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MODERN APPROACHES TO ESTIMATING THE OVARIAL RESERVE IN THE OLDER REPRODUCTIVE AGE

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✓ ***Resume***

The emergence and development of assisted reproductive technologies has become a new stage in the development of infertility treatment, in addition, they have provided a number of new opportunities in the study of pathogenetic, morphological, embryological, cytogenetic aspects of reproductive medicine. The question remains open, what is the cornerstone of age-related infertility - the quality of oocytes or impairment in implantation? This review discusses current approaches to assessing the ovarian reserve in older reproductive age, the remaining problems in this area, as well as promising areas of research designed to provide solutions to emerging challenges.

Key words: assisted reproductive technologies, in vitro fertilization, ovarian reserve, gametes

СОВРЕМЕННЫЕ ПОДХОДЫ К ОЦЕНКЕ ОВАРИАЛЬНОГО РЕЗЕРВА В СТАРШЕМ РЕПРОДУКТИВНОМ ВОЗРАСТЕ

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✓ ***Резюме***

Появление и развитие вспомогательных репродуктивных технологий стало новым этапом развития лечения бесплодия, кроме того они дали ряд новых возможностей в изучении патогенетических, морфологических, эмбриологических, цитогенетических аспектов репродуктологии. Открытым остаётся вопрос, что является краеугольным камнем возрастного бесплодия - качество ооцитов или нарушение в имплантации?. В настоящем обзоре обсуждается современные подходы к оценке овариального резерва в старшем репродуктивном возрасте, сохраняющиеся в этой сфере проблемы, а также перспективные направления исследований, призванные дать решение возникающим вызовам.

Ключевые слова: вспомогательные репродуктивные технологии, экстракорпоральное оплодотворение, овариальный резерв, гаметы

KECH REPRODUKTIV YOSHDAGI OVAR REZERVLARNI BAHOLASHGA ZAMONAVIY USLUBLAR

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Kalit so'zlar: yordamchi reproduktiv texnologiyalar, ekstrakorporal urug'lantirish, tuxumdonlar zaxirasi, jinsiy hujayralar

Relevance

The birth of children at a late reproductive age is a reality of modern civilized society, which causes a certain concern among doctors. The average age of primiparous mothers in the Netherlands rose from 24.4 years in 1970 to 29.2 years in 1999, with the majority of women giving birth over 30 years old. Based on an analysis of the birth rate in the UK for 2001-2003. revealed a tendency of increasing the age of primiparous women over 35 years old. There is a tendency for the age of women who prefer IVF to increase in different countries from 4.9 to 37.5% [2]. According to the WHO, the age of women is considered to be reproductive from 15 to 49 years [3]. It is customary to divide the reproductive age of women: 15-19 years - the period of early reproductive activity; 20-34 years - the period of the highest reproductive activity; 35-44 children - the period of fading reproductive activity; 45-49 years is the period of late reproductive activity [4]. The average age at menopause for most women is 50, but the ability to conceive begins to decline much earlier. By the age of 37, there is a decrease in the number of premordial follicles, which can be considered a physiological process [5].

Studies have shown that a slight decrease in reproductive ability is noted already from 27-28 years, more pronounced - between 35 and 40 years, and by 45 years of reproductive ability approaches zero [6].

The term ovarian reserve is used to describe the quantity and quality of the follicle pool. A decrease in ovarian reserve means a relative decrease in the number of follicles and / or a decrease in the quality of eggs [6]. In 1983, Garcia described for the first time the phenomenon of a decrease in ovarian reserve as a decrease in estradiol levels below 300 pg / ml and a decrease in the number of punctured oocytes. To date, there is no standardized definition of the term "decrease in ovarian reserve" [7]. An inadequate assessment of ovarian reserve can lead to inadequate cancellation of the cycle, increased cost of treatment and stress for patients [8].

About 33.5% of women of older reproductive age require the use of donor oocytes [7]. Modifications to the superovulation induction regimens and the use of assisted hatching do not increase the effectiveness of the IVF program; the success of treatment is determined by the state of the ovarian reserve of patients. The ability of the ovaries to respond to gonadotropic stimulation has been termed ovarian reserve. There are no absolutely reliable tests in predicting premature ovarian aging.

Surrey et al. Proposed a decrease in follicles and / or the number of obtained oocytes less than 5 with a standard age-specific stimulation protocol as a criterion for a decrease in ovarian reserve [8]. The decrease in ovarian reserve is a biological, not a chronological factor, and it is different for each woman. Nevertheless, age is considered the most significant factor in assessing ovarian reserve [4]. To date, non-invasive methods for determining the ovarian reserve are determining the level of FSH, estradiol, AMH, inhibin B and counting the number of antral follicles on ultrasound. Some scientists believe that the level of FSH in women of older reproductive age indirectly estimates ovarian reserve, and inhibin B is an earlier and sensitive marker of decreased ovarian reserve, while other authors disagree with such data [23]. The results were quite contradictory. Seifer et al. Consider a decrease in inhibin B less than 45 pg / ml to be an indicator of a reduced ovarian reserve [22], and Creus considers inhibin B to be an insufficient predictive marker of ovarian reserve, in contrast to a woman's age and basal FSH [23]. Yong et al. Determined the correlation of inhibin Bc with the number of oocytes and suggested a significant probability of assessing the ovarian reserve upon stimulation of the ovaries with FSH preparations [24]. Fried et al. Also found a relationship between inhibin B levels and oocyte count, but did not find a relationship with pregnancy. The ratio between IGF-1: IGFBP-1 showed a significant increase in women who became pregnant [24].

Unlike age-related changes in FSH, LH, estradiol, inhibin B is currently not used in the routine diagnosis of infertility. The same applies to AMG, the insulin-like growth factor-1. Martinez suggested that low levels of peak gonadotropin reducing factor can be used as a marker of poor ovarian response [36], while vanRooij has shown that a decrease in AMH levels indicates follicular loss [24]. Other scientists consider an early marker of decreased ovarian reserve - increased FSH [53]. It has been suggested that an increase in FSH occurs in response to a decrease in the secretion of ovarian inhibins [23,24]. Thus, inhibins A and B together affect the restriction of FSH secretion.

The relationship between a decrease in fertility and a woman's age has been confirmed by many studies using ART methods. TseYeunTan, et al. [20] in a retrospective study

of 3412 IVF cycles in different age groups found that the frequency of pregnancy in women significantly decreases with increasing age. In women under 30, the pregnancy rate was 50%, the birth rate was 40%, and at 40-44 years old, it was 13.2% and 5.9%, respectively. Conclusion, pregnancy rate decreases with age, and pregnancy loss increases. This decrease was associated with the age of women, and not with the quality of sperm, proved a study based on the analysis of the results of 3990 cycles of intrauterine insemination in women of different age groups [21]. Another comparative study on IUI, which included an analysis of the outcomes of 4246 IUI cycles in women from 25 to 45 years old [22] showed that the older the woman, the total effectiveness of IUI decreased almost 3 times compared with younger patients. The conclusion of the study is that women of the older age group should be offered more effective methods of ART-IVF, ICSI. Studying a group of women entering the first IVF / ICSI protocol, scientists determined that the level of FSH and the age of women are more accurate in predicting the onset of pregnancy than inhibin V. the frequency of pregnancy [19]. The rise in serum FSH concentration is secondary to a decrease in inhibin levels. Inhibin is an indicator of the size of the population of growing follicles at the beginning of the cycle and is not detected in menopause, being a predictor of the onset of ovarian wasting. A mathematical model for calculating the total number of ovarian follicles revealed that the decrease in the number of follicles is biexponential to age. The rapid rate of decrease in the number of follicles leaves an average of 1000 follicles by 51 years of age. The effect of a stepwise reduction in the number of follicles on subsequent menstrual function was calculated by a mathematical model. So, with a decrease in the number of follicles by 50% before 30 years, it led to the achievement of a threshold of 44 years and + for six months after 37.5 years, when the rate of decrease increases, menopause is obtained at 48 years. A 90% decrease in follicle count before age 14 leads to early menopause at age 27. If the rate of atresia remained the same, the age of menopause would reach 71 years [6]. Thus, there is a theoretical possibility that slowing the rate of aging of the ovaries after the critical age will delay the onset of menopause and increase fertility in older reproductive years. The main conclusion of the work is that in order to predict the age of menopause, the ovaries must be measured biologically, not chronologically. The increase in LH occurs after 5-10 years. The factors influencing the decrease in the pool of antral follicles, according to Mitchell P. et al., Also affect the number of quality oocytes and the

There is a theory of a parallel decline in quantity and quality, which explains the significant variability in reproductive potential in women of the same age [17,20]. Patients of older reproductive age with a preserved rhythm of menstruation are heterogeneous in terms of the functional state of the reproductive system. Women with ovarian reserve parameters: FSH <10 IU / L, inhibin B - 35-40 pg / ml, ovarian volume - 5-7 ml, the number of antral follicles - 4-5 - are promising for the treatment of infertility by IVF, although the number of cases of onset pregnancy does not exceed 15%. Patients with FSH levels> 15 IU / L, inhibin-B <20 pg / ml, ovarian volume <3 ml and antral follicle count 0-1 are not promising for ovarian stimulation and obtaining their own oocytes. The influence of genetic factors and anamnesis, the environment on the ovaries of women has been proven. So, D. Nikolaou, G.S. Basir, M. Al-Ani, S. Andronikou showed a statistically significant effect of smoking and pelvic inflammatory disease on ovarian response to ovarian stimulation, also noting that body mass index, the presence of endometriosis, hepatitis and AIDS in their study had little effect on ovarian response to stimulation. The data provided by Johnson may change the concept of fertility treatment in the future. The scientist announced the discovery of ovarian stem cells in mice, which allow oocytes to renew during their life [1,3].

Perhaps the creation of an ovarian tissue bank in the future will give good chances to preserve the reproductive capabilities of women of older reproductive age, as well as in patients with cancer after chemotherapy and radiation therapy [24].

Conclusion

There is a theoretical possibility that a slowdown in the aging of the ovaries after a critical age will delay the onset of menopause and increase fertility in older reproductive age. It should be noted that not all methodological and theoretical issues in reproductive medicine remain resolved, but this, in turn, stimulates the emergence new promising directions and research.

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