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Morphofunctional conditions of the endometrium in the late reproductive age patients with infertility

S.M. Kornienko
State Institute of Pediatrics, Obstetrics and Gynecology

The purpose of this study was to examine the morphofunctional state of endometrium in women of late reproductive age with infertility before IVF. The study involved 197 patients with infertility. Were performed ultrasound, fluid hysteroscopy and endometrial biopsy to examine the state of its receptor system. Were found that the US is not sufficiently informative for diagnostics of endometrial pathology in this category of patients: diagnostic findings during hysteroscopy included: endometrial polyp – 6.1%, endometrial hyperplasia - 4.0%, saddle uterus – 2.5%, uterine adhesions – 0.5% of cases. In general, primary false negative diagnoses recorded in 18.7% of patients. Immunohistochemical study of the expression of receptors for estrogen and progesterone in the endometrium revealed a dissonance between the indices in the stroma and glands: if the level of estrogen receptors in the glands and stroma in the majority of patients was higher than the population norm (in 84 and 66% cases, respectively), the number of progesterone receptors in stroma was reduced in 46% of women, and in the glands – increased in 59%.

Key words*: infertility, hysteroscopy, endometrial pathology, assisted reproductive technologies.*

Changes in the social status of women in many countries of the world, no doubt, can be considered one of the most significant achievements of recent years. Education, career, achieving a certain social status demanded that they change the attitude towards such an important purpose, as a reproduction. Delaying childbirth to a later period of life has led to the fact that at the time when a woman decides to take this step, its capabilities in the implementation of reproductive function are limited. This problem has a social background, therefore, the numbers of women of the late reproductive age treat infertility are increasing, and this trend is growing.

However, there are a number of health issues that complicate childbirth later in life, namely, the state of physical and gynecological health of women, aging of the reproductive system, poor quality oocyte, a low percentage of achieving pregnancy, problems carrying a pregnancy and the birth of a healthy child [1–3]. Thus, the assessment of the effectiveness of remedial measures and development of the algorithm of treatment of infertility in this group of patients getting urge.

Traditionally, the aging of the reproductive system and the actual loss of reproductive and menstrual function (menopause), as well as «perimenopause», accompanied by a significant decrease infertility. Some signs of aging of the reproductive function begin to grow in the fourth decade of a woman's life. These include the general decrease in the ability to conceive per one menstrual cycle, increasing the probability of offspring with a variety of chromosomal abnormalities, reducing the effectiveness of programs assisting reproduction [3, 4].

In recent years, the problem of restoring fertility in women of late reproductive age has been studied extensively in almost all developed countries. However, further progress in this important medical and social problem is impossible without a detailed study of the endometrium, which depends on both the offensive and the favorable outcome of pregnancy. In connection with this, the large number of research works devoted to changes in the endometrium in various forms of reproductive disorders [5–7].

Detection of these changes enables a differentiated approach to the choice of treatment tactics in preparation for in vitro fertilization (IVF). The study of the quality of the endometrium in women with infertility allows you to predict the possible outcome of the methods of assisted reproductive technology, and ultimately affect the improvement of the effectiveness of treatment.

In this regard, the aim of this study was to examine morphological and functional condition of the endometrium in women of late reproductive age with infertility in preparation for IVF.

MATERIAL AND METHODS

The endometrium in 197 patients of late reproductive age (35 to 45 years) with infertility was tested to solve this issue. The research took place in the comprehensive examination department of diagnostic and treatment of infertile marriages at the Donetsk regional center of maternal health prior to use of assisted reproductive technologies.

All patients evaluated somatic, gynecological and reproductive history, perform a full examination in accordance with the order of the Ministry of Health of Ukraine [8]. All women in the framework of compulsory clinical and laboratory examination conducted ultrasonography (US) of pelvic organs on the unit Medison SA-8000 EX with multifrequency probe. Where tested the size and position of the uterus and ovaries, condition of the cervix, endometrial thickness and echogenicity, presence of fibroids, adhesions.

After full examination and treatment (if necessary) executed liquid hysteroscopy followed by morphological and immunohistochemical study of the endometrium. Liquid hysteroscopy (HS) was performed on day 7–8 of the menstrual cycle by standard methods (equipment of «KARL STORZ», the hard hysteroscope Hopkins, 30°, endomat Hamou II). The Turusola solutionbeen used as the liquid medium to expand the uterine cavity. At the diagnosted the space uterine payed attention to the color, the thickness of the endometrium, matching day cycle, the state of the mouths of the Fallopian tubes, the presence of pathology.

The study of the expression level of the estrogen receptor-α and progesterone receptors in endometrial glands and stroma was performed by immunohistochemistry using test systems «Pakocytomation En Vision» (USA), HRP in accordance with the manufacturer's instructions. The level of receptor expression was determined by semi-quantitative receptor peroxidase staining as follows: considered the proportion of positive cells (heterogeneity of receptor expression) and reaction intensity (from 0 to +++), and further by the formula:

$$H = 3x + 2x + 1x$$

where N – number of points, the numbers 3, 2, 1 – the intensity of the color of the core, x – the percentage of stained core.

The frequency of endometrial pathology in relation to the method used to study, n (%)

Diagnosis	As a result of ultrasound	As a result of the HS
Endometrial polyps	104 (52,8)	92 (46,7)
Endometrial hyperplasia	64 (32,5)	72 (36.5)
Adenomyosis	34 (17,3)	37 (18,8)
Atrophy of the endometrium	0	7 (3,6)
Adhesions	5 (2,5)	6 (3,0)
Submucosal fibroids	57 (28,9)	27 (13,7)
Malformations of the uterus	2 (1,0)	7 (3,6)
Remains of bone fragments and ligation in uterus	0	4 (2,0)
The absence of pathology	39 (19,8)	21 (10,7)

Statistical analysis was performed on a PC using Word and Excel software packages. The average value error of the mean and proportion calculated. Data were considered significant at $p<0,05$.

The average age of the surveyed patients was 38,4±0,3 years. The study of gynecological history has shown that every second woman had menstruation abundant (in 106 or 53.8%), one in three – painful (74 or 37.6%). Spotting before and / or after the menstrual period occurred in 31.0% (61) patients. Chronic adnexitis afflicted history of 90 or 45.7% of ovarian pathology – in 44 or 22.3%, ectopia of the cervix – at 72 or 36.6%, cervical dysplasia – at 3 or 1.5% endometrial polyp – 65, or 33.0%, cervical polyp – at 11, or 5.6%, uterine fibroids – 66 or 33.5%, endometrial hyperplasia – in 28 or 14.2%, endometriosis – 20 or 10.2 % breast pathology – in 10 or 5.1% of the patients. One-third of women (74 or 37.6%) had surgery on the genitals, including surgery on the ovary were performed in 55 (27.9%) patients in the womb – in 17 or 8.6%.

In the history of 58.9% (116) women had abortions, 14.7% (29) – spontaneous abortions, 7.1% (15) – ectopic pregnancy. Every third woman has never given birth – 34.0% (67). Most of the examinees were secondary infertility (at 63.5%, or 125 women). The duration of infertility ranged from 1 to 25 years and averaged 7,3±0,5 years.

RESULTS AND DISCUSSION

The main compliance of patients during treatment were infertility – 100.0%. Also registered giperpolimenoreya (61 or 31.0%), intermenstrual spotting (at 26 or 13.2%), and other menstrual irregularities (in 4 or 2.0%), recurrent pain in the lower abdomen (in 12, or 6.1%). In some women (32 or 16.2%) HS was conducted in connection with the fact that with ultrasound have been found endometrial hyperplastic changes mainly polyps (30 or 15.2%). High frequency of these findings confirms the data and others in favor of the feasibility of ultrasound scanning planned gynecological examinations of women of late reproductive and perimenopausal age for early diagnosis of endometrial pathology [9].

Diagnoses based on the conducted ultrasound research as follows (Table): endometrial polyp – 52.8%, endometrial hyperplasia – 32.5%, submucosal uterine fibroids – 28,9%, adenomyosis – 17.3%, uterine adhesions – 25%, malformations of the uterus (bicornuate womb) – 1.0%.

The hysteroscopic study shawn the following diagnoses: endometrial polyp – 46.7%, endometrial hyperplasia – 36.4%, submucosal uterine fibroids – 13,7%, adenomyosis – 18.8%, endometrial atrophy – 3.6%, adhesions cavity uterus – 3.0%, the remains of bone fragments and ligation in the uterus – 2.0%, malformations of the uterus (womb saddle – 2.5%, intrauterine septum – 1.0%) – 3.6% of cases. In addition, 15.8% of women were recorded indirect signs of chronic endometritis. The absence of intrauterine pathology during the HS was observed in 10.7% of patients, whereas according to US figure was twice as much.

Combined uterine pathology was detected in the GS more than half of women – 53.3%. Most often it was endometrial hyperplasia with polyps – 16,2%. In 11.7% of patients there was a combination of endometrial hyperplasia with uterine myoma, at 9.1% – with uterine polyps. It recorded as 8.1% of cases the presence of endometrial hyperplasia and adenomyosis with 7.1% – polyps with adenomyosis. The combination of chronic endometritis with hyperplasia was observed in 13.2% of women.

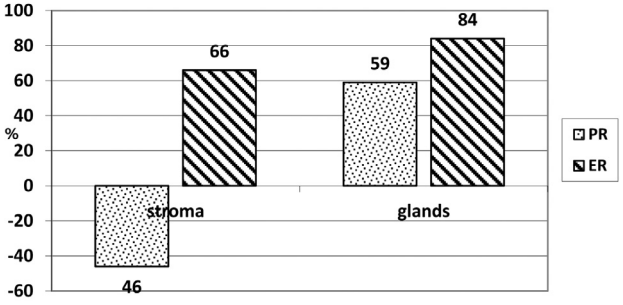
Diagnostic findings in the HS as follows: endometrial polyp – 6.1% endometrial hyperplasia – 4.0%, saddle-shaped womb – 2.5%, adhesions of the womb – 0.5% of cases. In general, primary false negative diagnoses were recorded in 18.7% of patients.

In addition, 9.6% of women the presence of GE endometrial polyps were not confirmed, at 2.5% – of endometrial hyperplasia in 15.2% – submucous uterine fibroids who are diagnosed by ultrasound. In total, the diagnoses were not confirmed in nearly 40% of cases.

The findings suggest that women of late reproductive age in preparation for infertility treatment by assisted reproductive technologies is mandatory conduct diagnostic hysteroscopy to reduce the time and improve the effectiveness of treatment.

Immunohistochemical study of the expression of receptors for estrogen and progesterone in the endometrium revealed a dissonance between the indices in the stroma and glands (Figure). It should be noted that almost two-thirds of women of late reproductive age had abnormalities on these parameters. It can be seen that if the level of б-ER and in the glands and stroma in the majority of patients had higher rate of population (84 and 66%, respectively), that the amount of PR in the stroma was reduced in 46% of women, and glands – have increased 59%.

Similar data were obtained by many other authors who have studied the question of endometrial pathology in infertility and endometrial receptivity changes established in women with infertility [10, 11]. However, it should be noted that it vary for different authors. Thus, according to A. Samoilova, with endometrial hyperplastic processes there is enough progesterone



The proportion of women with impaired receptors content in endometrium

receptors in the stroma and glands, while the estrogen receptor – decreased [12].

Violation of the expression of receptors for steroid hormones in the endometrium leads to disruption of implantation in patients with infertility, and the resulting study data indicate a change receptivity of the endometrium in women of late reproductive age with infertility, which should be considered when developing programs for managing these patients.

CONCLUSIONS

Thus, the study showed that:

1. The ultrasound performed only in women of late reproductive age with infertility before using assisted reproductive technology does not give a reliable picture of the state of the endometrium, as in 18.7% of cases when the hysteroscopic endometrial pathology found not diagnosed by ultrasound.

2. Hysteroscopy conducted with further immunohistochemical studies to determine the endometrial expression of steroid hormone receptors should be a mandatory component of the survey late reproductive age patients with infertility, which will optimize the preparation to the programs of assisted reproductive technologies and to increase the effectiveness of treatment.

Морфофункциональное состояние эндометрия у пациенток позднего репродуктивного возраста с бесплодием

С.М. Корниенко

Целью настоящего исследования явилось изучение морфофункционального состояния эндометрия у женщин позднего репродуктивного возраста с бесплодием на этапе подготовки к экстракорпоральному оплодотворению. Проведено обследование 197 пациенток с бесплодием. Всем пациенткам выполняли УЗИ, жидкостную гистероскопию и биопсию эндометрия для изучения состояния его рецепторного аппарата. В результате исследования установлено, что УЗИ является недостаточно информативным для диагностики состояния эндометрия и матки у данной категории пациенток: диагностические находки при гистероскопии включали полип эндометрия – 6,1%, гиперплазию эндометрия – 4,0%, седловидную матку – 2,5%, синехии полости матки – 0,5% случаев. В целом, первичные ложноотрицательные диагнозы зафиксированы у 18,7% пациенток. Иммуногистохимическое исследование экспрессии рецепторов к эстрогенам и прогестерону в эндометрии выявило диссонанс между показателями в строме и железах: если уровень рецепторов к эстрогенам в железах и в строме у большинства пациенток был выше популяционной нормы (у 84% и 66% соответственно), то количество прогестероновых рецепторов в строме было снижено у 46% женщин, а в железах – повышено у 59%.

Ключевые слова: *бесплодие, гистероскопия, патология эндометрия, вспомогательные репродуктивные технологии.*

Морфофункціональний стан ендометрія у пацієнток пізнього репродуктивного віку з безпліддям

С.М. Корнієнко

Метою даного дослідження було вивчення морфофункціонального стану ендометрія у жінок пізнього репродуктивного віку з безпліддям на етапі підготовки до екстракорпорального запліднення. Проведено обстеження 197 пацієнток з безпліддям для вивчення стану ендометрія. Для цього всім пацієнткам виконували УЗД, рідинну гістероскопію і біопсію ендометрія з метою вивчення стану рецепторного апарату. У результаті дослідження встановлено, що УЗД є недостатньо інформативним для діагностики стану ендометрія і матки даної категорії пацієнток: діагностичні знахідки при гістероскопії включали поліп ендометрія – 6,1%, гіперплазію ендометрія – 4,0%, сідлоподібну матку – 2,5%, синехії порожнини матки – 0,5% випадків. В цілому, первинні ложнонегативні діагнози зафіксовані у 18,7% пацієнток. Імуногістохімічне дослідження експресії рецепторів до естрогенів і прогестерону в ендометрії виявило дисонанс між показниками в стромі і залозах: якщо рівень рецепторів естрогенів і в залозах і в стромі у більшості пацієнток був вище популяційної норми (у 84% і 66% відповідно), то кількість прогестеронових рецепторів в стромі була знижена у 46% жінок, а в залозах – підвищена у 59%.

Ключові слова: *безпліддя, гістероскопія, патологія ендометрія, допоміжні репродуктивні технології.*

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