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Original article

The estimation of the quantity and quality of oocytes and embryos in the IVF protocols in women with uterine fibroids with and without surgical treatment

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Abstract: Myoma periodically leads to infertility by causing impaired blood flow, aseptic inflammation in the endometrium, increased uterine contractility, impaired sperm migration with cervical myoma nodes and obstruction of the proximal fallopian tubes.
Objective — The estimation of the quantity and quality of oocytes and embryos in the IVF (in vitro fertilization) protocols in women with uterine fibroids with and without surgical treatment.
Material and Methods — The retrospective study included 37 IVF cycles from 37 patients that had infertility combined with myoma. The Group 1 patients were subjected to the IVF procedure without previous treatment of the myoma, while the Group 2 patients were subjected to IVF after myomectomy.
Results — The total quantity of oocytes and the percentage of mature (MII) oocytes obtained during the ovarian puncture of the patients in the compared groups were slightly higher in the group without surgical treatment (p>0.05). Any significant differences in the frequency of formation of high-quality embryos (p=0.43) and good-quality embryos (p=0.22) between the groups were not obtained. The number of embryos suitable for embryo transfer to the uterine cavity and/or cryopreservation in the women with myomectomy was 9% higher than the one in the group without surgical treatment.
Conclusion — Surgical treatment of uterine fibroids does not significantly affect the quantity and quality of oocytes and embryos obtained in the IVF procedure.

Keywords: infertility, uterine fibroids, IVF, myomectomy.

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Introduction

Infertility is currently one of the most important public health problems. Over the past decade, the yearly increase in the use of assisted reproductive technologies has reached approximately 5-10% all over the world. Uterine fibroids often occur in women with infertility of various genesis, and about 20-40% of women of reproductive age are diagnosed with them [1,2].

Uterine fibroids do not always negatively affect the onset of pregnancy [3]. However, they can lead to infertility by causing impaired blood flow, aseptic inflammation in the endometrium and increased uterine contractility.

Inadequate blood supply of the uterus has a serious impact on fertility and is one of the most significant consequences of fibroids. In women with fibroma, the level of blood flow in the uterine artery increases, as well as the blood perfusion does at the site of the myoma node, thereby creating an imbalance of blood in the myometrium. Uterine fibroid cells synthesize pro-angiogenic factors (VEGF, bFGF and PDGF), which stimulate angiogenesis and increase vascular density in the normal muscle layer of the uterus surrounding the myoma node, and that can intensify the growth and progression of tumor [4,5]. Submucous and intramural fibroids lead to changes at the border of the endometrium and myometrium due to an increase in the level of macrophages and natural killer cells, changes in steroid hormone receptors, and, as a result, they induce chronic inflammation. The chronic inflammation is supported by cytokines that influence proliferation, fibrosis, and angiogenesis, which, in turn, stimulate the formation and growth of the myoma [6]. The excess of cytokines, growth factors, neurotensin, neuropeptides, enkephalin, oxytocin modulators, and chronic inflammation of the fibrous can lead to an increased myometrial contractility. The chronic inflammatory response caused by fibroids and the increased myometrial contractility may prevent embryo implantation, thereby affecting fertility and the IVF outcomes [6].

The specificity of the location and the growth of myoma nodes may also lead to difficulties in sperm penetration in women with cervical myoma due to the deformation of the uterine cavity and cervical canal [7], and the obstruction of the proximal fallopian tubes if the fibroid is located in the area of the uterine tube orifices.

All of the above lead to a decrease in reproductive potential, impaired transport of gametes, a decrease in embryo’s ability to implant and the creation of an unfavorable environment for pregnancy [8].

Current studies are mainly dedicated to the effect of the myoma, which does not deform the uterine cavity, on the outcomes of IVF. However, the results of these studies are ambiguous. For instance, there has been noticed no significant effect of the size and number of myoma nodes on the outcomes of the IVF program in the study conducted by Somigliana E. et al. [9]. Martynova A.E. et al. has demonstrated that the frequency of pregnancy as a result of IVF in patients after laparoscopic myomectomy is comparable to that in women without fibroids [10]. And, according to the systematic review and meta-analysis of 19 studies, including 6087 IVF cycles, the frequency of pregnancy and live births in patients with fibroids that do not deform the uterine cavity is lower than those in women without fibroids [11]. For this reason, the results of the research by Klatsky P.C. et al. [12] should also be noted. It has detected no significant difference in the frequency of implantation and clinical pregnancy rates after the IVF procedure using donor oocytes between the women with and without uterine fibroids. At the same time, the estimate of the quantity of intrinsic oocytes and the fertilization rate in patients with uterine myoma is cited only in several studies. So, according to the data of Ramzy A.M. et al. [13] and Christopoulos G. et al. [14], there were no significant differences in the quantity of obtained oocytes and fertilization rate, as well as in the frequency of transfer of high-quality embryos in the IVF cycles in patients with uterine myoma and without ones. Also, there are no available data on the effect of myomectomy on the quality of oocytes and embryos in the IVF protocols in the modern literature.

The objective of the present study is the estimation of the quantity and quality of oocytes and embryos in the IVF protocols in women with uterine fibroids with and without surgical treatment.

Material and Methods

Study design

The retrospective single-center study of 133 IVF cycles was performed at the Department of Assisted Reproductive Technologies (ART) of the Perinatal Center of the Federal State Budgetary Educational Institution of Higher Education, St. Petersburg State Pediatric Medical University, St. Petersburg, Russia, Ministry of Health of Russia, in 2016-2018.

Patient inclusion and exclusion criteria

In this study, all patients were thoroughly selected according to the inclusion and exclusion criteria. They had to demonstrate the presence of infertility, and either the presence of uterine fibroids, according to the ultrasound procedure performed by the attending physician at the time of the IVF protocol, or the presence of myomectomy in the anamnesis, confirmed by the hospital discharge summary. The exclusion criteria encompassed the presence of external genital endometriosis, acute conditions and exacerbation of chronic diseases, along with anomalies in the development of the genital organs.

Data collection

Based on the evaluation of 133 medical records, the study included 37 IVF cycles in 37 women with infertility and uterine fibroids (27.8 %). The patients were divided into two groups: Group 1 underwent IVF without treatment of fibroids (n=20), while Group 2 underwent IVF after myomectomy (n=17).

All patients signed the informed voluntary consent for the IVF procedure before entering the IVF protocol. The presence of a formal consent is not required for conducting a retrospective research.

Table 1. The main clinical characteristics of the patients in comparison groups

	Group 1 (n=20)	*Group 2 (n=17)*	*P*
Age, years old	37.4±3.0	37.0±4.0	0.365
IBM, kg/m²	24.9±3.7	25.2±4.3	0.417
Infertility factor (ICD-10):			
Female infertility associated with anovulation (N 97.0)	21%	6%	0.054
Female infertility of tubal factor (N 97.1)	25%	44%	0.027
Female infertility of uterine origin (N 97.2)	0%	6%	1.746
Female infertility associated with male factors (N 97.4)	50%	38%	0.133
Female infertility, unspecified (N 97.9)	4%	6%	0.455
Myoma size:			
Under 1 cm	5	3	0.298
1-3 cm	11	8	0.321
Over 3 cm	4	6	0.159

Table 2. Evaluating the quantity and quality of oocytes and embryos in comparison groups

	Group 1 (n=20)	*Group 2 (n=17)*	*P*
Quantity of oocytes			
The total quantity of oocytes (N)	6.8±5.2	5.7±3.2	0.215
Mature oocytes (MII), cells per cycle	5.6±3.8	4.7±3.0	0.216
Immature oocytes (MI), cells per cycle	0.8±1.4	0.6±1.5	0.329
Mature oocytes (MII), %	77.2±35.1	74.3±37.9	0.405
Immature oocytes (MI), %	9.9±22.8	6.7±24.3	0.343
Fertilization rate, %	71.3±34.5	74.7±27.2	0.371
Quality of embryos			
High quality, %	27.8±26.8	29.5±26.7	0.433
Good quality, %	17.3±24.8	24.9±33.7	0.222
Low quality, %	4.8±10.9	6.6±9.8	0.303
Relative number of embryos suitable for embryo transfer to the uterine cavity and/or cryopreservation, %	45.4	54.6	0.307
Extent of arrested embryo development in comparison groups: number of embryos per every IVF cycle	2.5±2.8	1.3±1.6	0.066

The number and size of myoma nodes were assessed on the basis of the data provided by the ultrasound study carried out by the attending physician during the initial inspection before the IVF procedure in patients with unoperated uterine myoma and on the basis of the description of the preparation in the surgery protocol.

Obtaining and assessing the quality of oocytes and embryos

In all patients, oocytes were obtained by transvaginal puncture of ovarian follicles after the induction of superovulation using the standard doses of recombinant and urinary gonadotropins preparation in protocols with gonadotropin-releasing hormone (GnRH) agonists and antagonists. The quantity and quality of the obtained oocytes and embryos were assessed on the basis of the data of the embryological protocol.

The appearance of the obtained oocyte-cumulus complexes, the size and the "degree of loosening" of the cumulus and radiant crown cells were taken into account in the course of assessing the quality of obtained oocytes. During the microscopy, the oocyte was considered mature (MII) if it was at the stage of metaphase of the second meiotic division, and if it demonstrated the presence of the first polar body and an overgrown cumulus with a cellular structure, along with the rays of the radiant crown. The oocyte was considered immature if it was at the stage of metaphase of the first meiotic division (MI) and if it demonstrated both the absence of the oocyte nucleus and the absence of the first polar body. Also, the oocyte was considered immature if it was at the stage of prophase of the first meiotic division (GV) and if it demonstrated a small size of the oocyte-cumulus complex, the firm adherence of the cumulus and the radiant crown cells to the oocyte, and the presence of a nucleus in the oocyte.

The fertilization of oocytes was carried out by methods of classical IVF and sperm injection into the oocyte cytoplasm (ICSI) according to medical indications. The embryos were cultured using standard commercial environment. The fertilization was estimated 18 hours after the insemination by calculating the number of pronuclei and polar bodies. The oocytes were considered normally fertilized if they have demonstrated the presence of two pronuclei in the cytoplasm and two polar bodies in the perivitelline space.

Only the normally fertilized oocytes were taken into account when the percentage of oocyte fertilization was estimated. The evaluation of the embryo quality was carried out on the day of embryo transfer to the uterine cavity (the 5th day of embryo cultivation).

The high-quality embryos possessed multiple densely packed cells of internal cell mass (ICM) and many trophectoderm cells, which formed cohesive epithelium. The good-quality embryos demonstrated either many, or several loosely grouped, ICM cells and some trophectoderm cells, which formed free epithelium. The low-quality embryos possessed very few non-grouped ICM cells and a few trophectoderm cells of crescent form.

Statistical analysis

The statistical analysis of the results was carried out using the statistical software of the Microsoft Office Excel 2016. Means (M) and standard deviations (δ) were calculated as quantitative indicators, whereas frequencies (%) were used as qualitative indicators. Quantitative data were checked for normal distribution using Shapiro-Wilk test. All quantitative data were normally distributed. In order to test the hypothesis of equality of the sample means, Student's t-test for two independent samples was employed. All differences between sample means were considered significant at $p<0.05$.

Results

The patients in the comparison groups had similar ages. The average age of the patients in Group 1 was 37.4±3.0 years, while in Group 2 it constituted 37.0±4.0 years (Table 1). The main causes of the patient infertility in the study groups were tubal and male factors (*Table* 1).

In our study, obesity was detected in 15.0% of the patients in Group 1 vs. 23.5% in Group 2. Fibrocystic mastopathy was diagnosed in nearly half of the women included in the study - i.e., in 55.0% of the patients in Group 1 vs. 41.2% of the patients in Group 2.

According to the results of our study, chronic endometritis was detected in 45.0% of women without surgical treatment and in 23.5% of women with surgical treatment of uterine myoma.

All patients in Group 1 were diagnosed with single myoma nodes of small diameter (in 80% of cases they were less than 3 cm), which did not deform the uterine cavity (Table 1). In Group 2, before the myomectomy, 58.8% of the patients had single myoma nodes and 41.2% of the patients were diagnosed with multiple nodes, mainly (in two-thirds of the total number of cases) with the diameter of up to 3 cm (*Table* 1). All patients in Group 2 underwent myomectomy performed laparoscopically.

The induction of superovulation in 5.3% of women in Group 1 vs. 6.2% in Group 2 was carried out using the long protocol. The short protocol with GnRH antagonists was performed in 68.4% of the patients in Group 1 vs. 81.3% in Group 2. The stimulation of superovulation using the short protocol with GnRH agonists was performed on 26.3% of women in Group 1 vs. 6.2% in Group 2. We identified no significant differences in the quantity and quality of the obtained oocytes and embryos when using different schemes of induction of superovulation in patients with uterine myoma.

The total number of oocytes and the proportion of mature (MII) oocytes obtained through the ovarian puncture from the patients in comparison groups were not significantly different, although they were higher to some extent in the group without surgical treatment. Along with this finding, a tendency of reduced quantity of immature (MI) oocytes was noted in the patients who underwent surgical treatment of uterine fibroids (*Table* 2).

The fertilization rates of the patients with surgical treatment of uterine fibroids were not significantly different, although they were slightly higher if compared to the group, which did not undergo the treatment for myoma (*Table* 2).

We did not observe any statistically significant differences between the groups in the frequency of formation of high-quality embryos and good-quality embryos (*Table* 2).

However, among women with surgical treatment of uterine fibroids, embryos, suitable for embryo transfer to the uterine cavity and/or cryopreservation, were obtained by 9% more often than among the women without surgical treatment of myoma (Table 2). Herewith, low-quality embryos formed more frequently during IVF in the patients after surgical treatment (*Table* 2).

In the patients of Group 1, more than a third of the received embryos (35.1%) stopped developing in vitro, which amounted to 2.5±2.8 embryos per each IVF cycle vs. 1.3±1.6 in Group 2 ($p=0.066$) (*Table* 2).

Discussion

Many researchers noted that uterine fibroids develop predominantly against the background of overweight, obesity and neuroendocrine disorders [15]. The accumulation and active conversion of androgens into estrogens occur in adipose tissue, while the quantity of estrogens increases tenfold against the background of obesity, and, consequently, a relative hyperestrogenism develops [15]. Hyperestrogenism leads to hyperproliferation in the ductal and lobular epithelium of the mammary glands, which underlies the pathogenesis of mastopathy [16]. In our study, less than a third of the patients with uterine myoma was diagnosed with obesity, while almost half of all examined women had fibrocystic mastopathy. According to the literature, chronic inflammation in the endometrium accompanies uterine fibroids as well [15]. Our study showed that chronic endometritis was detected twice as much in patients without surgical treatment of uterine myoma.

According to published sources, the presence of fibroids affects neither the quantity of obtained oocytes, nor the frequency of their fertilization and transfer of high-quality embryos in the IVF cycles: they do not differ significantly from those in women without fibroids [13, 14]. Our study detected a decline in the quantity of immature oocytes, along with an increase in the fertilization rate and the quantity of high-quality and good-quality embryos in women, who underwent conservative myomectomy performed laparoscopically, compared with the patients without surgical treatment.

Despite absence of any significant differences in the quantity and quality of oocytes and embryos obtained in the IVF programs in patients with both unoperated and operated uterine myoma, the identified trends suggest the necessity of further research.

Conclusion

The analysis of collected data has implied that surgical treatment of uterine fibroids did not significantly affect the quantity and quality of obtained oocytes, as well as embryos produced during the IVF procedure.

Conflict of interest

The authors declare that they have no conflicts of interest.

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