MedCrave
Step into the World of Research
Obstetrics & Gynecology International Journal

Research Article
Open Access
CrossMark

Insulin resistance in patients with endometrial polyps and its relationship with the expression of InR, IGF-1R, and IRS in the endometrium

Abstract

Objective: This study investigates the insulin resistance (IR) status in patients with endometrial polyps (EP) and analyzes its correlation with the endometrial expression of insulin receptor (InR), insulin-like growth factor-1 receptor (IGF-1R), and insulin receptor substrate-1 (IRS-1) and IRS-2, so as to preliminarily explore the potential molecular association between EP and IR.

Methods: A total of 170 patients who underwent hysteroscopy due to abnormal uterine bleeding or ultrasonic evidence of intrauterine abnormal echoes or space-occupying lesions were divided into Polyp group (endometrial polyps, n=84) and Control group (normal endometrium, n=86) based on endometrial pathology results. Clinical data and IR-related indicators [fasting plasma glucose (FPG), fasting insulin (FIN), and homeostasis model assessment-insulin resistance index (HOMA-IR)] were compared between the two groups. Immunohistochemistry was performed to compare the expression differences of InR, IGF-1R, IRS-1, and IRS-2 in endometrial tissues.

Results: Patients with endometrial polyps had significantly elevated FIN and HOMA-IR compared to the control group; the incidence of IR was slightly higher in the polyp group without statistical significance. There were no statistically significant differences in the expression of InR, IGF-1R, IRS-1, and IRS-2 among endometrial polyps, peri-polyp endometrium, and normal endometrium. No significant inter-group differences of the four target proteins were observed between proliferative and secretory phases in either group. Within both the polyp and control cohorts, endometrial expression of the four molecules showed no obvious difference between insulin-resistant (IR subgroup) and non-insulin-resistant (NIR subgroup) patients.

Conclusion: Patients with endometrial polyps tend to exhibit insulin-resistant metabolic profiles. However, the expression levels of InR, IGF-1R, IRS-1 and IRS-2 in polyp tissue show no significant difference compared with adjacent peri-polyp endometrium and normal endometrium. Combined with previous research focusing on downstream insulin signaling cascades, we hypothesize that the pathogenesis of endometrial polyps may be associated with abnormalities in post-insulin-receptor signaling pathways; further mechanistic experiments detecting downstream signaling proteins are required to verify this hypothesis.

Keywords: endometrial polyps, insulin resistance, insulin receptor, insulin-like growth factor-1 receptor, insulin receptor substrate

Volume 17 Issue 3 - 2026

Jian Yan-sen,[1] Hong Yu,[1] Xiao Gang,[2] Li Chun-ke,[1] Liang Hai-qi,[1] Chen Qing-ye[1]
[1]Department of Obstetrics and Gynecology, Kiangwu Hospital, Macau
[2]Department of Pathology, Kiangwu Hospital, Macau

Correspondence: Dr. Hong Yu, Department of Obstetrics and Gynecology, Kiangwu Hospital, Macau

Received: June 21, 2026 | **Published:** July 02, 2026

Introduction

Endometrial polyps (EP) are one of the most common benign diseases in women of reproductive age.[1] They may trigger abnormal uterine bleeding and infertility, accompanied by high recurrence risk and a certain malignant transformation tendency.[2] The exact etiology of EP remains unclear, which may be related to genetic factors, dysregulated estrogen and progesterone receptors, imbalance of cell proliferation and apoptosis, and immune inflammatory stimulation.[3,4] Accumulating clinical data indicate that patients with obesity, impaired glucose tolerance, diabetes, hyperlipidemia etc. Belong to the high-risk population of EP.[5,6] The core patho-physiological feature of these metabolic diseases is insulin resistance, suggesting that IR plays an important role in EP development. Previous studies have demonstrated that insulin/insulin-like growth factor-1 binds to corresponding receptors (InR/IGF-1R) to activate intracellular signaling, followed by phosphorylation of insulin receptor substrate (IRS) to form a tight signal complex. Phosphorylated IRS acts as a docking protein to activate multiple downstream proteins containing Src homology domain 2 (SH2), thus mediating corresponding biological effects.[7] On this basis, the occurrence of endometrial polyps may be linked to functional defects at key nodes of the insulin signaling pathway. Therefore, this study detects the expression of InR, IGF-1R, IRS-1 and IRS-2 in endometrial tissues of EP patients, to preliminarily explore the potential association between EP and IR.

Materials and methods

Subjects

Clinical data of patients who underwent hysteroscopy at the Department of Obstetrics and Gynecology, Kiangwu Hospital, Macau, from October 2024 to March 2026 were collected.

Inclusion criteria:

1) Patients with hysteroscopy indications and no contraindications

2) Endometrial pathology confirmed the diagnosis of normal endometrium or endometrial polyps.

Exclusion criteria:

1) Previously diagnosed diabetes or impaired glucose tolerance, hyperlipidemia, or polycystic ovary syndrome
2) Hormonal medication within the past 3 months
3) Hysteroscopy contraindications
4) Recurrent endometrial polyps
5) Pathological results showing endometrial hyperplasia, endometrial cancer, submucous fibroids or endometritis.

All enrolled participants signed informed consent forms. This study was approved by the hospital ethics committee (approval number 2024-003).

Serum measurement and IR-related indicators

All patients fasted for more than 8 hours before surgery. Elbow venous blood was collected on admission morning. Serum fasting insulin (FIN) was measured via chemiluminescence immunoassay analyzer, and fasting plasma glucose (FPG) was measured using a Toshiba automated biochemical analyzer. Homeostatic model assessment-insulin resistance index (HOMA-IR) was calculated by the formula: HOMA-IR = FINxFPG/22.5 to evaluate IR status. In this study, IR diagnostic criteria were defined as FIN $\geq$ 10 mIU/L or HOMA-IR $\geq$ 2.14. This threshold was derived from our previously published research focusing on Chinese reproductive-age women with endometrial polyps.[6] It should be noted that HOMA-IR cut-off values vary greatly across ethnicities, age groups and clinical guidelines; the standard used herein is only applicable to the current study population and cannot be generalized to other cohorts without external validation.

Histopathological and Immunohistochemical Analysis

Specimens obtained during hysteroscopy were fixed, dehydrated, embedded in paraffin and sliced for HE staining and immunohistochemical staining.

HE staining and routine morphological observation: Sections were routinely dewaxed, stained with hematoxylin-eosin, gradient alcohol dehydrated, xylene cleared and sealed with neutral resin for microscopic morphological observation to determine endometrial histological phase.

Immunohistochemical staining methods: The EnVision two-step method with DAB staining was adopted, and all operations were completed on a fully automated immunoassay system (Ventana Benchmark Ultra). Rabbit anti-human polyclonal InR antibody, rabbit anti-human polyclonal IGF-1R antibody, rabbit anti-human polyclonal IRS-1 antibody, and rabbit anti-human monoclonal IRS-2 antibody were purchased from ABCAM company (USA). Positive expression of InR, IGF-1R, IRS-1, and IRS-2 were mainly localized in cytoplasm.

Result evaluation: Semi-quantitative scoring referred to the scoring system established by Yu et al., combining staining intensity and positive cell distribution range. Two blinded senior pathologists independently scored all sections without access to patients' clinical and metabolic data. Discrepant scoring results were re-observed under double-headed microscope to reach consistent conclusions. Inter-rater reliability was calculated as Cohen's Kappa coefficient (κ=0.82), showing excellent consistency between evaluators. Staining intensity scoring: negative staining (0), weak staining stronger than negative control (1), moderate clear staining (2), strong staining (3). Distribution range scoring: positive cells <10% (0), 10%–30% (1), 31%–60% (2), >60% (3). Total score summation standard: 0–1 points (-), 2 points (+), 3–4 points (++), 5–6 points (+++).

Exclusion criteria for immunohistochemical staining: A total of 170 patients were enrolled for clinical serum index analysis, but partial paraffin specimens were excluded from IHC detection due to insufficient tissue volume, severe tissue autolysis, massive loss of glandular epithelium after sectioning or failed antigen retrieval. Finally, valid IHC samples were obtained from 52 polyp lesions with matched peri-polyp endometrium and 33 normal endometrial specimens from the control group, forming the final IHC analysis cohort. All excluded patients were retained in the clinical serum indicator comparison without removal.

Statistical processing

SPSS 22.0 statistical software was used for data statistical analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$). Normally distributed two-group data were compared by independent samples t-test; one-way analysis of variance (ANOVA) with Tukey's post-hoc test was applied for three-group comparison (polyp tissue / peri-polyp endometrium / normal endometrium). Enumeration data were presented as percentages (%) and analyzed using χ^2 tests. Bonferroni correction was used for multiple pairwise comparisons to reduce type I error. Effect sizes (Cohen's d for t-test, η^2 for ANOVA) and 95% confidence intervals were reported for all primary outcomes. $P < 0.05$ was considered statistically significant.

Results

Comparison of clinical data between two groups

All subjects were divided into Polyp group (n=84) and Control group (n=86) according to pathological diagnosis. As shown in Table 1, FIN and HOMA-IR levels in EP patients were significantly higher than those in the control group; the IR prevalence was slightly higher in the polyp group without statistical difference. There were no significant intergroup differences in age, gravidity, parity, menstrual cycle, hypertension proportion, BMI, FPG and endometrial phase distribution.

Expression of four antibodies and differences between different groups

InR, IGF-1R, IRS-1, and IRS-2 were expressed in both glandular epithelial cells and stromal cells, mainly located in cytoplasm and cell membrane, with weaker interstitial expression.

Comparison of four proteins expression among poly tissue, peri-poly endometrium and normal endometrium: No statistically significant differences were observed in InR, IGF-1R, IRS-1 and IRS-2 expression among endometrial polyps, peri-polyp endometrium and normal endometrium (P>0.05), as shown in Table 2.

Comparison of protein expression in proliferative and secretory phases: The expression levels of four proteins showed no significant difference between proliferative and secretory phases in both polyp group and control group (P>0.05). See Table 3.

Comparison of protein expression between IR and NIR subgroups: Within both polyp and control cohorts, there were no significant differences in endometrial InR, IGF-1R, IRS-1 and IRS-2 expression between IR patients and non-IR patients (P>0.05). See Table 4.

Table 1 Comparison of clinical data between two groups

Item	Category	Polyps group (n=84)	Control group (n=86)	t/χ^2	P
Age (years)		39.04±8.11	37.95±7.23	0.92	0.36
Gravidity	≤1 time	38	41	0.101	0.75
	≥2 times	46	45		
Parity	≤1 time	59	62	0.071	0.79
	≥2 times	25	24		
Menstrual cycle	Regular	58	68	2.22	0.136
	Irregular/Amenorrhea	26	18		
High blood pressure (mmHg)	Yes	4	4	0.108	0.74
	No	80	82		
BMI (kg/m^2)		23.03±3.02	21.86±5.41	1.786	0.076
FPG (mmol/L)		5.41±0.84	5.30±0.69	0.936	0.351
FIN (mIU/L)		8.59±2.08	7.37±1.96	12.43	<0.001
HOMA-IR		2.01±1.44	0.96±0.75	6.33	<0.001
IR prevalence (%)		23.8(20/84)	15.1(13/86)	2.05	0.15
Endometrial staging	Proliferative phase	45	55	1.89	0.17
	Secretory phase	39	31		

Table 2 Comparison of the expression of four antibodies in the Polyp group and Control group

	Polyps group		Control group (n=33)
	Polyps (n=52)	Peri-polyp endometrium (n=52)	
InR	2.27±0.56	2.40±0.57	2.15±0.57
IGF-1R	2.25±0.52	2.29±0.61	2.03±0.53
IRS-1	2.25±0.52	2.40±0.53	2.06±0.61
IRS-2	2.23±0.61	2.35±0.59	2.12±0.65

Table 3 Protein expression across endometrial phases in two groups

	Polyps group		Control group	
	Proliferative phase (n=28)	Secretory phase (n=24)	Proliferative phase (n=21)	Secretory phase (n=12)
InR	2.18±0.55	2.38±0.58	2.14±0.57	2.17±0.58
IGF-1R	2.29±0.54	2.21±0.51	2.05±0.50	2.00±0.60
IRS-1	2.14±0.45	2.38±0.58	2.10±0.54	2.00±0.74
IRS-2	2.25±0.52	2.21±0.721	2.10±0.70	2.17±0.58

Table 4 Protein expression in IR and NIR subgroups of two cohorts

	Polyp group		Control group	
	IR group (n=20)	**NIR group (n=32)**	**IR group (n=13)**	**NIR group (n=20)**
InR	2.25±0.64	2.27±0.52	2.23±0.44	2.10±0.64
IGF-1R	2.30±0.57	2.24±0.50	1.95±0.49	2.10±0.55
IRS-1	2.30±0.57	2.24±0.50	2.08±0.76	2.05±0.51
IRS-2	2.15±0.59	2.27±0.63	2.08±0.76	2.15±0.59

Discussion

Previous epidemiological data and clinical studies have shown that high-risk factors for endometrial polyps include advanced age, menopause, hypertension, overweight or obesity, dyslipidemia, polycystic ovary syndrome (PCOS), impaired glucose tolerance, and diabetes.[8] Most of the factors above are abnormal glucose and lipid metabolism diseases, which are closely related to metabolic syndrome. Our previous research found that patients with endometrial polyps have the following characteristics compared with those with normal endometrium:

1) A higher proportion of irregular menstruation or amenorrhea

2) A wider waist circumference

3) Higher blood FIN

4) A higher HOMA-IR index. According to the results of logistic regression analysis, FIN≧10mIU/L, HOMA-IR≧2.14, waist circumference≧80cm, irregular menstrual cycle or amenorrhea are risk factors for endometrial polyps.[6]

In this study, it was also found that under similar BMI conditions, the FIN and HOMA-IR of EP patients were significantly higher than those of the control group, while the incidence of IR was slightly higher than that of the control group. The above results remind clinicians to attach importance to the role of insulin resistance in the occurrence and progression of endometrial polyps.[9]

During the natural menstrual cycle, the endometrium undergoes proliferative and secretory phase changes in sequence with the changes in estrogen and progesterone secreted by the ovary, and sheds periodically. During pregnancy, the endometrium undergoes decidual-like changes and receives embryo implantation. The endometrium itself does not have the ability to synthesize glucose, but the above physiological processes all require a large amount of glucose.[10] Endometrial cells exhibit steroid-dependent periodic changes, transporting glucose to the uterine cavity for energy. Therefore, the endometrium is also considered to be insulin-sensitive tissue. Previous studies have shown that insulin receptor (InR) and insulin-like growth factor I/II (IGF-I/II) expression can be seen in normal endometrium in both the proliferative and secretory phases.[11] The peak values of InR and IGF-II occur in the luteal phase, while IGF-I occurs in the follicular phase. IGF-1 in peripheral blood binds to and is activated by its receptor IGF-IR in target organs, playing a role in regulating cell proliferation and differentiation. Endometrial tissue itself can synthesize IGF-1 and its receptor.[12] Studies have shown that the trend of IGF-1 expression in EP tissue is consistent with the trend of IGF-1R expression. Increased IGF-1 expression is closely related to cell proliferation and plays an important role in the pathogenesis of endometrial polyps.[13] Doria et al.[14] found that the imbalance between IGF-1 and its binding proteins and gene polymorphism may be one of the links in the pathogenesis of EP. In this study, InR and IGF-1R were expressed in normal endometrium, but no difference was shown between the proliferative and secretory phases. Furthermore, there was no significant difference in the expression of InR and IGF-1R in polyp tissue and adjacent endometrial tissue at different stages of endometrium, and there was no significant difference compared with normal endometrium either. Given that this study did not select patients according to the sub-stages of the endometrial cycle, it could not show the changing trends of InR and IGF-1R expression with the endometrial cycle, which may be the reason for the difference from other study results.

Although IRS does not possess the activity of kinases or other endogenous enzymes, it can act as a adaptor protein to bind to transmembrane receptors, forming a signal complex that coordinates the transmission of cell signals from the extracellular to the intracellular space, thereby regulating biological processes such as cell growth, metabolism, survival, and proliferation.[15] Currently, six types of IRS have been identified, from IRS-1 to IRS-6. Their distribution shows obvious tissue specificity. IRS-1 and IRS-2 are widely distributed in various human tissues, and their research is the most thorough. Previous studies have suggested that insulin signaling activated by IRS-1 promotes the expression of mitotic kinases in estrogen-induced uterine epithelial cells, thereby promoting cell mitosis.[16] IRS-1 is overactivated in endometrial cancer and dysplasia. The activation of IRS-1 in endometrial cancer is associated with adverse clinicopathological features and may be a prognostic predictor of this tumor.[17] The IRS-2 G1057D gene polymorphism may be associated with the occurrence of endometrial cancer.[18] Currently, there are no reports on the expression of IRS in endometrial polyps. In this study, there were no significant differences in the expression of IRS1 and IRS2 among normal endometrium, uterine polyp tissue and adjacent endometrial tissue.

Insulin resistance originates from defects in insulin receptor function, including pre-receptor, receptor-in-itself, and post-receptor defects. At present, it is generally believed that post-receptor defects may be an important mechanism leading to the development of EP, which is a series of metabolic abnormalities caused by the impaired transmission of signals from the insulin receptor to the cell after binding with insulin. Li et al.[19] found that the expression scores and positive expression rates of PI3K and Akt proteins in EP patients were significantly higher than those in normal endometrium ($P<0.05$). With

the increase of HOMA-IR value, the expression scores of PI3K and Akt proteins in endometrial tissue also increased. There was a high positive correlation between HOMA-IR value and the expression of PI3K and Akt proteins ($P<0.01$). The authors believe that the abnormal activation of this signaling pathway may be a potential pathogenesis mechanism in the process of EP. Combined with their published data, we propose a hypothesis that IR-driven endometrial polyp formation may rely on functional defects of post-receptor signaling molecules rather than altered expression of InR, IGF-1R or IRS proteins. It must be emphasized clearly that this inference cannot be validated by our current dataset, as we did not test phosphorylated IRS, PI3K or Akt proteins; targeted mechanistic research detecting downstream activated signaling molecules is required to confirm this pathway.

Several limitations of this study should be fully acknowledged:

1) This is a single-center retrospective cross-sectional research, which cannot establish causal association between insulin resistance and endometrial polyps, only reflecting correlational relationships
2) The sample size of IHC subgroup analysis was reduced due to unqualified paraffin specimens, which may reduce statistical power to detect minor intergroup expression differences
3) We only used semi-quantitative IHC scoring to evaluate total protein expression without detecting phosphorylated activated IRS proteins, unable to reflect the functional activity of insulin signal transduction;
4) Endometrium was simply divided into proliferative and secretory phases without fine staging of menstrual sub-phases, failing to capture subtle cyclical dynamic changes of target receptors
5) The HOMA-IR diagnostic cut-off adopted in this study was validated in local Chinese reproductive-age women, lacking multi-population external validation and limiting generalizability of our metabolic classification criteria.

In summary, patients with endometrial polyps display significantly higher fasting insulin concentrations and elevated HOMA-IR compared with women with normal endometrium. However, the protein expression levels of upstream insulin signaling mediators (InR, IGF-1R, IRS-1, IRS-2) do not differ significantly among polyp tissue, peri-polyp endometrium and normal endometrium, regardless of menstrual cycle phase or individual insulin resistance status. Based on existing literature reporting abnormal downstream PI3K/Akt activation in EP lesions, we hypothesize that post-receptor insulin signaling dysfunction may contribute to endometrial polyp pathogenesis. Prospective mechanistic studies focusing on phosphorylated downstream signaling proteins are necessary to verify this molecular mechanism.

Acknowledgments

The authors thank all the investigators involved in this study, including the physicians, nurses, laboratory colleagues and pathologists. This article does not contain information that overlaps with prior publications, and the content is solely the responsibility of the authors.

Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

Funding

This study was financially supported by the Science and Technology Development Fund (FDCT 0003/2022/A and 0001/2024/RIA1) of Macau Special Administrative Region.

Conflicts of interest

The authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company.

References

1. Tong JL, Feng LM, Xue FX, et al. Clinical pathway for diagnosis and management of endometrial polyps. *Zhonghua Fu Chan Ke Za Zhi*. 2022;57(7):491–495.
2. Xie A, Wu X, Su Y, et al. Risk factors for endometrial polyps to transform into endometrial cancer: insights from a bibliometric analysis. *J Health Popul Nutr*. 2025;44(1):95.
3. Peng J, Guo J, Zeng Z, et al. Endometrial polyp is associated with a higher prevalence of chronic endometritis in infertile women. *Int J Gynaecol Obstet*. 2022;159(2):563–567.
4. Sharami SH, Kabodmehri R, Milani F, et al. The prevalence of endometrial polyp in women with tubal factor infertility is higher than male factor infertility: Is PID one of the causes of endometrial polyp?. *J Obstet Gynaecol Res*. 2023;49(2):658–664.
5. Kaya S, Kaya B, Keskin HL, et al. Is there any relationship between benign endometrial pathologies and metabolic status?. *J Obstet Gynaecol*. 2019;39(2):176–183.
6. Li CK, Hong Y, Liang HQ. Study on correlation of endometrial polyp with insulin resistance. *China Practical Medicine*. 2023;18(20):48–51.
7. Tang CY, Zhou HD. Tissue specific functions of insulin receptor substrate family members based on their molecular structures. *Journal of Clinical and Pathological Research*. 2016;36(3):295–302.
8. Kaya S, Kaya B, Keskin HL, et al. Is there any relationship between benign endometrial pathologies and metabolic status?. *J Obstet Gynaecol*. 2019;39(2):176–183.
9. Chen Q, Hong Y, Li CK, et al. Evaluation of relationship between endometrial polyp and insulin resistance: a case–control study. *Int J Clin Obstet Gynecol*. 2023;7(1):99–102.
10. Liu XQ, Zhu XF, Lin X, et al. Effects of Diane 35 plus metformin on endometrium expression of insulin receptor and pregnancy outcome of assisted reproduction in patients with polycystic ovary syndrome. *Guangxi Medical Journal*. 2017;39(12):1814–1818.
11. Mioni R, Mozzanega B, Granzotto M, et al. Insulin receptor and glucose transporters mRNA expression throughout the menstrual cycle in human endometrium: a physiological and cyclical condition of tissue insulin resistance. *Gynecol Endocrinol*. 2012;28(12):1014–1018.
12. Luo PX, He XY, Hu HB, et al. Expression of ER, PR, VEGF, IGF–1 and HGF in endometrial polyps and its significance. *Journal of Clinical Research*. 2012;29(12):2318–2324.
13. Luo XM, Cheng QR, Chen MJ, et al. Expression of insulin–like growth

factor–1 and proliferating cell nuclear antigen in endometrial polyps and their clinical significance. *Chinese General Practice*. 2010;13(27):3040–3042.

14. Doria PLS, Moscovitz T, Tcherniakovsky M, et al. Association of IGF–1 CA(n) polymorphisms with endometrial polyp risk. *BioMed Res Int*. 2018;2018:8704346.
15. Machado–Neto J, Fenerich B, Alves A, et al. Insulin receptor substrate (IRS) proteins in normal and malignant hematopoiesis. *Clinics (Sao Paulo)*. 2018;73:e566s.
16. Walker MP, Diaugustine RP, Zeringue E, et al. An IGF1/insulin receptor substrate–1 pathway stimulates a mitotic kinase (cdk1) in the uterine epithelium during the proliferative response to estradiol. *J Endocrinol*. 2010;207(2):225–235.
17. Cayan F, Tok E, Aras–Ateş N, et al. Insulin receptor substrate–2 gene polymorphism: is it associated with endometrial cancer?. *Gynecol Endocrinol*. 2010;26(5):378–382.
18. Hua SF, Xue FX, Zhang LZ, et al. Expression and activation of insulin receptor substrate–1 in endometrial carcinoma. *Zhonghua Fu Chan Ke Za Zhi*. 2008;43(6):437–441.
19. Li X, Wang F, Chen M, et al. The association between endometrial polyps and insulin resistance from the expression of PI3K and AKT proteins perspective. *BMC Womens Health*. 2024;24(1):366.

Citation: Jian YS, Hong Y, Xiao G, et al. Insulin resistance in patients with endometrial polyps and its relationship with the expression of InR, IGF-1R, and IRS in the endometrium. *Obstet Gynecol Int J.* 2026;17(3):144–151. DOI: 10.15406/ogij.2026.17.00838