis Patients according to the Severity of the Disease after Using a Combined Approach of Laparoscopy, GnRH Agonist Treatment and in vitro Fertilization

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## Key Words

Endometriosis · GnRH agonists · Infertility · In vitro fertilization · Laparoscopy

## Abstract

**Aim:** To evaluate the effects of combined treatment approaches on endometriosis-associated infertility in different stages of endometriosis using laparoscopy, gonadotropin-releasing hormone (GnRH) agonist (GnRHa) therapy and in vitro fertilization (IVF). **Methods:** This retrospective study was carried out on 179 women with surgically confirmed endometriosis. Patients were divided into subgroups: group 1 (stage I–II, n = 121) and group 2 (stage III–IV, n = 58). Patients eligible for IVF, who were found to have adenomyosis or moderate to severe endometriosis, were also given postoperative GnRHa. Pregnancy and delivery rates were cumulatively calculated during 5 years according to the severity of the disease. **Results:** The overall pregnancy, delivery and miscarriage rates were 66.5, 56.4 and 15.1%, respectively, for all patients following spontaneous and assisted conception. There were no significant differences in reproductive outcomes between the study groups. The pregnancy and delivery rates were also comparable within group 1 between the patients with and without GnRHa treatment. **Conclusion:** Pregnancy and delivery rates at different stages of endome-

triosis were not affected by the different approaches used for infertility treatment, with >60 and >50% of patients having conceived and delivered a baby, respectively, in both groups. The usefulness of GnRHa treatment for endometriosis patients with minimal to mild forms is questionable and deserves further studies.

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## Introduction

Endometriosis is one of the most frequent benign chronic gynecological disorders, and it influences female health negatively by causing abdominopelvic pain and infertility. It has been estimated that endometriosis affects approximately 10% of women of reproductive age and up to 50% of infertile women [1]. Endometriosis-associated infertility is poorly treatable, and treatment mainly consists of surgical approaches, hormonal medication and in vitro fertilization (IVF) or their combination.

The purpose of surgery is to remove all visible implants of endometriosis and adhesions. Women surgically treated at any stage of endometriosis have an approximately 50% chance of spontaneous conception 1–2 years after surgery [2]. Previously, it has been confirmed that surgical treatment improves fertility and has a positive effect on

pregnancy rate at all stages of the disease [3]. Large-scale randomized controlled trials and meta-analyses have shown higher pregnancy rates in women with minimal and mild-stage endometriosis-associated infertility who underwent surgical treatment compared with diagnostic laparoscopy [4]. However, the real value of surgical approaches in women with early-stage endometriosis-associated infertility remains unclear [5]. Surgery for moderate to severe endometriosis is mainly aimed at the alleviation of pain classically associated with these lesions [6] and the restoration of distorted pelvic anatomy [7]. The negative aspect of moderate to severe endometriosis surgery is that it could harm the ovaries, especially in women with bilateral endometriomas, and impair the ovarian reserve [8].

Previous studies have shown that gonadotropin-releasing hormone (GnRH) treatment without laparoscopy for women with minimal to mild and moderate to severe endometriosis seems to be ineffective for endometriosis-related infertility and does not improve the pregnancy rates among infertile women. GnRH therapy may even worsen the situation as a result of treatment delay [9]. Long-term pituitary downregulation, using GnRH therapy, after surgery in women with endometriosis-associated infertility has often been advocated to improve the pregnancy rate, but its real value is still uncertain [10]. However, surgically diagnosed endometriosis patients had better pregnancy rates if pretreated with GnRH analogues for 3 months before IVF [11]. Also, a meta-analysis of 165 women has confirmed the benefit of a 3- to 6-month administration of GnRH analogues before initiation of IVF [12].

When surgery and hormonal medication fail, or when spontaneous conception is impossible due to tubal or male factor infertility, the use of IVF is recommended [13]. Thus, controlled ovarian hyperstimulation and IVF are commonly used for the treatment of endometriosis-associated infertility. The effect of surgery for ovarian endometriomas on IVF outcome is still unclear [14]. Nevertheless, in cases of several unsuccessful IVF attempts, surgical treatment could improve the pregnancy rate [15].

The aim of this retrospective study was to evaluate the effects of combined treatment approaches on endometriosis-associated infertility in minimal to mild and advanced stages of endometriosis using laparoscopy, GnRH agonist (GnRHa) therapy and IVF. In addition, we were interested in the usefulness of applying the GnRHa treatment in minimal to mild stages of endometriosis by calculating the cumulative pregnancy and delivery rates for patients with and without GnRHa treatment.

## Materials and Methods

This retrospective study was carried out among 179 infertile women (22–42 years of age) with surgically confirmed endometriosis, who underwent curative laparoscopy at the Elite Clinic from 2005 to 2008. In our clinic, diagnostic-curative laparoscopy is the first choice of treatment for all patients with endometriosis-associated infertility.

Laparoscopy was performed using a 10-mm laparoscope in the umbilical position and two 5-mm trocars. After a thorough check of the pelvic and abdominal organs, adnexal adhesions were removed. All visible foci of endometriosis, most commonly on ligaments, peritoneum, cavum Douglasi and less frequently on ovaries, parametrium and fossa ovarica, as well as superficial foci on the bowel and bladder were coagulated by bipolar diathermy. The appendix was removed if endometriotic foci were found on it. Out of 58 patients with moderate to severe endometriosis, 32 (55%) had endometriomas. When endometriotic lesions were found on the uterus, or the presence of adenomyosis had previously been diagnosed by ultrasonography, the whole exterior uterine wall was coagulated. Vascular extensions of the uterus and the fallopian tube angle region were also coagulated. However, in our clinical practice, we do not support the surgical treatment of adenomyosis alone, and this procedure is performed only in case of laparoscopy for endometriosis. We did not perform bowel and bladder resection, and a maximum of 6 months of GnRHa treatment was prescribed in these patients.

The patients were divided into group 1 (stage I–II endometriosis,  $n = 121$ ) and group 2 (stage III–IV endometriosis,  $n = 58$ ) according to the American Society for Reproductive Medicine (ASRM) classification system [16]. The patients of group 1 and group 2 were further divided according to the GnRHa treatment status (with and without GnRHa treatment). There were no patients without GnRHa treatment in group 2.

Patients eligible for IVF, or who were found to have adenomyosis or moderate to severe endometriosis, were postoperatively given a GnRHa, either Diphereline (Ipsen Pharma Biotech, France) or Zoladex (AstraZeneca UK, Ltd., UK). The first dose of GnRHa was administered on the first postoperative day, and each following dose was administered after every 28 days for 3–6 months. Some patients received GnRHa treatment, but did not undergo IVF treatment because they spontaneously achieved pregnancy prior to the scheduled IVF treatment. In patients scheduled for IVF, GnRHa treatment and pituitary suppression were continued by IVF without waiting for a menstrual period.

Natural conception was recommended for couples with patent fallopian tubes and normal sperm quality. IVF, intracytoplasmic sperm injection (ICSI) and slow embryo freezing were performed according to standard protocols. Pregnancy was documented by the presence of gestational sac(s) at 6–7 weeks of gestation, with miscarriages occurring between the detection of a pregnancy and the 22nd week of gestation. The cumulative pregnancy rate for all IVF/ICSI/frozen embryo transfer (FET) cycles was calculated for patients participating in the IVF program until December 2009. The study involved only those women for whom we had a complete pregnancy follow-up, including both natural and assisted conceptions and deliveries.

All statistical tests were performed using the R2.14.1 environment (Free Software Foundation, Boston, Mass., USA). The unpaired  $t$  test, Wilcoxon's rank sum test and the  $\chi^2$  test were applied to compare the groups. Logistic regression analysis adjusted for

**Table 1.** General characteristics and laparoscopic findings in the study groups

Characteristics	Group 1	Group 2
Patients, n	121	58
Age, years	33.2±4.4	32.5±4.4
BMI	22.4±2.9 <sup>a</sup>	21.5±2.6 <sup>a</sup>
Regularity of menstruation	105 (86.8)	53 (91.4)
Secondary dysmenorrhea	31 (25.6) <sup>b</sup>	24 (41.4) <sup>b</sup>
Primary infertility	41 (33.9)	25 (43.1)
Secondary infertility	80 (66.1)	33 (56.9)
Duration of infertility, years	6.1±3.3 (n = 111)	6.3±3.6 (n = 55)
Previously laparoscopically diagnosed endometriosis	19 (15.7) <sup>c</sup>	30 (51.7) <sup>c</sup>
Adenomyosis	44 (36.4) <sup>d</sup>	36 (62.1) <sup>d</sup>
Chronic and adhesive pelveoperitonitis	53 (43.8)	34 (58.6)
At least one fallopian tube permeable	91 (75.2)	45 (77.6)
Myoma of uterus	21 (17.4)	7 (12.1)

Values for age, BMI and duration of infertility are expressed as mean ± standard deviation. Figures in parentheses indicate percentages unless otherwise indicated. Groups with common superscript are different: <sup>a</sup>  $p = 0.041$ ; <sup>b</sup>  $p = 0.032$ ; <sup>c</sup>  $p < 0.001$ ; <sup>d</sup>  $p = 0.001$ .

age, body mass index (BMI), presence of adenomyosis and severity of endometriosis was used to assess pregnancy and delivery outcomes in different study groups.

The study was approved by the Research Ethics Committee of the University of Tartu, Tartu, Estonia.

## Results

General characteristics and laparoscopic findings for the two groups are presented in table 1, with no statistically significant differences between the groups regarding age, regularity of menstruation, pelveoperitonitis, fallopian tube permeability or the reproductive characteristics. The mean BMI value was higher in group 1 than in group 2 ( $p = 0.041$ ). Secondary dysmenorrhea was observed more often in the group with moderate to severe endometriosis ( $p = 0.032$ ). Also, the women in group 2 had adenomyosis ( $p = 0.001$ ) more often than those in group 1, while the incidence of myomas (size up to 3 cm) was similar in both groups.

Comparisons and the results of GnRHa treatment and IVF used for the study groups are presented in table 2. The average duration of GnRHa therapy after surgical treatment was longer in group 2 ( $p = 0.021$ ). More than 75% of the women had undergone IVF treatment; the value was the highest (89.7%) in the group with moderate to severe endometriosis who had also received GnRHa therapy. The total number of IVF and FET cycles and the average number of IVF/FET cycles per patient were similar in all groups.

Although the number of retrieved oocytes was statistically higher in group 1 ( $10.1 \pm 5.8$  vs.  $7.4 \pm 4.3$ ,  $p = 0.008$ ), two embryos were transferred in IVF/FET cycles in both groups.

During this retrospective study, until 2009, 119 (66.5%) patients became pregnant, 33 (18.4%) conceived spontaneously, and 86 (48.0%) conceived through IVF. Patients with minimal to mild endometriosis conceived similarly to patients with moderate to severe endometriosis. Twenty-four (19.8%) patients from group 1 and 9 (15.5%) patients from group 2 conceived spontaneously; 25 of them (16 patients from group 1 and 9 from group 2) had undergone previous GnRHa treatment. Fifty-seven (47.1%) patients from group 1 and 29 (50.0%) patients from group 2 conceived through IVF; 66 of them (37 patients from group 1 and 29 from group 2) had undergone previous GnRHa treatment. Seventy-seven patients (89.5% of all IVF pregnancies) conceived during the first two IVF attempts.

The overall clinical pregnancy rate for all patients was 66.5%, and altogether 81 (66.9%) patients with minimal to mild endometriosis and 38 (65.5%) patients with moderate to severe endometriosis achieved pregnancy. Seventy-one (58.7%) patients in group 1 and 30 (51.7%) patients in group 2 delivered. There were no significant differences in miscarriage and delivery rates between the groups with milder and more severe forms of the disease.

We were unable to demonstrate any statistical differences in total pregnancy, miscarriage and delivery rates between the patients with and without GnRHa treatment

**Table 2.** Results of treatment of endometriosis patients

Characteristics	GnRH treatment after laparoscopy			
	group 1			group 2
	GnRH+/-	GnRH+	GnRH-	GnRH+
Patients, n	121	76 (62.8)	45 (37.2)	58
Age, years	33.2±4.4	33.3±4.7	33.0±3.9	32.5±4.4
Duration of postoperative GnRH treatment, months	-	4.3±1.4 <sup>a</sup>	-	4.9±1.6 <sup>a</sup>
Patients with IVF/FET treatment per all patients	89 (73.6)	57 (75.0) <sup>b</sup>	32 (71.1)	52 (89.7) <sup>b</sup>
Total IVF cycles	142	89	53	71
IVF cycles per IVF patient	1.6	1.6	1.7	1.4
Total FET cycles	15	13	2	8
FET cycles per IVF patient	0.2	0.2	0.1	0.2
Retrieved oocytes	10.1±5.8 <sup>c</sup>	9.7±5.5	10.7±6.4	7.4±4.3 <sup>c</sup>
IVF/FET cumulative pregnancies per IVF patient	57 (64.0)	37 (64.9)	20 (62.5)	29 (55.8)
Conceived during I-II IVF attempt per all IVF/FET pregnancies	51 (89.5)	33 (89.2)	18 (90.0)	26 (89.7)
Spontaneous pregnancies per all patients	24 (19.8)	16 (21.1)	8 (17.8)	9 (15.5)
Total pregnancy rate per all patients	81 (66.9)	53 (69.7)	28 (62.2)	38 (65.5)
Total miscarriage rate per all pregnancies	10 (12.3)	6 (11.3)	4 (14.3)	8 (21.1)
Total delivery rate per all patients	71 (58.7)	47 (61.8)	24 (53.3)	30 (51.7)

Values for age, duration of postoperative GnRH treatment and retrieved oocytes are expressed as mean ± standard deviation. Figures in parentheses indicate percentages. GnRH+/- denotes patients with and without GnRH treatment. Groups with common superscript are different: <sup>a</sup> p = 0.021; <sup>b</sup> p = 0.030; <sup>c</sup> p = 0.008.

in group 1. This observation was equally true for those women who became pregnant following IVF as well as for those who conceived spontaneously.

## Discussion

In the present retrospective study, we evaluated the effects of combined treatment approaches on endometriosis-associated infertility using laparoscopy, GnRHa therapy and IVF. Treatment of endometriosis-associated infertility is complicated and depends largely on patient age, previous treatment, duration of infertility and the severity of the disease. Optimal treatment is often difficult to choose as the course of the disease is unpredictable and sometimes causes no complaints, while on other occasions it can be aggressive and cause severe pelvic pain and infertility, being referred to as 'active endometriosis' [17]. The ASRM classification system, which is widely used, provides the stage of endometriosis but does not always correlate with the activity of the disease and the degree of pelvic pain, nor is it predictive of fertility after treatment [2, 18, 19].

The results of studies focusing on treatment options for different stages of endometriosis are conflicting, even when involving identical treatment approaches [9, 20,

21]. Thus, it is possible that the patients with the same disease stage according to the ASRM classification are actually not comparable when it comes to symptoms and activity of endometriosis [2, 22]. The ideal management approach should involve the consideration of the course of the disease, and for very active forms of endometriosis early combined treatment is recommended. It is common practice that a combination of surgery, hormonal medication and IVF is usually recommended to women with endometriosis-associated infertility. However, there are limited data about the efficiency of the various forms of treatment because the number of randomized controlled trials has so far been too small [23].

Many studies have demonstrated the benefit of curative laparoscopy in endometriosis-associated infertility treatment. The pregnancy rate achieved after operative laparoscopy was shown to be similar at all stages of endometriosis [2], which was also observed in our study. In another study, the removal of visible foci of endometriosis during laparoscopy enhanced fertility in infertile women [4]. Sometimes, endometriotic lesions may be located in places (e.g. the myometrium of the uterus or the pararectal region) where surgical removal is technically impossible or associated with an increased risk of complications; in such cases, a combined treatment approach

could prove valuable. The following treatment options have been used: (a) surgical removal of endometriotic lesions, (b) laparoscopy and hysteroscopy when endometrial changes are expected (e.g. endometrial hyperplasia, uterine polyps, adenomyosis or repeated IVF failure), (c) postoperative GnRHa therapy depending on the severity of the endometriosis, and (d) in cases with indication for IVF, immediate postoperative GnRHa therapy continuing with IVF [3, 11, 12, 24, 25].

GnRH supplements are often used in the treatment of endometriosis. In cases of minimal and mild endometriosis, there is no clear view about the usefulness of GnRH therapy [20, 21]. Furthermore, the information available about the activity of endometriotic lesions in minimal to mild endometriosis is very scarce [9]. However, GnRH therapy alone without laparoscopy might be ineffective to alleviate endometriosis-associated infertility [26].

The results of our study further raised the question about the benefit of using GnRHa treatment in cases of milder forms of endometriosis unless laparoscopic surgery is continued with IVF. According to our results, with similar pregnancy and delivery rates in endometriosis patients with/without GnRHa treatment, the GnRHa treatment seems to be not advocated for patients with less severe forms of endometriosis. However, further studies are required before any final conclusion can be made about the recommended treatment protocols for endometriosis patients with milder forms.

When it comes to moderate and severe endometriosis and associated infertility, GnRH therapy after surgery should be considered the 'first-line' treatment and IVF is only indicated as a second treatment option [27]. Furthermore, several case studies where endometriosis was combined with adenomyosis have shown the efficacy of GnRHa therapy in enhancing pregnancy rate [28–30], although its exact fertility-improving impact is not yet entirely clear [29]. In our study, GnRHa therapy in patients with minimal to mild stages of endometriosis was mainly used when adenomyosis was observed during transvaginal ultrasonography. Thus, in our opinion, the reason for administering GnRHa medication after laparoscopy is the regulation of the menstrual cycle before starting IVF as well as the improvement in implantation in cases when endometrial pathology is detected during hysteroscopy.

Consensus opinion on the benefit of medical treatment after surgery in women with endometriosis-associated infertility has never been reached, and its real value in improving pregnancy rate and in preventing recurrence of endometriosis is uncertain [10]. According to the latest ASRM committee opinion [18] and the Royal College of

Obstetricians and Gynaecologists guidelines (2006; <http://www.rcog.org.uk>), postoperative GnRH treatment is not recommended as no proven value is available in terms of a better pregnancy rate. Furthermore, the prolonged GnRH treatment prior to IVF may decrease the ovarian reserve as patients become older and thereby may have a deleterious effect on the pregnancy outcome. As such, urgent IVF after surgery might have some benefit over the postoperative GnRH treatment. However, other studies have still reported contrasting results and have proposed that women who are postoperatively pretreated with analogues of GnRH prior to IVF show better pregnancy rates [11, 12, 31].

Our results confirm that the use of combined treatment can lead to good pregnancy rate, even in patients with moderate to severe endometriosis. Namely, the percentage of women who conceived after treatment of endometriosis in our study (overall pregnancy rate of 66.5%) is comparable to that reported by other authors [32, 33]. Also, our findings emphasize the importance of using combined treatment for infertility patients affected by endometriosis of different stages and in the case of coexisting adenomyosis. In contrast, there is evidence that adenomyosis has a negative impact on the pregnancy outcome [34]. However, the results of our study suggested that the pregnancy rate was not affected by the higher frequency of adenomyosis in the patients with more severe stages of endometriosis compared to the patients with minimal to mild endometriosis.

Certain limitations of this study must be underlined. Firstly, it is a retrospective follow-up study, with patients undergoing curative laparoscopy during 4 years. Secondly, there were no patients without GnRHa treatment in the group with severe endometriosis. This is because the benefits of the GnRHa treatment in cases of severe endometriosis are clearly proved [12, 27]. Therefore, we were unable to estimate the pregnancy rate in patients with more severe stages of the disease, but without the GnRH treatment.

However, the strong point of this study is that all patients were treated by one gynecologist, eliminating the differences in surgery techniques and biases in diagnosing and interpreting the occurrence and progression of the disease.

In conclusion, we found that the outcome of infertility treatment among patients with different stages of endometriosis was not affected by the different approaches used. Sixty-six percent of the studied endometriosis-associated infertility patients conceived and 56% delivered during the study period. Patients with minimal to mild endometriosis conceived similarly (either spontaneously or through IVF) to those who had moderate to severe endometriosis.

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## Disclosure Statement

The authors have no conflicts of interest to disclose.

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