PREGNANCY AND RECURRENCE RATES IN INFERTILE PATIENTS OPERATED FOR OVARIAN ENDOMETRIOSIS

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PREGNANCY AND RECURRENCE RATES IN INFERTILE PATIENTS OPERATED FOR OVARIAN ENDOMETRIOSIS (Abstract): Aim: The study deals with the preoperative ultrasound diagnosis of ovarian endometriosis, postoperative ultrasound reassessment, laparoscopic surgical resolution of ovarian endometriosis, estimation of recurrence risk 12 months after surgery by ultrasound, reappearance of clinical symptoms (such as pain) or second-look laparoscopy, and pregnancy rate 2 years after surgery. Material and methods: 140 patients with endometriosis and infertility admitted to the last “Cuza-Vodă” Clinical Hospital of Obstetrics and Gynecology between the years 2009-2011 were included in the study. The patients were divided into 2 groups: group 1 - 59 cases that refused in vitro fertilization procedures, did not afford in vitro fertilization (IVF) or had minimal endometriosis and young ages and thus a possibility of delaying treatment, and group 2 - 62 cases which underwent IVF procedures immediately after surgery. Results: No significant differences in the chance of becoming pregnant were found between the two groups ($\chi^2=2.06$, p=0.0891, 95% CI); in group 1, 11.86% pregnancies were obtained while in group 2 the pregnancy rate was 11.29%. Based on the nonparametric method of analysis of contingency tables we could estimate the odds of becoming pregnant in the study groups, obtaining an odds ratio (OR=1.16, CI: 1.04-2.23, 95% CI). This result indicated that in group 1 the odds of becoming pregnant was not significantly higher, and the estimation was made for a confidence interval of 95%. The study had in view the assessment of pregnancies obtained in the study groups and the time interval (number of weeks) from the time of intervention until the occurrence of pregnancy. The Kaplan-Meier analysis enabled the assessment of the mean value and the median value of the number of weeks until becoming pregnant, and these values did not show significant differences ($\chi^2=1.55$, p=0.212, 95% CI). Conclusions: For endometriosis associated with infertility, hormonal suppression does not improve fertility, and therefore surgery followed by controlled ovarian hyperstimulation and intrauterine insemination (IUI), provided the anatomy of the pelvis is preserved in early cases or in vitro fertilization in severe cases is preferred. Keywords: ENDOMETRIOSIS, INFERTILITY, PELVIC PAIN, LAPAROSCOPY.

Endometriosis is a benign disease characterized by the growth of the endometrium outside the uterus under the influence of estrogen. This cyclical growth followed by bleeding in the surrounding tissue determines symptoms such as pain and infertil-
The only form of endometriosis diagnosed preoperatively by noninvasive means is the ovarian endometrium, which is the formation of a cyst full of blood inside the ovary. The most common forms are the intraperitoneal ones, but distance localizations are not excluded. Optimal treatment is surgical laparoscopy to remove the endometrial tissue by ovarian stripping or hormonal suppression. In most cases it is followed by relapses.

Endometriosis is a hormone-dependent progressive disease, which can be responsible for symptoms like: dysmenorrhea, dyspareunia, chronic pelvic pain and infertility. After 150 years of research, when multiple hypotheses were issued, the etiology of endometriosis remains unknown. No theory can fully explain the clinical manifestations; therefore, endometriosis can rather be viewed as a syndrome. The diagnosis is often established macroscopically by laparoscopy; histological confirmation is essential because in several cases the endometrial origin of these lesions is invalidated. In the literature, the prevalence of endometriosis varies significantly according to the method of diagnosis: 2-78% in infertility, 0.7-43% in celioscopy for tubal ligation and 4.5-82% in patients who underwent surgery for pain (1). In teenagers with severe dysmenorrhea or pelvic pain, endometriosis is diagnosed by celioscopy in 50% of the cases (2). There are no relevant epidemiological data regarding the incidence of endometriosis in the general population.

The study dealt with the preoperative ultrasound diagnosis of ovarian endometriosis, ultrasound reassessment after surgical treatment, laparoscopic surgical resolution of ovarian endometriosis, estimation of recurrence risk 12 months postoperatively by ultrasound, reoccurrence of clinical symptoms such as pain or by second-look laparoscopy, and the pregnancy rate 2 years after surgery. The aim was to highlight the role of conservative surgery in the treatment of endometriosis-related infertility and the increase of recurrence rate following ovarian hyperstimulation.

**MATERIAL AND METHODS**

One hundred and forty cases of endometriosis and infertility admitted to the Iași “Cuza–Vodă” Hospital of Obstetrics and Gynecology between the years 2009-2011 were included in this study. The age distribution showed that 25% of the patients were older than 33 years (quartile interval Q75-33 years) with a mean age of 29.7 years ±4.9SD, while 50% of these were younger than 26 years (median – 26 years). We did not use the R-AFS classification because of its known subjectivity, and the cases were classified according to the size of the endometriomas: 100 cases of unilateral or bilateral endometriomas less than 5 cm in size and 40 cases with endometrial cysts over 5 cm.

The patients included in the study had a ultrasound diagnosis of unilateral or bilateral ovarian endometriosis histologically confirmed after laparoscopy. The conventional ultrasound diagnostic criteria were: presence of ovarian cysts with characteristic appearance, with a non-homogenous “ground glass” appearance and/or hyperechogenic wall foci with absence of vascularization on power Doppler. The cyst size ranged from 2 cm to 11 cm. The ultrasound signs of deep endometriosis were not looked for. Doctors explained to all patients the pathophysiology of the disease and its repercussions on fertility and quality of life. Patients who refused any intervention or did not come back for consultation were excluded from the study.
Inclusion criteria: age above 18 years, endometrioma over 3 cm and infertility, absence of pregnancy, absence of associated pathologies that do not indicate laparoscopic intervention, the patient’s expressed wish for immediate diagnosis, history of previous IVF failure, association of other causes of infertility. Exclusion criteria: pregnancy, patients who opted for hysterectomy with bilateral adnexectomy, patients with endometriomas not associated with infertility or who did not want children, endometriomas less than 2 cm in size (oral birth control pills were recommended), relapse after a new intervention.

Informed consent for the participation in this clinical study was obtained from all patients after the diagnosis of ovarian endometriosis was made. The consent for laparoscopy was obtained upon admission for the surgical intervention.

All participants in the study were included in a database where the following were recorded: age, weight, menarche, last menstruation, duration of cycles and interval between cycles, previous hormonal treatments, duration of symptoms, ultrasound cyst size, unilaterality or bilaterality, presence or absence of hydrosalpinx, clinical stability or mobility of cysts, previous admissions, preoperative CA125 levels and possibly preoperative AMH levels, and type of surgery. The pre-anesthesia consultation included the laboratory exam, the cardiological consultation and the chest X-ray.

Of the 140 patients with ultrasonographically suspected endometriosis, only 121 cases (86.43%) were operated of which 7 opted (5%) for hysterectomy with bilateral adnexectomy and 12 patients (8.57%) had other diagnoses (dermoid cyst: 4, hemorrhagic cyst: 8). These 121 patients who remained in the study were then divided into two groups depending on a series of factors which influenced decision making in the performance of laparoscopic surgery: history of infertility and other possible causes (male sterility); size of the endometrioma and the anatomic distortion of the pelvis; unilateral or bilateral hydrosalpinx; history of tubal or ovarian surgery; age, presence of the pelvic pain syndrome, other coexisting factors influencing the couple fertility, the patient’s wish, if the patient can afford the costs knowing that in Romania the fertilization procedures are not reimbursed by the Health Insurance Fund.

Group 1 - 59 patients who did not want IVF, did not afford IVF or had minimal endometriosis and young ages with possibility of delaying the treatment. Characteristics of the group: infertility without other associated causes: adherences, hydrosalpinx, preservation of pelvic anatomy, bilaterally positive methylene blue test, no history of inflammatory disease.

Group 2 - 62 patients who underwent IVF procedures immediately after surgery. Characteristics of the group: infertility, changes of pelvic anatomy by adherences or unilateral or bilateral hydrosalpinx, other associated causes of infertility. The group consisted of: 59 patients (95.16%) aged between 25 and 39 years with primary infertility and 2 cases (3.22%) with primary infertility and male infertility. The mean duration of infertility was 4 years. Tubal infertility was associated with unilateral or bilateral hydrosalpinx in 10 cases (16.13%), previous surgery in 3 cases (4.84%) and history of failed IVF in 6 cases (9.68%).

The 2 groups were compared with respect to the recurrence of endometriosis one year postoperatively (based on MRI, ultrasound, repeat laparoscopy, or reoccurrence of pain) and pregnancy rate following various treatment methods.
RESULTS
We conducted a comparative study of two homogenously distributed groups of patients with endometriosis and infertility. The 121 patients (86.43%) who had infertility and unilateral or bilateral ovarian endometriosis were advised to try to conceive as soon as possible after surgery, either naturally or by IVF. In the 62 patients (51.23%) in group 2, bilateral hydrosalpinx followed by tubal coagulation, older age, large cysts with multiple adherences, low preoperative AMH level or patient’s desire for fertility were the main indications for recommending reproductive medicine immediately after interventional laparoscopy. In milder cases, with unilateral endometriomas of small sizes, preserved tubal permeability at the methyl blue test, younger age under 30 years, the patient’s financial situation or lack of desire for immediate fertility, were indications for getting pregnant naturally.

During laparoscopy, the cysts were removed by ovarian stripping, the endometrial implants were coagulated and the adher- sions were totally or partially lysed; in case of hydrosalpinx, the tubes were cauterized or even removed by salpingectomy for successful IVF. In 3 instances laparoscopy was re-converted to laparotomy: in the first case, for large bilateral cysts, with multiple adhesions, in the second case, for suspicion of ovarian neoplasm, confirmed by extemporaneous exam, and in the third case, for difficult hemostasis. The excision of endometriomas was made with observing the ovarian vascularization, without excessive coagulation and with observing the remaining ovarian cortex to preserve the follicular reserve. Tubal permeability was tested in all cases in order to make a decision regarding the possibility of becoming pregnant by natural way after the removal of endometriosis. All cases with proximal obstruction were counselled for immediate reproductive medicine. The study had in view particularly the chances of becoming pregnant and the occurrence of recurrences (fig. 1).

![Fig. 1. Pregnancies and recurrence rate](image-url)
In group 1, 3 (5.08%) natural pregnancies were obtained. The expectancy for pregnancy was 1 year. At the end of the year, the patients were called for ultrasound and clinical re-assessment and reconsidering the therapeutic decision. Pain reoccurred after 1 year in 15 cases (25.42%), and endometrioma in 3 cases (5.08%), but in all 3 cases its size was under 2 cm. The hydrosalpinx occurred postoperatively in 2 cases (3.39%) probably as a result of adhesions and change in pelvic anatomy. The remaining 56 patients were counselled for reproductive medicine, 2 pregnancies being obtained following hyperstimulation with clomiphene, without intrauterine insemination (IUI), 1 pregnancy following hyperstimulation with gonal and IUI and only one pregnancy following 17 IVF procedures performed in 10 patients. The total number of obtained pregnancies was 7 (of 59 patients - 11.86%). Clinically or ultrasonically detected recurrence occurred in 3 cases (5.08%).

In group 2, 240 IUIs were performed of which only 20 by natural cycle without ovarian hyperstimulation and only 2 pregnancies were obtained, and 4 twin pregnancies were obtained from 80 IVFs; therefore, the pregnancy rate was 6 of 61. Recurrences occurred in 7 cases by reoccurrence of pelvic pain and ovarian endometriosis. A laparoscopic reintervention for adhesions lysis was performed in all 7 cases. In the 2 cases with recurrence of endometriosis stripping was difficult because of adhesions and postoperative fibrosis. In the 7 re-operated cases IVF was performed, but only one pregnancy was obtained. Patients older than 35 years with recurrence did not get pregnant (the patient who got pregnant was 28 years old).

From the point of view of becoming pregnant, no significant differences between the two groups were found ($\chi^2=2.06$, $p=0.0891$, 95% CI); in group 1, 11.86% pregnancies were obtained while in group 2 the pregnancy rate was 11.29%. Based on the nonparametric method of analysis of contingency tables we could estimate the odds of becoming pregnant in the study groups, obtaining an odds ratio (OR=1.16, CI: 1.04-2.23, 95% CI). This result indicates that the odds of becoming pregnant in group 1 was not significantly higher, and the estimation was made for a confidence interval of 95%.

**TABLE I**

Estimated parameters in the Kaplan-Meier analysis of pregnancy rate in the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Mean$^a$</th>
<th>Median</th>
<th>Std. Error</th>
<th>95% Confidence Interval</th>
<th>St. Error</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (weeks)</td>
<td>95% Confidence Interval</td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td>Estimate (weeks)</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Group 1</td>
<td>27.663</td>
<td>1.345</td>
<td>25.028</td>
<td>30.299</td>
<td>24.000</td>
<td>.571</td>
</tr>
<tr>
<td>Group 2</td>
<td>30.951</td>
<td>1.652</td>
<td>27.714</td>
<td>34.188</td>
<td>24.000</td>
<td>1.171</td>
</tr>
<tr>
<td>Overall</td>
<td>29.572</td>
<td>1.113</td>
<td>27.391</td>
<td>31.754</td>
<td>24.000</td>
<td>.446</td>
</tr>
</tbody>
</table>

a. Estimation is limited to the largest pregnancies time if it is censored.

The study had in view the assessment of pregnancies obtained in the study groups and therewith, the time interval (number of weeks) from the time of intervention until the occurrence of the pregnancy. The Kaplan-Meier analysis (fig. 2) enabled the assessment of the mean value and the median value of the number of weeks until
becoming pregnant, and these values did not show significant differences ($\chi^2=1.55$, $p=0.212$, 95% CI).

The mean time interval (weeks) between intervention and becoming pregnant was 29.5 weeks, and the median valued indicated that 50% of cases got pregnant in the first 24 weeks after the intervention (table II). The Kaplan-Meier curves clearly showed an absence of significant differences between the pregnancy rates in the two study groups (fig. 2).

![Kaplan-Meier curves of pregnancy rate in the two study groups](image)

**Fig.2.** Kaplan-Meier curves of pregnancy rate in the two study groups

<table>
<thead>
<tr>
<th>TABLE II</th>
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<tbody>
<tr>
<td><strong>Result of comparison tests regarding the rate of becoming pregnant</strong></td>
</tr>
<tr>
<td><strong>Overall Comparisons</strong></td>
</tr>
<tr>
<td>Log Rank (Mantel-Cox)</td>
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<tr>
<td>Breslow (Generalized Wilcoxon)</td>
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<tr>
<td>Tarone-Ware</td>
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</tbody>
</table>

**DISCUSSION**

In two cohort prospective studies on infertile women with moderate and severe endometriosis (AFS classification) who underwent laparoscopic surgery, the pregnancy rate was 57–69% (moderate endometriosis) and 52–68% (severe endometriosis) (3, 4). In our study, the pregnancy rate was much lower (maximum 11.86%), but we did not use the R-AFS classification.

Data in the literature suggest that cystectomy increases the pregnancy rate compared to drainage and electrocoagulation of the cyst (5). In our study, following cystectomy 7 patients got pregnant although they had a history of infertility of 2 to 16 years.
Pregnancy and recurrence rates in infertile patients operated for ovarian endometriosis

(mean 4 years) and of drained endometriomas without cystectomy. One patient who was infertile for 16 years and had bilateral endometrial cyst got spontaneously pregnant 3 months after the surgical intervention. Both surgical techniques, ablation and drainage, can affect the ovarian reserve, but it appears that pregnancy rate is higher after cystectomy (6).

There are no comparative studies on pregnancy rate between the expectant management after laparoscopic surgery and the active management by human assisted reproduction techniques. In our case, there were no significant differences in pregnancy rate between the two groups (6.78% group 1 vs. 9.68% group 2). A bias would be related to the fact that no intracytoplasmic sperm injection (ICSI) was performed in any of the patients and another one by the fact that patients with an AMH lower than 1 ng/ml were not accepted for IVF. A meta-analysis on 22 studies (7) demonstrated that women with endometriosis have a pregnancy rate below 35%. Our study confirmed this finding.

The therapeutic approach depended on the desire and individual characteristics of the patient: age, number of previous interventions, failure or success of previous therapies, endometrioma size, tubal damage, and exclusion of occult malignancies.

Human assisted reproduction as a first choice before laparoscopy has a low success rate and high costs, being the first choice only in women older than 35 years (8, 9). Postoperator therapeutic management can be used to delay surgery until fertility is desired (10). In Romania the reported endometriosis rate has increased alarmingly, either because of the advances in diagnosis (ultrasound diagnostic laparoscopy) or because more women who have chronic pelvic pain or infertility seek medical advice (11). Therefore, gynecologists should be prepared to counsel such patients. It is the doctor’s duty to make a diagnosis as early as possible and to inform the patient about the possibility of disease recurrence and the associated infertility. After making the diagnosis, which most of the time is late, it is necessary to establish a treatment protocol, which most of the time does not consider the Hippocratic principle *primum non nocere*, because the disease is so invalidating through the chronic pelvic pain that the only therapeutic option is total hysterectomy. Affected women are usually nulliparous, and the recommendation of a radical surgical procedure for removing all endometrial fragments, which practically would lead to the relief of pain caused by the endometrial implants, would put the patient in the impossibility of conceiving a child in the future (12,13,14).

**CONCLUSIONS**

In our study, in spite of a strong relation of causality between endometriosis and infertility, it is clear that treatment of endometriosis may improve fertility in some cases. Expectant management can by a reasonable approach in younger patients with less severe disease and a shorter period of infertility.

Laparoscopic surgery seems a better approach compared to medical therapy in endometriosis increasing the odds of spontaneous pregnancies by reconstructing the pelvic anatomy after adhesiolysis.

The pregnancy rate after immediate post-cystectomy procedures is equal to that of patients on postoperative expectant management. Expectant management should be indicated only in younger patients with perfect pelvic anatomy and...
without associated causes for obtaining a spontaneous pregnancy. Recurrence risk is equally high after expectant management or human assisted reproduction.

In women with minimal to mild endometriosis, IUI with controlled ovarian stimulation may be effective in increasing live birth rate, compared with expectant management. Furthermore, IUI with controlled ovarian stimulation may be more effective in increasing pregnancy rate than IUI alone, and may be as effective in women with minimal or mild endometriosis within 6 months of surgical treatment as in women with unexplained infertility.

Based on the conducted study we can recommend controlled ovarian hyperstimulation treatments followed by intrauterine insemination which are better, cheaper and easier options than IVF, only if the surgical anatomy of the pelvis is corrected by the lysis of adhesions, removal of cysts and positive bilateral dye test. Postoperative active intervention through procedures of assisted reproductive medicine increases the pregnancy rate (11.86%) regardless of the size of the endometrioma compared to the passive management.

REFERENCES
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