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PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330
Int J Hum Genet, 26(1): 59-66 (2026)
DOI: 10.31901/24566330.2026/26.01.932

Performance of CXC Chemokine Ligand 12 and Micro Ribonucleic Acid-31 in Assessing Endometrial Receptivity of Patients with Polycystic Ovary Syndrome-Induced Infertility

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KEYWORDS Clinical Studies. Endometrium. Genes. Infertility. MicroRNAs

ABSTRACT This study aimed to evaluate the potential of CXC chemokine ligand 12 (CXCL12) and microRNA-31 (miR-31) as biomarkers for assessing endometrial receptivity in patients with polycystic ovary syndrome (PCOS)-induced infertility. A total of 80 patients with PCOS-related infertility and 80 healthy controls were included. Serum levels of miR-31 and CXCL12 were measured using enzyme-linked immunosorbent assay and qPCR. The study found significantly lower serum levels of both biomarkers in the PCOS group ($P<0.05$). Logistic regression analysis revealed that decreased miR-31 and CXCL12 levels were risk factors for impaired endometrial receptivity [*odds ratio (OR)*>1, $P<0.05$]. The combination of these biomarkers showed a high diagnostic performance area under curve [(AUC)=0.920]. These results suggest that miR-31 and CXCL12 are promising biomarkers for evaluating endometrial receptivity in PCOS-induced infertility.

INTRODUCTION

Polycystic ovary syndrome (PCOS), a common endocrine and metabolic disorder in clinical practice, frequently occurs in females of reproductive age. It affects approximately 8 to 15 percent of women worldwide, and the prevalence varies by region and diagnostic criteria (Peng et al. 2025; Neven et al. 2024). The syndrome is characterised by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, and is often associated with insulin resistance, obesity, and an increased risk of type 2 diabetes and cardiovascular disease (Stañczak et al. 2024; Góral et al. 2024). The multifactorial etiology of PCOS involves genetic predisposition, lifestyle, and environmental influences, making it one of the leading causes of anovulatory infertility (Qin et al. 2024).

In the case of PCOS, irregular menstrual periods and persistent anovulation may occur, resulting in infertility and adversely affecting the physical and mental health of patients (Collée et al. 2021). For women with PCOS-related infertility, *in vitro* fertilisation-embryo transfer (IVF-ET) technology has become an effective strategy to achieve pregnancy with the development of assisted reproductive technologies. IVF-ET technology can accurately determine the optimal time for embryo transfer by assessing endometrial receptivity, thereby improving implantation and pregnancy success rates (Pathare et al. 2023). However, in PCOS-induced infertility, the implantation window of endometrial receptivity is not always fixed, which may contribute to lower implantation efficiency and poor pregnancy outcomes.

Therefore, exploring genes or proteins that can rapidly and accurately predict and evaluate endometrial receptivity in patients with PCOS-induced infertility remains a pressing research priority. Micro ribonucleic acid-31 (miR-31), a non-coding small RNA involved in post-transcriptional gene regulation, varies dynamically between the proliferative and secretory phases of the endometrium (Kresowik et al. 2014; Azhari et al. 2022). Other studies have manifested that CXC chemokine ligand 12 (CXCL12) and related chemokines serve as key mediators in reproductive processes such as follicular development, atresia and ovulation (Jin et al. 2021; Ao et al. 2020). Taken together, these findings suggest that both miR-31 and CXCL12 are potentially linked to reproductive function and may serve as biomarkers of endometrial receptivity. However, the associations of miR-31 and CXCL12 with endometrial receptivity in patients with PCOS-related infertility remain largely unexplored.

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Objectives

Despite advances in assisted reproductive technologies, implantation failure remains common in women with PCOS-related infertility, largely due to impaired endometrial receptivity. However, the molecular mechanisms underlying this dysfunction are still unclear. Given that miR-31 and CXCL12 play critical roles in regulating endometrial and ovarian function, their potential involvement in PCOS-induced infertility warrants investigation.

Therefore, this study aimed to determine the expression levels of miR-31 and CXCL12 in the endometrium of patients with PCOS-induced infertility and to evaluate their associations with endometrial receptivity, providing molecular evidence to support improved embryo implantation outcomes in assisted reproduction.

MATERIAL AND METHODS

Subjects

A total of 80 healthy people (control group) and 80 patients with PCOS-induced infertility (study group) who visited the researchers' hospital between June 2019 and July 2022 were recruited in this study. All procedures involving human participants were conducted in accordance with the Declaration of Helsinki and were approved by the Institutional Ethics Committee of The Second People's Hospital of Wuhu (Approval No.: IEC-20190102-056). Written informed consent was obtained from all participants prior to enrollment. In the study group, participants were aged 22-45 years (30.06±4.53 years), with a body mass index (BMI) of 22-26 kg/m^2 (24.24±0.35 kg/m^2). The systolic and diastolic blood pressures at admission ranged from 128-155 mmHg and 82-103 mmHg, respectively (135.20±5.16 mmHg and 96.60±3.05 mmHg). In the control group, participants were aged 20-46 years (30.08±4.52 years) with a BMI of 22-26 kg/m^2 (24.26±0.38 kg/m^2). Their systolic and diastolic blood pressures ranged from 125-156 mmHg and 80-105 mmHg, respectively (135.50±5.10 mmHg and 96.65±3.02 mmHg). The basic data were comparable between the two groups, with no significant differences observed (P>0.05).

Inclusion and Exclusion Criteria for the Study Group

The inclusion criteria included:

1. Women diagnosed with PCOS-induced infertility
2. Participants who were informed about the study, agreed to participate and provided written informed consent
3. Women with at least one unobstructed fallopian tube
4. Participants with normal mental state and communication abilities.

The exclusion criteria included:

1. Women with congenital uterine malformation or other uterine conditions affecting embryo implantation, such as adenomyosis and endometrial polyps
2. Participants with uncontrolled infectious or communicable diseases
3. Women who underwent hormone therapy recently within the past 3 months
4. Patients with autoimmune or immune system disorder
5. Women with a history of pelvic or ovarian surgery
6. Participants diagnosed with malignant tumours
7. Women with contraindications to pregnancy or those unsuitable for childbearing due to hereditary conditions
8. Participants exposed to teratogenic environments or substances during pregnancy.

Blood Sample Collection

Venous blood (5 mL) was drawn from each subject in a fasting and resting state. Samples from controls were collected during routine physical examination and from the study group before IVF-ET to ensure comparable physiological conditions. Samples were allowed to clot for 30 minutes at room temperature and centrifuged (2500 r/minutes, 10 minutes, 10 cm radius). Serum aliquots were stored at -80 °C. All samples were processed within 2 hours of collection to minimise RNA degradation.

Measurement of Serum miR-31 and CXCL12 Levels

Serum CXCL12 levels were determined using enzyme-linked immunosorbent assay kits

(Sino Biological Inc., China) following manufacturer instructions. For miR-31 detection, total RNA was extracted from 300 µL serum using Trizol reagent (Thermo Fisher Scientific). RNA concentration and purity were assessed by A260/A280 ratio using a UV spectrophotometer, ensuring values between 1.8-2.0. Reverse transcription was performed using a (complementary DNA) cDNA synthesis kit (Yeasen Biotechnology), and quantitative polymerase chain reaction (qPCR) amplification was conducted on a BIO-RAD CFX Connect system with SYBR Green detection. Reaction conditions were 95°C for 10 minutes, followed by 50 cycles of 95°C for 15 seconds and 60°C for 60 seconds. Primer sequences were: F: 5'-UUGUGU-CAGUUUUVU-CAAAC-3', and R: 5'-UUGAUAACU-GACA-CAA-3', and U6: F: 5'-CTCGCTTCGCAGCA-CA-3, and R: 5'-AACGCTTCACGAATTGCGT-3'. Relative expression was calculated by the $2^{-\Delta\Delta Ct}$ method, with each sample analysed in triplicate to ensure reproducibility.

Determination of Endometrial Receptivity

Endometrial biopsy was performed in the mid-luteal phase to observe pinopode morphology on epithelial cells using scanning electron microscopy, which is a standard marker of endometrial receptivity. Based on morphological and molecular findings, patients were subdivided into good and poor receptivity groups.

Measurement of Serum Laboratory Indicators

Serum levels of luteinising hormone (LH), estradiol (E2), follicle-stimulating hormone (FSH), progesterone (P) and testosterone (T) were measured using fluorescence immunoassay analyzers. Besides, a blood glucose analyser (Biosen C-Line, EKF) was used to measure the levels of glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG). Additionally, detection of the levels of triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) was performed using an automatic biochemical analyser (Beckman AU5811). Internal quality controls and calibrations were run daily to ensure analytical accuracy.

General Data Acquisition

Clinical data, including age, BMI, PCOS duration, endometrial volume, uterine artery pulsatility index (PI), and uterine artery resistance index (RI) were collected using a three-dimensional power Doppler ultrasound (3D-PDU). All measurements were performed by two independent sonographers blinded to group allocation to reduce observer bias.

Statistical Analysis

Statistical analysis was performed using SPSS 23.0. Data were expressed as mean ± standard deviation (SD). Group comparisons were performed using independent-sample t-tests for continuous variables and χ^2 tests for categorical variables. Multivariate logistic regression was applied to identify independent predictors of endometrial receptivity in PCOS patients. Receiver operating characteristic (ROC) curves were used to assess the diagnostic value of serum miR-31, CXCL12 and their combination. $P<0.05$ indicated statistical significance. All statistical methods were reviewed by an independent biostatistician.

RESULTS

Serum miR-31 and CXCL12 Levels in Study and Control Groups

As shown in Table 1, the serum levels of both miR-31 and CXCL12 were significantly decreased in patients with PCOS-induced infertility than in healthy controls ($P<0.001$ for both). The mean CXCL12 concentration in the study group was 98.80 ± 10.15 pg/mL, markedly lower than that of the control group (156.96 ± 15.10 pg/mL). Similarly, the mean serum miR-31 level

Table 1: Serum levels of miR-31 and CXCL12 ($\sum x \pm s$)

Group	*n*	*CXCL12 (pg/mL)*	*miR-31*
Control	80	156.96±15.10	0.80±0.23
Study	80	98.80±10.15	0.55±0.15
t		8.166	9.434
P		0.000	0.000

in the study group was 0.55 ± 0.15, compared with 0.80 ± 0.23 in the control group.

The t-test results (t = 8.166 for CXCL12; t = 9.434 for miR-31) further confirmed that these differences were statistically significant. These findings indicate that the expressions of miR-31 and CXCL12 are downregulated in patients with PCOS-induced infertility.

Endometrial Receptivity

According to endometrial biopsy results, 50 cases (62.50%) showed good endometrial receptivity while 30 cases (37.50%) had poor endometrial receptivity in the study group.

Relevant Indicators in Good and Poor Endometrial Receptivity Groups

As presented in Table 2, there were no significant differences between the two groups in age, BMI, PCOS course, endometrial volume, or serum levels of sex hormones (LH, E2, FSH, P, T) and metabolic indicators (FPG, HbA1c, LDL-C, HDL-C, TG, and TC) (all P > 0.05). However, the levels of serum miR-31 and CXCL12 were significantly lower in the poor endometrial receptivity group compared with the good receptivity group (miR-31: 0.52 ± 0.14 vs. 0.57 ± 0.09, t = 2.791, P = 0.004; CXCL12: 95.36 ± 9.26 pg/mL vs. 100.86 ± 10.98 pg/mL, t = 2.296, P = 0.024). These findings suggest that reduced serum miR-31 and CXCL12 levels are associated with impaired endometrial receptivity in patients with PCOS-induced infertility, indicating their potential roles as molecular predictors of endometrial function.

Risk Factors for Endometrial Receptivity in Patients with PCOS-induced Infertility

A binary logistic regression analysis was performed to identify factors influencing endometrial receptivity in patients with PCOS-induced infertility, with endometrial receptivity as the dependent variable (1=poor endometrial receptivity, 0=good endometrial receptivity) and the variables showing statistical significance. As shown in Table 3 and Figure 1, both serum miR-31 and CXCL12 were independently associated with endometrial receptivity. Decreased serum miR-31 levels were significantly correlated with a higher risk of poor endometrial receptivity [β = 0.218, P = 0.005; *odds ratio (OR)*: 1.331, 95% confidence interval (CI): 1.065-1.429]. Similarly, lower CXCL12 levels were also an independent risk factor (β = 0.027, *P* = 0.001; *OR*:

Table 2: Relevant indicators in good and poor endometrial receptivity groups (Σx ± s)

Indicator	*Good endometrial receptivity group (n=50)*	*Poor endometrial receptivity group (n=30)*	*Statistic value*	*P*
Age (year)	30 .63±3.85	30 .71±4.03	0.088	0.930
BMI (kg/m^2)	4 .63±0.39	4 .61±0.52	0.196	0.846
PCOS course (year)	3 .92±0.28	3 .86±0.27	0.940	0.350
Endometrial volume (mL)	79 .63±3.85	80 .02±4.53	0.410	0.683
Uterine artery PI (%)	2 .77±0.15	2 .80±0.16	0.845	0.401
Uterine artery RI (%)	0 .81±0.05	0 .82±0.06	0.803	0.425
Serum LH (U/L)	8 .85±0.13	8 .84±0.10	0.362	0.719
Serum E2 (U/L)	166.61±25.18	165.35±25.11	0.222	0.825
Serum FSH (U/L)	7 .15±0.23	7 .17±0.25	0.364	0.717
Serum P (nmol /L)	1 .46±0.25	1 .43±0.24	0.527	0.599
Serum T (nmol /L)	1 .55±0.12	1 .58±0.15	0.985	0.328
Serum FPG (mmol /L)	8 .29±0.30	8 .30±0.28	0.148	0.883
Serum HbA1c (%)	9 .20±0.25	9 .22±0.24	0.352	0.726
Serum LDL-C (mmol/L)	4 .95±0.42	4 .90±0.43	0.511	0.611
Serum HDL-C (mmol/L)	1 .16±0.03	1 .17±0.04	1.271	0.207
Serum TC (mmol/L)	6 .73±0.21	6 .76±0.19	0.641	0.524
Serum TG (mmol/L)	3 .25±0.68	3 .32±0.70	0.441	0.661
Serum miR-31	0 .57±0.09	0 .52±0.05	2.791	0.007
Serum CXCL12 (pg/mL)	100.86±10.98	95 .36±9.26	2.296	0.024

Table 3: Results of logistic regression analysis on endometrial receptivity in patients with PCOS-induced infertility

Variable	β	*Standard error*	*Wald*	*P*	*Odds ratio*	*95% confidence interval*
miR-31	0.218	0.079	8.169	0.005	1.331	1.065-1.429
CXCL12	0.027	0.029	15.423	0.001	1.213	1.052-1.383

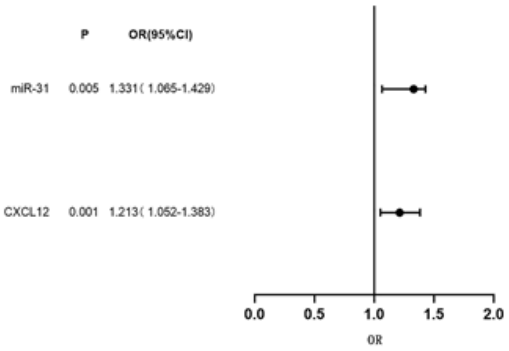

Fig. 1. Forest plot of clinical characteristics based on multivariate logistic regression analysis

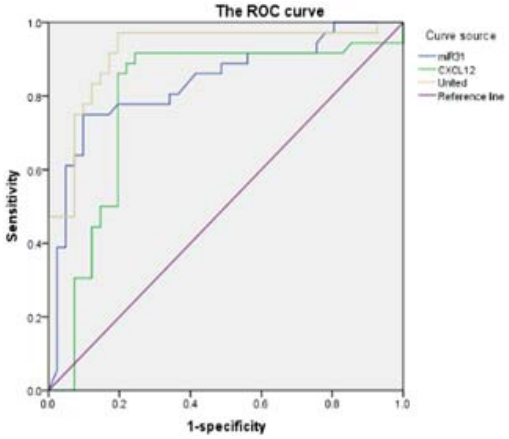

Fig. 2. ROC curves for predicting endometrial receptivity in patients with PCOS-induced infertility

1.213, 95% CI: 1.052-1.183). These results indicate that reduced expression of miR-31 and CXCL12 contributes to decreased endometrial receptivity in patients with PCOS-induced infertility.

Values of Serum miR-31 and CXCL12 for Predicting Endometrial Receptivity in Patients with PCOS-induced Infertility

ROC curve analysis was performed with endometrial receptivity as the state variable (0= good, 1= poor) and serum miR-31 and CXCL12 expression levels as test variables. As shown in Table 4 and Figure 2, both biomarkers demonstrated good diagnostic value for predicting endometrial receptivity in patients with PCOS-induced infertility. The area under the curve (AUC) for miR-31 was 0.837 (95% CI: 0.743-0.931, P < 0.001), with a sensitivity of 0.906 and a specificity of 0.705 at the optimal cutoff value of 0.550. The AUC for CXCL12 was 0.790 (95% CI: 0.676-0.904, P < 0.001), with a sensitivity of 0.892 and a specificity of 0.687 at the cutoff of 98.488 pg/mL. Notably, the combined detection of miR-31 and CXCL12 yielded the highest diagnostic performance, with an AUC of 0.920 (95% CI: 0.854-0.987), sensitivity of 0.924, and specificity of 0.870. These findings indicate that serum miR-31 and CXCL12 can effectively discriminate between good and poor endometrial receptivity, and their combined evaluation significantly enhances predictive accuracy.

Table 4: Values of serum miR-31 and CXCL12 for predicting endometrial receptivity of patients with PCOS-induced infertility

Item	*Optimum cutoff*	*Area under curve*	*Standard error*	*P*	*95% confidence interval*	*Sensitivity*	*Specificity*	*Youden index*
miR-31	0.550	0.837	0.048	<0.001	0.743-0.931	0.906	0.705	0.611
CXCL12	98.488pg/mL	0.790	0.058	<0.001	0.676-0.904	0.892	0.687	0.579
Combination	-	0.920	0.034	<0.001	0.854-0.987	0.924	0.870	0.794

DISCUSSION

PCOS is a common endocrine and metabolic disorder among women of reproductive age, and remains one of the leading causes of anovulatory infertility (Mirza et al. 2022). Although IVF-ET have improved conception rates, the success of implantation largely depends on adequate endometrial receptivity, which ensures synchronisation between the embryo and the endometrium (Palomba et al. 2021; Bahri Khomami et al. 2022). Recent studies highlight that impaired endometrial receptivity, rather than oocyte quality, is a major limiting factor in pregnancy outcomes for PCOS patients (Zeng et al. 2025; Singh et al. 2023). Therefore, identifying reliable, noninvasive biomarkers for evaluating endometrial receptivity has become a pressing clinical need.

Although endometrial biopsy remains the gold standard for assessing endometrial receptivity by observing pinopode development (Vitale et al. 2023), its invasiveness and procedural complexity hinder its routine use. Recent advances in molecular diagnostics and liquid biopsy techniques provide new opportunities for noninvasive evaluation of endometrial status (Tao et al. 2025; Kobayashi et al. 2025). Ultrasound-based assessments of endometrial volume and blood flow have also been employed, but their accuracy is often affected by operator experience and technical variability (Liu et al. 2019). Hence, circulating molecular markers, particularly miRNAs and chemokines, may serve as more objective tools for assessing receptivity.

MiR-31, an endogenous small non-coding RNA, has been shown to regulate multiple biological processes, including trophoblast invasion, proliferation and autophagy (Dong et al. 2020). Abnormal miR-31 expression has been linked to several reproductive disorders, including PCOS (Goharitaban et al. 2022; Jiang et al. 2022). Previous work demonstrated that miR-31 expression increases during the implantation window, facilitating a receptive endometrial phenotype (Bashti et al. 2018). Consistent with these observations, the study found that serum miR-31 levels were significantly lower in PCOS patients, particularly those with poor endometrial receptivity, compared with healthy controls.

Mechanistically, miR-31 directly targets Forkhead box P3 (Foxp3), a transcription factor essential for the differentiation of regulatory T (Treg) cells (Gao et al. 2022). Decreased miR-31 expression may downregulate Foxp3, leading to impaired Treg function and an imbalance between Th1 and Th2 cytokines, shifting the immune milieu toward a Th1-dominant inflammatory state. Such immune dysregulation is detrimental to embryo implantation and has been confirmed in recent immunoendocrine studies on PCOS (Martinez-Lopez et al. 2021; Lédée et al. 2025).

CXCL12, a CXC chemokine, is another molecule crucial for the establishment of endometrial receptivity. Animal experiment research showed that CXCL12 supplementation can improve the ovarian morphology and ovulation ability of rats (Koo et al. 2021). Besides, another study reported that immunomodulatory factors such as CXCL12 participate in the normal implantation of embryos into the endometrium (Freis et al. 2019). Moreover, it has been also confirmed that CXCL12/CXCR4 signalling facilitates endometrial repair and stromal remodelling (Wu et al. 2023; Zhang et al. 2023). The findings showed that serum CXCL12 levels were significantly lower in PCOS patients with poor receptivity.

Logistic regression analysis in the study confirmed that both miR-31 and CXCL12 were independent predictors of endometrial receptivity, with OR of 1.331 and 1.213, respectively. These findings highlight that dysregulation of immune-endocrine signaling, mediated by miR-31 and CXCL12, contributes to defective endometrial receptivity in PCOS. Furthermore, ROC curve analysis demonstrated that their combined detection achieved a superior diagnostic performance (AUC = 0.920), emphasising the clinical potential of these biomarkers for noninvasive evaluation.

Compared with earlier studies that focused primarily on morphological or hormonal indicators of receptivity (such as PI, RI, LH, E2), the study integrates molecular parameters that more directly reflect endometrial cellular function. A recent study similarly advocates the combined use of circulating miRNAs and chemokines for improving predictive accuracy in reproductive medicine (Ahmadi et al. 2024).

LIMITATIONS

Although the present study provides valuable insights into the relationship between miR-

31, CXCL12, and endometrial receptivity in PCOS-related infertility, the relatively small sample size may limit the generalisability of the findings. Future studies with larger, multicentre cohorts and functional validation experiments are warranted to confirm these associations and clarify their underlying mechanisms.

CONCLUSION

Collectively, these findings indicate that serum miR-31 and CXCL12 can serve as reliable biomarkers for assessing endometrial receptivity in PCOS-induced infertility.

RECOMMENDATIONS

Future research should validate these results in larger multicentre cohorts and explore targeted modulation of miR-31 and CXCL12 signalling as potential therapeutic approaches to enhance implantation success.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Yanmei Li contributed to the study design, methodology development, data analysis, and manuscript drafting, while also overseeing the research process. Huan Chen was responsible for data collection, experimental validation, and manuscript revision. Dan Peng performed data processing, visualisation, and project coordination. Li Li participated in methodological refinement, data verification, and critical review of the manuscript.

FUNDING

None.

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Paper received for publication in July, 2025
Paper accepted for publication in February, 2026