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TRENDS IN SAFE INFERTILITY TREATMENT WITH ASSISTED REPRODUCTIVE TECHNOLOGIES

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▪ The expansion of indications for assisted reproductive technology has led to significant implications for assisted reproductive technology (ART) programs worldwide. More than 7 million children in the world were born using ART. Modern clinical practice in the field of reproductive sciences is aimed not only at increasing the effectiveness, but also at the safety of treatment. ART, like any other type of therapy, may be combined with negative side effects. Both the correct prediction of the risks associated with treatment and a personalized approach ensure the absolute safety of infertility treatment using *in vitro* fertilization. In this regard, over the past decade, a number of new research approaches have been noted that use ART methods integrated into clinical practice: cycle segmentation with subsequent embryo transfer and the elective transfer of one embryo. New approaches provide a control in relation to ovarian stimulation and a reduction in the number of transferred embryos, which helps to minimize primarily adverse perinatal outcomes. Predicting the risks and outcomes of treatment using mathematical modeling is the application of good clinical practice.

▪ **Keywords:** assisted reproductive technology; infertility treatment; person-centered approach; single embryo transfer.

ПРИНЦИПЫ БЕЗОПАСНОГО ЛЕЧЕНИЯ БЕСПЛОДИЯ С ПОМОЩЬЮ ВСПОМОГАТЕЛЬНЫХ РЕПРОДУКТИВНЫХ ТЕХНОЛОГИЙ

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▪ Расширение показаний к использованию вспомогательных репродуктивных технологий (ВРТ) привело к значительному увеличению объемов программ ВРТ во всем мире. Более 7 млн детей в мире родились при помощи ВРТ. Современная клиническая практика в области репродуктологии направлена не только на повышение эффективности лечения, но и на безопасность лечения. Как и любой другой вид терапии, ВРТ может вызывать негативные побочные эффекты. Правильное прогнозирование рисков осложнения лечения и персонализированный подход обеспечивают абсолютную безопасность лечения бесплодия с помощью экстракорпорального оплодотворения. В последнее десятилетие разработан ряд новых подходов, интегрированных в клиническую практику методов ВРТ: сегментация цикла с последующим переносом эмбрионов и использование селективного переноса одного эмбриона. Новые подходы позволяют контролировать стимуляцию яичников и сократить число перенесенных эмбрионов, в результате удается минимизировать в первую очередь неблагоприятные перинатальные исходы. Прогнозирование рисков и исходов лечения путем математического моделирования способствует созданию оптимальной клинической практики.

▪ **Ключевые слова:** вспомогательные репродуктивные технологии; лечение бесплодия; пациент-ориентированный подход; перенос одного эмбриона.

Background

More than 7 million children in the world were born using assisted reproductive technologies (ART) [1]. These results have instilled confidence in ART efficiency to patients. At the same time, the issues of the ART methods safety and the health of future children are still relevant. Consequently ART, like other new technologies, should be aimed not only at efficiency, but also at the safety of treatment.

The process of creating the in vitro method of fertilization (IVF) was originally associated with tubal-peritoneal factors of infertility. However, in the future, the indications for the use of IVF began to expand. This led to the appearance of the intracytoplasmic sperm injection (ICSI) technique into the ooplasm, which was developed for the treatment of male infertility in the 1990s.

Today the indications for the use of ART are quite wide. These primarily include tubal or tuboperitoneal factors of infertility, relative infertility or subfertility, external genital endometriosis, polycystic ovary syndrome or other forms of anovulatory infertility, and older reproductive age. Despite the fact that the practice and results of IVF treatment differ in different countries, ART has undergone significant changes since its invention, primarily due to increase in the scope of ART programs.

A number of new approaches have been developed in the last decades, which were integrated into the clinical practice of routine ART methods aimed not only at increasing the efficiency of treatment, but also at ensuring the safety of treatment. These approaches include; segmentation of the cycle with subsequent transfer of embryos, the use of selective transfer of one embryo, and pre-implantation genetic testing of embryos.

The safety of treatment is a quality assurance of contemporary medicine. Like any other type of therapy, IVF can cause negative side effects. At the same time, knowledge of the risks of treatment helps to select the correct approach to the infertility therapy [2]. For this reason, in practice, possible complications associated with these types of procedures are necessary to identify.

There are two types of clinical complications arising from the treatment of infertility using ART. First, the general risks in case of any invasive procedure, namely bleeding and infectious complications. Second, risks associated with the treatment itself, namely with controlled ovarian stimulation, the development of ovarian hyperstimulation syndrome (OHSS).

Dominique de Ziegler et al. emphasize that the risks caused by treatment should be identified even before the start of the ART protocol [3]. Correct prediction of treatment risks and a personalized approach ensure absolute safety in the use of ART.

Ovarian hyperstimulation syndrome

Controlled ovarian stimulation is important for successful treatment. Several cohort studies have shown that the number of oocytes obtained by transvaginal puncture is a positive predictor of pregnancy and childbirth [4]. There is a relationship however between the numbers of oocytes obtained during transvaginal puncture and the severity of OHSS, as well as the risk of thromboembolic complications. For example, the incidence of OHSS is known to increase when the number of oocytes is 18 or more, and the risks of thromboembolic complications increase with a puncture of 15 follicles or more. The pregnancy rate increases when up to 11 oocytes are obtained during transvaginal puncture, and later remains unchanged. Therefore, the balance between efficacy and safety is a fundamental approach and of great importance for patients undergoing IVF treatment.

The incidence of severe OHSS varies from 2% to almost 9%. Thromboembolic complications are usually associated with OHSS which can develop into a life-threatening condition with an increased risk of thromboembolic complications. Ovarian hyperstimulation can theoretically occur in any woman undergoing ART treatment. However, some patients are at much greater risk. When assessing the risk of OHSS, patient's characteristics such as age, body mass index, and etiology of infertility should be considered. B. Luke et al. demonstrated that among 214,219 IVF cycles, women under 35 years of age, anovulatory infertility, and tubal factor were associated with an increased risk of ovarian hyperstimulation [5].

The risk of ovarian hyperstimulation can also be assessed by using ovarian reserve markers. In a prospective analytic study by R. Tal et al. (2014), 263 women underwent IVF, higher levels of anti-Müllerian hormone (threshold value 3.36 ng/ml) indicated more accurately the development of this complication than age and body mass index [6].

OHSS complicates controlled ovarian stimulation. In the ideal case, women at risk of this disorder should be identified prior to stimulation, and stimulation protocols that minimize the risks should be selected for them. The use of protocols with antagonists and replacement of the ovulation trigger with an agonist is a particularly effective strategy. Other strategies, which have some advantage, involve cryopreservation of all embryos rather than fresh embryo transfer. Severe forms of ovarian hyperstimulation are avoided in recent years through the "freezing of all embryos" strategy and cycle segmentation. Nevertheless, the balance between efficacy and safety in IVF stimulation, depending on the number of oocytes, is an urgent issue that should be discussed with patients before IVF.

An important point is the selection of the optimal starting dosage of drugs to stimulate ovulation. Thus, it is difficult to find the optimal balance of the starting dose in young patients with low body weight and a presumed high ovarian reserve.

To date, there are special prognostic models developed specifically for patients at high risk of OHSS in IVF. Their aim is to minimize and prevent treatment complications.

The reason for changing the stimulation protocol to minimize the risk of OHSS should be the presence of a high level of anti-Müllerian hormone or a large number of antral follicles, as determined by ultrasound examination. The foreign literature presents works devoted to personal stimulation, the correct choice of doses, and the correct work with patients with multifollicular ovaries [7, 8].

Treatment individualization is based on predicting ovarian response which is highly dependent on ovarian reserve. The most accurate and reliable markers of ovarian reserve are anti-Müllerian hormone and antral follicle count.

It is well known that IVF without a stimulation cycle, in the so-called natural cycle, is characterized by low efficiency. However, there are patients with a "favorable prognosis" for whom IVF without stimulation may be the best way to achieve pregnancy [9].

The most common and complicated group at risk of ovarian hyperstimulation is represented by patients with polycystic ovary syndrome. However, there are patients who do not belong to this group, but at the same time they may experience this type of complications. Attempts have been made to identify reliable prognostic markers for the development of OHSS during hormonal stimulation in the IVF protocol. Therefore, a model was developed, consisting of such predictors as the patient's reproductive history, the number of antral follicles, the etiology of the cause of infertility, and the presence or absence of hypothyroidism [10]. Using this model, the probability of OHSS can be calculated. The ability to anticipate and predict ovarian response is essential for a successful treatment outcome.

The use of mathematical algorithms prior to treatment initiation will provide control over ovarian stimulation [11], thus creating an optimal starting point for planned treatment.

Multifetal pregnancy

Due to the serious risks of complications for the mother and child [12, 13], as well as due to the high costs associated with the course of pregnancy [14], multifetal pregnancies are considered the leading complication of ART. Due to the large number of multifetal pregnancies in the world, there has been an increased need for strategies aimed at delivering one healthy child after ART.

The second principle of safe treatment is reduction in the number of multifetal pregnancies through the use of a Selective Embryo Transfer Policy (SETP).

The most effective way to reduce the frequency of multifetal pregnancies is by selective transfer of one embryo in the ART cycles [15]. However, the SETP strategy can affect overall pregnancy rates, so the use of this strategy must be mathematically justified. The individualized approach of embryo transfer is used to solve this problem, based on the determination of key clinical parameters affecting the onset of pregnancy using mathematical modeling. In this regard, interest has arisen in prognostic factors as a way to select patients for SETP.

Currently, the American Society for Reproductive Medicine recommends selective single embryo transfer for most patients under the age of 35 with a good prognosis. Although the likelihood of a successful ART cycle decreases with increase in age, patients of older reproductive age are also at risk of multifetal pregnancies, therefore, they should be considered candidates for single embryo transfer in the presence of excellent blastocytes [16].

The introduction of a national single embryo transfer policy in Sweden has reduced the frequency of twin births after IVF by 17% without performance degradation of pregnancy rates. In the absence of an appropriate legislative framework, clinics most often deviate from the strategy of selective transfer of one embryo and respond to the wishes of the patients. In 2013, the average number of embryos transferred in recent cycles in the United States amounted to 1.8 for women younger than 35 years old and 1.9 for women of 35 to 37 years of age. This means that, most centers still transfer two embryos in patients with a good prognosis [17].

At present, the experience of using the SETP approach enabled to identify groups of patients with a favorable prognosis. According to M.B. Jacobs and H. Klonoff-cohen, special attention should be paid to the reproductive history of women [18]. The authors point to predictive factors for IVF ineffectiveness in young patients. For example, the absence of previous childbirths, the presence of biochemical pregnancies or spontaneous miscarriages in a reproductive history should be considered as a marker of IVF treatment failure.

The SETP application will have a significant impact on reducing the number of multifetal births, and it should be followed during the planning phase of treatment. It is essential to remember that the infertility treatment should be aimed at birth of one healthy child. To introduce SETP into clinical practice, a multifaceted approach should be used, including education and counseling of patients, as well as tools for predicting IVF success.

Significant efforts have been made to minimize multifetal pregnancies and increase simultaneously the number of singleton pregnancies using an individualized approach to IVF treatment in line with the tendency of personalized medicine, over the past decade.

Conclusion

Prediction of treatment outcome is undoubtedly a very useful counseling tool of assisted reproduction specialists, as their clinical experience may not always contribute to safe prediction of the likelihood of pregnancy.

Fertility treatment specialists need to consider ART from two standpoints, namely success and possible complications. Control of ovarian stimulation and reduction of the number of transferred embryos present the right strategy to minimize adverse perinatal outcomes. The use of prognosis models will help ensure universally accepted best practices. The fact that IVF is a complex treatment and requires large financial and psychological expenditures further emphasizes the need for effective approaches in treatment of infertility.

Additional information

Conflict of interest. The authors declare no conflict of interest.

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