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Evaluation of the effectiveness of a proposed approach to treat infertility against the background of uterine leiomyoma, which includes treatment with a releasing hormone agonist, hysteroscopic resection or conservative myomectomy, and pre-pregnancy treatment in assisted reproductive technology programs

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There is much discussion about the effect of uterine leiomyomas on the outcomes of assisted reproductive technologies (ART). This study aimed to analyze the effectiveness of in vitro fertilization following the use of a therapy scheme we propose to treat infertility with the background of uterine leiomyoma. The therapy scheme includes the use of a releasing hormone agonist, hysteroscopic resection or conservative myomectomy and pre-pregnancy pre-treatment. The clinical study involved 175 women of reproductive age who had been diagnosed with uterine leiomyoma, and were divided into the groups as follows. The treatment group A included 137 women with uterine leiomyoma, and was further divided into subgroups. Subgroup A1 included 55 women with uterine leiomyoma after conservative myomectomy who underwent the proposed treatment scheme (TS); A2 included 45 women with uterine leiomyoma after hysteroscopic resection who underwent the TS; A3 included 37 women with uterine leiomyoma who underwent the TS but not the surgical removal of uterine leiomyoma. Control group B included 38 women with uterine leiomyoma after conservative myomectomy. All patients with intramural and submucosal myoma nodules underwent a hormonal preparatory treatment with a gonadotropin-releasing hormone (GnRH) agonist (Diphereline 3.75 mg intramuscularly once every 28 days for 3 months) prior to the myomectomy. After the surgery, patients were prescribed a combination therapy with a vitamin complex FT 500 plus, vitamin D3 and Pelvidol for three months before and during controlled ovarian stimulation (COS) protocol up to the follicle puncture. We determined that the incidence of pregnancy was the lowest (37.8 %) in women with infertility against the background of uterine leiomyoma, who surgically treated for the myomas, but underwent pre-pregnancy pre-treatment. The frequency of pregnancy did not differ between the A1 and A2 treatment groups, and was on average 7.0 % higher than in the control group, and 11.0 % higher than in the A3 group. The relative incidence of clinical pregnancies was the highest in A1 (45.5 %) and A2 (44.4 %) treatment groups. The frequency of live births in the A1 group was significantly higher than in A3 group (by 14.0 %), while the relative number of term live births in the A1 group exceeded that of A3 group by 26.0 %. Thus, both proposed therapy schemes to treat infertility against the background of uterine leiomyoma, which include the use of a releasing hormone agonist, either a conservative myomectomy or hysteroscopic resection and pre-pregnancy pre-treatment in addition to the ART protocol with a multi-vitamin complex with inositol, vitamin D3, alpha-lipoic acid and magnesium, had the equivalent effects on the incidence of clinical pregnancy, however the frequency of live births was highest after conservative myomectomy (84.0 %).

Keywords: uterine leiomyoma, myomectomy, pre-pregnancy treatment, effectiveness.

Introduction

Current research data addressing the issue of uterine leiomyoma and its impact on female reproductive function

indicate that uterine leiomyoma is a hormone-dependent benign formation of the myometrium. The tumor develops

from an abnormal cell that, after it mutates, gains the ability to grow uncontrollably. Uterine leiomyomas occur in up to 60 % of women under the age of 40 and in 80 % of women under 50 [17]. At the same time, uterine leiomyomas are found in 5 to 10 % of women with infertility and in 1-3 % of cases this pathology is the only factor contributing to infertility [1]. Uterine leiomyoma is also the cause of approximately 7 % of recurring miscarriages [15].

Sub-mucosal and intramural myomas in particular cause deformation of the lumen of the uterus and are the specific types of uterine leiomyomas that can reduce fertility [23]. Studies link the presence of sub-mucosal myomas to impaired fertility as well as pregnancy loss, but the effects of intramural myomas on reproductive outcomes are less clear [16].

Some studies failed to demonstrate an association between intramural myomas and successful *in vitro* fertilization [11], while the others conclude that the presence of intramural myomas reduces the effectiveness of *in vitro* fertilization cycles [17]. A meta-analysis study by Sunkara et al. revealed that intramural localization of myomas reduces the incidence of clinical pregnancy and fertility rate (0.85 and 0.79, respectively) in the cycles of *in vitro* fertilization [19]. There is still no consensus on the practicability of conservative myomectomy to treat these types of leiomyomas [12, 13, 24]. This surgical intervention can be performed, depending on the indications, using vaginal, trans-cervical, laparoscopic or abdominal access. However, surgical treatment can sometimes lead to infertility or deterioration of reproductive function if the connective tissue forms on the pelvic organs or scars form on the uterus. There are conflicting opinions on the effect of surgical treatment (conservative myomectomy) on the restoration of fertility. In particular, Zepiridis et al. [24] showed improved infertility treatment outcomes after any type of conservative myomectomy, while Samejima et al. [18] found that conservative myomectomy can address the issue of infertility only if the myomas were the only cause of infertility, in particular due to their sub-mucosal localization, and the removal of intramural nodules may not affect the effectiveness of infertility treatment. A combination therapy (aGnRH, pre-pregnancy treatment) increases the effectiveness of conservative myomectomy.

The aim of the study was to analyze the effectiveness of *in vitro* fertilization following a treatment for infertility against the background of uterine leiomyoma using a proposed scheme which includes administration of a releasing hormone agonist, hysteroresectoscopy or conservative myomectomy and pre-pregnancy treatment.

Materials and methods

The clinical study was performed during 2014-2020 at the medical center "The Clinic of Professor Stefan Khmil". The study group included 175 women of reproductive age who were diagnosed with uterine leiomyoma. The patients were divided into the treatment group A, which included 137

Fig. 1. Composition of the treatment group and its sub-groups.

women with uterine leiomyoma, and control group B, 38 women with uterine leiomyoma after conservative myomectomy. The group A was further sub-divided into the following subgroups: A1 - 55 women with uterine leiomyoma after conservative myomectomy who underwent treatment according to the proposed TS, A2 - 45 women with uterine leiomyoma after hysteroresectoscopy and TS, and A3 - 37 women with uterine leiomyoma who did undergo surgical removal of uterine leiomyoma but were administered the medication part of the TS (Fig. 1).

All patients with sub-mucosal, intramural and subserosal localization of the myoma nodules underwent hormonal pre-treatment with gonadotropin-releasing hormone (GnRH) agonists (*Diphereline* 3.75 mg intramuscularly once every 28 days for 3 months) before myomectomy. Such preoperative treatment with GnRH agonists is intended to reduce the size of myomas, supporting the organ-sparing approach. Surgical interventions were performed using different methods, depending on the localization of myomas.

Patients of the group A2 underwent hysteroresectoscopy, a modern organ-sparing minimally invasive surgical method to treat patients with uterine leiomyoma. Patients with sub-mucosal myomas were treated in one stage, and those with sub-mucosal/intramural localization of the myoma nodules, in two stages. Hysteroresectoscopy was performed on the 6th to 10th day of the menstrual cycle in the dorsal lithotomy position using mechanical and electrosurgical approaches with a hystero-resectoscope (Karl Storz) under a general anesthesia.

The operating field was pre-treated with antiseptic solutions, the cervix was exposed in mirrors in aseptic conditions; the anterior lip was gripped and stabilized using ball tips forceps. Os direction and length of the uterus were measured using a uterine probe, the degree of cervical canal extension using a Hegar 8 dilator. After that, a hysteroscope was inserted into the uterine cavity. Prior to the surgery, the condition of the uterine cavity and endometrium, angles of the uterus, openings of the fallopian tubes, the cervical canal and the presence and location of pathological formations, were examined and evaluated under a video camera control.

The choice of a surgery method was determined by localization and size of the myomas:

- mechanical surgery using a cutting loop was used to remove sub-mucosal myomas on a thin stalk, located on the uterine floor;
- electrosurgical approach with a loop electrode was used for resection of myoma nodules on a wide stalk with a sub-mucosal/intramural and sub-mucosal localization.

Following the surgery, all patients were prescribed appropriate hemostatic, antibacterial and hormonal therapy.

The other treatment groups of patients underwent conservative myomectomy with removal of intramural and subserosal myomas using laparotomy and laparoscopic approach.

After the surgery, all patients were prescribed a combination therapy for three months before the TS and, in the controlled ovarian stimulation (COS) protocol, before the follicle puncture. The combination therapy included: vitamin complex *FT 500 plus* (inositol (vitamin B8) - 2000 mg, vitamin C - 160 mg, vitamin E - 12 mg, folic acid - 400 µg, selenium - 55 µg, glutathione - 50 mg, zinc - 10 mg, and lutein - 3 mg), 1 sachet once a day for 3 months; vitamin D3 (in the form of *Eutilla vitamin D3*) 2000 IU 1- 2 times/day, depending on the 25(OH)D levels, for 3 months; and *Pelvidol* (alpha-lipoic acid - 600 mg and magnesium - 241.2 mg), 1 tablet once a day for 3 months.

Superovulation in the patients was stimulated with a recombinant gonadotropin corifollitropin-alpha *Elonva* starting on days 2-3 of the menstrual cycle. This drug has a prolonged effect produced by a modification of the carboxy-terminal peptide subunit of the beta chain of human FSH. On days 5-7 of the protocol, depending on the ovarian response, when the follicle size reached 14-15 mm, gonadotropin-releasing hormone antagonist (aGnRH) *Orgalutran* 0.25 mg/day was administered. On day 8 after *Elonva* administration, the stimulation was continued with a recombinant FSH *Puregon* and urinary medication *Menopur* until the final maturation of the oocytes (3 follicles at > 18 mm). Releasing hormone agonist *Diphereline* used was as a trigger (0.2 mg/mL once in the control group, and 0.2 mg/mL once and additionally 0.1 mg/mL after 12 hours in the treatment group). The duration of COS and medicine administration, including the ovulation trigger, were determined by ultrasound and hormone monitoring.

Follicle puncture and follicular fluid aspiration were performed under the control of a trans-vaginal sensor with Cook probes (USA) 36 h after ovulation trigger administration in a manipulation room. On day 5-6 the eggs were fertilized and embryos were cultured with subsequent vitrification in the IVF laboratory. One or 2 embryos were transferred into the uterine cavity using a Cook catheter, the remaining embryos were vitrified. Subsequently, the patients were prescribed a maintenance therapy with progesterone drugs to a positive β -HCG result. With a positive pregnancy result, the pre-pregnancy treatment was maintained for up to 10-12 weeks.

Ultrasound examination of the pelvic organs was performed on all patients included in the study using the *Voluson E8 Expert* system at the initial and each subsequent visit during COS, as well as for several days following the follicular puncture; and 28 days after the embryo transfer to visualize it in the uterine cavity and verify foetal heartbeat.

All patients received a standard comprehensive obstetric clinical and laboratory examination according to local protocols approved both in the Clinic for the management of patients with uterine infertility and by the Regulation of the Ministry of Health of Ukraine № 787 from 09.09.2013 "On the approval of the use of assisted reproductive technologies in Ukraine". This study utilises results of standard clinical and laboratory tests which were performed according to appropriate documents (local orders) regulating outpatient and inpatient obstetric and gynaecological care before and after myomectomy. The study was carried out in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine as well as relevant laws of Ukraine.

Statistical analysis was performed using a licensed software Statistica (version 10; Statsoft, USA). Quantitative values were compared using parametric statistics (the mean and standard error). The differences between parameters were considered statistically significant differences at $p < 0.05$.

Results

We used several parameters to evaluate the effectiveness of the proposed scheme to treat infertility against the background of uterine leiomyoma, and which includes administration of a releasing hormone agonist, hysteroscopy or conservative myomectomy and pre-pregnancy pre-treatment. We found that the incidence of pregnancy was the lowest (37.8 %) in women with infertility against the background of uterine leiomyoma, who did not undergo surgical myoma removal, but underwent pre-pregnancy pre-treatment. The frequency of pregnancy was not significantly different between the A1 and A2 treatment group and was on average 7.0 % higher than in the control group, as well as 11.0 % higher than in the A3 group.

It should be noted that in women with infertility against the background of uterine leiomyoma, who did not have myoma resection, but received pre-pregnancy pre-treatment, the relative number of biochemical pregnancies was 21.4 %, which significantly exceeded the same value in the patients with uterine leiomyoma who underwent conservative myomectomy together with the proposed treatment scheme (3.7 %) and in patients with uterine leiomyoma after hysteroscopy and the proposed treatment scheme (9.0%), as well as the values in the control group (12.5 %). Ectopic pregnancies were diagnosed in 1 woman each of the groups A1 and A3.

The relative incidence of clinical pregnancy was the highest in the A1 (45.5 %) and A2 (44.4 %) treatment groups, exceeding the same value in the A3 group, as well as control

Table 1. Clinical results in the study groups of patients (n,%).

Parameters	A1 group, n=55	A2 group, n=45	A3 group, n=37	Control group, n=38
Frequency of pregnancy	27 (49.1 %)	22 (48.9 %)	14 (37.8 %)	16 (42.1 %)
Frequency of biochemical pregnancy	1 (3.7 %)	2 (9.0 %)	3 (21.4 %)	2 (12.5 %)
Frequency of ectopic pregnancy	1 (3.7 %)	0 (0 %)	1 (7.1 %)	0 (0 %)
Frequency of clinical pregnancy	25 (45.5 %)	20 (44.4 %)	10 (27.0 %)	14 (36.8 %)
Frequency of aborted pregnancy	4 (16.0 %)	2 (10.0 %)	3 (30.0 %)	3 (21.4 %)
Frequency of a multiple pregnancy	4 (16.0 %)	3 (15.0 %)	1 (10.0 %)	2 (14.3 %)
Frequency of live birth	21 (84.0 %)	15 (75.0 %)	7 (70.0 %)	11 (78.6 %)
Frequency of term delivery	19 (76.0 %)	14 (70.0 %)	5 (50.0 %)	9 (64.3 %)
Frequency of a preterm delivery of live foetus	2 (8.0 %)	1 (5.0 %)	2 (20.0 %)	2 (14.3 %)

group. Among clinical pregnancies, the lowest proportion of aborted pregnancies was recorded in women with uterine leiomyoma who underwent hysteroscopy and TS (10.0 %); it was lower compared to the A1 and A2 groups by 6.0 % and 20.0 %, respectively, and to the control group by 11.4 %.

The lowest incidence of a multiple pregnancy was diagnosed in the group of women without surgical removal of uterine leiomyoma and pre-pregnancy pre-treatment (in 1 patient), while this value was comparably similar among other groups and ranged from 14.3 to 16.0 %. It should be noted, that in women who underwent surgery and pre-pregnancy pre-treatment according to the COS protocol, the frequency of live births did not differ from the control group, while it was even slightly higher (5.4 %) in the A1 group. The frequency of live births in the A1 group was significantly higher than in A3 group (by 14.0 %), while the relative number of term deliveries in the A1 group exceeded the same value in the A3 group by 26.0 %. Preterm deliveries with live fetuses were observed in 20.0 % of patients of the A3 group, which was higher compared to the A1 (by 12.0 %) and A2 (by 15.0 %) groups, as well as control group (by 5.7 %) (Table 1).

Discussion

Results of this study indicate the highest frequency of clinical pregnancy and the frequency of live birth were observed in women with uterine leiomyoma after conservative myomectomy who received the proposed treatment scheme. These results correspond to a number of other studies, which confirm higher effectiveness of *in vitro* fertilization after conservative myomectomy with removal of intramural and subserosal myomas [20]. For instance, Martynova et al. [14] found that patients who underwent laparoscopic myomectomy for intramural (or combined with subserosal) nodules with a diameter of over 4 cm before *in vitro* fertilization, the frequency of pregnancy was comparable to that in patients without uterine myomas, which confirms the need for myomectomy.

However, some studies indicate absence of a positive effect of conservative myomectomy on the results of *in vitro* fertilization caused by the changes in uterine blood supply

and endometrial receptivity [11]. In this study, we found almost the same frequency of clinical pregnancy in women of the A1 and A2 groups, but women who underwent hysterorectomy of uterine leiomyoma and received the proposed treatment scheme had a slightly lower incidence live foetus births. Hysterorectomy is known to have advantages such as organ preservation, significant reduction of surgical trauma, short duration of the surgery, and unproblematic postoperative period [10]. However, some research findings point out to a decrease in ovulatory activity after various cavitary interventions on the uterus or fallopian tubes [3, 7, 8]. Some authors that suggest that the risk scar tissue development in the uterine cavity after one hysteroscopy reaches 16 %, and after three or more up to 32 %, which leads to atrophic transformation of the preserved endometrium [2, 21], which may lower efficiency of *in vitro* fertilization. At the same time, the lowest incidence of clinical pregnancy in women of the A3 group, who did not undergo surgical removal of myomas, is fully warranted because of deformation of the uterine cavity, which leads to decreased blood flow, inflammatory changes and imbalance of pro- and antioxidant processes.

It should also be noted that patients in the groups A1, A2 and A3 underwent a course of pre-pregnancy pre-treatment before and into the COS protocol up to the follicle puncture. This combined therapy included inositol as part of the *FT 500 plus* vitamin complex, vitamin D3 in *Eutilia vitamin D3* and alpha-lipoic acid together with magnesium as components of *Pelvidol*. Research findings suggest that the use of medications with antioxidant properties allows not only to normalize the processes of free radical oxidation, which are activated in the cases of uterine leiomyoma, but also to balance the production of reproductive hormones [6, 9]. In addition, inositol and vitamin D3-containing medications enhance the efficiency of *in vitro* fertilization and increase the frequency of pregnancy by improving the quality of eggs and embryos, [22, 25]. Alpha-lipoic acid exhibits immunomodulatory and antioxidant activity, which improves embryo implantation and stimulates the production of local mediators that facilitate implantation. For instance, a study by Canosa et al. [5] showed that the intake of inositol,

alpha-lipoic and folic acids had a beneficial effect on the molecular organization of *zona pellucida* during follicle maturation, which is physiologically rearranged during oocyte maturation [4].

Conclusions

In women with infertility against the background of uterine leiomyoma, the proposed treatment scheme, which

includes either a conservative myomectomy or hysteroresectoscopy, administration a releasing hormone agonist and pre-pregnancy treatment for ART with a vitamin complex, vitamin D, inositol, lipoic acid and magnesium, has similar effects on the incidence of clinical pregnancy, but the frequency of live births is highest after conservative myomectomy (84.0%).

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