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PERSPECTIVE

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Can iron serve as oocyte quality indicator in endometriosis?

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Endometriosis (EMs) is a significant cause of female infertility, and recent attention has focused on the relationship between iron levels in follicular fluid (FF) and oocyte quality. This perspective summarizes the characteristics of altered FF iron content and oocyte quality in EMs-associated infertility patients, along with detection methods and correlative studies. Current research indicates that dysregulated iron levels in the FF of EMs patients may be associated with diminished oocyte quality. However, the clinical utilization of FF iron content as an evaluation indicator faces multiple challenges. Future investigations should prioritize elucidating the regulatory mechanisms of iron homeostasis in the FF of EMs patients, establishing standardized detection and evaluation protocols, and providing novel insights for assisted reproductive therapies in EMs-related infertility cases.

Endometriosis (EMs), a common gynecological disorder in women of reproductive age, impairs fertility through intricate mechanisms, among which the decline in oocyte quality is recognized as a pivotal factor. Follicular fluid (FF), serving as the microenvironment for oocyte growth and development, its compositional alterations may directly influence oocyte quality. In recent years, the role of trace elements, particularly iron, in FF has attracted significant attention from researchers.[1]

Iron, an essential trace element in the human body, plays a vital role in cellular metabolism and redox balance. EMs patients often exhibit changes in the pelvic microenvironment and chronic inflammation, which may lead to abnormal iron metabolism in FF. Investigating the variation in iron content in FF of infertile patients with EMs and its relationship with oocyte quality is of great significance for understanding the mechanism of infertility in EMs and improving the outcomes of assisted reproduction.

ASSOCIATION BETWEEN IRON DYNAMICS AND OOCYTE QUALITY IN EMS-ASSOCIATED INFERTILITY

The variation in iron content in FF of infertile patients with EMs may be related to the changes in the pelvic microenvironment caused by the disease itself. Cyclic bleeding of ectopic lesions leads to pelvic iron overload, which may impair oocyte quality by disrupting the follicular microenvironment. Studies have shown that FF iron levels in EMs patients are higher than those in controls and are positively correlated with disease severity.[2] Nevertheless, there are also conflicting findings. Some scholars believe that the iron content in follicular fluid of EMs patients may exhibit fluctuating changes, which are related to the menstrual cycle stage and ovarian stimulation protocol.[3] In addition, EMs patients often experience oxidative stress, which may affect the metabolism and distribution of iron.

Recent studies have explored the relationship between FF iron content and oocyte quality in infertile patients with EMs.[4] Elevated iron levels in FF are associated with impaired oocyte maturation, reduced fertilization rates, and poor embryo quality. High levels of iron may damage oocyte quality through mechanisms such as inducing oxidative stress, affecting mitochondrial function, and disrupting the meiotic spindle.

In addition, interactions between iron and other FF components may modulate its impact on oocyte quality. For example, studies have found that the level of antioxidants in FF of EMs patients is reduced, which may exacerbate the oxidative damage caused by iron overload.[5] The depletion of follicular antioxidant capacity in EMs patients impairs the ability to neutralize reactive oxygen species generated through iron-mediated Fenton reactions. Importantly, the observed reduction in follicular antioxidants may not only stem from iron overload-mediated suppression of antioxidant gene expression, but could also originate from paracrine secretion of pro-inflammatory cytokines by EMs lesions, which amplifies oxidative stress within the follicular microenvironment.

It is worth noting that most of the current studies on the relationship between the iron content in FF and oocyte quality in infertile patients with EMs are small-sample cross-sectional studies, lacking large-scale prospective studies. Future research needs to conduct more rigorously designed studies to clarify the relationship between the iron content in FF of EMs patients and oocyte quality and clinical outcomes (such as pregnancy rates and live birth rates).

DETECTION METHODS OF IRON CONTENT IN FF

The detection methods of iron content in FF mainly include atomic absorption spectrometry (AAS), inductively coupled plasma mass spectrometry (ICP-MS), and colorimetry.[6] AAS has the advantages of high sensitivity and good selectivity, but it can only measure one element at a time, resulting in relatively low efficiency. ICP-MS can simultaneously measure multiple elements with higher sensitivity, but the equipment is expensive and the operation is complex. Colorimetry is simple to operate and has a lower cost, but its sensitivity and accuracy are relatively poor. For EMs patients, ICP-MS is recommended to simultaneously detect multiple trace elements and comprehensively evaluate the FF microenvironment. Certainly, cost containment remains an important consideration for both ART clinics and patients. We propose a systematic evaluation of portable colorimetric assays through comparative cost-effectiveness analysis against conventional laboratory methods, with special consideration given to emerging innovations in Point-Of-Care Testing (POCT) platforms.[7] Building upon this foundation, future research should prioritize the development of next-generation diagnostic technologies that synergistically optimize three critical parameters: reduced cost, accelerated processing time, and improved analytical sensitivity.

Regardless of the method used, strict control of the sample collection, storage, and processing procedures is necessary. Special attention should be paid to avoiding sample hemolysis, as the rupture of red blood cells will release a large amount of iron, affecting the accuracy of the test results. In addition, establishing specific reference value ranges and quality control systems for EMs patients is crucial for ensuring the reliability and comparability of the test results.

FEASIBILITY AND CHALLENGES OF FF IRON CONTENT AS AN INDICATOR FOR OOCYTE QUALITY

FF iron content shows potential as an indicator of oocyte quality in EMs-related infertility. FF collection is minimally invasive and does not harm to oocytes, while iron detection is rapid and technically mature. If a specific reference value range for EMs patients can be established, the iron content in FF may become a useful indicator for evaluating oocyte quality.

However, this method also faces many challenges (Figure 1). Firstly, the heterogeneity of EMs (subtypes and classification) may lead to significant individual differences in the iron content in FF, requiring the establishment of standardized sampling and detection procedures. Secondly, patients often have other pathological changes, such as chronic pelvic inflammatory disease and ovarian dysfunction, which may affect the iron content in FF and require multivariate analysis to exclude the influence of confounding factors.

In addition, how to combine the iron content in FF with other evaluation indicators to improve the accuracy of evaluation is also a problem that needs to be solved in future research. Evidence from T2D studies shows heme iron is linked to metabolic alterations, including L-valine and uric acid pathways.[8] Additionally, our previous work revealed that iron-overloaded FF alters miRNA

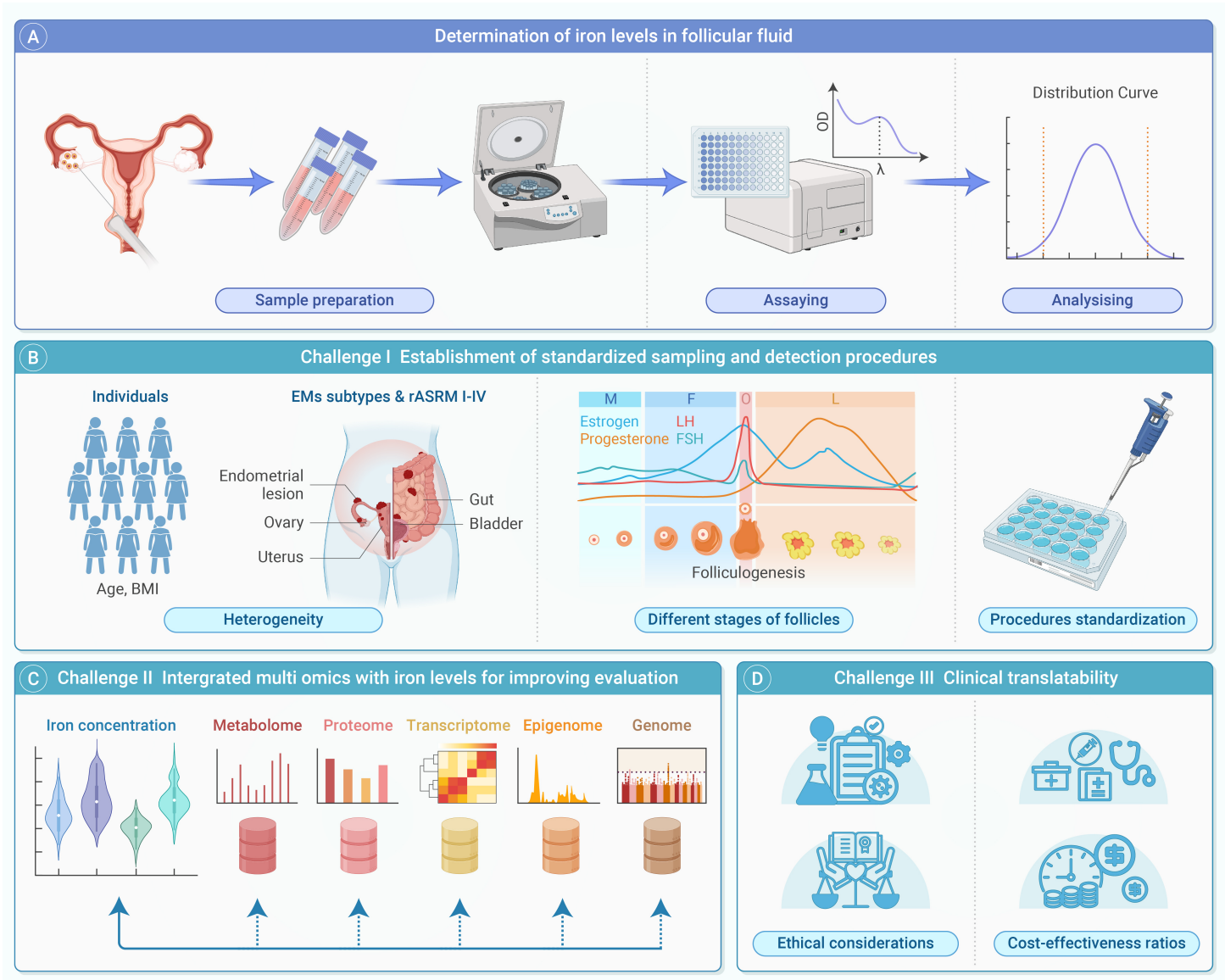

Figure 1. Challenges in assessing iron levels in follicular fluid (A) Determination of iron content in follicular fluid. Samples collected from individuals undergo preparatory processing, followed by quantitative measurement of iron concentrations. The acquired data are subsequently analyzed to ascertain iron levels in follicular fluid. (B) Challenge I: Establishment of standardized sampling and detection protocols. Individual heterogeneity arises from individual heterogeneity (age, BMI), pathological variations in endometriosis subtypes (manifesting as lesions in uterus, ovaries, intestines, and bladder) and classification (rASRM I-IV), folliculogenesis stages (M: menstrual phase, F: follicular phase, O: ovulation phase, L: luteal phase), and stage-specific hormonal regulation (estrogen, progesterone, LH, FSH). Standardized sampling protocols are essential to ensure analytical reproducibility in heterogeneous sample cohorts. (C) Challenge II: Integrated multi-omics with iron levels for improving evaluation. Multi-omics encompassing metabolomics, proteomics, transcriptomics, epigenomics, and genomics elucidate how iron concentrations modulate cellular metabolism, gene expression networks, DNA methylation patterns, and chromatin architecture, thereby enabling comprehensive understanding of iron's roles in follicular disorders. (D) Challenge III: Clinical Translatability. Systematic integration of ethical considerations with cost-effectiveness ratios for iron quantification in clinical environments is required to propel broad-scale clinical implementation.

profiles in granulosa cells.[9] This emerging "iron-multiomics" approach may not only clarify iron-related pathophysiology but also offers a novel framework for identifying biomarkers and developing precision intervention strategies.

An emerging question is whether FF iron content can serve as a guiding biomarker for individualized treatment in EMs-related infertility. While advanced-stage EMs is often linked to reduced oocyte quality due to chronic inflammation and oxidative stress, assisted reproductive technology (ART) outcome variability in early-stage EMs remains poorly understood. Some early-stage patients experience ART failure despite normal ovarian reserve, suggesting undetected microenvironmental disruptions. Elevated FF iron, a hallmark of EMs, may offer an objective, quantifiable marker to stratify oocyte developmental potential across disease stages. In advanced EMs, high FF iron may support clinical decisions such as early embryo freezing or antioxidant therapy. In early-stage EMs, it may help identify patients at risk of "silent" oocyte dysfunction before ovarian reserve declines.

Current evidence suggests that partial restoration of oocyte quality may be possible, but reversibility is highly context-dependent and requires careful consideration of clinical practicality.[10] Preclinical studies show that antioxidant interventions (e.g., melatonin, N-acetylcysteine, coenzyme Q10) can reduce oxidative stress, improve mitochondrial function, and enhance oocyte maturation in animal models. Mitochondrial augmentation (e.g., autologous mitochondrial transfer) shows promise in restoring energy metabolism in compromised oocytes, though raises concerns about mitochondrial heterogeneity and long-term safety. Ultimately, while partial recovery of oocyte quality is biologically plausible, its clinical feasibility hinges on resolving challenges related to efficacy, safety, and ethics through interdisciplinary efforts.

PROSPECTIVE STUDY ON FOLLICULAR IRON AND REPRODUCTIVE OUTCOMES IN EMS

Conducting a prospective cohort study in collaboration with ART clinics would be a robust validation approach. A prospective cohort study would

enroll EMs patients (stratified by rASRM stages I/II and III/IV) alongside age-matched controls. FF samples collected during oocyte retrieval will undergo parallel analysis via ICP-MS and portable colorimetry. In here, we establish a brief theoretical protocol for reference.

1. Sampling Timing

a) hCG-triggered cycles: Oocyte retrieval was strictly performed at 36.0 ± 0.5 hours after recombinant hCG administration, with real-time monitoring using ultrasound-guided follicle tracking.

b) Natural cycles: Fluid collection commenced only when urinary LH levels reached ≥25 mIU/mL, ensuring precise peri-ovulatory phase synchronization.

2. Endometriosis-Specific Adjustments

a) Aspiration needles maintained ≥5 mm clearance from cyst walls to avoid contamination.

b) Immediate exclusion of samples with: Brownish discoloration (indicative of chronic hemorrhage).

3. Standardized Centrifugation Protocol

a) Primary processing: 1,000 × g for 10 min at 4°C to separate granulosa cells (pellet) from supernatant.

b) Hemolysis control: Automated quantification using Chemical analyzer. Free hemoglobin acceptance thresholds: Control samples <50 mg/L; EM-associated samples <100 mg/L (adjusted for chronic intrafollicular bleeding).

4. Iron Quantification

a) Pre-treatment: Secondary centrifugation at 16,000 × g for 5 min to remove microparticles.

b) Hemoglobin correction: Final iron values normalized via free hemoglobin values.

Iron levels will be correlated with blastocyst formation through multivariate regression, and comparative analysis will contrast high-iron (>75th percentile) and low-iron (<25th percentile) groups using generalized linear mixed models. Machine learning algorithms will establish iron threshold predictability for blastocyst failure. Portable colorimetry's accuracy and sensitivity will be validated against ICP-MS, showing promise as a rapid, cost-effective clinical tool despite lower sensitivity. To facilitate clinical iron testing, and in the absence of superior market alternatives, a portable and PCOT device can be designed and developed based on practical needs.

CONCLUSIONS

Emerging evidence highlights the critical role of iron overload in the FF of EMs patients and its detrimental impact on oocyte quality. The utilization of FF iron concentration as a clinical evaluation index has certain feasibility but still faces many challenges. Future research should explore the regulatory mechanism of the iron content in FF of EMs patients, establish unified detection and evaluation standards, and conduct large-scale clinical studies to verify its predictive value. Combining other evaluation indicators and developing a multi-parameter evaluation model may provide new ideas for improving the accuracy of oocyte quality evaluation in infertile patients with EMs. In addition, exploring individualized treatment strategies based on the iron content in FF may open up new avenues for improving the assisted reproductive outcomes of infertile patients with EMs.

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AUTHOR CONTRIBUTIONS

C.Y. conceptualized and supervised this work. Z.N. and Y.L. drafted the manuscript and created figures. All authors read and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.