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"POOR RESPONDERS" – MODERN IDEAS, PRINCIPLES OF MANAGEMENT IN ART PROGRAMS. REVIEW

Ovarian reserve has an important role in the adequate ovarian response to ovarian stimulation and getting mature eggs in vitro fertilization programs (IVF).

Ovarian reserve is a functional reserve of the ovary, which determines its ability to develop a follicle with a mature egg and an adequate response to ovarian stimulation. Ovarian reserve reflects the number of follicles in the ovaries (primordial pool and growing follicles) and depends on physiological and pathophysiological factors [1]. The main problem for patients with low ovarian response is getting enough oocytes. Reducing the follicular reserve of the ovaries does not allow obtaining a sufficient number of embryos and, accordingly, the probability of implantation and pregnancy is reduced. De facto, due to the small number of obtained oocytes, and because of the low number of good quality embryos for transfer, the rate of pregnancy per transfer, as well as the cumulative pregnancy rate of per cycle are significantly reduced compare with patients with a normal ovarian reserve.

By the time of the formation of the menstrual function of the girl, the pool of primordial follicles in the ovaries is normal from 270 000 to 470 000 follicles. During the life of a woman, no more than 400-500 follicles reach to ovulation [2]. It is established that the rate of reduction in the number of primordial follicles with each menstrual cycle increases progressively, this is due to the mechanism of ovulation and atresia of a significant number of follicles. When the number of full-fledged follicles falls below a certain critical limit, menopause occurs, with significant changes in the hormonal background, accompanied by a final loss of the ability to conceive. It was found that the rate of follicle disappearance doubles when the primordial pool is reduced to 25 thousand follicles, which normally corresponds to the age of 37.5 years [3]. It follows that age is the most important physiological factor determining ovarian reserve.

In addition to physiological factors that affect the ovarian reserve, such as age and reduction of the follicle pool in the menstrual cycles for the entire reproductive period of the woman, there are other reasons for the decrease in the ovarian reserve.

In patients with "poor response" - "poor responders" ("PR"," poor"), the mechanisms of premature ovarian insufficiency turns on, which to date have not been fully studied. Some causes of ovarian reserve reduction were determined: ovarian surgery, especially in endometrioma [4-8], genetic defects, chemotherapy, radiation therapy, autoimmune disorders, presence of only one ovary, prolonged intensive smoking, obesity, as well as in cases of idiopathic infertility [9]. In recent years, risk factors for the development of "poor responders" included type I diabetes [10], transfusion-dependent b-thalassemia [11] and uterine artery embolization for the treatment of uterine leiomyoma [12, 13]. It was suggested that the reduced number of oocytes might be associated with the deterioration of their quality, which is clinically transformed into a decrease in the probability of implantation and an increase in the frequency of early miscarriages [14]. Conversely, due to the lack of a clear correlation between "quantity" and "quality", various authors have suggested that "poor responders" "themselves" do not represent a lesser chance of success in IVF, and the age of the woman is the most important factor in the likelihood of pregnancy and childbirth [15, 16]. However, a number of other studies have shown that the group of patients "poor

responders" had reduced pregnancy rates compared to ordinary patients regardless of the used treatment [17] and the age of the patient [18, 19]. Thus, in the group of patients "poor responders" to optimize the clinical results of IVF, it is necessary not only to predict ovarian reserve, but also, in particular, to determine and adapt the most optimal protocol of stimulation of superovulation, in order to make better use of ovarian reserves and optimize the number of oocytes to be fertilized.

Smoking plays a significant role in reducing ovarian reserve. Thus, studies have shown that actively smoking women had a reduced level of AMH and an earlier age of menopause [20]. These patients are 3 times more likely to experience a decrease in ovarian reserve compared to non-smokers (12.3% and 4.3%, respectively) [21].

Contained in tobacco smoke polycyclic aromatic hydrocarbons and metabolites of nicotine such as catenin, accumulate in the nucleus and cytoplasm of granulosa cells of the ovary. In turn, nicotine and cadmium trigger the process of egg death (apoptosis) by activating programmable cell death, which explains the decrease in AMH levels in smoking women [22, 23].

It was established that in diabetes mellitus oxidative stress is the cause of damage to the genetic material of granulosa cells of follicles, which can lead to a decrease in ovarian reserve [24, 25] and to DNA damage of granulosa cells of follicles [25]. In studies on the role of autoimmune disorders in the pathogenesis of gynecological diseases, it was noted that the combination of autoimmune oophoritis, autoimmune thyroiditis, type 1 diabetes and systemic lupus erythematosus leads to a decrease in ovarian reserve [23, 24,26].

Autoimmune oophoritis is an autoimmune organ-specific disease, the main role in the pathogenesis of which belongs to the incidence of autoantibodies steroidspropeciaei cells (theca cells) of the ovaries, which leads to inhibition of folliculogenesis [27].

Inflammatory diseases of the pelvic organs (IDPO) are not less important damage factor of the follicular apparatus of the ovary. IDPO can cause sclerotic changes in blood vessels, connective tissue growth in the stroma, the formation of small cysts. The destructive inflammatory process (purulent tubo-ovarian formation), developing in the uterus, may lower ovarian reserve as a result of purulent fusion of tissues of the ovary [28, 29].

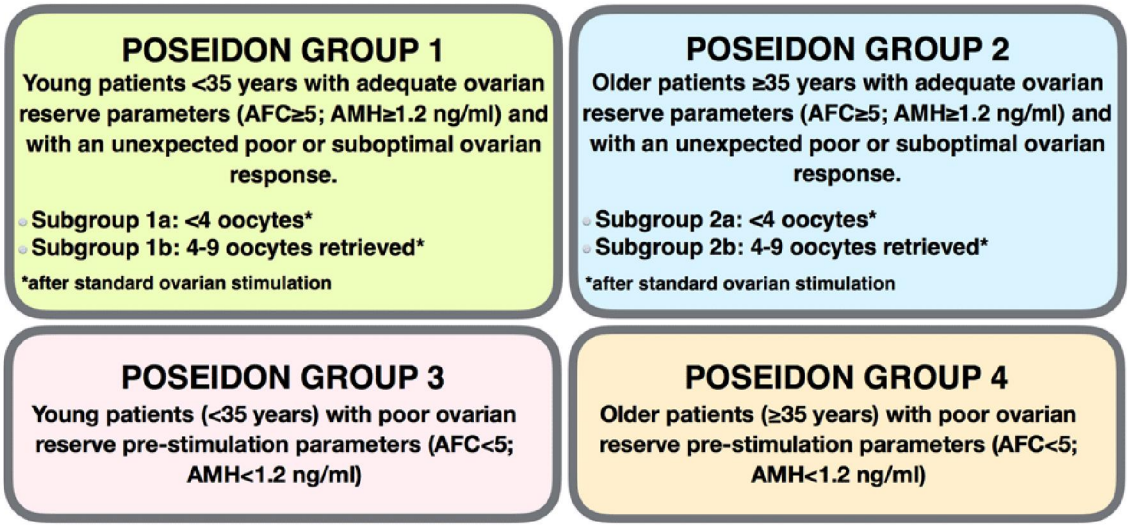
Endometriosis is diagnosed in 7-59% of women of reproductive age [30]. A common form of external genital endometriosis is ovarian endometriosis, which is 64% of the total number of other forms of this nosology [31]. It is shown that endometrioid cysts localized in the ovaries reduce the volume of functional ovarian tissue, while reducing the ovarian reserve of the woman [32]. In the pathogenesis of infertility in endometriosis, a major role is played by violations of the relationship between hormone secretion levels (estradiol, progesterone, LH, FSH, prolactin and testosterone), leading to defective ovulation and/or functional inferiority of the corpus luteum, endometrium. The cause of infertility in endometriosis may be a violation of steroidogenesis in granulosa cells of follicles, dystrophic processes in the granulosa and theca cells of the follicles, changes in the composition of the follicular fluid increased the apoptotic index of granulosa cells, degeneration of oocytes, which consequently disrupts folliculogenesis, and affects ovarian reserve [34-36]. It should be noted that its reduction may also be associated with a significant volume of ovarian resection, damaging its healthy tissue in the surgical treatment of endometrioid cysts [37, 38]. Also, a number of authors note that during electrocoagulation for hemostasis there is a violation of intraovarian blood flow, which leads to irreversible morphological and functional changes in ovarian tissue [39, 40].

Treatment of patients with "poor" ovarian response is the subject of numerous studies over the past twenty years. Despite the significant amount of published data, the definitions of POR are varied. From 1973 to 2018, 2037 randomized trials were published. The first systematic data on the definition of women who do not respond well to the stimulation of superovulation were developed by the European society of human reproduction and embryology (ESHRE) in 2011 and published in the form of the so-called "Bologna criteria». The prevalence of "poor" ovarian response to stimulation of superovulation is very high, and varies according to the literature from 9 to 24%. [41].

According to the ESHRE criteria, the "poor" ovarian response is the maturation of less than 3 follicles with stimulation of superovulation with large doses of gonadotropins (more than 300 ME/day). To diagnose a "poor" ovarian response, you must have at least two of the three criteria listed: 1) the age of the woman more than 40 years or the presence of other risk factors for a "poor" ovarian response; 2) an

indication of a "poor" ovarian response in the history (≤3 oocytes in standard stimulation protocols); tests indicating a decrease in ovarian reserve: the number of antral follicles less than 5-7, the AMH index in the blood less than 0.5-1.1 ng/ml [42].

The POSEIDON group (Patient Oriented Strategies Encompassing IndividualizeD Oocyte Number) proposed a new classification of patients with reduced ovarian reserve or unexpected incorrect ovarian response to exogenous gonadotropins. Four subgroups based on quantitative and qualitative parameters were proposed (figure).



POSEIDON Classification

The new classification introduces a more subtle distribution of "patients with poor ovarian response" into the ART using clinically relevant criteria that can help the physician best manage this group of patients.

POSEIDON group presented new data for the successful treatment of patients with poor response, namely, established a correlation between the age and the required number of oocytes to obtain one euploid embryo and transfer it into the uterine cavity (table 1).

Table 1 – Relationship between age and the required number of oocytes to produce one euploid embryo

Less than 35 years	39 – 40 years	More than 42 – 43 years
6 oocytes	11 oocytes	18 oocytes
5 adults	9 adults	16 adults
4 fertilized	7 fertilized	13 fertilized
2 blastocysts	3 blastocysts	5 blastocysts
1 euploid blastocyst	1 euploid blastocyst	1 euploid blastocyst

This table provides clear guidance on the number of controlled ovarian stimuli (COS) for physicians and allows the development of predictive models aimed at reducing the time to obtain a long-awaited pregnancy [43].

In addition to the long-known relationship between age and decreased ovarian response to gonadotropins, there are a number of other factors that have an important impact on the reproductive reserve.

Among them are premature depletion of ovarian reserve, adverse environmental factors and other conditions that may affect the ovarian response to gonadotropins. The situation may be even more complex, with differences in drug pharmacokinetics in many women and variability in biological activity between urinary gonadotropins up to 45%, while these problems can largely be overcome by new recombinant gonadotropins. In some cases, suboptimal responses remain unexplained, reflecting the complexities and subtleties of ovarian function. POR is often observed in patients with no apparent reason with normal ovarian reserve. Suggested mechanisms for poor ovarian response include a decreased number of FSH receptors in the granulosa cells; defective signal transduction after FSH receptor binding, an inappropriate local vascular network for the distribution of gonadotropins, the presence of autoantibodies against granulosa cells, an excess of VEGF will bind its target growth factor (VEGFR-1), abnormalities in the levels of IGF-I and IGF-II (insulin-like growth factor) and decreased bioactivity of circulating gonadotropic fator (GnSAF). Some numerical and structural abnormalities of the X chromosome and mutation of the FMR1 gene, or autoimmune damage to ovarian tissue, may be suspected pathogenetic factors of POR development in these women.

Nonrandom association of inactivation of the X chromosome, as well as structural changes in the area of its long arm (Xq) with the development of premature ovarian insufficiency was noted [44]. The FMR1 gene located on the long arm of the X chromosome at the xq27 locus.8, can contain different number of trinucleotides CGG repeats [45]. It was found that the number of CGG repeats, equal to 26-34 (average-30), is typical for half of the female population. A higher or lower number of CGG repeats is often associated with the development of premature ovarian depletion, decreased ovarian reserve and correlated with follicle stimulating hormone (FSH) and AMH levels, which affects ovarian function.

FSH exhibits its effects through a specific receptor (FSHR), which is located on the cells of ovarian granulosa. The fshr gene contains 10 exons and 9 introns and is located on chromosome 2p21. It is known that variants of FSHR changes are very rare [46, 47]; however, two polymorphisms: p.Thr307Ala (C.919A>G, rs6165) and p.Asn680Ser (C.2039A>G, rs6166), which were identified in exon 10, affect the ovarian reserve [48].

According to a prospective study of sun-dried key connection between Cumulus cells (CCs) and oocytes, which contributes to the change of gene expression of CCs in women with POR after adding DHEA and maturation of oocytes [49].

Currently, there is a dedicated line of major gene polymorphisms that can affect the outcome of the ART programs for the worse and for the better (table 2).

Table 2 – Association of gene polymorphism with outcomes of the ART programs.

Gene	Chromosome localization	Rs-number	Replacement of protein or coding sequence	The main hypotheses of the research on the association of gene polymorphism with the outcomes of the ART programs
FSHR	2p21	Rs6166	N680S	When carrying allele 680S requires higher doses of FSH in COS
		Rs1394205	-29G/A	Women with genotype-29G>A need higher doses of FSH, they have a lower level of estradiol, they produce fewer follicles and oocytes.
LHB	11p13	Rs1800447	W8R	Women with genotype W8R and I15T require the introduction of increased doses of FSH, marks the aspiration of a smaller number of oocytes
		Rs3439826	I15T	
LHCGR	2p21	Rs4073366	28G>C	Allele C carrier is associated with a threefold increase in the risk of PCOS
ESR1	6q25	Rs2234693	-397T>C	In carriers of genotype C/C notes receive a greater number of follicles, mature oocytes, good quality embryos
		Rs9340799	-351A>G	In carriers of genotype G/G higher chance of obtaining a larger number of oocytes and fertilization
		Rs3138774	(TA)n	Long repeats (TA) are associated with better superovulation stimulation outcomes
AMG	19p13	Rs10407022	I49S	Carriers of alleles AMH 49Ser and AMHR2-482G have increased sensitivity to FSH drugs
AMGR2	12q13	Rs2002555	-482A>G	

Prediction of poor ovarian response is possible with the help of biochemical and biophysical markers. There is a correlation between ovarian stock with biophysical markers (antral follicle count and ovarian volume) and biochemical markers (FSH, Inhibin B and AMH) and it is necessary to use these markers to predict poor ovarian response to stimulation. AMH value ≤1 ng/ml predicts poor ovarian reserve, poor ovarian response to stimulation and IVF results. AMH allows better assessment of the prospects of the art program to get a live child in women of different age groups. AMH level, counting the number of antral follicles together with age assessment together make up the best model for predicting ovarian response to ovulation stimulation.

One of the main steps for the success of the ART programs is still the number and quality of oocytes obtained after hormonal stimulation by gonadotropins in combination with GnRH analogues. The management and treatment of such patients with a suspected poor ovarian response is still an important issue in reproductive medicine. Almost all researchers share the view that the number of oocytes obtained after controlled ovarian stimulation (COS) of the ovaries largely determines the clinical outcome of treatment. For this reason, any COS should be aimed at optimizing the number of oocytes depending on the patient's ovarian reserve.

In the last 20 years, many protocols with different doses and types of gonadotropins for the treatment of patients with "poor responders" have been proposed in the literature, however, to date, a really effective method of treatment has not been chosen that can solve the problem of poor ovarian response to controlled ovulation stimulation [50].

With the aim of strengthening the influence of exogenous gonadotropins on follicular development was proposed a few alternative approaches that we present below.

Addition of estradiol in the luteal phase. In a meta-analysis published in 2013, 1227 studies with or without the addition of estradiol in the luteal phase were selected. It is shown that the addition of estradiol reduces the risk of cancellation of the cycle and increases the likelihood of clinical pregnancy in patients with poor reaction to COS [51]. The biological rationale may be that the priming of the luteal phase with estradiol may improve the synchronization of the pool of follicles available for controlled ovarian stimulation [52]. However, this meta-analysis has been criticized for possible methodological features and the quality of randomized trials [53].

Another meta-analysis published in 2013 [54] indicates that the addition of estradiol in the luteal phase prior to IVF in patients with poor COS response improved IVF results, including an increase in the number of oocytes obtained and a decrease in the cancellation of the cycle for one reason or another.

The addition of recombinant LH. To date, there is no clear answer about the need and feasibility of introducing recombinant LH. A study published in 2012 indicates a positive role of recombinant LH administration during gonadotropin stimulation in patients with poor ovarian response to COS [55]. However, two meta-analyses of 2012-2013 [56, 57] showed that the addition of recombinant LH did not increase the number of obtained oocytes, while the total dose of FSH, withdrawal rates and current pregnancy rates in patients with poor reaction to CBS did not change. On the other hand, a recent meta-analysis of 40 randomized controlled trials [58] found a significantly higher number of oocytes, and observed significantly higher clinical pregnancy rates in the treatment of r-hFSH plus r-hLH compared to r-hFSH in patients with low COS response, indicating a relative increase in clinical pregnancy rates in poor responders. The authors believe that adding r-hLH to r-hFSH may be beneficial for women with poor ovarian response.

The addition of growth hormone. It has been suggested that the use of growth hormone (GH) can modulate the effect of FSH on granulosa cells by enhancing local synthesis of insulin-like growth factor-I (IGF-I) [59-61]. IGF-I enhances FSH action in granulosa and theca cells [62, 63]. Two recent meta-analyses involving 6 randomized trials (a total of 128 patients) [64, 65] suggested that adding GH significantly increases the likelihood of having a child in poor patients. As for the addition of GH, the frequency and dosage varied markedly among the relevant studies. However, due to the small number of patients and the heterogeneity of the frequency and dosage of GH added among the studies, the fact that the addition of GH during ovarian stimulation increases the likelihood of pregnancy must be evaluated in further well-designed trials to prove or disprove this conclusion. In fact, until now there has been very reliable data indicating routine addition of GH to ovarian stimulation protocols for patients with poor COS response [66, 67].

The addition of androgens. Androgens produced mainly by theca cells play an important role for adequate follicular steroidogenesis [68] and for the proper development of early follicular and granulosa cells [69]. They are a substrate for the aromatase activity of granulosa cells, which converts androgens into estrogens. Moreover, androgens can enhance the expression of the FSH receptor in granulosa cells, enhancing the action of FSH, and thus potentially increase ovarian sensitivity to FSH [64, 69, 70]. In addition, inadequate levels of endogenous androgens are associated with decreased ovarian sensitivity to FSH and low pregnancy rate after IVF [64, 71].

Based on these observations, Casson et al. [72] first suggested that oral addition of dehydroepiandrosterone (DHEA) prior to superovulation with gonadotropin may improve ovarian stimulation response in patients with poor response. In the last decade, several uncontrolled studies have published improved clinical results after oral administration of DHEA before ovarian stimulation. A recent meta-analysis of four randomized controlled trials of androgens (DHEA and testosterone) in patients with poor response showed a significantly higher current pregnancy rate in the androgen supplementation group [73]. However, the included studies were too small and presented clinical and methodological heterogeneity to be definitive and guarantee their immediate application in practice. In fact, there is a need for reliable data from randomized controlled trials that could justify widespread use of DHEA before ovarian stimulation in patients with poor response, and it is time to evaluate the clinical cost-effectiveness of DHEA with large randomized controlled trials [74,75,76].

Adding aspirin. Ovarian circulatory disorders can contribute to poor response to ovarian stimulation [77, 78]. Therefore, a well-developed intravascular network improves the delivery of gonadotropins necessary for folliculogenesis [79, 80]. Based on this justification, vasoactive substances such as aspirin are used to strengthen the ovarian vascular system [81].

However, data confirming that the effect of low doses of aspirin in women undergoing IVF are not fully understood [82]. Although some studies have reported some positive effects of aspirin since embryo transfer [83, 84], others have not been able to confirm these results [85-87]. Prospective randomized trials have shown that widespread aspirin and prednisolone therapy did not improve uterine blood flow rate, implantation, and pregnancy rate [88]. The conclusion of the meta-analysis and systematic review [89] was that the clinical rate of pregnancy per embryo transfer did not differ between patients in the control group receiving aspirin at doses of 50-100 mg. Based on the updated data, a low dose of aspirin does not have a positive effect on pregnancy, and it should not be recommended for women undergoing IVF.

Natural IVF cycles. Natural IVF cycles with or without minimal stimulation can be seen as a simple and cheap approach to ovarian stimulation with a poor response. In fact, some authors have suggested that natural IVF cycles were an acceptable option for patients with poor response, as they have the same likelihood of pregnancy and implantation [90]. Some critical problems were noted: only 50% of the initiated cycles produced one embryo ready for transfer to the uterine cavity; the total clinical pregnancy rate was 10% for the initial cycle and 18% for embryo transfer [91]. Schimberni et al. [92] evaluated the IVF outcome in a large group of poor respondents (500 patients) who reported very encouraging results, especially in younger women (<35 years). In this group of patients with poor ovarian response to stimulation, the pregnancy rate was 18% for the initial cycle, 29% for transfer and 31% for one patient. On the contrary, in a recent article analyzed the effect of natural cycles IVF in women defined as poor by the respondents in accordance with the "Bologna criteria": unexpectedly the data showed that the cumulative live birth per patient does not exceed 8% [93]. Conflicting data may be very likely and associated with the diversity of patients selected using the "Bologna criteria".

Cryopreservation of oocytes. The freezing of oocytes has led to the breakthrough in the ART technologies, probably the most important of our decade. Recent evidence suggests that this approach is a highly effective procedure that can be applied in conventional infertility programs [94]. Major societies, including the European society of human reproduction and embryology(ESHRE), the American society of reproductive medicine (ASRM) and the American society of clinical oncologists (ASCO), have confirmed that recently oocyte cryopreservation is a procedure that provides the necessary legal and moral support for widespread use [95]. Different strategies are applicable for poor responders associated with oocyte cryopreservation. Some authors recently suggested obtaining a larger cohort of oocytes in these patients by accumulating frozen oocytes over several stimulation cycles, creating a similar situation as in patients

with normal response. According to the results presented in the study, it would be possible to obtain a higher fertility rate per patient and possibly reduce losses [96].

*Gonadotropins.*Gonadotropins cannot compensate for the lack of follicles in the ovary, so COS in "Poor" patients may be the optimal method of obtaining multiple follicles in a single cycle, for example, by stimulating the luteal phase or by double stimulation (follicular plus luteal) in the same ovarian cycle protocols (DuoStim).

DuoStim double stimulation is the most promising approach to increasing the number of oocytes collected in one ovarian cycle; however, this protocol requires further research and analysis of its economic efficiency. [97].

According to a systematic review of E. Labarta, D. Marin in patients with" Poor", minimal ovarian stimulation (MOS) is an alternative method if COS does not give the desired effect. In some cases, MOS is used as a first-line therapy [98].

Conclusion. A variety of anamnesis and baseline data in patients with poor response leads to a variety of outcomes of the IVF program, even with the use of the same treatment protocols. In patients with poor ovarian response to COS sometimes there are cycles in which it is possible to obtain a better response to braid compared to previous protocols. It is possible that the routine use of POSEIDON classification for "POR", will allow you to choose a more personalized methods of preparation for the COS and the choice of the COS. Despite the fact that in the last 20 years, many different protocols with different dosages and types of gonadotropins have been proposed for the treatment of POR patients, experts have not come to some most effective method of treatment that would solve the problem of poor ovarian response. It seems that the answers to these questions will be found in the near future using new methods of molecular genetics.

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“POORRESPONDERS” – СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ, ПРИНЦИПЫ ВЕДЕНИЯ В ПРОГРАММАХ ВРТ. ОБЗОР ЛИТЕРАТУРЫ

Аннотация. Состояние овариального резерва в течение жизни женщины претерпевает изменения. Начиная от воздействия физиологических факторов – возрастное уменьшение пула примордиальных фолликулов – до патологических состояний, ведущих к снижению овариального резерва – эндометриоз, операции на яичниках и другие факторы. Лечение пациенток с «бедным» овариальным ответом является предметом многочисленных исследований за последние двадцать лет. Существующие на сегодня классификации и схемы лечения не удовлетворяют в полной мере специалистов, нет какого-либо эффективного метода лечения, позволившего бы решить проблему бедного ответа яичников.

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“POORRESPONDERS” – СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ, ПРИНЦИПЫ ВЕДЕНИЯ В ПРОГРАММАХ ВРТ. ОБЗОР ЛИТЕРАТУРЫ

Аннотация. Овариалды қордың жағдайы әйел адамның өмірі бойында өзгеріске ұшырап отырады. Поримордиалдық фолликулалардың пуласының жас ерекшелігіне қарай азаюы сияқты физиологиялық факторлардың әсерінен бастап, эндометриоз, аналық бездерге ота жасау және т.б овариалдық қордың азаюына әкелетін патологиялық жағдайлар дейін. «Әлсіз» овариалдық жауапты әйелдерді емдеу соңғы жиырма жылда көптеген зерттеулердің негізі болып табылады. Қазіргі кездегі емдеу схемалары мен жіктеулер мамандарды канағаттандырмайды, аналық бездердің әлсіз жауап мәселесін шешетін эффективті емдеу әдісі жоқ.

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