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Surgery for endometriomas within the context of infertility treatment

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ABSTRACT

Background: The presence of an endometrioma can often be accompanied by a clinical dilemma during the course of fertility treatment. The aim of this study was to evaluate anti-Müllerian hormone (AMH) levels and spontaneous pregnancy rate in infertility patients with endometriomas depending of initial AMH levels and cyst type.

Methods: This prospective cohort study included infertility patients with unilateral endometrioma (3–5 s m in diameter) aged 25–35. A total of them underwent laparoscopic cystectomy. All patients were divided into two groups due to AMH levels and cyst type during surgery. We investigated AMH levels and spontaneous pregnancy rate in 1,3 and 12 months after surgery.

Results: The majority of patients with normal AMH level had type II endometriomas (70%) compared with low AMH level group (30%). There were no significant differences between AMH levels in all the patients with type II endometriomas after surgery. AMH level decreased significantly at 1 month in patients with normal AMH level and type I endometriomas (P = 0.018). But at 3 months the AMH level was compared with initial parameters. Women with low AMH levels before surgery and type I cysts had a significant decrease of AMH level at 1 and at 3 months after surgery. All patients with a time interval of 6 months after surgery had the best outcomes with significantly higher pregnancy rate (PR) in patients with normal AMH level and type II cysts (P = 0.036) and with AMH less than 2 ng/ml and type I cysts (P = 0.021). The group with normal AMH level and type II endometriomas had a significantly higher ongoing cumulative PR than others (59.4%).

Conclusions: Our data suggest that laparoscopic surgery could affect ovarian reserve in case of initial low AMH levels and type I of endometriomas. We believe that the good surgical technique helps to increase pregnancy rate in infertility patients with endometriomas. Good prognosis group are the infertility patients with normal AMH level and type II endometriomas.

Introduction

Ovarian endometrioma(s) can be found in up to 17–44% of women with endometriosis and are often associated with the severe form of the disease [1]. Endometriotic ovarian cysts (known as 'endometriomas') are mostly thought to occur through invagination of endometriotic tissue/cells through the ovarian serosa, for example, during remodelling of the ovarian cortex after ovulation [2].

The previous study showed that ovarian endometrioma increases SRA, ERs, and TSP-1 but decreases VEGF levels in the surrounding ovarian tissues, which may affect biological behaviors of ovarian endometrioma [3]. Clinical data suggest that the presence of an ovarian endometrioma may cause per se damage to the surrounding otherwise healthy ovarian tissue. An endometrioma contains free iron, reactive oxygen species (ROS), proteolytic enzymes and inflammatory molecules in concentrations from tens to hundreds of times higher than those present in peripheral blood or in other types of benign cysts. The cyst fluid causes substantial changes in the endometriotic cells that it baths from gene expression modifications to genetic mutations [4]. The distinguishing cellular and molecular features of Serum anti-Müllerian hormone (AMH), day 3 levels have been proposed as markers of ovarian reserve [5].

The presence of an endometrioma can often present a clinical dilemma during the course of fertility treatment. For example, there can be uncertainty regarding the decision to operate or to manage conservatively, balancing the potential detrimental effect of surgery on the ovarian reserve against the potential benefit that may be gained [6,7].

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The effectiveness and safety of laparoscopic surgery in the treatment of painful symptoms and subfertility associated with endometriosis are still controversial [8]. Some authors suggest that laparoscopic cystectomy when performed for endometriotic cysts with accurate surgical technique leads to no significant ovarian tissue removal [9,10]. The main criterion for endometrioma treatment effectiveness is spontaneous pregnancy rate.

The aim of this study was to evaluate AMH levels and spontaneous pregnancy rate in infertility patients with endometriomas depending of initial AMH levels and cyst type.

Methodology

The local Ethics Committee of People's Friendship University of Russia approved this study protocol (no. 17-107). The publication has been prepared with the support of the "RUDN University Program 5-100". This prospective study included 131 consecutive patients with infertility and unilateral endometrioma who underwent laparoscopic cystectomy for the first time between January 2014 and January 2018. All surgeries were performed by the same surgeon. The endometrioma was verified histologically.

Inclusion criteria were age-group 25–35 years, unilateral endometrioma of 3–5 s m in diametre, body mass index (BMI) <30 kg/m^2, either primary or secondary infertility with a duration of more than 1 year, tubal factor of infertility screened by hysterosalpingography.

Patients with bilateral endometriomas, previous ovarian cyst surgery, with endometriomas less than 3 sm and more than 5 sm, or if they had any pelvic pathology, including uterine fibroids, ovarian cysts (other than endometrioma), and hydrosalpinx. and with male infertility factor were excluded. Women were also excluded if they had a general disease or were on any medication that could affect pelvic blood flow.

Preoperative assessment. Preoperatively on day 2–3 of menses AMH were checked. Colour Doppler in the 2-D mode was used to diagnose endometriomas. After clinical and laparoscopic classification, the cysts were evaluated histologically.

Surgical technique. All the ovarian cystectomies were performed by the same team of surgeons. Endometriosis was staged according to revised American Society of Reproductive Medicine classification.

During laparoscopy all cyst were categorised into two groups based on classification system proposed by Falik et al. [11]. This classification system identifies 2 types of endometriomas on the basis of their etiologies and characteristics. Type I, which arise from endometrial tissue implanted on the ovarian surface, are also called *true endometriomas*. These endometriomas have a densely adherent fibrous capsule [12]. Type II endometriomas arise from functional cysts involved in or invaded by cortical or pelvic sidewall endometrial implants or by type I endometriomas. Type II endometriomas have a cyst wall that is separated easily from ovarian tissue during surgery [13,14].

The cystectomy technique was as follows:

1) Adhesiolysis using scissors; in most cases, the cyst is ruptured during mobilisation of the ovary;

2) The incision of ovarian cortex with scissors on the anti-mesenteric surface;

3) Meticulous repeated irrigation to remove the spillage;

4) Bimanual opposite traction with two 5-mm atraumatic grasping forceps to strip the cyst wall from the inner surface of the ovarian tissue; bipolar, monopolar or laser should not be used for the stripping step;

5) When the densely adherented zone is achieved (the base of the cyst) in case of type I of endometriomas the traction should be stopped. The base should be coagulated and cut using scissors;

6) The bed of the cyst is inspected carefully to visualise the bleeders and to coagulate them pointwise (not *ad mass*) using neutral argon plasma energy. It's necessary to irrigate the bed of the cyst constantly to visualise the spots of bleeding.

Usually we use three 5-mm trocars: 2 – for surgeon, and 1 – for the assistant to irrigate and aspirate continuously.

Postoperative assessment. Systematic postoperative clinical examination was performed in 1 months and in 3 months after surgery. Ovarian reserve was rechecked by measuring AMH levels and stromal blood flow by ultrasound. Pregnancy rates were evaluated during the following 12 months. SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical calculations. Wilcoxon signed test and Pearson Chi-square test were applied. Significance level was $P < 0.05$.

Results and discussion

All included patients were divided into two groups: 71 (542%) patients with AMH level less than 2,0 ng/ml measured at least twice on day 2–3 of different menses and 60 (458%) patients with AMH levels more than 2,0 ng/ml were included (Fig.1).

atients baseline characteristics were similar (Table 1). The were no significant difference in age (P = 0.725), duration of infertility (P = 0.481), duration of menstrual cycle (P = 0.328) and BMI (P = 0.326). Women with normal AMH levels had a secondary infertility in 58.3% of cases. Dysmenorrhoea and dispareunia was strongly and positively correlated with the presence of normal AMH levels. The majority of patients with normal AMH level had type II endometriomas (70%) compared with low AMH level group (30%).

In the literature some authors use another criterion to check the hypothesis. The BC were used to define POR in 56 (51%) of the published and 44 (39%) of the unpublished/ongoing trials. The remaining preferred to use other arbitrarily defined criteria. The BC have not been widely accepted and the definition of poor responders remains vague [15]. Some authors used the same principle and chose AMH level 2 ng/ml to divide patients into 2 groups [16].

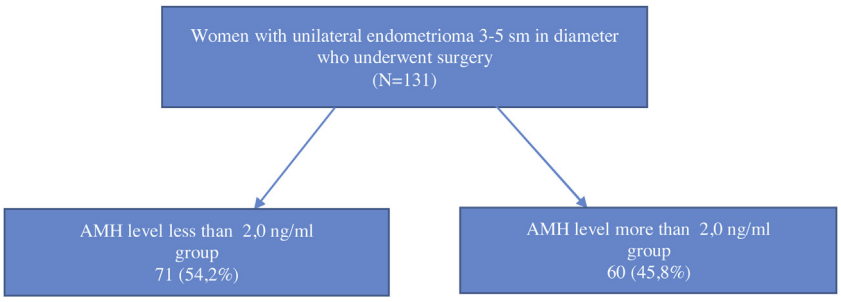

Fig. 1. Participant enrolment.

Table 1
Baseline characteristics for patients with low and normal AMH levels.

Demographic characteristics	Group with AMH less than 2 ng/ml N = 71	Group with AMH more than 2 ng/ml N = 60	P values
Age	24.5 ± 2.5	26.2 ± 3.1	0.725
BMI (kg/m)	24.4 ± 3.1	23.1 ± 2.7	0.326
Dispareunia	32 (45.1)	35 (58.4)	0.032
Dysmenorrhoea	29 (40.8)	37 (61.7)	0.029
Menstrual cycle	28.24 ± 1.41	28.57 ± 3.49	0.328
Infertility primary	50 (70.4)	25 (41.7)	0.019
Infertility secondary	21 (29.6)	35 (58.3)	0.017
Infertility duration	2.4 ± 1.1	2.5 ± 2.1	0.481
Type II Endometrioma	25 (35.3%)	42 (70%)	0.012
Type I Endometrioma	46 (64.7%)	18 (30%)	0.017
r-AFS I-II	36 (50.7)	38 (63.3%)	0.329
r-AFS III-IV	35 (49.3)	22 (36.4)	0.018
Pelvic adhesions stage I-II	42 (59.2)	38 (63.3)	0.453
Pelvic adhesions stage III-IV	29 (40.8)	22 (36.4)	0.453

Note: Data are mean ± standart deviation or n (%).
rAFS, the American Fertility Society revised classification of endometriosis.
Pelvic adhesions stage [35].

We compared AMH levels before surgery and at 1 and 3 months in patients depending on cyst type (Table 2). There were no significant differences between AMH levels in all the patients with type II endometriomas. AMH level decreased significantly at 1 month in patients with normal AMH level and type I endometriomas (P = 0.018). But at 3 months the AMH level was compared with initial parameters. Women with low AMH levels before surgery and type I cysts had a significant decrease of AMH level in 1 and in 3 months after surgery.

The results of pregnancy rate (PR) are presented at Table 3. All patients with a time interval of 6 months after surgery had the best outcomes with significantly higher PR in patients with normal AMH level and type II cysts (P = 0.036) and with AMH less than 2 ng/ml and type I cysts (P = 0.021). The group with normal AMH level and type II endometriomas had a significantly higher ongoing cumulative PR than others (59.4%). The group with AMH levels less than 2 ng/ml and type II had a significantly higher ongoing PR compared with those and type I cyst (37.5% versus 26.2%).

Our study demonstrates some important points. First, the patients with unilateral endometriomas of 3–5 s m in diameter are not the same. So, some of them have normal AMH levels, the others – decreased AMH levels. Probably, it depends on greater oxidative stress and frequent DNA mutations as some authors showed [17]. But our data suggest that AMH levels are associated with type of endometriomas. Secondly, our study was focused on AMH levels after surgery. We proved that the impact of cystectomy on AMH depends on cyst type. We classified cysts into two types because we had no explanation for controversies in the literature concerning ovarian reserve damage after surgery.

Thirdly, the results of the study proved that cystectomy in case of endometriomas of 3–5 s m in diametre increases spontaneous pregnancy rate. In patients with infertility 42.2% achieved pregnancy after surgery during 12 months. An additional explanation may arise from the correction of endometriosis and tubal patency during laparoscopy. The majority of studies investigate postoperative AMH levels [18], AFC [19], and the results of ART [20]. Keyhan et al. showed that the presence of an endometrioma does not appear to adversely affect IVF outcomes, and surgical excision of endometriomas does not appear to improve IVF outcomes [21]. But we tried to show that there is a need to stratify patients with endometriomas because the pregnancy rate depends on a lot of factors.

The damaging effects of endometriomas and cystectomy on ovarian reserve are still controversial. Several studies have shown that there is a loss of follicular density in ovaries with endometriomas compared with unaffected ovaries. Such studies have clearly shown that an endometrioma per se can have a gonadotoxic effect on the surrounding follicles. [21,22]. This fact could explain the differences between AMH levels in patients with endometriomas in present study. Our data suggests that the "aggressiveness" of cystectomy and its effect on ovarian reserve are determined by the technique of operative intervention and specificities of the cyst location [23].

Somigliana et al. showed reduced responsiveness to ovarian stimulation in women with unilateral endometriomas [24]. Benaglia et al. found that endometriomas have a detrimental impact on ovarian physiology by affecting ovulation. The rate of ovulation in ovaries with endometriomas was noted to be significantly less than that of unaffected healthy ovaries [25]. On the other hand, the presence of small endometriomas (<4 cm) does not appear to affect the results of ART [26,27]. Hart et al. summarised two randomised controlled trials (RCTs) which showed a beneficial effect of excisional surgery over drainage or ablation of an endometrioma in achieving a spontaneous pregnancy in subfertile women (OR 5.24, 95% CI 1.92–14.27; n = 88; two trials) [28].

Our data showed that the ongoing PR in patients with normal AMH levels and type II endometriomas achieved 60% after surgery.

Table 2
Comparison of AMH levels before surgery and in 1 and 3 months after depending on cyst localisation.

Groups		AMH levels, ng/ml			P < 0.05
		Before surgery	1 month Post-OP	3 months Post-OP	
Group with AMH more than 2 ng/ml N = 60	Type II endometrioma 42 (70%)	2.77 ± 0.54	2.26 ± 0.13	2.64 ± 0.33	p > 0.05
	Type I endometrioma 18 (30%)	2.42 ± 0.31	1.41 ± 0.11	2.26 ± 0.12	P = 0.018 (1-2) P = 0.023 (2-3)
Group with AMH less than 2 ng/ml N = 71	Type II endometrioma 25 (35.2%)	1.42 ± 0.09	1.18 ± 0.12	1.34 ± 0.16	p > 0.05
	Type I endometrioma 46 (64.8%)	1.24 ± 0.08	0.41 ± 0.06	0.48 ± 0.12	P = 0.025 (1-2) P = 0.031 (1-3)

Table 3
Spontaneous pregnancy rate during 12 months post-OP*.

Groups		Spontaneous uterine pregnancy 6 months post-OP	Spontaneous uterine Pregnancy 6-12 months post-OP	P-value
Group with AMH less than 2 ng/ml N = 66	Type I endometriomas N=42	7 (16.7%)	4 (9.5%)	0.021
	Type II endometriomas N=24	5 (20.8%)	4 (16.7%)	NS
Group with AMH more than 2 ng/ml N = 53	Type I endometriomas N=16	4 (25%)	3 (18.7%)	NS
	Type II endometriomas N= 37	14 (37.8%)	8 (21.6%)	0.036

Note: NS- not significant using Fisher's exact test.
Twelve patients changed the reproductive life plans and didn't desire to become pregnant.

The highest ongoing pregnancy was achieved in patients during first 6 months after cystectomy. So, these patients did not need IVF using. Our data were in agreement with previous studies [34], but demonstrates that PR is propotional to AMH levels and cyst type.

The debates about the most appropriate technique for surgical treatment of endometriomas, comparing the most commonly used techniques: cystectomy, fenestration and bipolar coagulation, or fenestration and laser vaporisation of the cyst wall or two or three step techniques are still continuing [29,30]. But we strongly agree with some authors who showed that laparoscopic endometriotic cystectomy of ovary when performed with accurate surgical technique leads to no significant ovarian tissue removal and thus does not result in reduction of ovarian reserve (Rajeshwari et al., 2014). Our data proved that surgery could affect ovarian reserve in case of initial low AMH levels and special type of cyst. In spite of this, in the group with low AMH levels PR were 37.5% in patients with type II and 26.2% in case of type I cyst.

Some studies state that the removal of ovarian tissue depends on cyst diameter [31], the others are controversial [32]. Muzi L. et al. suggest that the removal of ovarian tissue can be minimised with surgeon's expertise [33]. But we believe that the main evaluating results in patients with infertility should be pregnancy rate.

Conclusion

In summary, the present study reported the relationship between AMH levels and endometriotic cyst type. We suggest that laparoscopic surgery could affect ovarian reserve in case of initial low AMH levels and special type of cyst. We believe that the good surgical technique helps to increase pregnancy rate in infertility patients with endometriomas. The information about AMH levels and cyst type should be provided more systematically to all treated patients by medical staff, especially in terms of success rate of infertility treatment.

Authors' contributions

E.D. Dubinskaya: project development, data collection, manuscript writing, surgery performing; A.S. Gasparov: data collection, manuscript writing, A.A. Dutov: data collection, manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate: The local Ethics Committee of People's Friendship University of Russia approved this study protocol (no. 17-107). All patients gave written informed consent for enrolment in the present study.

Conflict of interest

None declared.

Availability of data and materials

Not applicable.

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