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Comparative Analysis Of Pregnancy Rates In ART In Young Women With Uterine Fibroids After Different Approaches To Organ-Preserving Treatment

Abdurakhmanova Sitora Ibragimovna

PhD, Associate Professor, Tashkent State Medical University, Department of Obstetrics and Gynecology, Pediatric Gynecology and Mediofarm IVF Clinic, Tashkent, Uzbekistan

Abstract: Background. Myomatous nodes can impair embryo implantation, alter blood supply to the endometrium, cause an inflammatory response and lead to a decrease in the effectiveness of assisted reproductive technologies (ART). Material and methods. A total of 106 patients with uterine myoma and infertility were examined and divided into 3 groups: 1-group consisted of 35 patients who received drug therapy, 2-group - 32 patients who underwent uterine artery embolization, and 3-group - 39 patients after myomectomy. Conclusion. The choice of the treatment method should take into account the individual characteristics of the patient and her reproductive plans. The frequency of pregnancy after ART varies depending on the method of myoma treatment. Drug therapy - 22.8%, EMA - 12.5%, the best indicators were noted after myomectomy - 30.7%.

Keywords: Uterine myoma, infertility, assisted reproductive technologies (ART), uterine artery embolization (UAE), myomectomy, organ-preserving treatment, pregnancy.

1. Introduction: Uterine myoma is one of the most common benign tumor diseases in women of reproductive age. According to various studies, myoma occurs in 20-40% of women, and among patients presenting for infertility, its incidence can reach 5-10% [1][17]. The effect of myoma on reproductive function

depends on its localization, size and number of nodes. Myomatous nodes can interfere with embryo implantation, alter blood supply to the endometrium, cause an inflammatory response and lead to a decrease in the effectiveness of assisted reproductive technologies (ART) [2][4][8]. In this regard, the choice of myoma treatment tactics before ART remains an urgent task. Since the field of ART in Uzbekistan is developing relatively recently and a number of unresolved problems remain, we conducted this study for the first time to compare the frequency of pregnancy after ART in women of reproductive age who underwent various methods of uterine myoma treatment: drug therapy, uterine artery embolization and myomectomy.

The use of selective progesterone receptor modulators (SRMRs), in particular ulipristal acetate, has attracted particular attention in recent years among drug therapies. Conservative therapy is an important component of treatment tactics, especially in women planning pregnancy or preferring organ-preserving treatment [9][13]. Mechanism of action of ulipristal acetate. Ulipristal acetate (UA) is an SMPR, a selective progesterone receptor modulator with tissue-specific action. It blocks progesterone receptors in myomatous nodules, causing cell apoptosis, decreased proliferation and reduced vasculature. This leads to a reduction in myomatous nodule volume and the relief of menorrhagia. At the same time ulipristal preserves estrogen background and does not cause hypoestrogenemia, unlike GnRH agonists [6][10].

Clinical efficacy. In a number of large clinical trials (PEARL I-IV) high efficacy of ulipristal acetate in uterine myoma was confirmed:

- PEARL I, II: showed significant reduction in the size of myomas and control of uterine bleeding when administered 5 mg/day for 3 months;

- PEARL III, IV: long-term courses of therapy were studied (repeated 3-month courses), which confirmed to a sustained clinical effect with good tolerability [11].

UA demonstrated improvement in the quality of life of patients, decreased need for surgical intervention, and increased probability of fertility preservation [9-11].

Safety and limitations of the drug. Despite the pronounced therapeutic effect, the use of ulipristal has been restricted since 2020 due to identified cases of severe drug-induced liver damage. According to the European Medicines Agency (EMA), cases of acute hepatitis and liver transplantation have been reported.

As a result:

- The EMA has recommended limiting the use of UA;
- The drug is not used for long-term treatment;
- Contraindicated in patients with hepatic pathology;
- Regular liver function tests are mandatory before starting therapy and during treatment.

After a long pause and expert opinion, ulipristal is back on the market in some countries from 2022, but with stricter precautions. Since the approval of ulipristal acetate for the therapy of symptomatic uterine myoma, many clinical and observational studies have been published confirming its efficacy and safety in the short term. A systematic review and meta-analysis by Murji et al (2017) included more than 10 randomized trials and showed that UA was superior to placebo and gonadotropin-releasing hormone (GnRH) analogues in terms of bleeding control, improved quality of life, and tolerability of therapy. Other reviews (e.g., Whitaker et al., 2017) indicate the promising use of UA as a non-invasive alternative to myomectomy, especially in preoperative preparation or patient refusal of surgery. However, despite the positive data, most authors emphasize the need for further studies regarding safety in long-term use, as well as when used in women planning pregnancy.

Role in reproductive medicine. Because uterine myoma is often associated with reproductive dysfunction, UA is important in the treatment of women preparing for pregnancy or assisted reproductive technology (ART) procedures. Ulipristal is considered first-line therapy in women planning pregnancy when myomas interfere with embryo implantation or are accompanied by bleeding. The advantage of UA is that it does not induce the hypoestrogenic state characteristic of GnRH analogs, which makes it more favorable for fertility [13].

The main advantages of UA in this context are:

- Preservation of ovarian function;
- Absence of hypoestrogenic side effects as with GnRH analogs;
- Reduction in the volume of submucosal and intramural myomas interfering with implantation.

Nevertheless, after completion of UA therapy, monitoring of menstrual cycle recovery and myoma control is required before planning pregnancy. Some authors also recommend not to use UA immediately

before the ART program and to wait 1-2 cycles after therapy.

Future prospects include:

- Development of new SPRMs with an improved safety profile;
- Individualization of therapy based on myoma molecular markers;
- Use of UA in combination regimens with other drugs.

Ulipristal acetate represents an effective organ-preserving treatment for symptomatic uterine myoma. Despite the potential hepatotoxic risk, the drug can be used in carefully selected patients if the guidelines are strictly followed. UA remains an important alternative to surgical techniques, especially in preoperative preparation and reproductive medicine [9-13][15].

One of the modern and important organ-preserving treatments for uterine myoma is uterine artery embolization (UA). The procedure involves selective catheterization of uterine arteries with subsequent injection of embolizing particles that cut off the blood supply to myomatous nodes, causing their ischemia and reduction in size. The mechanism of action of the procedure is that the blockage of arterial blood flow leads to ischemic necrosis of myoma tissue, which causes its regression. At the same time, the integrity of the uterus is preserved, which makes EMA an alternative to surgical treatment, especially for women who do not want to undergo hysterectomy [5].

According to numerous studies, the clinical efficacy of EMA allows achieving an average 50-60% reduction in the volume of myomatous nodes within 6 months after the procedure. Reduction of menorrhagia and reduction of pelvic pressure are observed in 80-90% of patients.

Reproductive aspects. Despite its high efficacy in symptom relief, there are concerns about the effects of EMA on reproductive function. Reduced uterine blood flow may adversely affect endometrial receptivity and embryo implantation. According to the literature, the pregnancy rate after EMA is about 10-20% and is accompanied by an increased risk of obstetric complications such as miscarriage, abnormal placental attachment, and preterm labor. The procedure is considered safe, but side effects are

possible: postembolization syndrome (fever, pain, weakness), premature depletion of ovarian reserve (especially in women over 40 years of age), and rarely infection or necrosis of the uterus [16].

Myomectomy is an organ-preserving operation, but in some cases with an unfortunate location of the node (intramural-submucosal localization of a large node) leads to the opening of the uterine cavity, which requires radical surgery - amputation of the uterus in a young woman. In addition, the operation is accompanied by bleeding of the node bed, increased blood loss and requires hemostasis by suturing [3]. Today myomectomy is performed by laparotomy or laparoscopic access, and when it is difficult to remove the removed node, colpotomy access or minilaparotomy is used, i.e. if necessary, combined access is performed. It should be emphasized that the widespread introduction of laparoscopy in the practice of gynecological departments for myomectomy allows to make the operation minimally invasive, less traumatic, with less blood loss. This contributes to the reduction of bed days, rapid rehabilitation and restoration of labor capacity of patients after laparoscopy, as well as rapid restoration of fertility [7][14].

Another effective method for nodule removal is the use of hysteroscopy for submucosal nodules, which allows not only to visualize submucosal myomas, but also to remove them by hysteroscopy if conditions exist [15].

The current methods of surgical treatment of uterine myoma can mostly contribute to the removal of myomatous nodes and preservation of the uterus. However, it is known that recurrence of myoma after myomectomy reaches 30-45%. Consequently, removal of myoma nodes alone does not solve the problem of treating the disease. Only combined complex treatment can contribute to organ-preserving treatment.

Thus, the problem of myoma treatment optimization in patients of reproductive age is not finally solved. The priority tasks remain the development of an individual approach to planning of surgical or combined treatment of myoma in order to predict the formation of qualitative and complete scar, absence of negative influence on the state of ovarian reserve, which will contribute to the improvement of the outcomes of ART programs.

Table 1.**Comparison of different methods of uterine myoma treatment and impact on reproductive function.**

Parameter	Ulipristal acetate (UPA)	GnRH agonists	Myomectomy	EUA
Action mechanism	Blockade of progesterone receptors	Suppression of the pituitary-ovarian axis	Surgical removal of nodes	Embolization of uterine arteries
Effect on ovarian function	Remains	Suppressed	Part of it may be disrupted	Persistent, but possible risks
Bleeding control	Fast (5-10 days)	In 2-3 weeks.	Immediately after surgery	In 2-3 weeks
Myoma volume reduction	30–50%	Till 50–60%	Complete removal	40–60%
Side effects	Cycle disorders, nausea, hepatotoxicity	Hypoestrogenism, osteopenia	Risks of surgery, adhesions	Pain, risk of necrosis, infection
Return of symptoms after therapy	Possible	Often after withdrawal	Depends on the radicalization	Often with partial blood flow
Use in planning pregnancy	Yes, after a course of therapy	Limited	Yes (after uterine recovery)	With caution

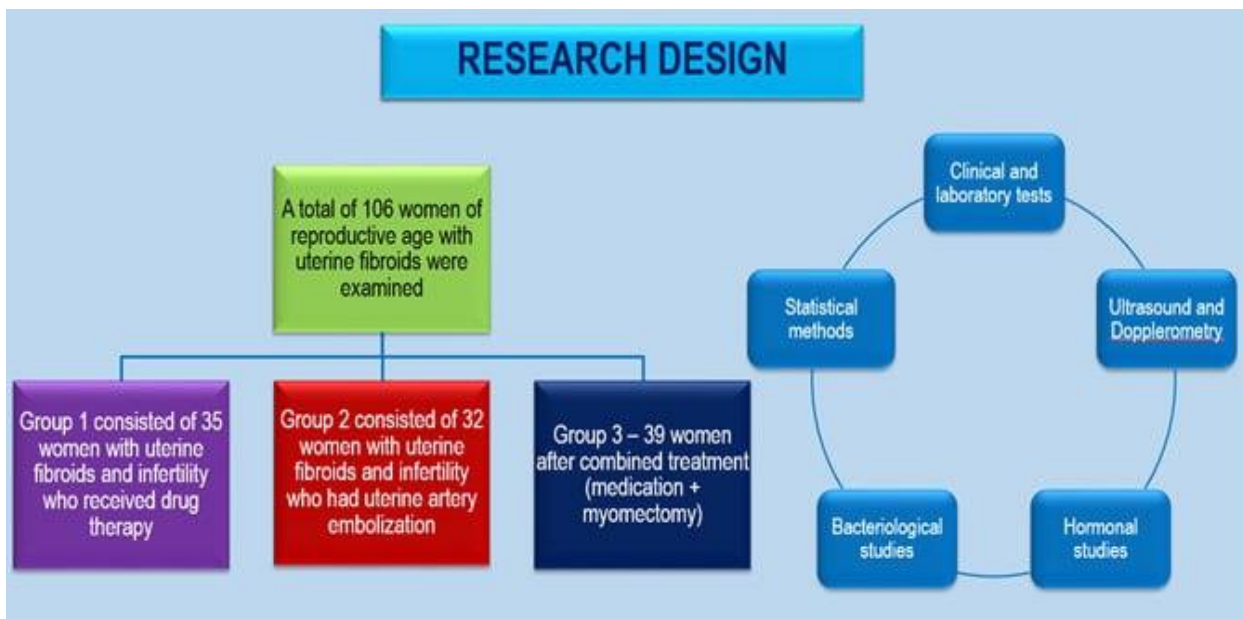
The aim of the study was to perform a comparative analysis of the pregnancy rate in women with uterine myoma after different treatment approaches: drug therapy, uterine artery embolization (UAE) and myomectomy.

2. Methods

The study was conducted in 2024-2025 at the Department of Obstetrics and Gynecology at the National Medical Center of Tashkent State Medical University, in the Department of Gynecology, as well as at the Mediopharm IVF Clinic (Tashkent), where assisted reproductive technology (ART) procedures were performed. In order to compare different treatment methods and determine their effectiveness, we formed three groups of patients with different

types of uterine myoma who underwent ART:

- Group 1 - 35 women with uterine myoma and infertility (primary or secondary infertility in the anamnesis) who received medical therapy. Myomatous nodes were solitary, FIGO classification 3, 4, 5, 6, small in size (≤ 5 cm).
- Group 2 - 32 women with uterine myoma and infertility who underwent uterine artery embolization (FIGO nodes 1, 2, 3).
- Group 3 - 39 women after combined treatment (medication + myomectomy) (FIGO nodes 5, 6, 7).



Laboratory studies

All women underwent general clinical investigations (OAC, blood biochemistry, gross coagulogram, OAM), hormonal investigations (AMH, FSH, LH, estradiol, progesterone, TTG), gynecological examination (gynecological smear, smear femoscreen, bacterial culture of vaginal discharge), infectious investigations (HIV, RW, hepatitis B and C), determination of the patient's blood groups and Rh factor.

Instrumental methods. Ultrasound examination of uterus and ovaries, Dopplerometry of intranodular and perinodular blood flow of myomatous nodes were performed.

Exclusion criteria were women older than 35 years of age, women with multiple myomatous nodes, nodes of large size more than 5 cm, combined forms of uterine myoma and adenomyosis, and women with extragenital diseases.

Statistical studies were performed according to the standard technique using Student's t test (t). Nominal variables were presented as numbers and frequencies, and continuous variables were presented as medians and interquartile ranges. Values of $P < 0.05$ were considered statistically significant.

3. Results

The age of the patients ranged from 23 to 35 years, with the mean age in all three groups being 30.9 ± 1.3 years. The choice of therapy method was made individually taking into account the localization of myomatous nodes and patient's preferences. Thus, among all patients the frequency of primary infertility

was 29%, secondary infertility - 71%, which may indicate the presence of myomatous nodes during the first pregnancy, which contributed to their growth due to the increase in progesterone level. The pregnancy rate in each group was assessed after embryo transfer. Group 1 patients (with myomatous nodes of FIGO types 3, 4, 5, 6) were treated with SMPR (ulipristal acetate) and/or gonadotropin-releasing hormone antagonists (Buserin) for 6-12 months. In group 1 of women who received conservative therapy, the pregnancy rate after ART was 22.8% (n=8). Women in group 2 with myomatous nodes of FIGO classification types 1, 2, 3 were referred to uterine artery embolization (UAE) as a minimally invasive method of treatment, since the effectiveness of this approach is higher for this node localization compared to subserosal nodes. It also reduced the risk of complications such as nodal necrosis after EMA. In this group, embryo transfer was performed 3-6 months after the procedure, but the pregnancy rate was low - only 12.5% (n=4) of 32 women. In the third group of patients with myomatous nodes FIGO 5, 6, 7, myomectomy was performed on the basis of the Department of Obstetrics and Gynecology of TGSI (Department of Gynecology). All patients underwent cryopreservation of oocytes and embryos before EMA and myomectomy at the Mediofarm IVF clinic. Six months after myomectomy, the patients were referred back to Mediofarm IVF to prepare for embryo transfer. This group had the highest pregnancy rate among all groups - 30.7% (n=12).

4. Discussion

The results confirm the effect of different uterine myoma treatment methods on the effectiveness of HRT.

1. Conservative therapy. Recent studies have shown the

effectiveness of conservative therapy of uterine myoma, especially in women of reproductive age, including those with unrealized reproductive function. Modern approaches to the treatment of uterine myoma in women of reproductive age are characterized by organ-preserving orientation, preservation or restoration of impaired reproductive function. Prescription of gonadotropic releasing hormone agonists (a-GnRH) is considered to be one of the effective methods of conservative treatment in terms of clinical effect on the size of nodules, which leads to a decrease in the volume of large and disappearance of small nodules. However, the effectiveness of these drugs varies from patient to patient, which is associated with the hormonal and receptor properties of nodules, their type and size, there is often a recurrence of myoma after withdrawal of the drug.

Esmia, which is a selective progesterone receptor modulator (SMPR - ulipristal acetate), is recognized as a new and quite effective drug. It is of interest to determine the effectiveness of various schemes of conservative treatment of uterine myoma leading to regression of myomatous nodes, preservation of the uterus and restoration of reproductive function.

There were 35 women with uterine myoma under our observation who received medical treatment. Depending on the therapy, the patients were divided into 2 subgroups: 1a - subgroup - 22 women who received Esmia 5 mg for 3 months; 1b - subgroup - 13 women (after unsuccessful Esmia treatment) who received Buserelin-depo 3.75 mg (Pharm Synthesis) for 3 months.

The effectiveness of conservative treatment was monitored by monthly ultrasound to measure the size of the nodes with simultaneous Dopplerometric study of blood flow in the vessels of the nodes. Deterioration of blood flow was assessed by an increase in the value of the resistance index (RI), a relative index characterizing the quality of blood flow before the beginning and in the dynamics of treatment, which provided an objective assessment of the treatment. All women included in the study had subserosal, intramural-submucosal and/or intramural uterine myomatous nodes. All patients were treated with Esmia for three months. Dynamic observation of the clinical picture and ultrasound indicators of uterus and myoma node size showed that the effect of the drug was different. Clinical manifestations in the patients were characterized by amenorrhea, first reduction and then disappearance of pains. During the treatment period, no exacerbation of chronic inflammatory diseases was detected among the examined. Signs of hypoestrogenemia against the background of receiving esmia were noted only by 3 (13.6%) patients, characterized by insignificantly expressed feeling of "hot flashes". All other patients did not present such complaints.

The results of uterine ultrasound and Dopplerometry of blood flow in the nodes were of interest. Dynamic observation of the condition of the nodes showed that in group 1 the use of esmia for 3 months caused a decrease in their size by 35-50% of the initial size, and deterioration of peri- and intranodular blood flow especially at medium-sized myoma nodes. Thus, in the 1-a subgroup IR before treatment ranged from 0.48 to 0.55, after treatment - 0.68-0.87, which was combined with a decrease in node size (Table 2.).

Table 2.

Effectiveness of myoma treatment with Esmia and a-GnRH for 3 months.

Group	Node size (mm)		Node reduction in %	Resistance index			
	before treatment	post- treatment		before treatment		post-treatment	
				around the node	in the node	around the node	in the node
1-a	51x47	25x22	55%	0,48	0,53	0,79	0,87
	49x45	22x17	56%	0,55	0,59	0,68	0,78
	44x48	41x27	36%	0,51	0,57	0,78	0,81
1-b	34x30	21x17	39%	0,63	0,71	0,70	0,81
	52x47	27x25	49%	0,65	0,69	0,75	0,80

	38x29	26x24	32%	0,69	0,75	0,74	0,83
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Deterioration of blood flow was also observed in nodes measuring 5 cm in diameter, although no significant reduction in node size was detected in 21.1% of patients. These patients underwent surgical removal of the nodes by laparoscopy. Also, 26.4% of patients who had nodes measuring 3 cm or more, which deformed the uterine cavity were offered surgical treatment - myomectomy. In two patients (15.4%) of group 1b after 3 injections of a-GnRH the size of the nodes decreased only by 8-11.5% of the initial size, which indicated a low effect of the treatment. Such cases were considered as a risk of myomatous node growth recurrence, which was an indication for surgical treatment of ME. After a-GnRH treatment patients with nodes with diameter from 4 cm to 5 cm underwent myomectomy by laparoscopic surgery taking into account the large size of the nodes. After completion of a-GnRH treatment, oral contraceptive preparations (OC) were prescribed to prevent myoma recurrence. For this purpose, we chose low-dose single-phase Novinet, the treatment course of which was from 4 to 6 months. Dynamic ultrasound monitoring of uterine size and blood flow in the area of nodules showed that the transfer of patients of the 1-b subgroup to the second course of treatment with OC did not cause recurrence of nodule formation, did not lead to improvement of blood supply and decrease of IR in 59.3%. However, in 40.7% of the patients, although the size of the nodules did not change, but the IR increased by 42% from the initial value. This was considered by us as a risk of myoma recurrence, which was also an indication for myomectomy. Thus, treatment of myoma with a-GnRH is most effective in small myomas. The drug esmia showed that it has better results compared to a-GnRH drugs in terms of the rate of involution of nodes, better tolerability of the drug. The economic aspect of treatment is also important, as the cost of Esmium is lower than the cost of a-GnRH preparations. Patients with small myomatous nodes (up to 5 cm) of subserosal and intramural localization (FIGO 4, 5, 6) had a 22.8% probability of pregnancy. This confirms the literature data, according to which myomatous nodes can influence implantation, even if their size is relatively small [7].

2. Uterine artery embolization. EMA is often considered as an alternative to surgical treatment, but its effect on reproductive function remains controversial. In this group 18.7% of women had necrosis of myomatous nodes, as a consequence of which these patients underwent laparotomic myomectomy. Recurrent uterine bleeding was registered in 9.3% of patients. In 34.4% of cases, the endometrial thickness did not correspond to the phase of the menstrual cycle. In this group, the pregnancy rate after EMA was 12.5%, which may be associated with impaired blood supply to the endometrium and decreased receptivity after the procedure. According to studies, EMA increases the risk of intrauterine fusion and endometrial atrophy, which may negatively affect implantation [5].

3. Myomectomy. In the choice of treatment method for patients with uterine myoma we implemented a differentiated approach, which is determined by many factors: clinical manifestations, size and localization of myomatous nodes, intensity of tumor growth and other parameters. Combined medical and surgical treatment helps to increase the number of organ-preserving operations on the uterus, as well as lead to the restoration of fertility. Meanwhile, the efficacy of these drugs is not always unambiguous in women of reproductive age, and the question of the timing of hormonal treatment and myomectomy to restore fertility is debated. Under our observation there were 39 women with uterine myoma, who had previously received drug treatment and underwent surgical treatment - myomectomy. The technique of performance, duration, as well as blood loss during the operation in patients of both groups attracted attention. The average duration of node removal by laparoscopy in patients who received esmia (19.2±0.7 min.) was 2 times shorter than in patients who received a-GnRH (38.1±0.65min.). Undoubtedly, one of the reasons was increased bleeding of the node bed during enucleation due to the difficulty of their isolation, as well as their number (Table 3.). Blood loss during the operation in women who received esmia was (49.2±5.3 ml), which is 2 times less than in patients after a-GnRH (99.6±2.86 ml). Reduced blood flow in the nodes, established by Dopplerometry, provided less blood loss during node enucleation.

Table 3.

Peculiarities of myomectomy performance at different types of preoperative treatment preoperative treatment

Indicators	a-GnRH for 3 months, n=30	Esmia for 3 months, n=10	P
Duration, min	38,1±0,65*	19,2±0,7*	p>0.05
Blood loss, ml	99,6±14,7*	49,2±15,3*	p>0.05

Consequently, the peculiarity of surgery in patients who received esmium for 3 months prior to surgery was a marked decrease in blood loss during node removal compared with pretreatment with a-GnRH. Nodules were released from the bed easily, blood loss was minimal and significantly less than after a-GnRH. The possibilities of modern treatment of uterine myoma allow to reduce the frequency of radical operations. The results of our studies indicate that early diagnosis and pathogenetic therapy of uterine myoma can replace surgical intervention with drug intervention or significantly reduce its volume before myomectomy. All this has made it possible to put conservative measures and endoscopic surgery in the first place in the treatment of uterine myoma, which allowed to restore fertility and improve the quality of

life of women. Women who underwent myomectomy showed the best results - 30.7% of pregnancies after ART. This is in line with studies where surgical removal of myoma, especially for intramural and subserosal nodes (FIGO 5, 6, 7), increases the chances of a successful pregnancy. However, possible risks associated with surgery, including uterine scar formation and adhesions, should be considered [7]. In this pregnancy outcome group, we decided to publicize in another article.

5. Conclusion

The results of this analysis demonstrate that the pregnancy rate after ART varies according to the method of myoma treatment:

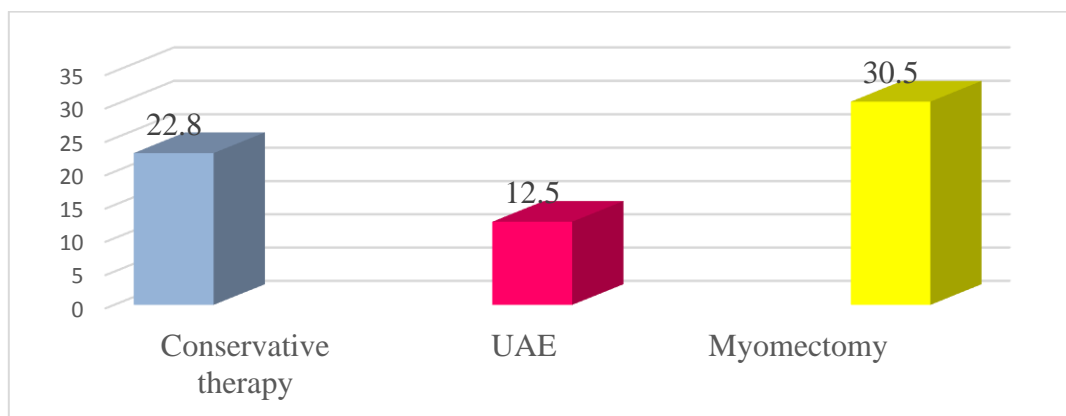


Figure 1. Pregnancy on ART after different methods of myoma therapy

- Conservative therapy - 22.8%, - UAE - 12.5%, - Myomectomy - 30.7%.

Treatment of uterine myoma in young women has its own peculiarities. Conservative organ-preserving therapy with buserelin is most effective for small nodes. To determine the effectiveness of treatment and to decide on the need for ME, Doppler blood flow of myoma nodes before and after treatment is informative. Myomectomy after esmiya is characterized by less blood loss, better mobilization of

the nodes, which is due to a more significant deterioration of blood flow in the nodes compared to a-GnRH. The best indicators were noted after myomectomy, which confirms the expediency of surgical removal of myoma in women planning ART. EMA, despite its minimal invasiveness, may adversely affect the receptivity of the endometrium. Thus, the choice of treatment method should take into account the individual characteristics of the patient and her reproductive plans.

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