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Oxidative balance in follicular fluid: correlation with hormonal profile and ovarian response in IVF cycles

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The objective: **to evaluate the oxidation-reduction potential (ORP) of follicular fluid (FF) in ovaries as a biomarker of the intrafollicular microenvironment and its association with oocyte maturation and *in vitro* fertilization (IVF) outcomes.**
***Materials and methods*. A retrospective analysis of 212 IVF cycles during 2020–2023 was conducted. ORP in FF was measured using MiOXSYS. The concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, anti-Müllerian hormone and prolactin were measured in blood serum. Correlations between ORP and gonadotropin levels, stimulation parameters, and oocyte outcomes were assessed.**
***Results*. The mean ORP value in FF was 86.42 ± 23.23 mV, with wide interindividual variations. Weak but statistically significant positive correlations were observed between ORP and baseline FSH ($\rho = 0.166$, $p = 0.016$) and LH levels ($\rho = 0.148$, $p = 0.032$). Patients with basal FSH ≥ 8 IU/L exhibited higher ORP levels compared to women with FSH concentration < 8 IU/L (median 93.26 mV vs 81.70 mV, $p = 0.041$). However, ORP values did not differ significantly between groups stratified by total FSH dose, estradiol levels on chorionic gonadotropin day, or total number of retrieved oocytes. Notably, patients achieving ≥ 12 mature oocytes had a significantly higher oocyte maturation rate (86.19% vs 77.78%, $p < 0.001$), although their median ORP values were not significantly different (84.17 mV vs 89.68 mV, $p = 0.849$).**
***Conclusions*. ORP in FF reflects subtle endocrine influences but was not directly predictive of oocyte number or maturity. Stable ORP values together with optimal stimulation (≥ 12 mature oocytes) were associated with better oocyte maturation, suggesting ORP as a potential marker of follicular health in IVF.**
Keywords: *oxidation-reduction potential, follicular fluid, anti-Müllerian hormone, ovarian stimulation, in vitro fertilization.*

Окиснювальний баланс у фолікулярній рідині яєчників: кореляція з гормональним профілем та відповіддю яєчників у циклах екстракорпорального запліднення

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Мета дослідження: оцінка окиснювально-відновного потенціалу (ОВП) фолікулярної рідини (ФР) яєчників як біомаркера внутрішньофолікулярного мікросередовища та його зв'язок із дозріванням ооцитів і результатами екстракорпорального запліднення (ЕКЗ).
***Матеріали та методи*.** Проведено ретроспективний аналіз 212 циклів ЕКЗ за період 2020–2023 рр. ОВП у ФР визначали за допомогою системи MiOXSYS. У сироватці крові визначали концентрації фолікулостимулювального гормону (ФСГ), лютеїнізувального гормону (ЛГ), естрадіолу, антимюллерового гормону та пролактину. Проведено оцінку кореляції ОВП з рівнями гонадотропінів, параметрами стимуляції та результатами отримання ооцитів.
***Результати*.** Середнє значення ОВП у ФР становило 86,42 ± 23,23 мВ із широкими міжіндивідуальними варіаціями. Спостерігалися слабкі, проте статистично значущі позитивні кореляції між ОВП та вихідними рівнями ФСГ ($\rho = 0{,}166$, $p = 0{,}016$) та ЛГ ($\rho = 0{,}148$, $p = 0{,}032$). Пацієнтки з базальним рівнем ФСГ ≥ 8 МО/л демонстрували вищі рівні ОВП порівняно з жінками, в яких концентрація ФСГ була до 8 МО/л (медіана 93,26 мВ проти 81,70 мВ відповідно, $p = 0{,}041$). Однак значення ОВП суттєво не відрізнялися між групами, стратифікованими за загальною дозою ФСГ, рівнем естрадіолу в день введення хоріонічного гонадотропіну або загальною кількістю отриманих ооцитів. Примітно, що пацієнтки, які досягли ≥ 12 зрілих ооцитів, мали значно вищий рівень їхнього дозрівання (86,19% проти 77,78%, $p < 0{,}001$), хоча медіанні значення ОВП у них суттєво не відрізнялися (84,17 мВ проти 89,68 мВ, $p = 0{,}849$).
***Висновки*.** ОВП у ФР відображає незначні ендокринні впливи, але не є прямим прогностичним показником кількості або зрілості ооцитів. Стабільні значення ОВП разом з оптимальною стимуляцією (≥ 12 зрілих ооцитів) асоціювалися з кращим дозріванням ооцитів, що свідчить про потенційну роль ОВП як маркера функціонального стану фолікулів при ЕКЗ.
Ключові слова: *окиснювально-відновний потенціал, фолікулярна рідина, антимюллерів гормон, стимуляція яєчників, екстракорпоральне запліднення.*

Ovarian follicles are fluid-filled structures which enclose the oocyte, representing dynamic microenvironments essential for oocyte development and maturation. The follicular fluid (FF) plays a pivotal role in this process, providing not only nutrients and hormonal signals but also acting as a biochemical interface for paracrine and endocrine regulation. The granulosa cell lines (somatic cells) play an important role in responding to differences in gonadotropin stimulation and contribute to the differences observed in the FF [1, 2]. FF comprises a complex mixture of steroids, cytokines, growth factors, and redox-active molecules, reflecting the physiological state of the follicle and the surrounding ovarian milieu [3]. Abnormal factors in women could have altered the components of the FF and affected the quality of assisted reproductive treatment [4–6]. The coordinated

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interaction between the oocyte and its surrounding granulosa and theca cells, mediated by gonadotropins – primarily follicle-stimulating hormone (FSH) and luteinizing hormone (LH) – drives follicular growth, dominant follicle selection, and ovulation. These hormones and their downstream molecular mediators accumulate within FF and are considered predictive of oocyte quality and subsequent *in vitro* fertilization (IVF) outcomes [7]. In addition to FF-related factors that affected oocyte quality, abnormalities during folliculogenesis also altered the environment and morphology of uterine and cervical tissues, and impacted the reproductive process of infertile couples seeking to have a child [8].

Among various biochemical markers, oxidation-reduction balance within the FF, often quantified via oxidation-reduction potential (ORP), has attracted increasing attention. ORP reflects the net balance between oxidants, such as reactive oxygen species (ROS), and antioxidants, which collectively influence cellular homeostasis. Excess ROS production or impaired antioxidant defense can lead to oxidative stress, which impairs meiotic competence, disrupts mitochondrial function, and compromises oocyte maturation and fertilization potential [9, 10].

While oxidative stress has been widely investigated in male infertility, research on its role in the female reproductive tract, particularly within the ovarian follicular environment, remains limited. This gap may stem from the invasive nature of FF sampling and limited standardization of oxidative stress measurement in women. Some studies suggest that elevated FF-ROS is associated with poorer oocyte quality and IVF failure, but findings remain inconsistent across populations and protocols [11, 12].

To date, few studies have explored the correlation between follicular ORP and specific hormonal parameters or oocyte competence in a clinically meaningful manner. Moreover, most existing studies are limited by small sample sizes or heterogeneous populations. There is the potential clinical utility of ORP as a non-invasive surrogate marker for oocyte competence and ovarian health.

The objective: to evaluate the ORP of FF as a potential biomarker reflecting the intrafollicular microenvironment, to estimate the relationship between ORP levels and oocyte maturation, and investigate the interplay between baseline hormonal profiles, stimulation-induced endocrine changes, and oxidative imbalance in FF.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at the Center for Reproductive Endocrinology and Infertility, Hue University of Medicine and Pharmacy Hospital, Vietnam. The study included infertile couples undergoing IVF cycles from December 2020 to October 2023. A total of 201 patients met the inclusion criteria and participated in the study. Eligible participants were those receiving IVF with intracytoplasmic sperm injection (ICSI) and extended blastocyst culture. Inclusion criteria consisted of female partners under 45 years of age, with a serum anti-Müllerian hormone (AMH) level of at least 1 ng/mL. Participants were required to have no clinical or ultrasonographic signs of endometriosis. Male partners presented with either normal semen parameters or mild oligozoospermia. Only cycles using autologous gametes and including blastocyst culture were considered eligible.

Exclusion criteria: the women diagnosed with endometriosis, pelvic adhesions, or a history of pelvic inflammatory disease, cycles involving donor oocytes or donor sperm, as well as those using frozen-thawed sperm. Clinical data were collected for each patient, including female and male age, body mass index (BMI), causes of infertility, baseline hormone levels (FSH, LH, AMH, estradiol (E2)), and markers of ovarian reserve.

FF samples were analyzed from 212 IVF cycles in this retrospective study conducted. Controlled ovarian hyperstimulation was initiated on the 2nd day of the menstrual cycle using a gonadotropin-releasing hormone (GnRH) antagonist protocol. Recombinant FSH (follitropin alfa) was administered at doses ranging from 150 to 300 IU/day, determined by baseline antral follicle count (AFC). Follicular development was monitored via transvaginal ultrasound. When the dominant follicles reached a diameter of at least 18 mm, final oocyte maturation was triggered by a subcutaneous injection of 0.2 mg GnRH agonist (triptorelin).

Baseline reproductive hormone assessments, including serum FSH, E2, AMH, and prolactin, were performed on the 2nd day of the menstrual cycle. In addition, serum FSH and E2 levels were measured again on the day of human chorionic gonadotropin (hCG) administration. All hormone levels were analyzed using blood plasma samples that had been processed on the cobas 8000 system, employing the Elecsys® e602 immunoassay module (both from Roche Diagnostics GmbH, Mannheim, Germany). The Elecsys® kits used for these assays had been pre-calibrated and included integrated calibration curves, which made them highly suitable for precise hormone quantification in the context of IVF protocols.

Oocyte retrieval was scheduled 35 to 36 hours after the trigger, under transvaginal ultrasound guidance, using a single-lumen aspiration needle (Kitazato, Japan). The first 2 mL of FF collected from leading follicles, free of blood contamination or culture medium, were designated for analysis of oxidation-reduction status. Subsequent follicles were aspirated into tubes containing G-MOPS (Vitrolife, Sweden) supplemented with 7 IU heparin to prevent coagulation.

ORP of the FF was measured using the MiOXSYS® system (Aytu BioScience, Englewood, CO, USA). A 30 µL sample of cell-free FF was introduced into the system's sensor, and the resulting ORP value, expressed in millivolts (mV), reflected the balance between oxidant and antioxidant activity within the follicular environment.

Retrieved cumulus-oocyte complexes were identified under a stereomicroscope and rinsed in G-MOPS PLUS medium. Oocytes were preincubated for 2 hours in G-IVF PLUS medium (Vitrolife, Sweden) at 37 °C in a tri-gas incubator (Galaxy 170S, Eppendorf, UK). Cumulus cells were removed using HYASE 80 IU enzyme (Vitrolife, Sweden) and gentle mechanical aspiration through a series of glass pipettes with decreasing diameters (1.5 mm to 140 µm). Oocyte maturation was determined by the presence of the first polar body, and only mature oocytes at the metaphase II (MII) stage were selected for ICSI.

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The oocyte maturation rate, defined as the number of mature oocytes divided by the total number of retrieved oocytes, was calculated for each cycle. Statistical analysis was conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables were reported as mean (M) ± standard deviation (SD) and compared using independent-sample t-tests. Non-normally distributed variables were expressed as median (Me) and interquartile range (IQR) and compared using the Mann–Whitney U test. Correlation analyses were performed using Pearson's test (r) for parametric data and Spearman's test (ρ) for nonparametric data. A p-value of less than 0.05 was considered statistically significant.

This study was approved by the Ethics Committee of Hue University of Medicine and Pharmacy (approval number H2023/016). Written informed consent was obtained from all participants prior to enrollment and sample collection.

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The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

RESULTS AND DISCUSSION

The clinical and cycle characteristics of the participants are summarized in Table 1. The mean age of female participants was 31.90 ± 3.54 years, with an average infertility duration of 4.94 ± 2.42 years. Most cases (60.8%) were classified as primary infertility. The baseline hormonal profile showed mean levels of FSH, LH, and E2 on 8.25 ± 3.47 IU/L, 6.31 ± 3.91 IU/L, and 24.43 ± 26.95 pg/mL, respectively. During ovarian stimulation, the average total FSH dose administered was 2,186.91 ± 403.40 IU over a mean of 8.08 ± 0.99 days. The mean number of oocytes retrieved was 14.60 ± 5.37, with 11.50 ± 4.66 mature oocytes. On average, 3.19 ± 2.69 high-quality blastocysts were formed per cycle. The mean ORP level in FF was 86.42 ± 23.23 mV.

Table 2 presents the correlations between patient characteristics and the oxidative balance in FF. A weak but statistically significant positive correlation was found between the 2nd day FSH levels and ORP (ρ = 0.166, p = 0.016), as well as between the 2nd day LH and ORP (ρ = 0.148, p = 0.032). No significant correlations were found between ORP and other variables such as age, AMH, BMI, total FSH dose, or E2 levels on hCG day. These findings suggest that basal gonadotropin levels may have a modest effect on the oxidative environment of the FF.

Further analysis in Table 3 revealed that patients with basal FSH levels ≥ 8.00 IU/L exhibited significantly higher ORP values in FF compared to those with FSH < 8.00 IU/L (93.26 mV vs 81.70 mV, p = 0.041). However, no statistically significant differences in ORP were observed when patients were stratified by age, LH, or E2 levels. Regarding oocyte maturation, although a higher basal FSH tended to be associated with improved maturation rates (83.33% vs 78.57%), this difference did not reach statistical significance.

Table 1

Baseline characteristics and clinical parameters of study participants (N = 212)

Characteristics	M ± SD	Range
Female age, years	31.90 ± 3.54	22.00–38.00
Infertility duration, years	4.94 ± 2.42	1.00–15.00
Basal FSH, IU/L	8.25 ± 3.47	0.83–23.00
Basal LH, IU/L	6.31 ± 3.91	0.00–27.55
Basal E2, pg/mL	24.43 ± 26.95	2.00–218.40
Total FSH dose, IU	2,186.91 ± 403.40	750.00–3,525.00
Stimulation duration, days	8.80 ± 0.99	7.00–13.00
E2 on hCG day, pg/mL	3,006.77 ± 1,623.89	274.40–10,017.00
FF oxidation, mV	86.42 ± 23.23	27.00–182.95
Retrieved oocytes, n	14.60 ± 5.37	5.00–33.00
Mature oocytes, n	11.50 ± 4.66	5.00–29.00
Normally fertilized oocytes, n	8.22 ± 3.98	1.00–23.00
Blastocysts formed, n	4.94 ± 3.36	0.00–19.00
Good-quality blastocysts, n	3.19 ± 2.69	0.00–16.00
Male age, years	34.98 ± 4.51	26.00–51.00
Normal semen analysis, n (%)	18 (8.5)	
Primary infertility, n (%)	129 (60.8)	
Secondary infertility, n (%)	83 (39.2)	

Notes: M – mean; SD – standard deviation; FSH – follicle-stimulating hormone; LH – luteinizing hormone; E2 – estradiol; hCG – human chorionic gonadotropin; FF – follicular fluid.

Table 2

Correlation between patient characteristics, ovarian stimulation, and hormonal profile in FF with ORP

Characteristics	Correlation coefficient (ρ)	p-value
Female age, years	0.018	0.799
AFC, n	–0.008	0.904
Basal FSH, IU/L	0.166	0.016
Basal LH, IU/L	0.148	0.032
Basal E2, pg/mL	–0.095	0.167
Prolactin, ng/mL	–0.093	0.177
AMH, ng/mL	0.026	0.704
Initial dose of FSH, IU	0.165	0.016
Total dose of FSH, IU	–0.015	0.826
E2 on hCG day, pg/mL	0.040	0.562
Number of dominant follicles, n	–0.118	0.086
Number of retrieved oocytes, n	–0.077	0.267
Number of mature oocytes, n	–0.044	0.521
Mature oocyte rate, %	0.056	0.417

Notes: FF – follicular fluid; ORP – oxidation-reduction potential; AFC – antral follicle count; FSH – follicle-stimulating hormone; LH – luteinizing hormone; E2 – estradiol; AMH – anti-Müllerian hormone; hCG – human chorionic gonadotropin.

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Table 3

Influence of female endocrine characteristics on ORP in FF

Characteristics	Subgroup	n	ORP (mV), Me (IQR)	p-value (ORP)	Mature oocyte rate (%), Me (IQR)	p-value (MII)
Female age, years	< 35	159	89.05 (32.05)	0.576	80.00 (22.92)	0.151
	≥ 35	53	85.74 (24.51)		84.62 (24.51)	
Basal FSH, IU/L	< 8.00	124	81.70 (24.38)	0.041	78.57 (27.15)	0.082
	≥ 8.00	88	93.26 (36.97)		83.33 (17.85)	
Basal LH, IU/L	< 5.00	78	83.03 (29.27)	0.051	79.29 (25.64)	0.636
	≥ 5.00	134	87.97 (30.79)		81.82 (21.72)	
Basal E2, pg/mL	< 20	113	91.52 (33.56)	0.210	80.77 (25.00)	0.347
	≥ 20	99	82.98 (24.78)		82.35 (20.64)	

Notes: ORP – oxidation-reduction potential; FF – follicular fluid; FSH – follicle-stimulating hormone; LH – luteinizing hormone; E2 – estradiol; MII – metaphase II; Me – median; IQR – interquartile range; variables were expressed as Me and IQR and compared using the Mann–Whitney U test.

Table 4

Impact of ovarian stimulation parameters on ORP in FF and oocyte maturation rate

Parameters	Subgroup	n	ORP (mV), Me (IQR)	p-value (ORP)	Mature oocyte rate (%), Me (IQR)	p-value (MII)
Total FSH dose, IU	< 2200	118	87.15 (31.21)	0.493	80.00 (25.64)	0.403
	≥ 2200	83	87.14 (28.90)		83.33 (20.15)	
Stimulation duration, days	< 9	85	89.62 (32.18)	0.276	81.82 (26.47)	0.750
	≥ 9	127	86.64 (28.31)		81.82 (23.08)	
E2 on hCG day, pg/mL	< 3000	141	87.59 (28.21)	0.787	81.82 (23.56)	0.443
	≥ 3000	71	86.45 (34.90)		80.77 (19.41)	
Number of oocytes retrieved, n	< 15	116	89.68 (28.24)	0.521	83.98 (19.58)	0.045
	≥ 15	96	85.60 (30.88)		79.29 (24.81)	
Number of mature oocytes, n	< 12	120	89.68 (31.37)	0.849	77.78 (26.08)	< 0.001
	≥ 12	92	84.17 (30.25)		86.19 (18.01)	

Notes: ORP – oxidation-reduction potential; FF – follicular fluid; FSH – follicle-stimulating hormone; E2 – estradiol; hCG – human chorionic gonadotropin; MII – metaphase II; Me – median; IQR – interquartile range; variables were expressed as Me and IQR and compared using the Mann–Whitney U test.

Table 4 evaluates the effect of ovarian stimulation parameters on oxidative balance and oocyte maturation. No statistically significant differences in ORP values were found between subgroups stratified by total FSH dose, stimulation duration, E2 level on hCG day, or number of retrieved oocytes. However, differences in oocyte maturation rates were observed. Specifically, patients with ≥ 15 retrieved oocytes had a significantly lower median maturation rate compared to those with fewer than 15 oocytes (79.29% vs 83.98%, p = 0.045), while patients with ≥ 12 mature oocytes had a significantly higher maturation rate than those with fewer mature oocytes (86.19% vs 77.78%, p < 0.001).

Overall, these findings suggest that while the oxidative status of FF, as measured by ORP, may be modestly influenced by basal gonadotropin levels, its correlation with ovarian stimulation intensity and maturation outcomes is less pronounced. Nonetheless, certain stimulation-related factors, such as the number of retrieved and mature oocytes, do appear to impact oocyte maturity, even in the absence of strong changes in ORP levels.

The MiOXSYS system is a device used to measure ORP, an indicator reflecting the electron transfer process from reducing agents (antioxidants) to oxidizing agents. ORP is measured in millivolts and provides an overall assessment of oxidative stress. Unlike individual biochemical markers that quantify specific oxidants or reductants, ORP offers a composite index that reflects the balance between both components. It is thus a clinically meaningful parameter in cases of unexplained infertility associated with oxidative stress [13].

In this study, we explored the relationship between the ORP value in FF and the endocrine characteristics of women undergoing IVF treatment. A total of 212 IVF cycles were included. FF was aspirated directly from follicles without blood contamination and was immediately analyzed using the MiOXSYS system. This approach avoided pre-analytical sample handling and enabled rapid, direct assessment of oxidative status. The observed ORP values ranged from 27.00 to 182.95 mV, with a mean of 86.42 mV, which was slightly lower than the average of 107.74 mV reported by N. Sallam et al. in 2021 [14]. This suggests that individual patient characteristics and ovarian stimulation protocols may influence the redox status of FF.

Among baseline hormones, FSH levels demonstrated a weak but statistically significant positive correlation

with ORP values (ρ = 0.166, p = 0.016). In women with FSH ≥ 8 IU/L, median ORP values were significantly higher (93.26 mV) compared to those with lower FSH (81.70 mV, p = 0.041). This finding implies that elevated endogenous FSH levels may contribute to altered oxidative balance in the follicular environment [15]. While FSH is known to stimulate mitochondrial respiration and ROS production in granulosa cells, these ROS are primarily localized to mitochondria and may not elicit widespread oxidative stress [16]. This aligns with N. Lin et al., who demonstrated that FSH-induced ROS increases do not result in detrimental oxidative stress within the cells [16]. Furthermore, in our study, elevated FSH did not reduce the oocyte maturation rate, which remained within the acceptable range for Key Performance Indicator benchmarks [17, 18].

Ovarian hyperstimulation syndrome (OHSS), driven by vascular endothelial growth factor overexpression, has been linked to increased vascular permeability and fluid accumulation, potentially affecting the redox microenvironment of FF [19, 20]. Although previous studies have associated OHSS with oxidative stress and impaired oocyte quality [21, 22], our findings did not show significant ORP elevation in women with E2 levels ≥ 3000 pg/mL on the day of hCG administration. There was not a significant reduction in oocyte maturation rate. These observations may indicate the preservation of antioxidant defense mechanisms and absence of microvascular injury during controlled ovarian stimulation [23–25].

Regarding follicular response, although ORP values did not significantly differ between groups with varying oocyte yields, the oocyte maturation rate was lower in women with ≥ 15 oocytes retrieved (79.29% vs 83.98%, p = 0.045). Conversely, women with ≥ 12 mature oocytes exhibited a significantly higher maturation rate (86.19% vs 77.78%, p < 0.001), with no ORP elevation. This supports the role of redox homeostasis in promoting optimal oocyte development and suggests that maintaining stable ORP values may enhance the quality of ovarian response even when oocyte numbers are high [26, 27].

CONCLUSIONS

Our study demonstrated that FF ORP values exhibit a weak correlation with basal FSH and LH levels. No significant association was observed between ORP and the number of oocytes retrieved or matured. However, higher oocyte maturation rates were found in cases with ≥ 12 mature oocytes, regardless of ORP levels. These findings suggest that maintaining stable redox balance in FF supports oocyte maturation and reflects effective ovarian stimulation outcomes.

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

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