A Real-world Study of Changes in Preoperative and Postoperative CA125, A and M H in Patients with Endometriosis

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Abstract: To investigate the changes of ovarian reserve function in real-world of patients diagnosed endometriosis with different stages, preoperative and postoperative, respectively. Ananlysis the relationship between anti-mullerian hormone (AMH) and CA125. A total of 50 patients operatived because of uterine myoma and 185 patients diagnosed endometriosis from 2014 to June 2020 were inrolled. Of the endometriosis patients, 70 patients with stage I-II and 115 patients with stage III-IV. The groups were redivided into group A(≤35years) and group B (>36) based on age. The serum CA125 and AMH was tested preoperative, retested the AMH1 and 6 months postoperaive. Then analyzed these data by statistical methods. ① There is no statistical significance in the same age groups versus preoperative blood AMH in patients with I-II stage endometriosis groups and in the myoma patients (P> 0.05), compared to the III-IV stage of endometriosis, the AMH were high in the myoma groups and I-II stage endometriosis groups (P <0.05); ② There was no significantly change of serum AMH in the uterine myoma groups between preoperative and postoperative, the differental has no statistical significance (P>0.05)in the I-II stage endometriosis a groups, the AMH decreased 1 month after operation, whereas there was no significant decrease 6 months after operation compared to preoperative, and the difference had not statistically significance (P> 0.05). In the III-IV stage endometriosis groups, the AMH decreased after operation in 1 and 6 months, and the difference had statistically significance (P <0.05). ③ The CA125 was significantly higher in advanced endometriosis stages compared to the I-II stage groups and uterine myoma groups, and was negatively correlated with preoperative AMH.

Keywords: Anti-mullerian hormone; Ovarian endometriosis cyst; CA125; Ovarian reserve function

1. Introduction

Endometriosis is a common and frequently occurring disease in women of childbearing age. In recent years, with the increase of the proportion of cesarean section, the incidence rate of endometriosis is gradually increasing. Ovarian endometriosis is the most common endometriosis, with an incidence of 17%-44% [1]. In addition to dysmenorrhea, infertility is also one of its important hazards. The main cause of infertility caused by endometriosis is the infiltration, erosion and destruction of ovarian tissue, which has a certain impact on the reserve function of ovary. Therefore, it needs active treatment. Laparoscopic ovarian exfoliation is currently recognized as the 'gold standard' for the treatment of ovarian endometriosis. However, whether the operation itself will damage the ovarian tissue and destroy the reserve function of the ovary is still controversial [2].

In recent years, anti-M üllerian hormone (AMH) has attracted much attention in the evaluation of ovarian reserve. It is composed of two dimer monomers with a relative molecular mass of 72,000, which are connected to homodimeric glycoproteins by disulfide bonds, belonging to the transforming growth factor-β superfamily members, these members play a very important role in tissue growth and differentiation. The synthesis of AMH in women is derived from follicular granulosa cells in the early stages of follicular development and is a crucial hormone in the regulation of follicular maturation [3]. There is a good correlation between AMH and the number of antral follicles and the number of primordial follicles present in ovarian tissue [4], whereas in ovarian endometriosis undergoing cyst enucleation, part of the primordial follicles in the ovarian cortex may be destroyed, thus affecting the function of the ovary,

and because it is not affected by the regulation of the hypothalamic pituitary ovarian axis, thus making it better stable and non-cycle dependent, convenient to detect clinically. There have been a large number of studies confirmed that serum AMH level is a good indicator for evaluating ovarian reserve function [5-7], and it is able to predict the slight damage to the ovary at an early stage to predict and evaluate various situations that make the ovarian function impaired.

CA125 is a high molecular glycoprotein surface antigen derived from coelomic epithelial cells, which mainly exists in human endometrial, cervical epithelium, fallopian tube, decidua, peritoneum and other glandular organs. Its elevated expression in serum is commonly found in endometriosis, acute pelvic inflammatory disease, early pregnancy, and ovarian and fallopian tube cancer. The main source is the endometrium, and its concentration is closely related to the biological activity of the endometrium [8]. A large number of clinical studies have shown that the preoperative serum CA125 concentration in patients with endometriosis is related to the stage. In patients with early or no obvious clinical symptoms, serum CA125 is generally within the normal range. With the progress of endometriosis, its expression is on the rise, and it can be significantly increased in patients with mid-late stage or typical symptoms. Therefore, for patients with endometriosis, the level of blood CA125 indicates the disease degree of endometriosis, but it is unknown whether its concentration is related to the change of postoperative ovarian reserve.

In this study, in the real world, 50 patients with uterine fibroids and 185 patients with ovarian endometriosis underwent preoperative and postoperative blood AMH and CA125 monitoring to evaluate the ovarian endometriosis itself. Whether it has any effect on ovarian reserve function and whether laparoscopic ovarian endometriosis cystectomy has any effect on ovarian reserve function. The research results are now reported as follows.

2. Materials and methods

2.1. Subjects and groups

A total of 50 patients who underwent laparoscopic myomectomy due to uterine fibroids at the Affiliated Hospital of Chengde Medical College from 2014 to June 2020 and 50 patients who underwent laparoscopic ovarian myomectomy due to ovarian endometriosis were selected as study subjects, among which 70 patients with endometriosis were divided into stages I-II according to ASRM revised endometriosis staging method and 115 patients were divided into stages III-IV. The groups were further divided into group A (≤ 35 years) and group B (> 36 years) based on age. Inclusion criteria of uterine fibroid group: ①uterine fibroids were suggested by color ultrasound before operation, and they were pathologically confirmed after operation as uterine fibroids without degeneration; ②Menstruation was regular preoperatively, and timing of surgery was chosen 3-7 days after clean menstruation; ③No history of taking hormone drugs in recent half a year; ④There were no other serious medical and surgical comorbidities affecting surgery or hormone determination. Inclusion criteria for the ovarian endometriosis group: ①preoperative color ultrasound suggested an ovarian cyst, the diameter of the cyst was ≥ 4 cm, predominantly cystic, and dense punctate weak echogenicity was seen in it, which was pathologically confirmed as ovarian endometriosis after surgery; ② Menstruation was regular preoperatively, and timing of surgery was chosen 3-7 days after clean menstruation; ③ No history of taking hormone drugs in recent half a year; ④ There were no other serious medical and surgical comorbidities affecting surgery or hormone determination. All surgical approaches for patients were performed laparoscopically and were performed by associate chief physicians with extensive experience in our hospital and those with job titles above. Two methods of hemostasis after ovarian cystectomy include bipolar coagulation and suture hemostasis. The uterus was shaped by suture after myomectomy. Postoperative pathology was diagnosed by the experienced chief physician of our hospital. The procedures followed in this study conformed to the ethical standards established by the Affiliated Hospital of Chengde Medical College, and were approved by the committee, and the patients themselves signed an informed consent form for clinical research.

2.2. Methods

2.2.1. Ovariohysterectomy and myomectomy

Ovarian endometriosis cystectomy: All endometriosis patients underwent laparoscopic EMS conservative surgery, including ovarian cystectomy, pelvic adhesion release, ectopic lesion resection and electrocautery technique. The operation is carried out 3-7 days after menstruation is clean. Specific steps:

① Insert laparoscope for comprehensive exploration and progressive clinical staging. ② Perform adhesion release and cystectomy to expose the operative field, and then suture the ovary with absorbable sutures to stop the bleeding and perform ovarian shaping. If there is still bleeding, use bipolar coagulation at last. ③ After the operation, the basin and abdominal cavity should be washed repeatedly with a large amount of normal saline. The resected tissue was sent for histopathological examination.

Myomectomy: all enrolled patients with uterine fibroids underwent myomectomy laparoscopically. Surgery was performed within 3-7 days after clean menstruation. Specific steps: ① Laparoscopy was placed for full exploration. ② Monopolar incision of the serosal layer of the uterine fibroid to expose the fibroid nodule, such as bleeding from coarse blood vessels during stripping to give timely electrocoagulation and hemostasis, combined with bending forceps to completely denude the fibroid. ③ The fibroid is pulverized by a fibroid rotator, and removed. The uterus was sutured by barbed thread to stop bleeding and shaped. As there was still oozing blood at the needle eye, and finally hemostasis with bipolar electrocoagulation. ④ The application of a large amount of normal saline repeatedly rinses the basin and abdominal cavity. The resected tissues were sent for histopathological examination.

2.2.2. Serum anti-mullerian hormone test

All patients were given an empty stomach before surgery and in the early morning of 1 and 6 months after surgery, 5 ml of venous blood was drawn, and the serum was separated by centrifugation after standing for 2 hours at 3500 rpm and AMH was detected by Roche E411 automatic chemiluminescence analyzer.

2.2.3. Serum CA125 Detection

5ml of venous blood was drawn from all patients on an empty stomach in the early morning before surgery, and after standing for 2 hours, the serum was separated by centrifugation at a speed of 3500 rpm, and CA125 was detected.

2.3. Follow up

Serum AMH levels were measured in all patients preoperatively at 1 day, 1 month, and 6 months postoperatively, and long-term follow-up of pregnancy outcomes was performed at 2 years by using 2 methods: regular review with telephone follow-up, in which the follow-up of pregnant patients was completed just before, and in some patients, the follow-up was lost.

2.4. Statistical analysis observation indicators

SPSS 19.0 software was used for data processing, and the measurement data were expressed as mean $\pm$ standard deviation one-way analysis of variance was used, the relationship between two variables was analyzed by correlation, and the comparison between groups was performed by T-test. Inspection of the level of $\alpha=0.05$ and $P < 0.05$ were considered statistically significant.

3. Results

3.1. General information on the study population

A total of 235 patients were included in this study, including 50 patients with uterine fibroids, 24 patients in group A, 26 patients in group B, and 70 patients with stage I-II endometriosis, including 25 patients in group A, there were 45 patients in group B and 115 patients with stage III-IV endometriosis, including 55 patients in group A and 60 patients in group B. In group A and group B, there were no statistically significant differences in age and BIM between the groups. However, there was no statistically significant difference in AMH in preoperative blood AMH between the uterine fibroids group and the stage I-II group in the same age group (P>0.05,); compared with the stage III-IV group Compared with the uterine fibroids group and the I-II stage endometriosis group, the preoperative blood AMH was higher, and the difference was statistically significant (P<0.05). The preoperative general information and serum AMH values are shown in Table 1 and Table 2, respectively.

Table 1: General data and serum AMH levels of the patients in group A.

Group	Age (years)	BIM (kg/m^2)	AMH (ng/ml)
uterine myoma	27.38±4.89	20.59±0.54	4.33±1.19
I-IIendometriosis	28.44±4.67	21.23±0.33	4.12±0.92
III-IVendometriosis	28.02±4.02	20.86±0.31	3.05±1.02
P	>0.05	>0.05	<0.05

Table 1: General data and serum AMH levels of the patients in group B.

Group	Age (years)	BIM (kg/m^2)	AMH (ng/ml)
uterine myoma	40.46±3.17	21.32±0.58	3.42±0.85
I-IIendometriosis	40.22±3.21	20.82±0.61	2.69±0.93
III-IVendometriosis	41.8±3.82	21.93±0.71	1.84±0.84
P	>0.05	>0.05	<0.05

3.2. Correlation

There was no significant correlation between the preoperative blood CA125 level and AMH in the patients with stage I-II endometriosis, while there was a positive correlation between the preoperative blood AMH and CA125 level in the patients with stage III-IV endometriosis (Figure 1).
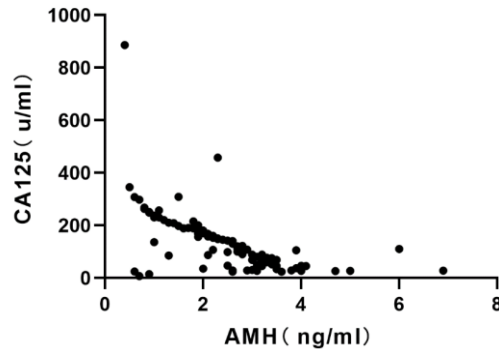

Figure 1: Preoperative blood AMH and CA125 in the stage I- V endometriosis group

3.3. Statistics of changes in blood AMH

There was no significant decrease in blood AMH in the uterine fibroids group at 1 month and 6 months after operation, and the difference was not statistically significant (P>0.05). Monthly blood AMH decreased compared with that before operation, and the difference was statistically significant (P<0.05), but there was no significant decrease compared with preoperative 6 months after operation, and the difference was not statistically significant (P>0.05). The blood AMH in stage III-IV group decreased at 1 month and 6 months after operation, and the difference was statistically significant (P<0.05) (Figure2).
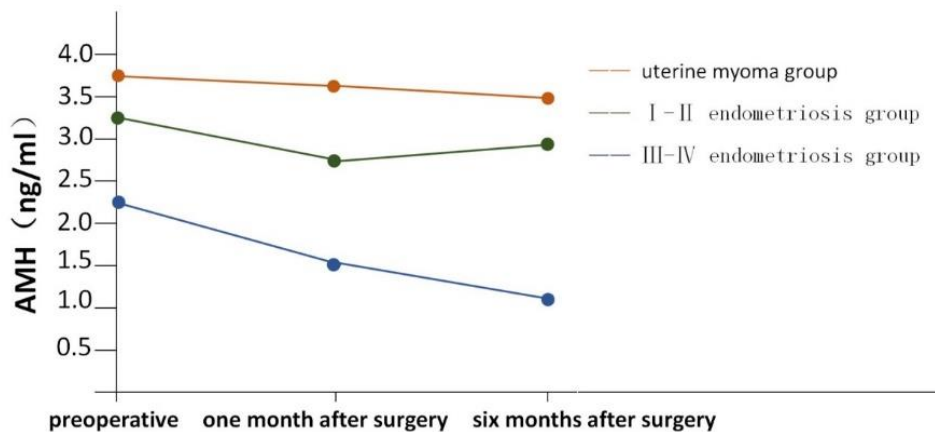

Figure 2: Preoperative and postoperative changes of the patient's AMH

4. Conclusions

(1) Compared with other patients of the same age group, patients with advanced endometriosis have lower preoperative blood AMH and higher blood CA125. Considering that advanced endometriosis itself has an impact on ovarian reserve function, it is negatively correlated with the level of CA125.

(2) In the early and young patients with endometriosis, the blood AMH decreased in a short period of time compared with that before the operation, but the effect on ovarian function was reversible, and there was no significant difference between the two after six months. Postoperative blood AMH in patients with late endometriosis has a greater decline. Considering that surgery has a serious impact on the decline of ovarian reserve, and the effect is irreversible, the degree of AMH decline is negatively correlated with the preoperative CA125 level.

(3) For women with reproductive needs, patients with endometriosis should undergo surgery as soon as possible to avoid the progression of the disease, which will eventually affect ovarian function and lead to infertility.

5. Discussion

Endometriosis refers to the growth of endometrial tissue with growth function in other parts of the uterus. According to its anatomical location, it can be divided into three categories: pelvic adhesion type, ovarian cyst type and deep infiltration type. Among them, ectopic endometrial cysts located in the ovarian parenchyma can directly affect the female ovarian reserve [9]. The number of primordial follicles in the ovaries affected by endometriotic cysts decreases, while the number of atretic follicles and primary follicles increases. The results in this experiment are consistent with this theory. The explanation for this phenomenon is that the ovaries affected by ovarian endometriotic cyst lesions have an inflammatory response, which stimulates more primordial follicles that should have been dormant to be recruited into the growth and development track, and the inflammatory response of local lesions makes Ovarian fibrosis affects its blood supply, so that the follicles entering the growth stage cannot receive sufficient nutritional support, thus leading to atresia. Hence the seemingly contradictory phenomenon that both primary follicles entering the growth phase are increased in atretic follicles in the ipsilateral ovarian cortex [10]. This forms a vicious circle and accelerates the depletion of the diseased follicle reserve. In recent years, many experimental results have shown that the content of inflammatory mediators such as IL-6, IL-8, IL-18, TNF-a and monocyte chemotactic factor-1 in the follicular fluid, peritoneal washing fluid and blood of patients with endometriotic cysts is significantly increased, which further confirmed the scientific hypothesis that ovarian endometrioma cysts increase the recruitment of follicles through the inflammatory response, thereby promoting the depletion of ovarian reserve.

The serum CA125 concentration is closely related to the biological activity of the endometrium. The serum CA125 concentration of women in menstrual period is higher than that in non-menstrual period, and the serum CA125 concentration in endometriosis is higher than that in non-endometriosis. Pan[11] selected 60 observers who were diagnosed with endometriosis by surgery and 60 control subjects with normal physical examination, and detected serum CA125 in the two groups respectively. The results showed that the average level of serum CA125 in the control group was (13.32 ± 6.24) IU/ ml, while the stage I-II endometriosis was (42.91 ± 20.13) IU/ml, and the stage III-IV was (55.91 ± 39.20) IU/ml, and the difference was statistically significant. Consistent with the results of this experimental study, this experiment further analyzed the correlation between the preoperative serum CA125 concentration and the postoperative serum AMH decrease, and concluded that the two were negatively correlated.

Both AMH level and Antral Follicle Count (AFC) have good predictive value for ovarian reserve, and AMH is the gold standard for predicting ovarian reserve [12]. Through a prospective cohort study, some researchers found that compared with the control group, the AMH levels and AFC in the patients with ovarian endometriosis of reproductive age were decreased [13]. This experiment further confirmed that the serum AMH decreased in patients with advanced endometriosis before surgery, but there was no obvious change in the early stage. After laparoscopic endometriosis cystectomy, the postoperative AMH decrease was more obvious in patients with advanced endometriosis, while the decrease in postoperative AMH was not obvious in patients with early stage and loose adhesions.

Real-world research is a study that collects real diagnosis and treatment data of patients in real clinical, community or family environments to evaluate the real impact of treatment measures on patients' health. A powerful supplement [14]. The subjects in this study are all from the real clinical environment. Compared with randomized controlled clinical studies, the criteria for inclusion and exclusion are

relatively loose. Endometriosis and the effects of surgery on ovarian function are useful supplements to prospective randomized clinical studies.

Endometriosis cystectomy: The surgical indication for ovarian endometriosis is asymptomatic, and surgery is feasible for patients with a diameter greater than 4 cm. In fact, the statement that surgical treatment of early ovarian endometrioma is a 'double-edged sword' has been controversial in recent years. In recent years, with the opening of the country's 'second child' and 'third child', especially for patients with ovarian endometriosis cysts who have reproductive needs, the risk of delaying surgery is that the disease progresses after the diagnosis is delayed, resulting in aggravation of pelvic adhesions. The involved ovarian lesions are further destroyed and fibrotic, resulting in egg loss and decreased ovarian reserve. This experiment also confirmed that patients with advanced endometriotic cysts had lower blood AMH than in the early stage. However, at the same time as the operation, the ovarian cortex is inevitably damaged, thereby destroying the ovarian reserve function. This experiment also confirmed this point of view. Therefore, the operation requires higher requirements for the operator, and more attention should be paid to the protection of the ovary. The results of this experiment show that the early excision of ovarian endometriomas has relatively little effect on the ovary because of its slightly loose adhesion, and it is reversible. Surgical treatment can better protect the ovarian reserve function, and at the same time, it can also be diagnosed early, inform the patient of the disease, plan the time of birth, and reduce the risk of malignant transformation.

Acknowledgements

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