Future perspectives of non-invasive techniques for evaluating oocyte and embryo quality

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Despite significant advancements in assisted reproductive technology, there is still high demand for improvements in the clinical pregnancy rate and reductions in the time needed to achieve a live birth. One bottleneck issue is the effective selection of oocytes and/or embryos of better quality in the laboratory. The quality of oocytes and embryos cannot be accurately assessed with routine clinical methods. Thus, assessment methods that are more objective, accurate, quantifiable, non-invasive, rapid, and repeatable are needed in the clinic. This perspective highlights the latest developments in non-invasive assessments of oocyte and embryo quality and presents new trends and insights into the biomedical engineering technologies used to evaluate oocyte and embryo quality.

INTRODUCTION

According to the innovation conference of 2023, women’s health plays a crucial role in shaping the future of humanity. Due to social, environmental and many other factors, infertility has become a key issue plaguing women’s health. To combat this issue, assisted reproductive technology (ART) has emerged as a viable solution. ART encompasses various fertility treatments including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), with more than seven million children estimated to have been born through ART. However, the efficacy of ART remains relatively low. According to the statistics, among 100 oocytes collected, only 31 become high-quality embryos, and only 5 result in the birth of offspring. Due to the lack of objective parameters for evaluating oocyte or embryo quality, multiple embryos are transferred into the uterus to ensure an acceptable clinical pregnancy rate, resulting in a higher risk of multiple pregnancy from the IVF cycle.

There is no doubt that the goal of an IVF/ICSI cycle is to achieve one healthy baby per transfer. Selection of high-quality oocytes and/or embryos is the crucial initial step toward ensuring the success of an ART procedure. Oocyte quality, or oocyte developmental competence, refers to an oocyte’s ability to undergo successful meiosis, fertilization, preimplantation embryo development, implantation, and ultimately result in the birth of a healthy offspring. Human oocytes and embryos are small in size (~120 μm). In addition, they are quite vulnerable to tiny changes in culture conditions, such as fluctuations in temperature, pH, osmolarity and toxicity. As a result, the assessment of oocytes and embryos is challenging. Clinically, the assessment involves both non-invasive morphological evaluation and invasive preimplantation genetic testing for aneuploidy screening (PGT-A). PGT-A is invasive in nature and requires additional manipulation and expense. In addition, consumption due to embryo biopsy, chromosome screening, and vitrification cannot be neglected. Therefore, more objective, accurate, quantitative, non-invasive, rapid, and repeatable evaluation methods are clinically demanded.

Recent developments in the technology of ultrastructure observation, autofluorescence detection, and microfluidic chips, among others, may provide a novel opportunity to overcome current limitations in the evaluation of oocytes and embryos. Here, we present various non-invasive techniques for evaluating oocyte and embryo quality (Figure 1), such as mechanical, optical, and cell metabolism secreted factor-based methods. Additionally, we introduce the use of automation and artificial intelligence (AI) approaches to increase the efficiency and precision in assessing oocyte and embryo quality, ultimately aiming to increase the efficiency of ART.

MECHANICAL-BASED METHODS

The mechanical properties of cells, such as elasticity, viscoelasticity, and shear modulus, play crucial roles in various cellular functions including cell growth, division, motility, and adhesion. Assessing the mechanical properties of oocytes may provide valuable insights into their quality and developmental potential for successful use in ART.

One commonly used method for assessing oocyte mechanics is analysis of the zona pellucida, which is the protein coating surrounding the oocyte plasma membrane. Techniques such as indentation force, micropipette aspiration, and atomic force microscopy are utilized to measure the hardness, elasticity, and viscosity of the zona pellucida. Typically, these non-invasive techniques involve the use of glass tubes of various sizes or probes to place pressure or suction on the zona pellucida. The resulting deformation of the zona pellucida is then analyzed to assess its mechanical properties. Several mechanical methods can also be conveniently applied during ICSI, facilitating the integration of these methods into clinical research. I Yanez et al., reported that the viscoelastic properties of embryos can be indicative of their viability for blastocyst development. Embryos with moderate levels of softness and hardness were identified as having higher chances of successful development. Excessive force applied via mechanical methods may cause deformation and damage to oocytes or embryos, so determining the appropriate amount of force is an important area for future research on mechanical methods.

OPTICAL-BASED METHODS

Optical-based methods, including absorption, refractive index, and autofluorescence, are used to measure various properties of oocyte development. A lab-on-a-chip (LOC) system combined with an optical sensor was previously developed to measure absorption and the refractive index at different stages of oocyte development. This system automates the capture, movement, and trapping of a single human oocyte using a microfluidic device. The amount of light absorbed and transmitted by the oocyte was measured using two illumination and collection optical fibers. Higher quality oocytes with a homogeneous cytoplasm had a lower absorbance ratio, in contrast, lower quality oocytes with heterogeneous cytoplasm and inclusions exhibited a higher absorbance ratio.

Optical-based methods are also utilized to assess the localization, shape, and refringence of the meiotic spindle using polarized light. The meiotic spindle plays a crucial role in aligning and separating chromosomes during meiosis, thus making it a key focus in the examination of oocyte quality. There is a correlation between meiotic spindle length and oocyte quality. Oocytes with a birefringent spindle, as observed under polarized light, tend to have better embryonic development than those with a nonbirefringent spindle. Additionally, oocytes lacking a visible meiotic spindle under polarized light are linked to lower rates of fertilization and blastocyst formation.

The autoluminescent metabolic factors NADH and FAD are currently receiving increasing amounts of attention in relation to oocytes and embryos. These factors are directly linked to mitochondrial activity, and the fluorescence intensity of NADH and FAD has been used to quantify mitochondrial activity and metabolic changes in oocytes and embryos. To capture these autoluminescent metabolic cofactors, laser scanning confocal microscopy and fluorescence lifetime microscopy (FLIM) are commonly used. Confocal microscopy allows for 3D imaging of mitochondria in oocytes and embryos. FLIM has been successfully used to assess the metabolic processes of
Figure 1. Non-invasive assessments for selection of high-quality oocytes and embryos.

Automations and AI methods

With the advantage of time-lapse embryo culture technology, consecutive images have been automatically captured in recent years. However, no universal algorithm has been developed for the selection of viable embryos for transfer, indicating that current morphological parameters may not be enough, and clinical factors, such as female age, ovarian reserve, infertility etiology, and ovarian stimulation protocol, should be considered. AI techniques have gained attention for their applications in medical imaging diagnostics by incorporating deep learning, computer vision image processing techniques, and clinical data. It has been applied in prediction, diagnosis, information management, data collection, and clinical practice. Moreover, AI can supplement existing conventional morphological indicators used clinically and integrate new indicators in the future to improve the accuracy of quality screening. Recently, a prediction model for ovarian reserve or polycystic ovary syndrome has been reported. It is promising to develop an AI model for oocyte and embryo quality assessment based on a large amount of clinical and laboratory data for model training.

Improving Oocyte Quality Methods

In addition to selecting high-quality oocytes and embryos, improving oocyte quality is crucial for the success of ART procedures. Clinically, doctors typically rely on different ovarian stimulation protocols to enhance oocyte quality. Mitochondria have garnered increased attention due to their significant role in regulating oocyte metabolism and epigenetics. Antioxidants such as coenzyme Q10 are orally administered or added to culture media during IVF/ICSI treatment to improve oocyte quality. The development of AI and cell metabolism secreted factor-based methods may also benefit the enhancement of oocyte quality. This approach may benefit the development of a more personalized ovarian stimulation protocol for specific patients. In addition, small molecule substances discovered through secreted factor methods may be orally consumed or added to culture media to improve oocyte quality.

Conclusion

In the field of ART, selecting high-quality oocytes and embryos is a crucial step. The exploration of new non-invasive methods for evaluating oocytes and embryos is clinically demanded. The future of non-invasive assessment of oocytes and embryos lies in physics, microscopy, incorporating genomics, microfluidics, AI, and other biomedical technologies into the study of oocyte and embryo biology. However, there are still challenges to overcome, particularly in terms of technology and clinical applications. To address these challenges, it is important to encourage interdisciplinary research and collaboration between medicine and industry. Doing this will expand our understanding of unexplored ultrastructural fields and change traditional methods to develop more reliable techniques for the assessment of oocyte and embryo.
developmental competence.

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DECLARATION OF INTERESTS
The authors declare no competing interests.