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MODERN MORPHOKINETIC ASSESSMENT OF EMBRYO QUALITY (literature review)

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✓ ***Resume***

The embryological stage of ART programs is one of the most important, since the assessment of the quality of oocytes, their fertilization and in vitro cultivation to the stage of preimplantation embryos largely determine its success. Morphological evaluation of embryos remains the main method of embryo selection. Time-lapse microscopy is one of the modern methods of selecting a high-quality embryo for transfer. In the analysis of many retrospective and prospective studies, they emphasize the advantage and lack of differences compared to traditional morphological assessment of embryo quality Almost all publications devoted to time-lapse microscopy have focused on determining the timing of specific events of embryo division and then using this information to create algorithms to help select embryo for transfer.

Key words: assisted reproductive technologies, infertility, elective blastocyst transfer, time-lapse microscopy.

EMBRYO SIFATINING MODERN MORFOKINETIK BAHOLASHI (Adabiyot sharhi)

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ART dasturlarining embriologik bosqichi eng muhimlardan biri hisoblanadi, chunki oositlar sifatini baholash, ularni urug'lantirish va ekstrakorporal usulda etishtirish embrionlarning preimplantatsiya bosqichiga qadar. Embrionlarni morfologik baholash embrion tanlashning asosiy usuli bo'lib qolmoqda. Vaqt o'tishi bilan mikroskopiya - bu ko'chirish uchun yuqori sifatli embrionni tanlashning zamonaviy usullaridan biridir. Ko'pgina retrospektiv va istiqbolli tadqiqotlarni tahlil qilishda ular embrionlarning sifatini an'anaviy morfologik baholash bilan taqqoslaganda afzallik va farqlarning yo'qligini ta'kidlaydilar. time-lapse mikroskopiya bo'yicha deyarli barcha nashrlarda embrionning bo'linishining aniq vaqtlarini belgilashga va keyinchalik ushbu ma'lumotdan foydalanish uchun embrionni tanlashga yordam beradigan algoritmlarni yaratish uchun foydalanilgan.

Kalit so'zlar: yordamchi reproduktiv texnologiyalar, bepushtlik, elektif blastotsist ko'chirilishi, time-lapse mikroskop

СОВРЕМЕННАЯ МОРФОЛОГИЧЕСКАЯ И МОРФОКИНЕТИЧЕСКАЯ ОЦЕНКА КАЧЕСТВА ЭМБРИОНОВ

(Обзор литературы)

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✓ ***Резюме***

Эмбриологический этап программ ВРТ является одним из важнейших, поскольку оценка качества ооцитов, их оплодотворение и куль¬тивирование in vitro до стадии преимплантационных эмбрионов во многом определяют ее успех. Морфологическая оценка эмбрионов остается основным методом селекции эмбрионов. Time-lapse микроскопия является одним из современных способов выбора качественного эмбриона на перенос. При анализе многих ретроспективных и проспективных исследований подчеркивают преимущество и отсутствие различий по сравнению с традиционной морфологической оценкой качества эмбрионов Почти все публикации, посвященные time-lapse микроскопии, были сфокусированы на определении времени конкретных событий деления эмбриона и последующем использовании этой информации для создания алгоритмов, помогающих выбрать эмбрион для переноса.

Ключевые слова: вспомогательные репродуктивные технологии, бесплодие, элективный перенос бластоцисты, time-lapse микроскопия.

Relevance

The most effective method of infertility treatment today is the use of assisted reproductive technologies (ART). The introduction of new assisted reproductive technologies into clinical practice has significantly expanded the possibility of obtaining offspring with seemingly previously incurable forms of infertility in marriage. Every year, assistive technologies are only improving, and today medicine and embryology have stepped far beyond the thinking of the 20th century [17]. The embryological stage of ART programs is one of the most important, since the assessment of the quality of oocytes, their fertilization and in vitro cultivation to the stage of preimplantation embryos largely determine its success. Morphological assessment of embryos remains the main method of embryo selection, according to which embryologists evaluate a number of parameters: the number of blastomeres, the correspondence of their size and shape to the developmental stage, the percentage of fragmentation, the degree of compaction of the embryo and an increase in the blastocyst cavity, the characteristics of the cells of the inner cell mass and trophoblast. Evaluation of the quality of cultured embryos is extremely in demand, since it is a kind of tool for selecting an embryo that has the highest chances of implantation [1]. Some clinics have introduced advanced technology for continuous monitoring of embryos, which allows you to examine, assess the quality and rate of development of embryos without opening the incubator and without removing them outside. The system is based on the use of the innovative time-lapse video technology Time-lapse TLT technology, during which every embryo is photographed at a given frequency from the moment of fertilization and throughout the entire incubation period. But this is not the only value of time-lapse technology [7, 8, 9]. In IVF cycles, the embryologist most often deals with several embryos. These embryos differ: some are ideal, others are less promising, and some are abnormal. One of the most important tasks facing the embryologist is the selection of the most promising embryos for transfer into the uterine cavity. To solve this problem, the embryologist evaluates the appearance of the embryos - he studies certain morphological signs. During the entire cultivation time (up to 120 hours), the embryologist can afford only a very limited number of examinations of the embryos - usually 2-4 short examinations. We can say that with the traditional method of assessment, the embryologist had only a few “frames” from the early life of the embryos, on the basis of which he must select the best ones. The rest of the time, the development of embryos was hidden from the embryologist. Traditional methods of embryo selection are still associated with a relatively low IVF success rate with a clinical pregnancy rate (PR) of ~30% per transfer [1]. This often results in more than one embryo transfer at a time, which increases the risk of multiple pregnancies and associated neonatal complications and health problems associated with maternal pregnancy [2, 3, 4]. With the advent of the technology of continuous monitoring of embryos, the embryologist receives the most detailed video chronicle of the early development of each individual embryo. In the course of its development, the embryo goes through a number of key events (stages of development) and the time it takes for the embryo to move from one stage of development to the next is an important indicator in assessing its quality and implantation potential - the kinetics of development. Thanks to the time-lapse technology, a new tool has

appeared in the embryologist's arsenal, which makes it possible to improve the selection of the most promising embryos and thereby increase the likelihood of pregnancy. Clinical researchers have focused on finding non-invasive embryonic markers that improve embryo selection and offer a consistent embryo protocol without compromising overall IVF success. Payne and colleagues [7] first applied time-lapse observations in 1997, when they documented the processes during fertilization and the first steps in the development of 38 oocytes. A decade later, Mio and Maeda [18] extended the analysis period to the blastocyst stage and characterized dynamic and morphokinetic events from fertilization to blastocyst hatching in 286 embryos. Using negative and positive predictive variables, an embryo selection algorithm based on morphokinetics was determined, categorizing embryos into 10 categories. The clinical significance of these promising results has not been confirmed, and prospective randomized trials are needed. In addition, both algorithms require large datasets to develop an embryo model, as well as validating the model in a separate dataset. Quality markers for early embryos are of particular value in clinics where extended embryo culture is not possible. Following a groundbreaking study by Payne et al., TLT allowed Coticchio and colleagues to draw up a detailed map of events during fertilization that could be putative indicators of embryo quality [2]. Twenty-eight parameters were described that were previously unknown or poorly documented. The time intervals between four morphokinetic events have been shown to predict the quality of the embryo on day 3 [2]. Further research is needed to evaluate these markers as predictors of day 5 embryo quality and clinical outcome, but TLT is the only technology available that allows embryos to be assessed based on such criteria. A comprehensive literature review has recently been published on the predictive value of morphokinetic parameters for embryo ploidy status [3]. A total of 13 studies were included that had significant heterogeneity in terms of design, inclusion criteria, embryo biopsy, statistical approach, and outcome measures. Although most studies found significant differences in the morphokinetic parameters of euploid and aneuploid embryos, none of them provided sufficient evidence to recommend the clinical use of TLT to assess embryo ploidy. To the same conclusion, another recent review was made, which discussed the relationship between morphokinetics and aneuploidy [4]. However, the combination of PGT-A with morphokinetic analysis can help in the selection of the embryo with the highest implantation potential [5]. Currently, automatic annotation has not resolved the issue of the accuracy of morphokinetic analysis. Automation requires human oversight to correct possible but recurring annotation inaccuracies that could affect the performance of prediction models for embryo selection. Therefore, as with other activities, each laboratory must implement appropriate quality control and quality assurance programs [6]. As with any new intervention, TLT should be introduced into routine clinical practice only after rigorous tests demonstrating patient benefit [7,8]. However, a clear increase in the number of successful IVF attempts using TLT has yet to be proven. The most recent Cochrane review (nine RCTs, 2955 women) [9] reported insufficient evidence for differences in live birth rates (odds ratio (OR0 1.12, 95% CI 0.92–1.36), miscarriage rate (OR 0.63 , 95%).% CI 0.45-0.89) or percentage of clinical pregnancy (OR 0.95, 95% CI 0.78-1.16) for TLT in combination with software for embryo selection versus traditional incubation and evaluation. Likewise, the putative benefit of TLT has not been demonstrated by meta-analyzes [9,10,11]. Conversely, one meta-analysis using a different methodological approach suggested a beneficial effect of TLT compared to conventional incubation and scoring, respectively, reporting significantly higher rates of ongoing pregnancy (51.0 versus 39.9%; OR 1.54, 95% CI 1.21–1.97), a significantly lower number of early pregnancy loss cases (15.3 versus 21.3%; OR 0.66, 95% CI 0.47–0.94), and a significantly increased frequency of live births (44.2 versus 31.3%; OR 1.67, 95% CI 1.13–2.46) [12]. The cumulative live birth rate was estimated in a recent retrospective study of 1882 cycles comparing interval versus routine incubation / score [15]: the study showed similar cumulative live birth rates for interval and standard incubation / score (51.7 versus 51.2%; OR 1 , 02, 95% CI: 0.85-1.22), although the rate of live births with fresh embryo transfer was higher for TLT cycles (36.8 versus 33.9%, adjusted OR 1.28, 95% CI: 1. 05-1.57). The main reason for controversy over the effectiveness of TLT is that it involves two distinct components, namely a continuous incubation environment and selection of embryos using imaging software. In this respect, these two components were not effectively separated in most studies, possibly masking the weight of the effect of better culture conditions or improved embryo selection on the reported results [9]. Importantly, no safety

concerns have been reported following culture of embryos in TLT incubators, and obstetric and perinatal outcomes such as duration of pregnancy, congenital malformations and birth weight are comparable [13,16,14] or better [15] compared to standard incubation.

Conclusion

Thus, the study of the morphology and rates of development of embryos made it possible to develop morphokinetic criteria for assessing the quality of embryos, which significantly complements the traditional approaches. Although there is currently no evidence from RCTs for the clinical benefit of TLT, it is reasonable to assume that, compared to static observation, continuous monitoring of the embryo in an undisturbed environment will provide more information about embryo development and is expected to improve the identification of good outcomes - embryo prognosis for clinical use. To firmly establish the presumed beneficial effect of TLT, more well-designed and powerful enough RCTs are needed that report live births and perinatal outcomes.

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