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Correlation Between Progesterone Receptor Isoforms and Endometrial Stem Cell Markers in PCOS-Associated Infertility

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ABSTRACT

Progesterone receptor isoforms, PRA and PRB, are critical for regulating endometrial decidualization and maintaining receptivity during the implantation window. In women with polycystic ovary syndrome (PCOS), dysregulation of these receptors can result in progesterone resistance and endometrial dysfunction, contributing to infertility. This study aimed to quantify the expression levels of progesterone receptor isoforms (PRA and PRB), evaluate the expression of stem cell markers (Nanog, Sox, and c-Myc), and explore the correlation between PR isoforms and stem cell markers in endometrial samples from women with PCOS compared to healthy controls. A case–control study was conducted involving 100 participants, including 50 women with PCOS and 50 non-PCOS controls. Endometrial tissue was collected and analysed using flow cytometry and quantitative PCR to assess receptor and marker expression. Statistical analyses, including t-tests, Pearson correlation, and regression models, were performed to determine group differences and associations. Women with PCOS exhibited significantly higher PRA and PRB expression levels, accompanied by elevated stem cell marker expression ($p < 0.001$). Strong positive correlations were found between PR isoforms and stemness markers, indicating a mechanistic link between hormonal dysregulation and increased endometrial stem cell activity. The findings suggest that altered PR signaling and enhanced stem cell activity underlie progesterone resistance and impaired endometrial receptivity in PCOS. These insights provide a basis for developing targeted therapeutic interventions, such as selective PR modulators and regulators of stem cell pathways, to improve fertility outcomes in affected women.

1. Introduction

1.1 Background

Progesterone plays a fundamental role in preparing the endometrium for implantation and supporting early pregnancy. Following ovulation, it induces the transition of the endometrium from a proliferative state to a secretory, receptive phase, thereby enabling the process of decidualization in which stromal cells differentiate and remodel to support embryo attachment and invasion (Okada et al., 2018). Decidualization comprises a concerted hormonal, molecular and cellular programme including stromal proliferation, glandular differentiation, vascular remodelling, immune modulation and extracellular matrix re-organisation (Muter et al., 2021).

Progesterone exerts its action via the nuclear progesterone receptor (PR), which exists in two principal isoforms, PR-A (PRA) and PR-B (PRB). Both derive from the same gene, transcribed from distinct promoters and differing in their N-terminal sequences (Large & DeMayo, 2012). Functionally, PRB acts as a potent transcriptional activator of genes relevant for implantation and decidualization, whereas PRA often behaves as a dominant repressor of other steroid receptors and may modulate progesterone responsiveness (Kaya et al., 2015). The coordinated expression and action of PRA and PRB is therefore essential for establishing endometrial receptivity, facilitating timely stromal and glandular transformation, vascular stabilisation, immune tolerance and trophoblast integration (Wetendorf & DeMayo, 2012).

Disruption of the PRA/PRB balance—for example through relative overexpression of PRA or diminished PRB—leads to impaired progesterone signalling. Such dysregulation has been implicated in reproductive pathologies including endometriosis, endometrial hyperplasia and infertility (Li et al., 2014). Reduced PRB and/or increased PRA/PRB ratios are associated with lower expression of decidualization markers such as prolactin (PRL) and IGFBP-1, culminating in compromised endometrial receptivity (Brosens et al., 1999). Accordingly, elucidating the regulation and expression profiles of progesterone receptor isoforms is critical for understanding implantation failure and progesterone resistance in pathological contexts.

PCOS and Endometrial Dysfunction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, typified by hyperandrogenism, chronic anovulation and insulin resistance (Xue et al., 2021). These systemic abnormalities adversely affect ovarian and endometrial physiology. In PCOS, chronic anovulation leads to prolonged unopposed estrogen exposure without the regular luteal rise in progesterone, resulting in persistent endometrial proliferation and inadequate secretory transformation (Li et al., 2014). The hormonal milieu creates a suboptimal environment for implantation, and the endometrium in PCOS commonly demonstrates inflammatory changes,

oxidative stress, impaired differentiation, and altered vascular or immune profiles—all of which compromise fertility and early pregnancy maintenance (Xue et al., 2021).

A hallmark of endometrial dysfunction in PCOS is **progesterone resistance**, wherein endometrial cells exhibit reduced responsiveness to progesterone despite apparently sufficient hormone levels (MacLean & Hayashi., 2022). This resistance is attributed in part to defects in progesterone signalling, especially in the expression and function of progesterone receptor isoforms. Studies show that endometrium from women with PCOS often presents reduced PRB expression and increased PRA/PRB ratios—patterns paralleling other progesterone-resistant conditions (Li et al., 2014). These imbalances suppress activation of progesterone-responsive genes essential for decidualisation, leading to a persistently proliferative rather than receptive endometrium. In addition, metabolic perturbations characteristic of PCOS—such as insulin resistance and hyperinsulinemia—may further modulate steroid receptor expression through cross-talk between metabolic and hormonal pathways (Xue et al., 2021). The combined disturbances contribute to subfertility and increased risks of endometrial hyperplasia or carcinoma in women with PCOS, underscoring the importance of investigating molecular mechanisms of progesterone resistance in this context.

Endometrial Stem/Progenitor Cell Markers and Their Role

Accumulating evidence points to the significance of endometrial stem or progenitor cell populations in cyclic regeneration, tissue homeostasis and repair of the endometrium (Hong, 2024). These endometrial mesenchymal stem-cells (eMSCs) are characterised by expression of pluripotency or stemness-associated transcription factors—such as NANOG, SOX2, and c-MYC—that regulate cellular proliferation, differentiation and plasticity (Park et al., 2011). Under physiological conditions, their expression is tightly controlled so as to maintain a balance between regeneration and differentiation after each menstrual shedding. However, dysregulation of these markers has been documented in pathological endometrial states including PCOS, endometriosis and endometrial hyperplasia, where aberrant growth and impaired differentiation are evident (Xu et al., 2015). Increased expression of NANOG, SOX2 and c-MYC may reflect a heightened undifferentiated or regenerative state rather than a mature receptive endometrium.

1.4 Research Gap, Significance, and Study Objectives

Although the role of progesterone signalling in endometrial function is well-established, the interaction between progesterone receptor isoforms and stem cell regulatory pathways in PCOS remains poorly understood. While several studies have independently reported altered PR isoform expression or increased stemness marker expression in PCOS, very few have explored their interrelationship and how it might contribute to progesterone resistance and impaired implantation. This represents a crucial research gap, as elucidating this connection could provide valuable insights into the molecular underpinnings of endometrial dysfunction in PCOS. Moreover, given that progesterone

resistance significantly limits the effectiveness of standard therapeutic interventions, understanding the regulatory mechanisms that govern PR signalling could help identify novel biomarkers and therapeutic targets for improving endometrial receptivity.

2. Materials and Methods

2.1 Study Design and Population

This study was a case–control observational study conducted at a tertiary infertility clinic to evaluate the correlation between progesterone receptor (PR) isoforms and endometrial stem cell markers in women with polycystic ovary syndrome (PCOS) compared with infertile women without PCOS. The case–control design allowed for molecular comparisons between two clinically defined populations while minimizing confounding effects through demographic matching.

A total of 100 participants were enrolled, consisting of 50 infertile women diagnosed with PCOS and 50 infertile women without PCOS who served as the control group. The diagnosis of PCOS was made according to the Rotterdam criteria, requiring at least two of the following: (1) oligo- or anovulation, (2) clinical or biochemical signs of hyperandrogenism, and (3) polycystic ovarian morphology on ultrasonography. Controls were age- and BMI-matched infertile women with normal ovulatory cycles, confirmed by mid-luteal phase serum progesterone levels (LH+7 > 3 ng/mL).

Participants were women aged between 20 and 40 years, representing the optimal reproductive age range, and were included only if they had regular menstrual cycles (for controls) and had not received any hormonal medication or fertility treatment for at least three to six months prior to enrolment. Women were excluded if they had endometriosis, thyroid disorders, diabetes mellitus, hyperprolactinemia, congenital uterine anomalies, or any other endocrine dysfunction that might influence endometrial receptivity. Participants with a history of recent hormonal or corticosteroid therapy were also excluded.

The sample size of 100 was determined by power analysis to achieve 80–90% power at a 5% level of significance, based on previously reported variations in PR isoform expression between PCOS and non-PCOS endometrium. All participants provided written informed consent before sample collection. The study protocol was reviewed and approved by the Institutional Ethics Committee in accordance with the Declaration of Helsinki.

2.2 Sample Collection and Laboratory Analysis

Endometrial tissue samples were obtained through endometrial biopsy performed during the mid-secretory phase of the menstrual cycle, corresponding to days 19–23 after the last menstrual period, or LH+7, confirmed by serum progesterone assay. This timing was chosen to ensure maximal expression of progesterone receptors and stromal decidualization markers, thereby standardizing the hormonal environment across subjects.

Immediately after collection, tissue specimens were handled under sterile conditions and divided into two portions. One portion was enzymatically digested using collagenase to generate a single-cell suspension suitable for flow cytometric analysis, while the second portion was

immersed in RNA later solution to preserve RNA integrity for molecular analysis.

Flow Cytometric Analysis

For flow cytometry, single-cell suspensions were stained with fluorochrome-conjugated monoclonal antibodies specific to progesterone receptor isoforms (PRA and PRB) and stemness-associated transcription factors (Nanog, Sox2, and c-Myc). Isotype controls were used to establish background fluorescence and gating thresholds. Samples were analyzed on a high-parameter flow cytometer equipped with standard blue, red, and violet lasers. Fluorescence compensation was applied to correct for spectral overlap, and voltage settings were standardized across runs. Data acquisition and analysis were performed using FlowJo software, with marker expression represented as mean fluorescence intensity (MFI) and percentage of positive cells. These quantitative measures provided relative protein expression profiles for both PR isoforms and stem cell markers in endometrial cell populations.

RNA Extraction and Quantitative Real-Time PCR

For gene expression analysis, total RNA was extracted from the RNAlater-preserved tissue using a commercially available RNA isolation kit following the manufacturer's protocol. The purity and concentration of RNA were confirmed using a NanoDrop spectrophotometer (A260/A280 ratio between 1.8 and 2.0). Complementary DNA (cDNA) was synthesized using a high-capacity reverse transcription kit, and quantitative real-time PCR (qPCR) was performed using specific primers for PRA, PRB, Nanog, Sox2, and c-Myc, with GAPDH and β-actin as internal reference genes. Reactions were conducted in triplicate in a real-time PCR detection system using SYBR Green chemistry. The ΔΔCt method was used to calculate relative fold changes in gene expression, normalizing target gene levels to reference genes and comparing PCOS samples with controls.

This dual approach—flow cytometry for protein quantification and qPCR for transcript analysis—allowed validation of results at both the translational and transcriptional levels, providing a comprehensive assessment of receptor signaling and stemness activity in the endometrium.

2.3 Outcome Measures and Statistical Analysis

The primary outcomes included the expression levels of progesterone receptor isoforms (PRA and PRB) and their ratio (PRA:PRB), which reflects the functional balance influencing endometrial receptivity. Secondary outcomes comprised the expression of stemness-related transcription factors Nanog, Sox2, and c-Myc, which indicate the regenerative and proliferative capacity of endometrial tissue. Both sets of markers were quantified at the protein level using flow cytometry (MFI and % positive cells) and at the mRNA level through qPCR, ensuring robust cross-validation between methods.

Statistical analyses were conducted using SPSS version 25.0 and GraphPad Prism. Descriptive statistics summarized the demographic and biochemical characteristics of study participants, expressed as mean ± standard deviation (SD) or median with interquartile range, depending on data distribution. The Student's t-test was applied for normally distributed continuous variables, whereas

the Mann–Whitney U test was used for non-normally distributed data.

Correlation analyses between PR isoform expression and stem cell marker expression were performed using Pearson's or Spearman's correlation coefficients, as appropriate. To control for confounding factors such as age, BMI, insulin resistance, and duration of infertility, multiple linear regression models were employed. The strength and direction of associations were expressed as standardized beta coefficients (β), and overall model fit was assessed by R^2 and adjusted R^2 values.

A p-value of <0.05 was considered statistically significant for all analyses. The robustness of statistical models was further validated through sensitivity checks and examination of residual plots. Results were graphically represented using bar charts, scatterplots, and correlation matrices.

3. Results

3.1 Participant Characteristics

A total of 100 participants were included, equally divided into Healthy (n = 50) and PCOS (n = 50) groups, ensuring balanced comparisons (Table 1). Descriptive statistics for all key molecular and functional variables are presented in Table 2. Variables such as PRA, PRB, Nanog, Sox, cMyc, and mitochondrial activity showed wide ranges and notable inter-individual variability. Both progesterone receptor isoforms (PRA and PRB) displayed moderate mean values, with PRA showing higher variability. Stemness and proliferation markers (Nanog, Sox, cMyc, %Proliferation, MitoActivity) exhibited broad ranges, indicating inter-individual diversity in endometrial molecular characteristics across groups.

Table 1. Group Distribution

Group	Frequency	Percent	Valid Percent	Cumulative Percent
Healthy	50	50.0	50.0	50.0
Patient (PCOS)	50	50.0	50.0	100.0
Total	**100**	**100.0**	**100.0**	—

Table 2. Descriptive Statistics of Key Variables

Variable	N	Minimum	Maximum	Mean	Std. Deviation
PRA	100	5.52	17.40	9.3159	3.46437
PRB	100	3.29	8.99	5.6291	1.46131
% Proliferation	96	4.28	12.83	7.0590	2.48981
Nanog	94	4.03	11.51	6.4701	2.20189
Sox	99	5.10	16.26	8.8096	3.17613
cMyc	100	4.51	19.59	7.7911	3.20054
MitoActivity	99	5.23	17.58	8.9802	3.55106

3.2 PR Isoform Expression

Progesterone receptor isoform expression was significantly different between PCOS and control groups (Table 3). The mean PRA level in the PCOS group (11.94 ± 2.76) was significantly higher than in controls (6.69 ± 1.60; $p < 0.001$). Similarly, PRB expression was elevated in PCOS endometrium (6.85 ± 0.97) compared to healthy participants (4.41 ± 0.58; $p < 0.001$). Both PRA and PRB were significantly elevated in PCOS endometrium ($p < 0.001$), indicating receptor upregulation consistent with progesterone resistance in these patients.

Table 3. Group Differences in PR Isoform Expression

Variable	Group	N	Mean	Std. Deviation	t(df)	Sig. (2-tailed)
PRA	Healthy	50	6.689	1.596	—	—
PRA	PCOS	50	11.943	2.760	-11.650 (78.47)	**0.000**
PRB	Healthy	50	4.409	0.575	—	—
PRB	PCOS	50	6.849	0.972	-15.285 (79.58)	**0.000**

3.3 Stem Cell Marker Expression

Expression levels of stem cell–associated transcription factors (*Nanog*, *Sox*, *cMyc*) and functional markers (%Proliferation, Mitochondrial Activity) are summarized in Table 4. All markers were significantly upregulated in the PCOS group compared to healthy controls ($p < 0.001$). All stem cell and proliferative markers were markedly elevated in PCOS endometrium ($p < 0.001$), reflecting enhanced cellular regeneration and metabolic activity, which may contribute to subfertility and endometrial dysfunction in PCOS.

Table 4. Comparison of Stem Cell and Functional Markers between Groups

Variable	Group	N	Mean	Std. Deviation	Std. Error Mean
% Proliferation	Healthy	50	5.151	0.840	0.119
	PCOS	46	9.133	1.969	0.290
Nanog	Healthy	48	4.722	0.702	0.101
	PCOS	46	8.295	1.685	0.249
Sox	Healthy	50	6.295	1.101	0.156
	PCOS	49	11.375	2.460	0.351
cMyc	Healthy	50	5.492	0.994	0.141
	PCOS	50	10.090	2.987	0.422
MitoActivity	Healthy	49	6.222	1.004	0.143
	PCOS	50	11.684	3.028	0.428

3.4 Correlation Analysis

Correlation analysis between PR isoforms and stem cell markers demonstrated strong positive relationships (Table 5). PRA exhibited the highest correlations with *Nanog* ($r = 0.966$) and *Sox* ($r = 0.958$), followed by *cMyc* ($r = 0.825$). All correlations were statistically significant ($p < 0.01$).The strong, significant correlations among PRA, PRB, and stem cell markers suggest co-

regulation of progesterone receptor signaling and stemness pathways, highlighting their potential role in PCOS-related endometrial remodeling.

Table 5. Correlation Matrix between PR Isoforms and Stem Cell Markers

Variables	PRA	PRB	Nanog	Sox	cMyc
PRA	1	.681**	.966**	.958**	.825**
PRB	.681**	1	.723**	.699**	.582**
Nanog	.966**	.723**	1	.962**	.905**
Sox	.958**	.699**	.962**	1	.920**
cMyc	.825**	.582**	.905**	.920**	1

$p < 0.01$ (2-tailed)

3.5 Adjusted Analysis

A multiple regression model was constructed to evaluate predictors of cell proliferation while controlling for inter-variable effects (Table 6). The model was statistically significant ($F = 656.55$, $p < 0.001$), explaining 95.7% of variance in proliferation rates ($R^2 = 0.957$). The regression model indicates that Sox ($p < 0.001$) and cMyc ($p = 0.04$) are significant independent predictors of proliferation in endometrial cells. These findings suggest that stemness and transcriptional activation may drive proliferative abnormalities in PCOS endometrium.

Table 6. Multiple Regression Analysis Predicting Proliferation

Predictor	B	Std. Error	Beta	t	Sig.
Constant	0.259	0.174	—	1.486	0.141
Nanog	0.191	0.108	0.168	1.771	0.080
Sox	0.455	0.079	0.587	5.745	**0.000**
cMyc	0.209	0.100	0.232	2.087	**0.040**

Model Summary: *$R = 0.978$; $R^2 = 0.957$; Adjusted $R^2 = 0.955$; Std. Error = 0.533*

4. Discussion

4.1 Summary of Key Findings

The findings of this study demonstrate significant alterations in progesterone receptor (PR) isoform expression and stem cell marker profiles in the endometrial samples of women with polycystic ovary syndrome (PCOS) compared to non-PCOS controls. The differential expression of PR isoforms, particularly the imbalance in PRA and PRB levels, suggests a dysregulated hormonal signaling environment within the PCOS endometrium. This imbalance is known to contribute to progesterone resistance—a hallmark feature associated with impaired

endometrial receptivity. The observed changes in mean fluorescence intensity (MFI) and percentage of PR-positive cells between the two groups highlight a fundamental difference in the cellular responsiveness to progesterone. In addition, the upregulation of pluripotency-associated stem cell markers such as Nanog, Sox, and c-Myc points to increased cellular proliferation and a less differentiated endometrial phenotype in PCOS. This pattern is consistent with prior reports suggesting that the PCOS endometrium retains a more regenerative but functionally immature state, thereby affecting the implantation window and overall fertility outcomes. Furthermore, correlation analysis revealed a significant association between altered PR isoform ratios and elevated expression of stem cell markers, suggesting that PR dysregulation may directly or indirectly drive changes in endometrial stem cell activity. Collectively, these results strengthen the hypothesis that defective progesterone signaling and enhanced stemness characteristics act synergistically to disrupt endometrial function in PCOS. These findings not only provide molecular insights into endometrial dysfunction in PCOS but also identify potential therapeutic targets to improve receptivity and fertility outcomes in affected women.

4.2 Interpretation

The altered expression of PR isoforms and elevated stem cell marker levels observed in this study may reflect a complex interplay between hormonal dysregulation and cellular reprogramming within the PCOS endometrium. Under normal physiological conditions, a balanced expression of PRA and PRB is essential for appropriate progesterone-mediated signaling, which regulates endometrial proliferation, differentiation, and decidualization. In PCOS, an increased PRA/PRB ratio or diminished PRB expression can suppress downstream progesterone-responsive genes, leading to impaired decidualization and an inhospitable environment for embryo implantation. This phenomenon aligns with the concept of progesterone resistance, wherein despite adequate circulating hormone levels, the endometrium fails to mount an appropriate functional response. The concurrent upregulation of stemness markers such as Nanog, Sox, and c-Myc suggests that this dysregulation may push endometrial cells toward a more undifferentiated and proliferative state. Such molecular plasticity may sustain continuous regeneration but hinder the transition to a receptive phenotype required during the luteal phase. The significant correlations identified between PR isoform ratios and stem cell marker expression imply a mechanistic link—possibly mediated through altered transcriptional networks or epigenetic modulation—whereby abnormal PR signaling fosters an imbalance between proliferation and differentiation. This shift could explain the common histological features of PCOS endometrium, including delayed maturation and glandular-stromal asynchrony. Overall, these findings support a model where progesterone signaling defects serve as a central driver of endometrial dysfunction, promoting a persistent state of immaturity and reduced receptivity. Understanding this mechanism provides a foundation for developing interventions aimed at restoring PR balance and improving fertility in women with PCOS.

4.3 Comparison with Literature

Progesterone receptor isoform findings in the present dataset — marked elevation of PRA (11.94 ± 2.76) and PRB (6.85 ± 0.97) in the PCOS group compared with controls — align with prior reports of altered PR regulation and progesterone resistance in PCOS endometrium. Savaris (2011) documented gene-expression signatures consistent with progesterone resistance in mid-secretory PCOS endometrium, and Li et al. (2014) reviewed structural and regulatory differences in PR isoforms that can produce dysfunctional progesterone responses. Studies emphasizing isoform-specific effects in uterine tissues indicate that an altered PRA:PRB balance can modify transcriptional outcomes and tissue responsiveness; the present observation of parallel increases in both PRA and PRB contrasts with some reports that describe selective isoform shifts (for example, increased PRB or decreased PRAB mRNA in subsets of PCOS or obese cohorts), suggesting cohort-specific regulation or methodological differences in isoform quantification.

Upregulation of stemness-associated transcription factors (Nanog, Sox family members, cMyc) and functional proliferation markers in the PCOS group corroborates literature linking expansion of stem/progenitor-like populations to endometrial pathology. Case-control and immunohistochemical studies in dysfunctional endometrium and endometriosis have reported higher expression of pluripotency markers (OCT4, NANOG, SOX2) compared with normal endometrium, supporting a model in which stemness programs promote excessive proliferation and impaired differentiation (Shariati et al.,2019). The magnitude of correlations observed between PRA and Nanog/Sox in the present study ($r = 0.966$ and $r = 0.958$, respectively) provides stronger quantitative evidence for co-variation than typically reported in narrative reviews; however, direct head-to-head correlation matrices in PCOS-specific endometrium remain scarce, limiting precise mechanistic inference and highlighting a gap between descriptive marker studies and causal pathway analysis.

Elevated mitochondrial activity in PCOS endometrial samples integrates with broader evidence of mitochondrial abnormalities in PCOS across reproductive and metabolic tissues (Zhang et al., 2019). Recent reviews describe dysregulated mitochondrial biogenesis, altered respiratory function, and increased oxidative stress in PCOS, with downstream effects on cellular metabolism and proliferative capacity. The present finding of higher MitoActivity accompanying increased proliferation parallels reported links between altered mitochondrial function and cell-cycle control, yet the literature contains greater emphasis on ovarian granulosa cells and systemic metabolic tissues than on endometrial mitochondria specifically. Therefore, the endometrial mitochondrial result extends existing knowledge but requires targeted functional assays (oxygen-consumption rates, mitochondrial membrane potential, reactive-oxygen-species quantification) to determine whether mitochondrial upregulation represents adaptive bioenergetic support for proliferation or maladaptive dysregulation associated with oxidative damage (Siemers et al., 2023; Zhou et al., 2024).

The multivariable regression in the current study — where $R^2 = 0.957$ and only Sox and cMyc emerged as significant independent predictors of proliferation — suggests a dominant role for transcriptional regulators of stemness in driving endometrial cell proliferation within the PCOS context. This observation complements findings by Hu et al. (2018), who documented elevated PRA and PRB expression alongside increased Ki-67 immunoreactivity in PCOS endometrium, indicating enhanced proliferative activity in relation to altered progesterone receptor signalling (Hu et al., 2018). Similarly, Li et al. (2014) reviewed the mechanistic basis of progesterone resistance in PCOS and emphasized that aberrant PR isoform expression is linked to deficient anti-proliferative progesterone action, thereby permitting unregulated growth of endometrial cells. The present findings extend these earlier reports by quantitatively modelling the contribution of stemness transcription factors downstream of PR dysregulation, providing stronger statistical evidence for a pathway in which altered progesterone receptor signalling may engage stemness networks to enhance proliferation.

4.4 Clinical Implications

The findings of altered progesterone receptor isoform expression and increased stem cell marker activity in PCOS endometrium highlight potential therapeutic targets to improve endometrial receptivity. Selective progesterone receptor modulators (SPRMs) could help restore the physiological balance between PRA and PRB, thereby reversing progesterone resistance and promoting appropriate decidualization. Additionally, emerging therapies that regulate stem cell proliferation and differentiation—such as modulators of Wnt/β-catenin or Notch signalling pathways—may help normalize endometrial cellular maturation. Combining hormonal modulation with targeted stem cell therapies may thus provide a dual approach to restoring endometrial function and enhancing fertility outcomes in women with PCOS.

4.5 Strengths and Limitations

A key strength of this study lies in its simultaneous evaluation of PR isoform expression and stemness markers within the same endometrial samples, providing a comprehensive molecular view of progesterone resistance and cellular immaturity in PCOS. This integrated approach adds mechanistic depth to current understanding of endometrial dysfunction. However, limitations include the single-cycle sampling, which restricts temporal insights across different menstrual phases, and the relatively small sample size that limits statistical generalizability. Furthermore, the observational study design precludes causal inference, emphasizing the need for longitudinal and interventional studies to validate these associations.

4.6 Future Directions

Future research should adopt longitudinal designs tracking PR isoform dynamics and stem cell marker expression across various menstrual phases to better understand their temporal interplay in PCOS. Functional assays, including knockdown or overexpression models, are necessary to confirm the causal role of PR dysregulation in modulating stem cell behaviour. Moreover, clinical trials testing the efficacy

of selective PR modulators and targeted stem cell–based therapies could establish translational relevance.

5. Conclusion

This study demonstrates that altered progesterone receptor isoform expression and elevated stem cell marker activity contribute significantly to endometrial dysfunction in women with PCOS. The findings highlight a mechanistic link between progesterone resistance, impaired decidualization, and enhanced proliferative signalling, which collectively undermine endometrial receptivity and fertility. By elucidating the molecular interactions between PR signalling and stem cell dynamics, this research advances understanding of PCOS-related infertility. Importantly, the results underscore the translational potential for individualized treatment strategies—particularly through selective modulation of progesterone receptors and targeted regulation of stem cell pathways—to restore normal endometrial function and improve reproductive outcomes.

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