

SURGICAL TREATMENT (MYOMECTOMY) VERSUS MEDICAL TREATMENT FOR SYMPTOMATIC LEIOMYOMA IN INFERTILE PATIENTS

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Abstract

The treatment of uterine fibroids in sterile patients is yet to be clarified. In the present study (retrospective), we aimed to examine the effectiveness of two therapeutic approaches: medical treatment (3,75 mg Agonist GnRh) and surgical treatment (laparoscopic or hysteroscopic myomectomy) from an implantation consequences point of view.

There were 64 patients included in the study - 32 patients for medical treatment and 32 patients for surgical treatment (out of which 10 laparoscopic interventions and 22 hysteroscopic interventions).

The results confirm a superior effect of the medical treatment on the junction area thickness (3.9 mm vs 4.9 mm $p < 0.008$). As far as the rate of pregnancy is concerned, there is a clear tendency in favour of the surgical treatment (46.8% vs 25%) but without crossing the statistical relevance threshold $p < 0.1$.

The surgical treatment appears to be more effective in the implantation procedure compared to the medical treatment.

Rezumat

Tratamentul fibroamelor uterine la pacientele sterile ramane un subiect neclarificat. In studiul prezent (retrospectiv) ne-am propus sa examinam eficienta a doua abordari terapeutice : tratament medical (Agonist GnRh 3,75 mg – 3luni) respectiv tratament chirurgical (miomectomie laparoscopica sau histeroscopica) prin prisma consecintelor asupra implantarii. Au fost incluse in studiu 64 de paciente – 32 de paciente pentru tratamentul medical, respectiv 32 de paciente pentru tratamentul chirurgical – 10 interventii laparoscopice, 22 interventii histeroscopice).

Rezultatele obtinute confirma un efect superior al tratamentului medical asupra grosimii zonei de jonctiune (3,9 mm vs 4,9 mm $p < 0,008$). In privinta ratei de sarcini exista o tendinta clara in favoarea tratamentului chirurgical (46,8 % vs 25%), fara a se atinge insa pragul de relevanta statistica $p < 0,1$ Tratamentul chirurgical pare a fi mai eficient in privinta fenomenului implantarii comparativ cu tratamentul medical.

Cuvinte cheie: miomectomie, infertilitate, tratament

Introduction

The presence of the intrauterine fibroid is an unfavourable element in the equation of the implantation phenomenon. Sterile patients included

in IVF (In vitro fertilization) programs describing benign tumours such as the leiomyoma constitutes a separate subgroup of sterile patients. One of the major

features is the more important outlook that eventual endometrial or myometrial dysfunctions have in the implantation process compared to patients in whom uterine embryo passage occurs naturally.

The role of uterine fibroids' location has been analysed in a multitude of studies. There is a solid documentation of the negative definite impact of submucosal fibroids and to a significantly lower extent of intramural fibroids (1). Instead, there were no significant differences between patients with subserosal fibroids and the general population (1).

Mechanisms by which uterine fibroids alter implantation are only partially understood. It's generally accepted that both myometrial and endometrial function (local steroid metabolism, inflammatory cell behavior, interleukin behavior) may be altered but without establishing clinical relevance thresholds. Studies on adenomyosis - pathology with many similarities with fibroids - have revealed that the strongest pathogenetic alterations were best associated with the extent of clinical symptoms and not the size or location of the tumour.

Surgical treatment (myomectomy) has been shown useful in submucosal fibroids or at least in those that alter the uterine cavity (2,3). Medical treatment (GnRH agonists) induces a profound level of hypoestrogenemia that has been documented as being useful in the correction of multiple endometrial dysfunctions (4) - There are no studies to this day to compare the two therapeutic lines.

At the moment, there is a strong need to personalise the different types of therapies according to the particularities of each patient (biological potential, comorbidities) and the characteristics of the tumours (dimensions, endometrial involvement, association of clinical symptoms). In the present study we aim to examine two therapeutic approaches:

medical and surgical, in terms of the consequences of implantation in patients with uterine fibroids enrolled in an IVF protocol.

We also only selected patients with symptomatic uterine fibroids, thereby assuming endometrial dysfunctions that reach a clinically relevant level.

Material and methods

The present study (retrospective study) took place at the Obstetrics and Gynecology I Clinic and "Vth Surgical Clinic" in Cluj Napoca from 2015 to 2018.

Subjects were represented by sterile patients with symptomatic uterine fibroids (menorrhagia, dysmenorrhea) enrolled in the reproductive assistance protocol (IVF).

Patients over 37 years of age, with BMI over 30, uterine pathology (adenomyosis) or endometriosis, and diminished ovarian reserve (AMH < 1 ng / ml) were excluded from the study.

Patients were offered two options: medical treatment - Diphereline 3.75 mg intramuscular 1 per month for 3 months prior to IVF or surgical treatment (myomectomy or laparoscopy) followed by IVF after 2 to 6 months depending on the type of intervention.

Hysteroscopy was suggested to patients with submucosal fibroids, with dimensions less than 5 cm and laparoscopic myomectomy for patients with fibroids with no uterine cavity involvement or size greater than 6 cm.

The IVF procedure consisted of a suppression phase with GnRH agonists (for surgical patients) followed by ovarian stimulation with the starting dose determined by age, AMH, number of antral follicles, and BMI respectively. From day 6,

Table 1. Demographic characteristics of the study populations.

	Group A (n=32)	Group B (n=32)	p
Age (years) Median ± SD	32,13 ± 2,70	31,31 ± 3,28	0,283
BMI (kg/m ²) Median ± SD	23,50 ± 1,90	24,34 ± 2,25	0,1456
Duration of infertility (years)	4,53 ± 2,02	5,00 ± 1,88	0,3402
Fibroid diameter (cm)	4,25 ± 1,59	3,84 ± 1,95	0,3
Number of embrioc transfered	1,97 ± 0,59	2,00 ± 0,57	0,827

Group A – surgically treated patients, Group B – non surgically treated patients, SD – standard deviation, BMI – body mass index

doses were individualized based on the ovarian response.

Ovitrelle 250 mcg was administered once the leading three follicles have reached a mean diameter of 18 mm or more. The thickness of the endometrium and the junctional zone were assessed on the day of triggering the ovulation. 1-3 embryos were transferred, according to the patient's wishes.

Confirmation of pregnancy was done 14 days after transfer by beta hCG dosing (values above 25U).

Pregnancies were monitored up to 26 weeks - missed miscarriage during this time being equated with abortion.

The statistical analysis covered descriptive statistics elements, the data being presented using centrality, location and distribution indicators.

The Shapiro-Wilk test was used to test normal distribution. In the case of normal distribution data, the t (Student) test was used and in the case of non-uniform distribution values or ranks, the Mann-Whitney (U) nonparametric test was used. The $\div 2$ test was used in some cases in which the risk to the exposed (R_E), the non-exposed (R_N) and the RR (Risk Ratio) risk were also calculated. The significance threshold for the tests used was $\alpha = 0.05$ (5%), $\acute{\alpha} = 0.01$ (1%) or $\alpha = 0.001$.

Statistical processing was performed with the StatsDirect v.2.7.2 and OpenEpi v.3.03 applications.

Results

68 sterile patients enrolled in an IVF protocol were diagnosed with symptomatic uterine fibroid.

32 patients opted for the surgical approach: 22 patients required hysteroscopic intervention, 10 patients underwent laparoscopic surgery, while 36 patients opted for a medical treatment (4 of these patients subsequently quit the IVF procedure). The demographic data showed a very good homogeneity of the two groups (table 1).

We obtained an important statistically significant difference for the thickness of the uterine junctional zone: 4,9 mm vs 3,9 mm ($p < 0,00009$). The endometrial thickness was similar between the two groups: 9,4 mm vs 9,8 mm ($p 0,2$) (table 2).

The pregnancy rate was significantly higher in the surgically treated group 46,8% compared to the medically treated one 25%, but there was no statistically significant difference ($p = 0,11$) (table 3). The abortion rate was similar in the two groups.

Discussions

The results of the present study establish the favourable influence that the medical treatment (GnRH agonists) has on the junctional zone. At the same time, we were able to observe a clear trend (even if it did not reach the level of statistical

Table 2. Post therapeutic results

	Group A (n=32)	Group B (n=32)	<i>p</i>
Junctional zone thickness (mm) Median \pm SD	4,97 \pm 1,12	3,94 \pm 1,13	0,0009
Endometrial thickness (mm) Median \pm SD	9,44 \pm 1,61	9,88 \pm 1,60	0,2197

Group A – surgically treated patients, Group B – non surgically treated patients, SD – standard deviation

Table 3. Procedure results

Group	Pregnancy		<i>p</i>
	No	Yes	
A	17	15	0,1181
B	24	8	

Group A – surgically treated patients, Group B – non surgically treated patients

relevance) for a better implantation rate in the surgically treated group compared to the medically treated one.

The junctional zone is known as an independent factor in the implantation equation. Treatments that led to a reduction of the junctional zone below a 6 mm threshold have achieved at least partial improvement of clinical symptoms (5).

The presence of a larger pregnancy rate in the surgically treated group demonstrates the existence of additional pathogenetic lines involved in the process (outside the junction area), which were much better controlled by tumour excision.

Process analysis that governs the implantation phenomenon remains an open subject, both because of the complexity of the mechanisms and the large number of factors involved. Thus, the description of endometrial function implies the assessment of the local metabolism of steroids, the expression of interleukins / adhesion proteins, the local immune system or the local antioxidant system. Equally, uterine kinetics play an overwhelming role in this process and the means of quantification and evaluation are unfortunately relatively broad.

The presence of uterine fibroids has been frequently associated with dysfunction in all endometrial or uterine kinetics control systems (5,12,13). It was somewhat surprising that the strongest correlations between the presence of the tumour and the various endometrial dysfunctions were not conditioned by certain tumour sizes or location, but by the presence of clinical symptoms: dysmenorrhea or meno/metrorrhagia. This phenomenon was much better documented in the case of another uterine pathology: adenomyosis (4). The primary therapeutic solution in these cases (sterile patients with adenomyosis entering an IVF protocol) is the treatment with GnRH agonists. This is primarily due to the technical limitations that the infiltrative character of the adenomyotic tumour implies - myometrial mass destruction - which practically limits the surgical indication to exceptional situations. In contrast, in the case of uterine fibroids, myometrial mass is little affected by surgery (6-9) .

The only real shortcomings are the sometimes significant prolongation of the start of reproductive assistance procedures (6 months in the case of

laparoscopy) and the risk of uterine rupture in the last trimester of pregnancy (7-11).

The present study proves that surgical treatment (myomectomy) is a reasonable solution for symptomatic uterine fibroids in sterile patients. Medical treatment (GnRH agonists) is also an acceptable option, especially for patients who associate comorbidities such as adenomyosis or endometriosis.

The main limit of the study is the relatively small number of cases which, for some parameters, did not allow the statistical relevance threshold to be exceeded. Secondly, there is a high degree of subjectivity in determining whether the fibroids are symptomatic or not. A consistent analysis would involve the observation of some pathogenetic parameters (expression of endometrial aromatase, expression of NK cells, pattern of myometrial contractions)

Conclusions

To sum up, the present study supports the beneficial role of surgical treatment (myomectomy) in the context of implantation in sterile patients with symptomatic uterine fibroids. Clearly more extensive studies, with more precise distinctions between different types of fibroids (size, location, symptoms association) and easy to quantify pathogenetic parameters, are needed to provide a more individualised approach.

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