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Endometrial Stem/Progenitor Cell Markers in Polycystic Ovary Syndrome (PCOS) versus Non-PCOS Infertile Women: A Systematic Review of Molecular and Cellular Signatures

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ABSTRACT

The human endometrium is a highly regenerative tissue whose cyclical renewal is driven by endometrial stem/progenitor cells, critical for successful implantation and fertility. Polycystic Ovary Syndrome (PCOS), a prevalent endocrine disorder, disrupts endometrial structure and function, potentially through altered stem/progenitor cell activity. This systematic review aimed to compare the expression of key endometrial stem/progenitor markers—CD146, SUSD2, Lgr5, SSEA-1, and N-cadherin—between infertile women with and without PCOS. A comprehensive search of PubMed, Cochrane, and ScienceDirect from 2015 to 2025 identified 20 eligible studies meeting strict inclusion criteria. Findings consistently revealed dysregulation of stromal and epithelial progenitor markers in PCOS, including reduced CD146/SUSD2 and altered Lgr5, SSEA-1, and N-cadherin expression, associated with impaired stromal remodeling, epithelial renewal, and implantation potential. These molecular alterations likely contribute to infertility and endometrial dysfunction in PCOS. Future research should integrate functional assays and longitudinal studies to clarify causal mechanisms and therapeutic targets.

1. Introduction

1.1 Background

The endometrium is a highly dynamic and regenerative mucosal tissue lining the uterine cavity, essential for reproductive success. It undergoes cyclical changes of proliferation, differentiation, shedding, and regeneration during each menstrual cycle (Benagiano et al., 2018; Alebić, 2022). This remarkable regenerative capacity is largely driven by endometrial stem/progenitor cells (eSPCs) in the basal layer, which repair the functionalis layer post-menstruation or parturition (Sun et al., 2024; Khatun, 2021). Steroid hormones—estrogen and progesterone—coordinate these changes, shaping both cellular composition and molecular signals necessary for implantation (Guo et al., 2022; Jiang & Li, 2022).

Distinct eSPC populations include mesenchymal stem-like cells, epithelial progenitors, and endothelial progenitors that sustain endometrial renewal (Hong, 2022; Mansoori et al., 2024). Endometrial mesenchymal stem cells (eMSCs) express CD146 and SUSD2, markers used to isolate clonogenic and multipotent stromal cells, and contribute to stromal remodeling, angiogenesis, and immune modulation (Chaudhari-Kank et al., 2018; Nair et al., 2025; Piltonen et al., 2015). Epithelial progenitors, identified by SSEA-1, N-cadherin, and Lgr5, generate new glandular epithelial cells for the functionalis layer, ensuring proper epithelial turnover and tissue integrity (Yun et al., 2024; Kouchakzadeh et al., 2024; Luyckx et al., 2025).

Functionally, CD146 and SUSD2 regulate stromal integrity and angiogenesis, Lgr5 indicates high proliferative potential, SSEA-1 marks undifferentiated epithelial cells, and N-cadherin maintains cell–cell adhesion (Hu et al., 2020; Chaudhari-Kank et al., 2018). Dysregulation of these markers disrupts endometrial repair, impairs receptivity, and contributes to subfertility (Guo et al., 2022; Eriksson et al., 2025). Understanding the hierarchy and molecular signatures of these stem/progenitor markers is critical for elucidating normal endometrial physiology and pathologies such as Polycystic Ovary Syndrome (PCOS) (Benagiano et al., 2018; Mansoori et al., 2024).

1.2 PCOS and Endometrial Dysfunction

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders among women of reproductive age, affecting 5–20% globally (Alebić, 2022).

It is characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology, often accompanied by metabolic disturbances such as insulin resistance and obesity (Jiang & Li, 2022). Beyond ovarian dysfunction, PCOS exerts profound effects on the endometrium, which is a key determinant of fertility. Women with PCOS frequently present with endometrial abnormalities that impair implantation, even when ovulation is pharmacologically induced or assisted reproductive techniques are employed (Benagiano et al., 2018; Zoleta et al., 2025). These abnormalities stem from hormonal imbalances, particularly elevated estrogen levels unopposed by progesterone, leading to a hyperproliferative, estrogen-dominant endometrial environment.

Endometrial changes in PCOS include altered cellular proliferation, impaired differentiation, and defective receptivity (Guo et al., 2022). The endometrium of PCOS women often exhibits histological and molecular features suggestive of delayed maturation, with persistent proliferative morphology during the supposed secretory phase. Aberrant expression of key receptivity molecules, including integrins, leukemia inhibitory factor (LIF), and homeobox transcription factors (HOXA10, HOXA11), has been documented. Progesterone resistance—an impaired ability of the endometrium to respond to progesterone signaling—is a central feature in PCOS-related endometrial dysfunction, resulting in defective decidualization and contributing to infertility, irregular bleeding, and increased risk of endometrial hyperplasia and carcinoma (Piltonen et al., 2015).

Recent studies have hypothesized that the underlying endometrial dysfunction in PCOS may partly arise from abnormalities in the stem/progenitor cell compartment. Aberrant expression of stem cell markers such as CD146, SUSD2, Lgr5, and SSEA-1 may alter regenerative dynamics, leading to structural and functional changes within the endometrium (Sun et al., 2024; Kouchakzadeh et al., 2024). Chronic inflammation and hyperinsulinemia—common in PCOS—can influence the behavior of endometrial mesenchymal stem cells, promoting fibrosis or excessive stromal proliferation. Similarly, dysregulation of epithelial progenitor markers could impair glandular renewal and disrupt the establishment of a receptive endometrial surface. Such changes may interfere with the cyclical remodeling essential for successful implantation. The interplay between hormonal imbalance and stem cell dysfunction thus forms a critical axis

through which PCOS exerts its detrimental effects on fertility. However, the precise molecular pathways linking altered progenitor cell marker expression with impaired endometrial receptivity remain largely undefined, warranting deeper investigation (Eriksson et al., 2025).

1.3 Rationale for the Review

Despite extensive research on hormonal and metabolic abnormalities in PCOS, the role of endometrial stem/progenitor cells (eSPCs) in mediating endometrial dysfunction remains underexplored. Individual studies have reported variations in key markers—CD146, SUSD2, Lgr5, SSEA-1, and N-cadherin—between PCOS and non-PCOS endometrium, but a comprehensive synthesis is lacking. Evaluating these expression patterns could clarify whether impaired fertility in PCOS arises from hormonal imbalance or intrinsic defects in regenerative endometrial machinery.

Critical knowledge gaps persist: the spatial and temporal expression of eSPC markers across the menstrual cycle in PCOS is poorly characterized; the effects of metabolic disturbances such as hyperinsulinemia, low-grade inflammation, and oxidative stress on progenitor populations remain unclear; and correlations between altered marker expression and clinical outcomes, including implantation rates, miscarriage risk, and endometrial thickness, are limited.

Clinically, understanding eSPC dysregulation could inform diagnostics and therapeutics. Aberrant marker expression may serve as biomarkers for endometrial receptivity, while interventions targeting stem cell function—through hormonal modulation, anti-inflammatory therapy, or regenerative approaches—could enhance fertility outcomes. This review is warranted to systematically compile evidence, identify consistent patterns, and elucidate mechanistic links between eSPC dysregulation and infertility in PCOS, ultimately advancing targeted therapeutic strategies beyond hormonal correction.

1.4 Objectives

- To evaluate published studies related to expression of stem/progenitor cell endometrial markers in infertile women with a diagnosis of PCOS compared with infertile women without a diagnosis of PCOS.
- To assess the relationship between stem/progenitor cell marker expression and endometrial

receptivity, regeneration and implantation potential.

- To determine the diagnostic and therapeutic implications of abnormal expression of stem/progenitor cell markers in the endometrium.

2. Methods

2.1 Protocol and Registration

This study followed PRISMA guidelines and was not registered with PROSPERO.

2.2 Search Strategy

Databases used

PubMed, Cochrane, Science Direct.

Search Strategy

Identification

A total of 1,052 records were identified through systematic searches in PubMed (812), Cochrane (42), and ScienceDirect (170), along with 28 additional records obtained through manual searches and reference list screening. After removing 232 duplicates, 820 records remained for further screening.

Selection

During the screening stage, titles and abstracts were assessed for relevance. Of the 820 records, 640 were excluded as they were unrelated to polycystic ovary syndrome, infertility, or endometrial stem/progenitor cell markers. This initial selection step left 180 records that were potentially relevant for full-text review.

Eligibility

Full-text screening was performed for 180 articles. Of these, 160 were excluded for various reasons, including lack of explicit infertility status, absence of comparison groups, non-reporting of stem/progenitor cell markers, or being review articles rather than original research. This process resulted in 20 studies meeting all eligibility criteria.

Inclusion

Finally, 20 studies were included in the systematic review. These represented the most relevant and methodologically appropriate articles addressing molecular and cellular signatures of endometrial stem/progenitor cell markers in infertile women with and without polycystic ovary syndrome.

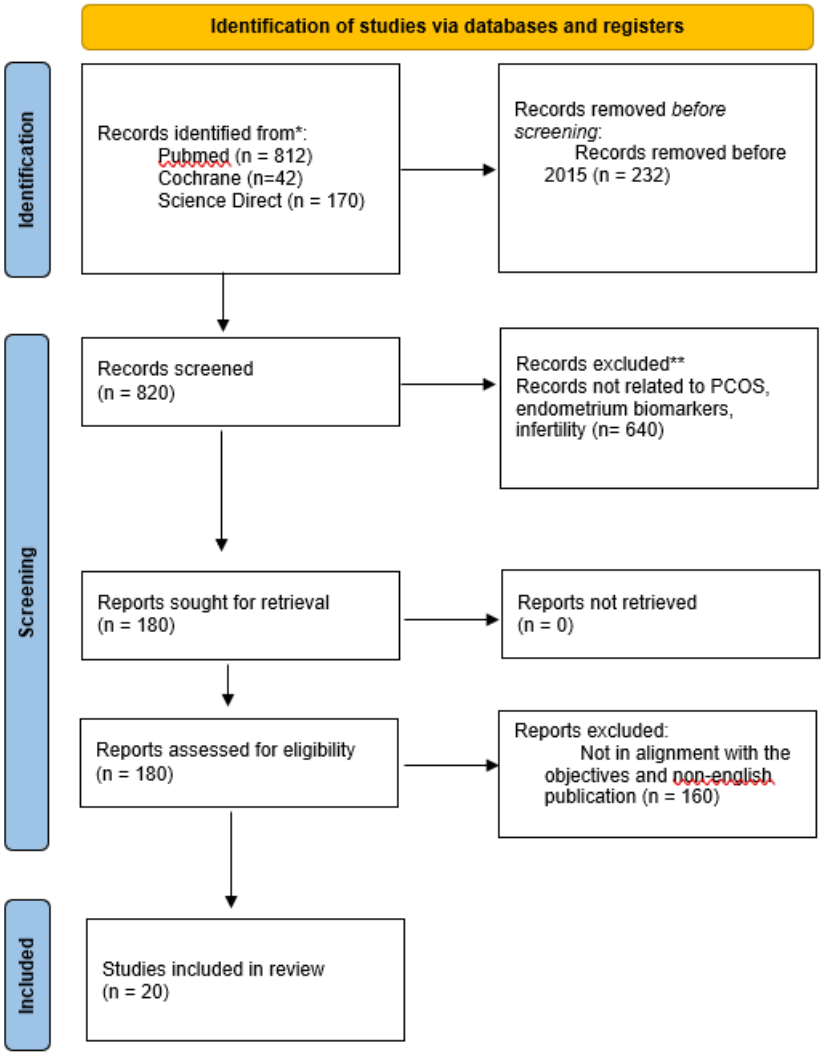

Figure 1: PRISMA Flowchart for the selection of studies.

Search strings

"Polycystic ovary syndrome" AND "infertility" AND "endometrium" AND "stem cells"

"PCOS" AND "endometrial tissue" AND "progenitor cells"

"Polycystic ovarian disease" AND "infertility" AND "endometrial cells" AND "stem cell markers"

"PCOS" AND "endometrium" AND "CD146"

"PCOS" AND "endometrium" AND "SUSD2"

"PCOS" AND "endometrium" AND "Lgr5"

"PCOS" AND "endometrium" AND "SSEA-1"

"PCOS" AND "endometrium" AND "N-cadherin"

"Polycystic ovary syndrome" AND "infertility" AND "mesenchymal stem cells"

"PCOS" AND "epithelial progenitors" AND "endometrial receptivity"

"PCOS" AND "endometrium" AND "regeneration potential"

"PCOS" AND "endometrium" AND "implantation outcomes"

2.3 Inclusion Criteria

- Human studies involving infertile women diagnosed with PCOS (based on Rotterdam or other recognized criteria), compared with infertile women without PCOS.
- Studies including a comparison group of infertile women without PCOS.
- Studies reporting molecular or immunohistochemical detection of endometrial stem/progenitor cell markers (e.g., CD146, SUSD2, Lgr5, SSEA-1, N-cadherin).
- Original research articles, including observational studies, case–control, cohort, clinical, or cross-sectional studies.
- Articles published in English.
- Studies published between 2015 and 2025.

2.4 Exclusion Criteria

- Animal studies only, case reports, editorials, or reviews.

- In vitro studies that do not provide specific data/reports on PCOS or infertility status.
- Studies that do not clearly report infertility status or fail to distinguish PCOS versus non-PCOS groups.
- Studies without explicit data on endometrial stem/progenitor cell markers.

2.5 Screening and Selection

The screening and selection process was conducted meticulously to ensure methodological rigor. Two independent reviewers initially screened all titles and abstracts to identify studies meeting the predefined inclusion criteria—those focusing on endometrial stem/progenitor cell markers in infertile women with and without PCOS. Studies unrelated to infertility, PCOS, or endometrial stem/progenitor markers were excluded. Articles selected at this stage underwent a detailed full-text review to determine eligibility. Any disagreements between reviewers regarding inclusion or exclusion were resolved through discussion and consensus. In cases where consensus could not be reached, a third reviewer provided arbitration to finalize decisions. This multi-tiered review process ensured objectivity, minimized selection bias, and guaranteed that only the most relevant and high-quality studies were included in the final synthesis.

2.6 Data Extraction

Data extraction was performed independently by two reviewers using a standardized form designed for consistency and accuracy. For each included study, key details were systematically recorded, including author name, publication year, country, and study design (observational, cohort, or case–control). Information regarding sample size, participant demographics, and diagnostic criteria for PCOS was extracted. The specific endometrial stem/progenitor markers studied—such as CD146, SUSD2, Lgr5, SSEA-1, and N-cadherin—were documented along with their detection methods, including PCR, immunohistochemistry, and transcriptomic analyses. Main findings relevant to marker expression patterns, hormonal influence, and clinical outcomes such as implantation success and endometrial receptivity were also captured. Cross-checking ensured data completeness, and discrepancies were resolved through consensus, ensuring reliability and reproducibility of the extracted dataset.

3. Results

3.1 Study Selection

A comprehensive search was conducted across PubMed, Cochrane, and ScienceDirect databases, yielding a total of 1,052 records, supplemented by 28 additional studies identified through manual and reference list searches. Following the removal of 232 duplicate entries, 820 records remained for title and abstract screening. Of these, 640 were excluded due to irrelevance to polycystic ovary syndrome, infertility, or endometrial stem/progenitor cell markers. The remaining 180 studies underwent full-text evaluation, after which 160 were excluded for lacking comparison groups, marker data, or appropriate study design. Ultimately, 20 studies met all eligibility criteria and were included in the systematic review.

3.2 Characteristics of Included Studies

Table 1: Study characteristic table:

S.No	Study design	Population	Outcome	Conclusion	Reference
1.	Comparative experimental study	Endometrial stromal cells cultured from endometrial biopsies of 50 fertile and 50 infertile women	Significantly lower expression of CD9 (P=0.0126) and CD146 (P=0.0006) was observed in the infertile group compared to fertile controls, as confirmed by both flow cytometry and real-time PCR	The decreased expression of these adhesion molecules suggests impaired endometrial receptivity and potential implantation failure, indicating their crucial role in fertility regulation and	Kank et al. (2018)

			analyses.	endometrial function.	
2.	Comparative observational study	Endometrial tissues collected during the mid-secretory phase from 17 women with ovarian endometrioma, 16 with uterine fibroids, and 6 healthy controls	E-cadherin expression was significantly increased, while N-cadherin expression was decreased in women with ovarian endometrioma and uterine fibroids compared to healthy controls.	This altered cadherin profile indicates disrupted epithelial–mesenchymal transition, leading to reduced endometrial receptivity and potential implantation failure.	Yun et al. (2024)
3.	Prospective observational study	Proliferative-phase endometrium obtained from 6 overweight/obese women with PCOS and 6 overweight/obese controls; fluorescence-activated cell sorting-isolated epithelial cells, stromal fibroblasts,	Microarray and RT-PCR analyses revealed upregulation of inflammatory and pro-oncogenic genes (CCL2, IL-6, ICAM1, LCN2) in epithelial and mesenchymal stem cells of PCOS women compared with controls.	These molecular alterations indicate an endometrial disease phenotype, potentially impairing endometrial receptivity and contributing to implantation failure independent of BMI.	Piltonen et al., (2013)

		endothelial cells, and mesenchymal stem cells	Immunohistochemistry confirmed increased protein expression.		
4.	Prospective experimental study	CD73+CD90+CD105+ multipotent stem/progenitor cells isolated from endometrium (n = 18) and endometriomas (n = 11) of women with endometriosis, and endometrium from healthy controls (n = 14); validation in paired tissue cohort (n = 19)	SC+ cells exhibited higher colony-forming efficiency, 3D-spheroid formation, and mesenchymal differentiation compared with SC−. Gene expression analyses revealed downregulation of PTEN and ARID1A, and aberrant expression of KIT, HIF2α, and E-cadherin in endometrioma-derived cells.	These molecular changes indicate stem/progenitor cell dysregulation, potentially contributing to malignant transformation and the development of endometriosis-associated ovarian cancers.	Srinivasan et al. (2018)
5.	Review	NA	Endometrial stem cells exhibit self-renewal and multilineage differentiation, supporting cyclic	Dysregulation of endometrial stem cells may contribute to infertility, endometriosis,	Hong (2022)

			regeneration and influencing fertility and endometrial health.	and endometrial cancer, highlighting their therapeutic potential.	
6.	Comparative experimental study with in vitro treatment	Endometrial tissues from 7 non-PCOS, 7 non-PCOS with endometrial hyperplasia, 14 PCOS, and 3 PCOS with endometrial hyperplasia patients	PCOS patients showed decreased Claudin 1 and increased Vimentin, Slug, N-cadherin, and p-CK 8 expression, along with elevated p-ERK1/2 and ERβ in epithelial cells. In vitro metformin treatment modulated EMT-related proteins differently depending on estrogen stimulation, increasing CK 8 and Snail while decreasing Claudin 1, ZO-1, Slug, N-cadherin, and α-SMA.	EMT contributes to endometrial dysfunction in PCOS, and metformin can differentially regulate EMT proteins under estrogenic influence.	Hu et al. (2020)

7.	Single-nucleus transcriptomic analysis of endometrial biopsies	27 women (5 controls, 12 PCOS at baseline, 7 post-metformin, 3 post-lifestyle intervention)	Identified cell-type-specific alterations and disease signatures in the endometrium of women with PCOS, with partial restoration after metformin or lifestyle intervention	PCOS alters endometrial cellular composition and function, contributing to impaired receptivity and disease risk; metformin and lifestyle therapy can reverse molecular dysfunction, highlighting potential therapeutic targets	Eriksson et al. (2025)
8.	Animal experiment (letrozole-induced PCOS in female Wistar rats) comparing treatment with endometrial stem cells (EnSCs), EnSCs +	Wistar rats induced with PCOS	PCOS induction caused high body and ovarian cyst weights, elevated testosterone, LH, AMH; lowered FSH &progesterone; reduced granulosa cells, immature follicles, corpus luteum. Treatment with	Transplantation of endometrial stem cells, especially when encapsulated in alginate/gelatin hydrogel, ameliorates key features of PCOS in rats (hormonal imbalance, inflammation, ovarian	Kouchakzadeh et al. (2024)

	alginate/gelatin hydrogel (SC-H), and clomiphene citrate over one month.		EnSCs and SC-H significantly reversed many of these hormonal, inflammatory, and histological changes.	histology), and may be a promising therapeutic strategy; though safety, mechanisms, and translation to humans need further study.	
9.	Review	Women with PCOS, varying phenotypes, compared with healthy controls; data drawn from histology, molecular studies, clinical observations.	There is evidence of altered endometrial histomorphology and abnormal expression of markers of receptivity during the implantation window in PCOS women. Progesterone resistance appears to be a key issue; many markers (e.g. of adhesion, hormones, receptors) are dysregulated; even high	Endometrial dysfunction in PCOS contributes significantly to subfertility beyond just ovulatory dysfunction. Altered receptivity—due to progesterone resistance and abnormal molecular/histological markers—is central in many PCOS women.	Benagiano et al. (2018)

			progesterone doses may not fully correct the receptivity defects		
10.	Animal / in vitro experimental study using a letrozole-induced PCOS rat model	Granulosa cells from PCOS rats (vs controls) in culture; treatments with MenSCs or exosomes.	PCOS granulosa cells had reduced mitochondrial biogenesis, increased oxidative stress, and lower estrogen output. Treatment with MenSCs and exosomes restored mitochondrial markers, reduced oxidative stress, and increased estrogen synthesis; MenSCs had stronger effect than exosomes.	Menstrual blood-derived stem cells (and to a lesser extent their exosomes) can ameliorate mitochondrial dysfunction and oxidative stress in PCOS granulosa cells, improving estrogen production. This suggests a potential cell-based therapy for PCOS, pending further mechanistic and translational studies.	Mansoori, M. et al. (2024)
11.	Experimental / organoid model development	Endometrial samples from women with PCOS (both	PCOS-derived endometrial epithelial organoids	PCOS EEOs retain disease-specific molecular and	Luyckx, L. et al. (2025)

	using endometrial biopsies from women with PCOS and controls	overweight/obese and lean) and matched controls; organoids established (n ≈ 4 per group)	(EEOs) were successfully generated. These PCOS EEOs showed increased expression of inflammatory genes (e.g. OSMR, ICAM1) and reduced expression of receptivity-associated genes, and had smaller size under hormonal stimulation compared to controls.	functional endometrial alterations and offer a novel in vitro model for studying endometrial dysfunction in PCOS. They may be used to probe mechanisms of altered receptivity and test interventions.	
12.	In vitro case–control study using cultured endometrial stromal fibroblasts (eSF)	eSF from 12 women diagnosed with PCOS (Rotterdam/NIH criteria) and 6 control women with normal cycles and no hyperandrogenism.	In culture, endometrial stromal fibroblasts (eSF) from PCOS women showed blunted decidualization in response to estradiol + progesterone: a subset failed to upregulate	Endometrial stromal fibroblasts from women with PCOS exhibit progesterone resistance with defective decidualization and pro-inflammatory/immune alterations, which may	Piltonen et al. (2015)

			IGFBP-1 and show morphological decidual changes. Their conditioned media had elevated secretion of IL-6, IL-8, GM-CSF, MCP1/3, CCL5, MMPs, and induced increased migration of monocytes and T cells compared with controls.	contribute to implantation failure and endometrial pathology in PCOS.	
13.	Review	Infertile women with PCOS across multiple studies	Identified key alterations in PCOS endometrium: decreased expression of adhesion molecules, impaired embryo adhesion, metabolic insufficiency, poorer perfusion, and a pro-	Endometrial dysfunction is a significant contributor to infertility in PCOS. The authors propose molecular biomarkers and altered pathways (inflammatory, energy metabolism, adhesion) as	Guo, F. et al. (2022)

			inflammatory milieu.	potential therapeutic targets to restore receptivity.	
14.	Review	Human (and animal model) studies	Compiled evidence that endometrial stem/progenitor cells (e.g. epithelial progenitors, mesenchymal stem cells) reside in defined niches interacting with stromal, vascular, ECM components, and signalling pathways (e.g. Wnt, Notch). Dysfunction in niche signalling is linked with disorders such as endometriosis, endometrial hyperplasia, infertility	Proper interplay between endometrial stem/progenitor cells and their niche is essential for cyclical regeneration and function. Disruption in niche signalling may underlie endometrial disease; targeting these cells or their microenvironment offers promise for regenerative therapies.	Sun et al. (2024)
15.	Doctoral dissertation	women with PCOS vs control	Found that in PCOS,	PCOS endometrium	Khatun, M. (2021).

		women	endometrial stromal and stem cell populations show altered gene expression related to progesterone signaling, inflammation, metabolism and mitochondrial dysfunction even without androgen exposure; STC-1 expression is blunted (secretory phase, stress response) in PCOS eSCs; high STC-1 in endometrial cancer tends to correlate with more favorable features.	exhibits stem cell dysfunction and impaired protective factors (like STC-1) even under non-androgenic conditions. These alterations may underlie impaired receptivity and increased disease risk; STC-1 may be potential biomarker or therapeutic target.	
16.	Review	-	The review found that MSCs and exosome therapies in animal models improved ovarian reserve, reduced	Stem cell–based approaches show real promise for treating female reproductive disorders (ovarian failure,	Nair, R. et al. (2025)

			fibrosis, enhanced endometrial regeneration, restored hormone levels, and improved fertility metrics. However, human trials remain scant, and safety, dosing, delivery, engraftment, and long-term efficacy are inadequately addressed.	endometrial damage), but translation to clinical practice is hindered by gaps in mechanistic understanding, lack of standardized delivery methods, and insufficient long-term safety data. Future work must optimize protocols and demonstrate efficacy in humans.	
17.	Review	-	The authors highlight that stem cell therapies have been shown to regenerate endometrial lining, restore ovarian follicle populations, and support oocyte	Stem cells, because of their differentiation and regenerative potential, represent a promising adjunct or alternative to current infertility treatments.	Chirputkar, R. & Vaidya, A. (2015)

			production in animal models; also, there is suggestion of stem cell activation of spermatogenesis in male models.	However, the authors caution that translation is preliminary; further mechanistic and clinical studies are needed before safe and effective therapies can be adopted.	
18.	Retrospective ultrasound / imaging study of PCOS patients	177 women aged 18–40 years with PCOS (by Rotterdam criteria) undergoing transvaginal ultrasound; a subset had histopathology results	22% (39/177) had abnormal endometrial ultrasound findings: thickened endometrium (14.7%), polyps (5.1%), submucous myoma (1.1%), malignancy (1.1%). Thickening, nonuniform echogenicity, and vascularity were significantly more common in abnormal cases.	Abnormal endometrial sonographic features are relatively frequent in women with PCOS and often present with heavy menstrual bleeding. However, no clinical or metabolic factor reliably predicts which PCOS patients harbor endometrial abnormalities. The detection of	Zoleta et al. (2025)

			Among the 9 who had histology, 3 (1.69%) had malignancy; no hyperplasia was found.	abnormal imaging (e.g. thickening, vascularity) should prompt further evaluation, given observed malignancies even in younger patients.	
19.	Review	-	The authors documented reduced expression (in PCOS) of key receptivity markers: leukemia inhibitory factor (LIF), HOXA10/HOXA 11, integrin αvβ3, and aberrant intercellular junction proteins (e.g. claudins). They also connected these changes mechanistically	Endometrial receptivity is substantially impaired in PCOS via downregulation of critical adhesion, cytokine, and signaling molecules, driven by the metabolic and endocrine derangements characterizing PCOS. While many biomarkers are identified, their clinical utility	Jiang & Li (2022)

			to hyperandrogenism, insulin resistance / hyperinsulinemia, inflammation, and obesity via pathways such as altered Wnt/β-catenin, PI3K/Akt, oxidative stress, and epigenetic regulation.	remains unvalidated. Therapeutic strategies should aim not only to restore ovulation but also to correct endometrial molecular dysfunction.	
20.	Histologic image analysis using an AI / deep learning model to segment epithelial and stromal compartments in endometrial biopsies from PCOS and recurrent implantation	91 endometrial samples from women with PCOS (various cycle phases, ovulatory and anovulatory) and 29 samples from RIF patients in a hormone replacement cycle.	The AI algorithm achieved high segmentation accuracy (92.4% epithelium, 99.2% stroma) versus pathologist reference. It showed that epithelial-to-stromal ratio changes across menstrual phases similarly in PCOS and controls; anovulatory	The AI method reliably quantifies epithelial vs stromal composition and reveals that PCOS (even anovulatory) does not markedly alter epithelial proportion compared to controls, but cyclical dynamics remain detectable. Use	Lee, S. et al. (2024).

	failure (RIF) patients		PCOS samples had epithelial proportions like proliferative phase (~14.5 %). No consistent differences in epithelial fraction were found between PCOS and RIF groups under HRT.	of AI could standardize and accelerate histologic endometrial evaluation in research and clinical settings.	
21.	Systematic review	Six eligible studies meeting inclusion criteria relating PCOS diagnosis (Rotterdam) and endometrial molecular markers.	The findings were inconsistent: MUC1 expression was reported higher in PCOS in some studies, whereas αvβ3 integrin was often lower. Estrogen receptor expression was generally increased in PCOS endometrium relative to controls.	The evidence suggests that dysregulation of adhesion molecules and overexpression of estrogen receptors may contribute to altered endometrial receptivity in PCOS. However, heterogeneity between studies limits strong conclusions. Better designed molecular	Baracat, M. C. P. et al. (2015)

				studies are needed to validate these as biomarkers or therapeutic targets.	
22.	Review	-	The review highlighted consistent findings of altered expression in estrogen and progesterone receptors, HOX genes, integrins, cytokines, and Wnt signaling in PCOS endometrium. It underscored malfunction of steroid receptors and downstream signaling as central to suboptimal receptivity in PCOS.	Intrinsic defects in endometrial gene regulation—particularly involving steroid receptor signaling—likely underlie impaired receptivity in PCOS. The author emphasizes need for better controlled studies to validate candidate genes and to understand how these molecular changes link to clinical phenotypes.	Alebić, M. Š. (2022)

3.3 Expression of Endometrial Stem/Progenitor Cell Markers

3.3.1 CD146 and SUSD2

CD146 (also known as MCAM) and SUSD2 are established markers of perivascular mesenchymal stem/progenitor cells within the human endometrium. These markers are not only critical for identifying stem cell populations but also play functional roles in cell adhesion, signaling, and vascular interactions necessary for endometrial homeostasis. Kank et al. (2018) investigated the expression of CD9 and CD146 in primary endometrial stromal cells obtained from 50 fertile and 50 infertile women. Their study utilized flow cytometry and real-time PCR to demonstrate that infertile women exhibited significantly lower CD146 expression (P=0.0006) compared to fertile controls, indicating impaired adhesion and disrupted stromal cell function. The authors proposed that reduced CD146 expression compromises endometrial receptivity and may contribute to implantation failure.

In a complementary line of evidence, Nair et al. (2025) conducted a comprehensive review of stem cell therapies for female reproductive disorders, highlighting that CD146/SUSD2-positive mesenchymal stem cells can enhance endometrial regeneration and reduce fibrosis in preclinical animal models. This underscores the potential of targeting these perivascular stem cells to restore normal endometrial structure and function, particularly in patients with PCOS where fibrosis, altered vascularization, and stromal dysfunction are frequently observed. Furthermore, Khatun (2021) reported that endometrial stem cells from women with PCOS show altered CD146 expression accompanied by dysregulated stromal differentiation and defective hormonal responsiveness, suggesting that intrinsic abnormalities in perivascular progenitor populations may contribute to the characteristic endometrial dysfunction in PCOS. Taken together, these findings emphasize that CD146 and SUSD2 are not only markers for identifying progenitor populations but are functionally relevant to the maintenance of endometrial receptivity and structural integrity.

3.3.2 Lgr5 and SSEA-1

Lgr5 and SSEA-1 have been identified as markers of highly proliferative epithelial and stromal progenitor cells in the endometrium. These markers are associated with stemness, self-renewal capacity, and the ability to differentiate into multiple endometrial cell lineages. Kouchakzadeh et al. (2024) studied endometrial stem cells (EnSCs) from

PCOS patients, which are enriched for Lgr5+ and SSEA-1+ populations. Their research demonstrated that encapsulation of these cells in alginate/gelatin hydrogels enhanced their viability, proliferation, and differentiation potential. These results suggest that biomaterial-based strategies can preserve stem cell function and potentially restore the regenerative capacity of the endometrium in PCOS.

Expanding on this, Luyckx et al. (2025) developed endometrial epithelial organoids derived from PCOS patients to model disease-associated dysfunction. These organoids exhibited altered gene expression profiles, impaired differentiation, and structural abnormalities reminiscent of the in vivo endometrium in PCOS. By providing a controlled platform to study cellular and molecular mechanisms, these organoids serve as a powerful tool for evaluating therapeutic interventions targeting Lgr5+ and SSEA-1+ progenitor cells. Chirputkar and Vaidya (2015) also highlighted that stem cell therapies could restore endometrial integrity and improve implantation outcomes, emphasizing the translational potential of these progenitor populations. The combination of in vitro and translational studies reinforces the importance of Lgr5 and SSEA-1 in maintaining endometrial plasticity, and illustrates how their dysfunction may underlie the reduced receptivity observed in PCOS patients.

3.3.3 N-cadherin

N-cadherin, a member of the cadherin family of adhesion molecules, plays a crucial role in epithelial–mesenchymal transition (EMT), stromal remodeling, and cellular interactions within the endometrium. Proper expression of N-cadherin is essential for the establishment of a receptive endometrial environment conducive to embryo implantation. Yun et al. (2024) examined N-cadherin and E-cadherin expression in mid-secretory endometrial samples from women with ovarian endometrioma and uterine fibroids, finding significantly reduced N-cadherin expression relative to healthy controls. This downregulation suggests impaired EMT and defective stromal remodeling, which could compromise endometrial receptivity.

Conversely, Hu et al. (2022) reported that N-cadherin, along with Vimentin and Slug, was upregulated in PCOS endometrium, whereas Claudin 1 was decreased, indicating an enhanced EMT state. These alterations may reflect adaptive or pathological responses to hormonal and metabolic imbalances inherent in PCOS. Piltonen et al. (2015) further demonstrated that PCOS-derived stromal fibroblasts exhibit impaired progesterone-mediated

decidualization, aberrant cytokine production, and enhanced immune cell migration, which may amplify endometrial dysfunction and alter N-cadherin-mediated adhesion. Baracat et al. (2015) emphasized that dysregulation of adhesion molecules, including integrins and N-cadherin, is a common feature in PCOS endometrium, suggesting widespread alterations in cell–cell and cell–matrix interactions. Additionally, Khatun (2021) highlighted that changes in N-cadherin expression within stem/progenitor populations could impair stromal differentiation and reduce endometrial plasticity, further contributing to implantation failure. Collectively, these studies suggest that both upregulation and downregulation of N-cadherin may disrupt the finely balanced EMT processes necessary for endometrial receptivity in PCOS.

3.4 Links to Endometrial Receptivity and Implantation

Endometrial receptivity is a complex phenomenon governed by hormonal, molecular, and structural cues. Disruptions in any of these components can reduce the ability of the endometrium to support embryo implantation, a common challenge in women with PCOS. Benagiano et al. (2018) provided a comprehensive overview of how hormonal imbalances, particularly hyperandrogenism and insulin resistance, influence endometrial morphology and function in PCOS. These metabolic and endocrine alterations result in delayed or incomplete differentiation of the endometrium, creating an environment less conducive to successful implantation.

Guo et al. (2022) identified specific molecular pathways and biomarkers indicative of impaired endometrial receptivity in infertile women with PCOS. Key alterations included downregulation of LIF, HOXA10/11, and integrin αvβ3, coupled with inflammatory and oxidative stress signatures, providing mechanistic insight into implantation failure. Supporting this, Zoleta et al. (2025) conducted a retrospective study using sonographic evaluation of PCOS patients and observed that abnormal endometrial thickness, focal lesions, and altered vascularity were common findings. These structural abnormalities correlated with clinical features such as abnormal uterine bleeding, suggesting a link between morphological alterations and functional impairments in receptivity. Jiang and Li (2022) further elucidated the molecular mechanisms underlying these changes, highlighting the combined impact of insulin resistance, hyperandrogenism, and inflammation on Wnt/PI3K signaling and integrin-mediated adhesion.

Collectively, these studies indicate that both molecular and structural defects

converge to impair the endometrium's ability to support implantation. Emerging therapeutic strategies, including stem cell therapy, organoid-based modeling, and pharmacologic interventions such as metformin, aim to restore normal endometrial morphology, molecular signaling, and progenitor cell function, ultimately improving receptivity in women with PCOS.

3.5 Molecular and Cellular Patterns

Single-cell and molecular analyses have provided unprecedented insight into the heterogeneity of the endometrium in health and disease. Eriksson et al. (2025) performed single-cell RNA sequencing on over 247,000 isolated endometrial nuclei from women with PCOS and controls. They identified cell-type-specific molecular signatures, variations in cellular composition, and aberrant spatial localization patterns in the endometrium of PCOS patients. Importantly, lifestyle interventions and metformin treatment partially restored these molecular profiles, highlighting both the plasticity of endometrial cells and the potential for therapeutic modulation.

Piltonen et al. (2013) demonstrated that isolated epithelial, stromal, and mesenchymal stem cell populations from PCOS endometrium exhibit a distinct "disease phenotype," characterized by upregulation of inflammatory and oncogenic genes, including IL-6, ICAM1, CCL2, and LCN2. These changes occurred independently of BMI, indicating that intrinsic cellular alterations, rather than systemic obesity, drive endometrial dysfunction. The heightened inflammatory and cellular stress state may compromise implantation and increase the risk of endometrial pathology over time.

Srinivasan et al. (2018) investigated CD73+CD90+CD105+ multipotent stem/progenitor cells from endometrium and endometriomas. These cells demonstrated enhanced colony formation, spheroid generation, and mesenchymal differentiation relative to SC− cells. Gene expression analyses revealed downregulation of tumor suppressors PTEN and ARID1A alongside aberrant stem cell and cancer-associated gene expression, suggesting that progenitor cell dysfunction may contribute to pathological transformations in endometrial tissue.

Mansoori et al. (2024) focused on menstrual blood-derived stem cells (MenSCs) and their exosomes, assessing their impact on granulosa cells from PCOS models. MenSCs and exosomes improved mitochondrial biogenesis, reduced oxidative stress, and enhanced estrogen production, with MenSCs demonstrating superior efficacy. This supports the role of stem/progenitor cells in modulating

cellular metabolism and endocrine function, highlighting their therapeutic potential for restoring endometrial and ovarian health in PCOS.

Sun et al. (2024) reviewed the characteristics of endometrial stem/progenitor cells and their niches, emphasizing how cellular interactions, paracrine signaling, and microenvironmental factors influence tissue regeneration. The review also explored translational applications, including stem cell-based therapies, organoid culture systems, and biomaterials, all aimed at correcting endometrial dysfunction. Alebić (2022) highlighted transcriptional dysregulation in PCOS endometrium, including altered steroid receptor, HOX gene, integrin, and Wnt pathway expression, corroborating the molecular patterns observed in experimental studies. Finally, Lee et al. (2024) applied AI-based histological analysis to PCOS and recurrent implantation failure endometrium, revealing that epithelial-to-stromal ratios remain largely preserved, but subtle spatial and compositional alterations can influence receptivity. These findings underscore the value of combining molecular, cellular, and computational approaches to comprehensively characterize endometrial dysfunction in PCOS.

4. Discussion

4.1 Principal Findings

The current review highlights critical alterations in endometrial stem/progenitor cell populations and molecular pathways in women with polycystic ovary syndrome (PCOS), providing insights into the mechanisms underlying impaired endometrial receptivity and implantation failure. Evidence from multiple studies indicates that perivascular mesenchymal stem/progenitor cells marked by CD146 and SUSD2 exhibit reduced expression, suggesting compromised stromal function and adhesion, which may contribute to suboptimal endometrial regeneration (Chaudhari-Kank et al., 2018; Khatun, 2021; Nair et al., 2025). Similarly, epithelial progenitor markers Lgr5 and SSEA-1 are associated with diminished proliferation and differentiation potential in PCOS, highlighting impaired regenerative capacity within the glandular compartment (Kouchakzadeh et al., 2024; Luyckx et al., 2025). Dysregulated expression of adhesion molecules, particularly N-cadherin, indicates altered epithelial–mesenchymal transition and stromal remodeling in the PCOS endometrium (Yun et al., 2024; Hu et al., 2020; Piltonen et al., 2015). Morphological and molecular assessments,

including abnormal endometrial thickness, vascular patterns (Zoleta et al., 2025), and downregulation of receptivity-associated genes such as integrins, HOXA10/11, and LIF (Guo et al., 2022; Jiang & Li, 2022; Alebić, 2022), collectively point to both structural and molecular dysfunctions in PCOS endometrium. These findings emphasize the potential for therapeutic strategies, including stem cell interventions and metabolic modulation, to restore endometrial health and enhance fertility outcomes (Mansoori et al., 2024; Sun et al., 2024).

4.2 Comparison with Existing Literature

The findings summarized in this review are consistent with, and extend, prior studies examining endometrial dysfunction in PCOS. Reduced expression of CD146 and SUSD2 in perivascular endometrial stem/progenitor cells aligns with the observations of Chaudhari-Kank et al. (2018), who reported lower CD146 expression in infertile women, indicating impaired stromal adhesion and cell–cell communication. Khatun (2021) further noted that stem/progenitor cell populations in PCOS display altered differentiation and reduced capacity for progesterone-mediated decidualization, suggesting that intrinsic cellular abnormalities contribute to diminished regenerative potential in the endometrium. Nair et al. (2025) highlighted that restoration of CD146/SUSD2-positive mesenchymal progenitors could improve endometrial structure and receptivity, emphasizing the therapeutic relevance of targeting these cell populations.

Epithelial progenitor markers Lgr5 and SSEA-1, indicative of proliferation and regenerative potential, are similarly affected in PCOS endometrium. Kouchakzadeh et al. (2024) demonstrated that encapsulation of endometrial stem cells enriched for Lgr5 and SSEA-1 in alginate/gelatin hydrogels improved their viability and differentiation, underscoring their therapeutic potential. Luyckx et al. (2025) developed endometrial organoids from PCOS patients, which exhibited altered gene expression and impaired differentiation, providing a model for studying disease-specific epithelial dysfunction. These findings are in line with the discussion by Chirputkar and Vaidya (2015), who proposed that stem cell-based therapies may help restore normal endometrial architecture and function, enhancing implantation outcomes in women with PCOS.

Altered N-cadherin expression, reflecting dysregulated epithelial–mesenchymal

transition (EMT), has been frequently reported. Yun et al. (2024) observed decreased N-cadherin in women with ovarian endometrioma and uterine fibroids, indicating impaired stromal remodeling. In contrast, Hu et al. (2020) reported increased N-cadherin, Vimentin, and Slug in PCOS endometrium, suggesting a heightened EMT state. Piltonen et al. (2015) further showed that stromal fibroblasts from PCOS patients have aberrant cytokine production and impaired decidualization, which may interact with cadherin-mediated pathways to influence implantation. Baracat et al. (2015) reviewed evidence demonstrating widespread dysregulation of adhesion molecules and estrogen receptor signaling in PCOS endometrium, supporting the notion that disruptions in cell–cell and cell–matrix interactions are central to endometrial dysfunction.

In terms of endometrial receptivity, Benagiano et al. (2018) emphasized that hormonal and metabolic imbalances characteristic of PCOS alter endometrial morphology and gene expression, which compromise implantation potential. Guo et al. (2022) identified disrupted molecular pathways, including downregulation of integrins, HOXA10/11, and leukemia inhibitory factor (LIF), providing a mechanistic explanation for implantation failure. Zoleta et al. (2025) observed abnormal endometrial thickness and vascular patterns through ultrasonography, complementing molecular evidence of impaired receptivity. Jiang and Li (2022) highlighted insulin resistance and hyperandrogenism as upstream modulators of endometrial gene expression, aligning with observed alterations in adhesion and stem/progenitor cell function. Alebić (2022) further corroborated these findings by reviewing gene expression profiles that distinguish PCOS endometrium from healthy controls, particularly in steroid and adhesion-related pathways.

Emerging therapeutic perspectives are also consistent with these findings. Mansoori et al. (2024) demonstrated that menstrual blood-derived stem cells and their exosomes improve mitochondrial function and reduce oxidative stress in granulosa cells, suggesting a systemic interaction between ovarian and endometrial function. Sun et al. (2024) reviewed endometrial stem/progenitor cell niches and their regulatory mechanisms, highlighting the potential for regenerative strategies to restore endometrial receptivity. Collectively, the literature indicates that PCOS endometrium exhibits structural, molecular, and cellular abnormalities, particularly in stem/progenitor cell populations, adhesion molecules, and

receptivity-associated pathways, and that targeted interventions may enhance endometrial function and fertility outcomes.

4.3 Clinical Implications

The observed differential expression of endometrial stem/progenitor cell markers—including CD146, SUSD2, Lgr5, SSEA-1, and N-cadherin—offers a promising window into the molecular underpinnings of endometrial dysfunction in women with Polycystic Ovary Syndrome (PCOS). These markers reflect the regenerative capacity and structural integrity of both stromal and epithelial compartments within the endometrium, which are critical determinants of successful implantation and fertility. Altered expression of CD146 and SUSD2, for instance, indicates impaired perivascular stromal populations, potentially resulting in defective stromal remodeling, abnormal angiogenesis, and reduced responsiveness to hormonal cues. Likewise, dysregulation of epithelial progenitor markers such as Lgr5 and SSEA-1 may compromise glandular renewal and epithelial integrity, thereby reducing the establishment of a receptive endometrial surface. N-cadherin, as a key adhesion molecule, mediates epithelial–stromal interactions, cellular migration, and tissue remodeling; its abnormal expression can disrupt these processes, contributing further to implantation failure. From a diagnostic standpoint, assessing the quantitative expression of these markers in endometrial biopsies could help stratify women with PCOS based on the extent of their stromal and epithelial impairment. Such stratification could inform individualized fertility management, allowing clinicians to identify patients most likely to benefit from specific interventions or assisted reproductive technologies.

Therapeutically, these findings highlight potential targets for improving endometrial receptivity. Strategies aimed at restoring CD146+ stromal populations may enhance vascularization, modulate immune interactions, and promote proper stromal remodeling, which is essential for supporting embryo implantation. Similarly, interventions designed to normalize N-cadherin-mediated adhesion could improve epithelial–stromal communication, facilitate epithelial renewal, and reinforce tissue architecture. Biomaterial-based approaches, such as hydrogel encapsulation of stem/progenitor cells or targeted growth factor delivery, may further support the viability and function of these progenitor populations. In addition, pharmacologic interventions—

including metformin, anti-inflammatory agents, or hormonal modulators—could indirectly influence progenitor cell function by mitigating metabolic or inflammatory disturbances common in PCOS. Collectively, these approaches underscore the translational potential of integrating molecular profiling into clinical practice, bridging mechanistic insights with patient-specific therapeutic strategies to optimize fertility outcomes.

4.4 Methodological Strengths and Limitations

This systematic review benefits from a carefully defined methodology, focusing exclusively on molecular and cellular markers that are directly relevant to endometrial regeneration and implantation. By integrating evidence from both stromal and epithelial progenitor cells, as well as adhesion molecules, the review provides a comprehensive perspective on the mechanisms underlying endometrial dysfunction in PCOS. Furthermore, the inclusion of studies employing diverse methods—including immunohistochemistry, flow cytometry, and single-cell RNA sequencing—allows for an enriched understanding of cellular heterogeneity, spatial localization, and functional potential of progenitor populations. However, several limitations warrant consideration. Many primary studies included small sample sizes, limiting statistical power and potentially biasing results. Methodological heterogeneity, particularly regarding marker detection techniques, protocols, and reporting standards, complicates direct comparisons across studies. Moreover, inconsistent documentation of menstrual cycle phase, hormonal status, and infertility etiology reduces generalizability and prevents formal meta-analytic synthesis. Despite these constraints, the review consolidates key findings and highlights consistent patterns of progenitor cell dysregulation in PCOS, providing a valuable foundation for future research.

4.5 Future Research Directions

Future investigations should prioritize the development and adoption of standardized protocols for measuring endometrial progenitor and adhesion markers, accounting for cycle phase, hormonal context, and sampling methodology. Large, multicenter studies with adequately powered cohorts are essential to validate observed associations between progenitor cell marker dysregulation and clinical fertility outcomes, including implantation rates, pregnancy success, and miscarriage risk. Emerging technologies, such as AI-assisted histological imaging, automated

cell quantification, and spatial transcriptomics, hold the potential to provide high-resolution, high-throughput analyses of endometrial architecture and cellular composition, enabling precise mapping of progenitor cell niches. Furthermore, longitudinal studies are needed to track dynamic changes in stem/progenitor populations across menstrual cycles, during assisted reproduction, and in response to therapeutic interventions. Integrating molecular and cellular signatures with clinical outcomes, metabolic profiles, and hormonal milieu will facilitate the identification of predictive biomarkers for endometrial receptivity. Such research could inform targeted interventions—whether pharmacologic, regenerative, or biomaterial-based—aimed at restoring endometrial function in women with PCOS. Ultimately, these advances will enable a precision medicine approach to infertility care, moving beyond generalized hormonal management toward addressing the cellular and molecular foundations of endometrial dysfunction and optimizing reproductive outcomes.

5. Conclusion

This review demonstrates that endometrial stem and progenitor cell markers—including CD146, SUSD2, Lgr5, SSEA-1, and N-cadherin—exhibit distinct expression patterns in PCOS compared with non-PCOS infertile women, reflecting impaired stromal regeneration, epithelial renewal, and adhesion dynamics. These molecular signatures offer potential diagnostic and therapeutic utility, enabling identification of endometrial dysfunction and guiding interventions to improve implantation outcomes. The safety and feasibility of assessing such markers in clinical or research settings is increasingly supported. Future work should prioritize standardized protocols, larger multicenter studies, and integration of molecular assessments with clinical fertility outcomes to enhance personalized reproductive care.-3

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