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Recent Advances in Biosensors for Ovum Maturity Detection: Technologies, Challenges, and Future Perspectives

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Abstract

Biosensors are advanced medical detection tools with pivotal applications in ovum maturity detection, providing accurate clinical experimental data and professional condition assessment. This paper deliberates three main types of biosensors in this field: electrochemical sensors, which measure electronic signal changes via nano-modified electrodes to detect estradiol levels in follicular fluid, thereby assessing ovum maturity; optical sensors, which test the intensity of fluorescent biomarkers to evaluate the dynamic change in mRNA; and piezoelectric sensors, which measure the changes in mass associated with ovum maturity.

Keywords

biosensors, ovum detection, electochemical sensors, optical sensors, piezoelectric sensors

1. Introduction

In clinical gynecology, infertility, premature ovarian failure, and polycystic ovary syndrome have become increasingly prevalent among female patients, which makes assisted reproductive technology a routine treatment choice for many fertility-seeking groups. Accurately assessing the actual maturity of ovarian follicles and oocytes is a core prerequisite for formulating targeted ovulation induction plans and ensuring the final success of in vitro fertilization (IVF). At present, most clinical teams still rely on microscopic morphological observation to assess oocyte maturity; this method relies heavily on the operator's subjective experience, and improper handling may cause irreversible damage to fragile oocyte samples. Besides morphological observation, other conventional testing approaches also have obvious practical limitations: they require large-scale laboratory equipment, tedious manual operations, and long waiting times for test results, and tend to introduce significant random errors due to human manipulation. These traditional testing schemes consume relatively large volumes of biological samples, and cannot support high-throughput batch screening either. In livestock and aquatic breeding industries, dissection sampling to detect ovarian development will directly cause the death of breeding parents, further limiting the practical value of classic detection methods. Taken together, these existing technical routes can barely meet current demands for bedside clinical testing, grassroots preliminary screening, and rapid field detection at breeding sites.

As practical tools for quantitative biological analysis, biosensors can capture clear imaging data and measurable physiological indicators from clinical samples when equipped with optimized sensing components,

enabling researchers to evaluate patients' reproductive physiological conditions more precisely. Such devices have demonstrated practical value in evaluating reproductive function in IVF, yet single biosensor units still fail to address the multiple limitations of traditional detection methods on their own.

In recent years, researchers have begun to combine microfluidic chips with biosensor modules to address bottlenecks in biochemical reproductive testing. Integrated microfluidic platforms combine microchannels, microvalves, micropumps, and independent droplet-control structures into a single testing chip, which can eliminate nearly all repetitive manual steps and enable a fully automated testing workflow covering sample loading, pretreatment, biochemical reaction, and signal output. Continuous-flow microfluidic structures can achieve dilution, target-substance enrichment, and impurity interception in complex body fluid samples; droplet and digital microfluidic technologies enable separate manipulation of tiny microdroplets and simultaneous testing of multiple indicators. Within enclosed microscale reaction spaces, experimenters can stably control reaction temperature, incubation duration, and reagent mixing ratios, thereby reducing test errors and improving the stability of quantitative results. Based on these practical technical strengths, this paper develops an integrated automatic detection system that combines microfluidic structures and biosensors and conducts targeted tests to assess its detection performance, technical merits, and practical application in oocyte maturity measurement.

2. Biomarkers for Ovum Maturation

Oocyte cytoplasmic and meiotic maturation is an indispensable prerequisite for normal fertilization and sustained embryonic development. Precise judgment of follicular maturity status relies heavily on specific, stable molecular biomarkers. Follicular fluid and granulosa cells together constitute the intrafollicular microenvironment, which mediates continuous crosstalk between somatic granulosa cells and oocytes. Therefore, soluble bioactive molecules accumulated in follicular fluid, together with functional mRNA transcripts expressed within granulosa cells, can directly and objectively reflect the real developmental stage of ovarian follicles. Among all validated molecular indicators derived from follicular compartments, inhibin-B, which is predominantly synthesized and secreted by proliferating granulosa cells, is the most representative marker for grading follicular maturity. Apart from inhibin-B, estradiol dissolved in follicular fluid is closely linked to cumulus expansion and the resumption of oocyte meiosis; granulosa cell-specific mRNA transcripts, including LHCGR and FSHR, can further reflect the functional activity of follicular somatic tissue. Moreover, small non-coding microRNAs isolated from follicular fluid have gradually been recognized as novel auxiliary biomarkers to discriminate immature follicles from pre-ovulatory ones. It is worth noting that detecting all the above follicle-derived markers requires invasive follicular puncture, which limits continuous, dynamic tracking of follicular growth and motivates further exploration of non-invasive detection approaches targeting peripheral substitutes for granulosa cell metabolites.

3. Classification and Applications

3.1 Electrochemical Sensors

Electrochemical sensors detect target substances by measuring changes in electrical signals, such as current, potential, or conductance, generated during oxidation and reduction. In detecting ovum maturity, they primarily target biomarkers associated with ovum maturation. For example, some studies use electrochemical sensors to detect the estradiol level in follicular fluid to infer oocyte maturity. Estradiol is one of the essential hormones that reflect follicular development and oocyte maturation. The research developed an electrochemical sensor with Nano-modified electrodes that significantly improves the sensitivity and accuracy of estradiol detection.

3.2 Optical Sensors

Optical sensors detect target substances based on changes in light signals. Among them, fluorescence sensors are widely used for detecting ovum maturity. Some studies design fluorescent probes that bind to specific molecules or biomarkers related to oocyte maturation, thereby altering fluorescence signals. A research team has developed a fluorescence sensor for a specific mRNA whose expression level changes significantly during oocyte maturation. By measuring fluorescence intensity, researchers can monitor dynamic

changes in this mRNA during oocyte maturation in real time and evaluate oocyte maturity. In addition, surface plasmon resonance (SPR) sensors are also applied. It uses surface plasmon resonance on a metal surface to detect biomolecular interactions without labeling. In detecting ovum maturity, it can detect protein-protein interactions or antibody-antigen reactions related to ovum maturation, providing information for assessing the ovum maturation stage.

3.3 Piezoelectric Sensors

Piezoelectric sensors detect substances by exploiting the property that piezoelectric materials generate electric charges in response to external forces. Ovum maturity can be detected by measuring mass changes associated with biomolecules involved in ovum maturation. For example, when a specific antibody is immobilized on the surface of a piezoelectric crystal and binds to the corresponding antigen in the follicular fluid, it increases the mass on the crystal surface, thereby changing the piezoelectric frequency. Piezoelectric sensors offer high sensitivity and label-free operation, providing a simple and efficient approach to detecting ovum maturity.

4. Current Challenges

4.1 Key Issue

Although biosensors have been a breakthrough, they still face a serious, unresolved problem: they remain immature in some respects, including technological issues, due to the scarcity of people trained to perform clinical detection. That shows the different sides of biosensors, not just the benefits; those problems need to be solved for a better future and the diverse development of biosensors. Current Challenges Although these sensors show promise, they are not yet widely used in hospitals. Three main challenges are holding them back:

4.2 Sensitivity

Human follicular fluid extracted alongside oocytes during IVF procedures contains dozens of endogenous biological components in addition to target reproductive hormones, including abundant serum albumin, immunoglobulin fragments, cellular debris, and various small metabolic molecules derived from granulosa cells. These coexisting substances tend to cause nonspecific adsorption at the recognition interface of electrochemical and optical biosensors. In repeated actual testing of clinical follicular fluid samples, adsorbed miscellaneous proteins will cover the specific capture probes fixed on the sensor surface, thereby weakening the binding efficiency between target hormone molecules and the probes. This matrix interference will lead to unstable baseline signals and pronounced signal suppression, causing the measured concentrations of key markers to deviate far from their in vivo levels. Even if researchers increase the incubation time of samples, the complex matrix background of follicular fluid cannot be eliminated by simple dilution alone, which severely limits the detection sensitivity and quantitative accuracy of unmodified biosensors used for oocyte maturity evaluation.

4.3 Sampling Difficulties

Sampling Difficulties: Egg cells are extremely small and very valuable. Collecting samples from them is difficult and requires specialized technology, such as microfluidics, to work properly. Individual human oocytes have extremely small volumes, and each viable oocyte obtained from clinical patients carries irreplaceable reproductive value, so researchers cannot obtain sufficient fluid samples from a single egg cell for repeated testing. Conventional laboratory hormone detection methods, such as chemiluminescence immunoassay, require microliter-level volumes for the reaction to proceed. Yet, the physiological fluid attached to the surface of one oocyte only reaches the nanoliter scale. Direct sampling with traditional pipettes can easily cause mechanical damage to fragile oocyte membranes or consume nearly all trace amounts of extracellular fluid, leaving no residual sample for repeated verification. Under this constraint, conventional detection equipment cannot produce a valid measurement. Microfluidic chips with microchannel structures are currently the only feasible technical route to achieve nanoliter-level trace sampling without causing excessive loss of precious oocyte-related samples.

4.4 Biocompatibility Concerns

When biosensor components come into direct contact with living oocytes or are placed within the ovarian microenvironment for in situ monitoring, all raw materials used in the sensing device must meet strict biological safety standards. Unmodified polymer or metal substrates may release trace amounts of toxic ions or small-molecule monomers under constant contact with follicular fluid; these leachable substances can trigger an oxidative stress response in oocytes, impair mitochondrial activity, and even block the normal maturation of gamete cells. For this reason, the substrate and surface coating materials of biosensors need to avoid inducing cytotoxic reactions and maintain stable chemical inertia in biological fluid environments. Only tissue-compatible modified materials can ensure the sensor does not cause irreversible harm to living egg cells during real-time maturity detection.

5. Future

Relying on microfluidic on-chip technologies and new sensing materials, modern biosensors have achieved miniaturization, full-process automation, and high-throughput capabilities, addressing the problems of traditional testing methods, which are cumbersome to operate, consume large sample volumes, and are prone to fluctuations. A microfluidic biosensing platform integrating microchannels, micropumps, miniature valves, droplet-control structures, sample pretreatment, biochemical reactions, and signal acquisition can be fully automated within a closed microsystem, effectively ensuring biosafety for clinical and pathogen sample testing. Beyond routine clinical diagnosis, this type of integrated device is increasingly used in assisted reproductive medicine. It enables quantitative analysis of reproductive hormones and objective evaluation of ovarian and oocyte maturity, showing great potential in clinical translation and large-scale propagation applications. This article will further elaborate on the automated working mechanism, technical advantages, and practical applications of microfluidic biosensors in ovarian maturity detection.

5.1 Integration with Microfluidics

Future biosensors would completely replace artificial operations and rely primarily on microfluidic microchannels, microvalves, micropumps, droplet control units, and other structures. On the one hand, sequential microfluidic system can finish diluting the samples, liquids phase mixing, target object enriching and the disposion before the washout and other steps, especially the whole blood, sputum,evironmental body of water and other complecated samples, sorting aggregative cells, the function of helding back the impurity, accessing the automatic pretreatment of the intricate specimen, solves the time-consuming and labor-intensive pain points of traditional sample processing. On the other hand, droplet microfluidics and digital microfluidics, which are based on upgraded electro-wetting technology, solve the pain point of traditional sample processing that was time-consuming and labor-intensive, and enable sequencing, standardized, and automated testing of multiple batches of samples. A microscale fluid environment can accurately regulate temperature, reaction duration, and reagent ratio, substantially reduce random error from artificial operations, and increase the quantitative accuracy and repeatability of the detection result. Therefore, the closed microfluidics channel is isolated from external pollution.

5.2 Non-invasive Detection

With continuous iteration in reproductive detection technology and the interdisciplinary integration of imaging science, molecular biology, and artificial intelligence, non-invasive detection of ovarian maturity will become the mainstream evaluation method for assisted reproductive therapy in the future. Breaking through the limitations of inconsistent diagnostic criteria and insufficient model verification in current clinical applications, future research will focus on optimizing multimodal detection systems that combine high-resolution ultrasound morphokinetic parameters, specific fluid biomarkers, and machine learning algorithms. The establishment of unified, standardized quantitative scoring criteria for ovarian follicle maturity will effectively eliminate individual diagnostic errors arising from physical differences and varying ovulation induction regimens, thereby greatly improving the accuracy and stability of non-invasive evaluation. With advances in portable, miniaturized detection equipment, this non-invasive technical system will enable widespread clinical and daily use, support long-term dynamic monitoring of ovarian function in infertile patients, and enable high-precision prediction of the ovulation window. Ultimately, the mature non-invasive

ovarian maturity assessment system will fully optimize the traditional ART diagnostic and treatment paradigm, reduce clinical reproductive complications, and provide safer, more accurate, and personalized technical support to improve oocyte quality and clinical pregnancy rate in infertility treatment.

5.3 AI & Data Analysis

Portable biosensors capture trace concentrations of follicle-derived biomarkers (inhibin-B, estradiol, and circulating miRNAs) from peripheral blood or saliva to enable non-invasive acquisition of signals of ovarian maturity. Integrated artificial intelligence algorithms first eliminate signal noise and baseline drift inherent to biosensor chips via denoising regression, correcting interference from individual endocrine differences. Machine learning models then fuse real-time quantitative biomarker readings from sensors with basic follicle morphological parameters, thereby generating continuous maturity-grading scores rather than relying on single molecular indicators. Lightweight embedded AI is further loaded into miniaturized biosensor equipment, enabling instant automatic interpretation of test results for outpatients and home fertility monitoring. With cumulative multi-center clinical biosensor datasets, deep learning can continuously optimize diagnostic thresholds for ovarian maturity and improve the accuracy of ovulation timing predictions.

6. Conclusion

Combining biosensors with microfluidic chips is an effective solution to the above bottlenecks by enabling automated trace-sample processing and stable, quantitative testing. In the future, the integration of microfluidic platforms, non-invasive peripheral biomarker detection, and artificial intelligence will become the core direction for development. AI algorithms can eliminate signal noise and generate comprehensive maturity scoring, while non-invasive testing avoids follicular puncture trauma. Integrated microfluidic biosensors deliver miniaturized, automated, and high-throughput detection, optimizing assisted reproductive diagnosis and treatment to raise pregnancy rates for infertile patients. Such portable devices also fit rapid detection for livestock and aquaculture breeding. Further research should optimize biocompatible modification materials and multi-index synchronous detection chips to build a low-cost, high-precision universal oocyte maturity detection system.

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Conflicts of Interest

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