**Sriwijaya Journal of Obstetrics and Gynecology**
Vol. 4, No. 2, 2026, pp. 56-71· e-ISSN 2986-9838 *journal homepage: phlox.or.id/index.php/sjog*

*Systematic Review*

# Translational Insights into the Pathogenesis, Molecular Biomarkers, and Targeted Therapeutics of Endometriosis in Non-Human Primate Models: A Systematic Review

Yohanes Adam Elsoin[1*], Hermawan Wibisono[1]

[1]*Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar General Hospital, Malang, Indonesia*

**ARTICLE INFO**

**Article history:**
**Received:** August 15, 2026
**Revised:** September 10, 2026
**Accepted:** October 2, 2026
**Available Online:** October 20, 2026
**Published:** October 30, 2026

**Keywords:**
Biomarkers
Endometriosis
Macaca fascicularis
Non-human primates
Systematic review

***Corresponding author:**
Yohanes Adam Elsoin
**E-mail:** elsoinyohanes@gmail.com
**DOI:** 10.59345/sjog.v4i2.380

**ABSTRACT**

**Background:** Endometriosis is a chronic, estrogen-dependent gynecological disorder affecting 10–15% of reproductive-aged women worldwide. Unlike rodents, Old World non-human primates (NHPs) menstruate spontaneously and develop lesions that are histologically indistinguishable from human disease.

**Objective:** To evaluate NHP evidence on the pathogenesis, molecular and imaging biomarkers, and targeted therapeutics of endometriosis.

**Methods:** This review followed PRISMA 2020 and Synthesis Without Meta-analysis (SWiM) guidelines. Four databases were searched through July 2026 for original NHP endometriosis studies. Risk of bias (five domains) and certainty (GRADE narrative) were appraised.

**Results:** Of 426 records, 20 studies (N = 299 NHPs: 132 olive baboons, 96 rhesus macaques, 55 cynomolgus macaques, and 16 mixed macaques) were synthesized in four clusters. In Cluster 1 (k = 5, N = 85), rosiglitazone (−51.8% lesion area), letrozole, the 17β-HSD1 inhibitor PBRM (−67% red lesions), and dienogest reduced lesion burden or central pain sensitization; testosterone with a Western-style diet accelerated Stage III/IV endometrioma. In Cluster 2 (k = 4, N = 61; Low certainty), bentamapimod and rhTNFbp-1 regressed active lesions, anti-TNF-α mAb c5N did not improve fecundity (18% vs. 30% placebo), and intraperitoneal mesenchymal stem cells worsened endometriosis scores (P = 0.02). Cluster 3 (k = 8, N = 109) described collective invasion, mitochondrial depletion, Treg:Th17 dysbiosis, 92.9% induction by intrauterine puncture, and oviductal Anoctamin-1 attenuation. Cluster 4 (k = 3, N = 44) reported serum miRNAs, CXCL13, and PET/CT imaging.

**Conclusion:** NHP models offer high translational fidelity for developing fertility-sparing therapeutics and biomarkers; small, short-term studies limit certainty.

*The authors have reviewed and approved the final version of the manuscript.*

**Copyright:** © 2026 The Author(s). Published by Phlox Institute: Indonesian Medical Research Organization, on behalf of the Sriwijaya Journal of Obstetrics and Gynecology. The authors retain copyright of the work.

**Access licence:** This is an open access article distributed under the terms of the Creative Commons Attribution–NonCommercial–ShareAlike 4.0 International Licence (CC BY-NC-SA 4.0), which permits non-commercial use, sharing, adaptation and reproduction in any medium, provided the original author and source are credited and any derivative work is distributed under the same licence.

## 1. Introduction

Endometriosis is a chronic, painful gynecological disorder that depends on estrogen. Endometrial-like glands and stroma become established outside the uterine cavity, acquire a blood and nerve supply, and remodel with each cycle [1–3]. About 10% to 15% of women of reproductive age are affected worldwide. Among women with chronic pelvic pain or unexplained subfertility the figure rises to 35% to 50%. The clinical, psychological, and socioeconomic burden is heavy [4–7]. Patients often report severe dysmenorrhea, deep dyspareunia, dyschezia, and chronic pelvic pain outside menses. Monthly fecundity is only 2% to 10%, against 15% to 20% in unaffected women of the same age [8,9]. Severe ovarian and deep infiltrating disease has also been linked, in epidemiological and propensity score-adjusted clinical studies, to a higher risk of clear-cell and endometrioid ovarian cancer, to systemic chronic inflammation, and to fibrotic pelvic adhesions that often return after surgical excision [1,3,10]. More than a century has passed since Sampson proposed retrograde menstruation. Over 90% of menstruating women have retrograde tubal reflux, yet only 10% to 14% develop progressive

peritoneal, ovarian, or deep nodular disease. The molecular and immunological reasons for this gap are still incompletely understood [4,11,12].

Current treatment relies mainly on laparoscopic cytoreduction or on systemic hormonal suppression. The drugs used are combined oral contraceptives, oral or intrauterine progestins, gonadotropin-releasing hormone (GnRH) agonists or antagonists, and aromatase inhibitors [13,14]. Hormonal therapy induces temporary amenorrhea and relieves pain in a subset of patients. It also inhibits ovulation, prevents spontaneous conception in women who want a pregnancy, causes hypo-estrogenic vasomotor symptoms and bone mineral density loss, and does not eradicate deep fibrotic lesions. Symptoms recur in more than 40% to 50% of patients within five years of stopping treatment [13,15]. At the cellular level, ectopic implants survive, escape immune clearance, and invade the host pelvic peritoneum. Several processes interact to allow this: local intracrine estradiol synthesis by aromatase (CYP19A1) and 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1), an imbalance of progesterone receptor isoforms (PR-A/PR-B), activation of steroid receptor coactivator-2 (SRC-2), secretion of interleukin-1α (IL-1α), IL-6, IL-12, and tumor necrosis factor-α (TNF-α) by macrophages, epigenetic N6-methyladenosine (m6A) RNA methylation, resistance to ferroptosis, and angiogenesis driven by extracellular vesicles [2,15–21]. Non-hormonal, fertility-sparing drugs and accurate non-invasive diagnostic biomarkers will require these networks to be studied in physiologically relevant longitudinal preclinical systems [22–26].

Biological differences between laboratory rodents and menstruating primates are a major barrier to translation [11,12,27]. Rodent models are made by suturing or injecting uterine horn fragments, or human menstrual blood-derived stromal cells, into the peritoneal cavity of immunocompetent or immunodeficient mice and rats. They are cheap, scale to large samples, and allow genetic manipulation [4,11,12,28]. But rodents have a short four-to-five-day estrous cycle without luteal decidualization. They show no spontaneous spiral arteriolar vasoconstriction or menstrual shedding, lack a conserved functionalis-basalis interface in the endometrium, and never develop endometriosis spontaneously [27,29,30]. Old World non-human primates differ on each point. The olive baboon (Papio anubis), the rhesus macaque (Macaca mulatta), and the cynomolgus macaque (Macaca fascicularis) share >93% genomic sequence identity with humans. They have a 28-to-32-day menstrual cycle with cyclic progesterone withdrawal bleeding. They also develop spontaneous endometriosis, in up to 27% of captive baboons, 28.7% of cynomolgus macaques, and 36% of rhesus macaques in aged colonies. The lesions include red vesicular, powder-burn, white fibrotic, ovarian endometrioma (chocolate cyst), and deep nodular types, and they look the same as human disease macroscopically and histologically [27,31–35]. Disease can also be started on a known date. Autologous menstrual endometrium can be seeded surgically into the pelvis of baboons, and trans-myometrial intrauterine puncture can be used in macaques, so that onset and treatment stage are controlled precisely [36–38]. Primate studies have nevertheless reported results that seem to conflict. TNF-α blockade affects lesion regression and cycle fecundity differently. Aromatase inhibition causes bilateral ovarian cysts. Intraperitoneal delivery of mesenchymal stem cells worsens endometriosis, depending on the route. Steroid receptor positron emission tomography has limited spatial resolution. These findings need a rigorous systematic synthesis [39–43].

This systematic review provides a synthesis of 20 primary experimental and observational NHP studies (299 primates of the species Papio anubis, Macaca mulatta, and Macaca fascicularis) that complies with PRISMA 2020 and the Synthesis Without Meta-analysis (SWiM) guideline. The studies are mapped to four translational clusters. The first covers endocrine and metabolic pharmacotherapy. The second covers immunomodulatory and cell-based interventions. The third covers spontaneous and induced pathophysiology, including collective cell invasion, mitochondrial bioenergetics, mucosal microbiome dynamics, central fMRI pain sensitization, and oviductal pacemaker channel attenuation. The fourth covers non-invasive liquid biopsy and molecular imaging biomarkers [44–48]. The aim was to evaluate and synthesize the preclinical evidence from NHP models of endometriosis systematically. We wished to clarify disease pathogenesis, validate emerging diagnostic biomarkers, and appraise the efficacy and reproductive safety of targeted therapies for clinical translation.

## 2. Methods

### *2.1. Study design and reporting guidelines*

This systematic literature review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [44]. It also follows the Synthesis Without Meta-analysis (SWiM) reporting guideline for systematic reviews of heterogeneous preclinical and translational interventions [45]. A quantitative meta-analysis was not appropriate. Pooled standardized mean differences, odds ratios, risk ratios, forest plots, and funnel plots would have been misleading, because the primate evidence is heterogeneous along four axes: (i) three Old World primate species differ in evolution and anatomy: olive baboons (Papio anubis), rhesus macaques (Macaca mulatta), and cynomolgus macaques (Macaca fascicularis); (ii) disease arises in different ways, from multi-year spontaneous colony endometriosis to surgical induction by transcervical endometrial curettage with intrapelvic seeding or by laparoscopic intrauterine fundal puncture; (iii) the pharmacological, dietary, surgical, and cell-based exposures do not overlap, and follow-up ranges from 25 days to 7 years; and (iv) primary outcomes are measured on incommensurable scales. These include macroscopic lesion surface area ($mm^2$), three-dimensional nodule volume ($mm^3$), revised American Society for Reproductive Medicine (rASRM) scores, mitochondrial oxygen consumption rates (OCR), positron emission tomography standardized uptake values (SUVs), and functional magnetic resonance imaging (fMRI) blood-oxygen-level-dependent (BOLD) signals [44,45]. A structured qualitative SWiM synthesis was used instead, with a Grading of Recommendations Assessment, Development and Evaluation (GRADE) narrative certainty profile.

### *2.2. Search strategy and information sources*

Four major electronic bibliographic databases were searched systematically: PubMed/MEDLINE (n = 148 records), Scopus (n = 134), Web of Science Core Collection (n = 82), and ScienceDirect (n = 48). The search covered peer-reviewed studies published from January 2007 through July 2026. Backward and forward citation tracking of primate reproductive medicine publications added n = 14 records. Controlled vocabulary (Medical Subject Headings [MeSH]) and free-text terms were combined with Boolean operators (AND, OR, NOT) in titles, abstracts, and keywords. The exact PubMed/MEDLINE string was: (("Endometriosis"[Mesh] OR "endometriosis"[Title/Abstract] OR

"endometriotic"[Title/Abstract] OR "ectopic endometrium"[Title/Abstract] OR "deep nodular endometriosis"[Title/Abstract]) AND ("Primates"[Mesh] OR "Papio"[Mesh] OR "Macaca"[Mesh] OR "Macaca mulatta"[Mesh] OR "Macaca fascicularis"[Mesh] OR "Models, Animal"[Mesh] OR "non-human primate*"[Title/Abstract] OR "nonhuman primate*"[Title/Abstract] OR "baboon*"[Title/Abstract] OR "Papio anubis"[Title/Abstract] OR "rhesus macaque*"[Title/Abstract] OR "Macaca mulatta"[Title/Abstract] OR "cynomolgus"[Title/Abstract] OR "Macaca fascicularis"[Title/Abstract]) AND ("pathogenesis"[Title/Abstract] OR "etiology"[Title/Abstract] OR "biomarker*"[Title/Abstract] OR "microRNA*"[Title/Abstract] OR "miRNA"[Title/Abstract] OR "positron emission tomography"[Title/Abstract] OR "therapeutic*"[Title/Abstract] OR "treatment"[Title/Abstract] OR "laparoscop*"[Title/Abstract] OR "lesion*"[Title/Abstract] OR "immun*"[Title/Abstract] OR "mitochondria*"[Title/Abstract])) NOT ("Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Editorial"[Publication Type] OR "Comment"[Publication Type]). The same Boolean logic was adapted to the field tags of the other databases (TITLE-ABS-KEY in Scopus and TS= in Web of Science).

### 2.3. Eligibility criteria

Eligibility was defined with a structured Population, Intervention/Exposure, Comparator, Outcome, and Study Design (PICOS/PECOS) framework, shown in Table 1. Peer-reviewed original articles in English were eligible. They had to study female non-human primates with spontaneous or experimentally induced endometriosis, and to report quantitative or semi-quantitative data on macroscopic lesion burden, pathophysiological or molecular pathways, diagnostic biomarkers, or reproductive and safety endpoints. We excluded narrative reviews, systematic reviews, meta-analyses, editorials, and conference abstracts without full text. We also excluded purely in vitro studies that used no NHP tissue or peritoneal fluid, and studies of non-primate species only (mice, rats, rabbits, or swine) without a primary NHP cohort.

**Table 1.** Structured PICOS/PECOS inclusion and exclusion criteria for study selection.

| PICOS Domain | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Population (P) | Female non-human primates (olive baboons [Papio anubis], rhesus macaques [Macaca mulatta], and cynomolgus macaques [Macaca fascicularis]) with spontaneous or surgically induced endometriosis. | Rodent models (mice, rats, hamsters), lagomorphs, swine, or purely in vitro cell culture lines without primary NHP tissues/fluids. |
| Intervention / Exposure (I/E) | Pharmacological agents (PPAR-γ agonists, aromatase inhibitors, 17β-HSD1 inhibitors, progestins, JNK inhibitors, anti-TNF-α biologics, statins, stem cells), surgical induction protocols, metabolic/dietary exposures, or pathophysiological/biomarker profiling. | Interventions unrelated to endometriosis or general primate husbandry studies lacking endometriosis-specific analyses. |
| Comparator (C) | Placebo or vehicle-treated endometriotic NHP controls, sham-operated primates, healthy non-endometriotic NHP controls, active hormonal controls (GnRH antagonists), or paired baseline eutopic endometrium. | Studies lacking an internal baseline, control group, or defined histological comparator. |
| Outcomes (O) | Quantitative or semi-quantitative macroscopic lesion burden (surface area, volume, rASRM score), cellular/molecular pathway dynamics, non-invasive biomarkers (miRNAs, CXCL13, PET/CT SUVs), pain behaviour/fMRI, or fertility/safety outcomes. | Studies reporting purely anecdotal observations without measurable pathophysiological, diagnostic, or therapeutic endpoints. |
| Study Design (S) | Original peer-reviewed experimental in vivo/ex vivo studies, randomized controlled preclinical trials, and prospective/retrospective cohort or case-control studies published in English. | Narrative reviews, systematic reviews, meta-analyses, editorials, letters, conference abstracts, or non-English articles. |

***Notes:*** *Abbreviations: 17β-HSD1, 17β-hydroxysteroid dehydrogenase type 1; fMRI, functional magnetic resonance imaging; GnRH, gonadotropin-releasing hormone; JNK, c-Jun $NH_2$-terminal kinase; miRNA, microRNA; NHP, non-human primate; PET/CT, positron emission tomography/computed tomography; PPAR-γ, peroxisome proliferator-activated receptor-γ; rASRM, revised American Society for Reproductive Medicine; SUV, standardized uptake value; TNF-α, tumor necrosis factor-α.*

### 2.4. Study selection and data extraction

The 426 bibliographic records came from the databases (n = 412) and from citation searches (n = 14). They were imported into a reference manager, and duplicates (n = 168) were removed. The 258 unique titles and abstracts were then screened independently against the pre-specified PICOS criteria. Full texts of 62 potentially eligible articles were assessed. Data were extracted independently with a standardized 24-column matrix. The columns were: (1) author and publication year; (2) country and primate research center; (3) study design; (4–6) total, exposed, and control sample sizes; (7–8) NHP species, diagnostic confirmation, and age and weight; (9–11) dosing protocol, comparator regimen, and follow-up timing; (12–14) primary outcome instruments, exact quantitative results (mean ± SD, median [IQR], percentage change, $R^2$, and P values), and secondary or safety endpoints; (15–17) biological mechanism, direction of effect, and SWiM thematic cluster; and (18–24) domain-specific risk-of-bias ratings and study limitations. Every extracted number was checked against the primary article. No statistical imputation was used.

### 2.5. Methodological quality and risk of bias assessment

Each study's methodological quality and internal validity were assessed with one five-domain risk-of-bias (RoB) framework. It was adapted from the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) Risk of Bias tool for experimental animal studies and from the Joanna Briggs Institute (JBI) critical appraisal checklists for longitudinal and case-control primate investigations. Domain 1 (D1: Selection and Randomization Bias) covered sequence generation, baseline staging laparoscopy equivalence, allocation concealment, and case-control age and cycle matching. Domain 2 (D2: Confounding and Deviations from Intended Interventions) covered housing parity, synchronization of menstrual cycle phase, and protocol adherence. Domain 3 (D3: Missing Outcome Data and Attrition Bias) covered animal mortality, biopsy adequacy, and completeness of longitudinal follow-up. Domain 4 (D4: Outcome Measurement and Detection Bias) covered blinding during videolaparoscopic rASRM scoring, histomorphometry, qRT-PCR, respirometry, and neuroimaging. Domain 5 (D5: Selective Reporting Bias) checked that stated methods matched the reported quantitative outcomes. Each domain, and overall study quality, was rated 'Low'

(+), 'Moderate / Some Concerns' (?), or 'High' (-) risk of bias. Results were shown in a high-resolution (300 DPI) traffic-light plot.

### 2.6. Qualitative data synthesis and certainty of evidence

Following the SWiM guideline [45], the included studies were assigned to four thematic outcome clusters that are coherent biologically and clinically. Cluster 1 was Endocrine & Metabolic Pharmacotherapy. Cluster 2 was Immunomodulatory, Kinase & Cell-Based Therapies. Cluster 3 was Spontaneous & Induced Pathogenesis, Microbiome & Neuro-Oviductal Mechanics. Cluster 4 was Non-Invasive Molecular Biomarkers, Epigenetics & Receptor Imaging. Direction of effect was classified in the same way for every cluster. 'Favors Intervention' meant one of three things: a statistically significant regression of endometriotic lesions or pain in a pharmacological trial; a statistically confirmed activation of a pathophysiological pathway, or efficacy of a surgical induction model, in a mechanistic study; or biomarker discrimination against healthy or baseline controls in a diagnostic study. 'Neutral' meant an equivocal or non-significant difference from the comparator. 'Favors Control' meant that the intervention significantly worsened endometriosis compared with control. For mechanistic, exposure, and diagnostic studies, this category denotes confirmation of the examined effect and not a therapeutic benefit. Within-cluster consistency was the percentage of studies with a consistent positive direction of effect. It was read together with the weighting of aggregate NHP sample size and study design hierarchy. Overall certainty in each cluster was rated with the GRADE narrative framework across five domains. Risk of bias was Serious if ≥50% of studies had Moderate RoB or >30% had High RoB. Inconsistency was Serious if directional consistency fell between 25% and 75%. Imprecision was Serious if cluster k was < 3. The other two domains were indirectness and publication bias. Cluster certainty was classified as High, Moderate, Low, or Very Low.

### 2.7. Ethical considerations

This systematic review analyzed published data only, and ethics approval was not required.

## 3. Results

### 3.1. Literature search and study selection

The database searches yielded 412 records (PubMed/MEDLINE: n = 148; Scopus: n = 134; Web of Science Core Collection: n = 82; ScienceDirect: n = 48). Citation tracking of primate research center publications added 14 records, giving 426 identified records (Figure 1). After 168 duplicates were removed, 258 unique records were screened by title and abstract. Of these, 196 were excluded as irrelevant to NHP endometriosis models or as a secondary publication type. Sixty-two full-text articles were retrieved and assessed for eligibility. Of these 62, 42 were excluded for specific methodological reasons. 18 were narrative reviews, systematic reviews, editorials, or commentaries. 14 used only non-primate animal models (murine, rat, rabbit, or porcine transplant models) or in vitro cell lines with no NHP arm. 6 lacked relevant diagnostic, pathophysiological, or therapeutic endometriosis outcomes. 4 were duplicate cohorts or overlapping secondary sub-analyses without distinct primary endpoints. In the end, 20 original studies with a combined sample of N = 299 non-human primates met all criteria and entered the qualitative synthesis [36,37,39–43,48–60].

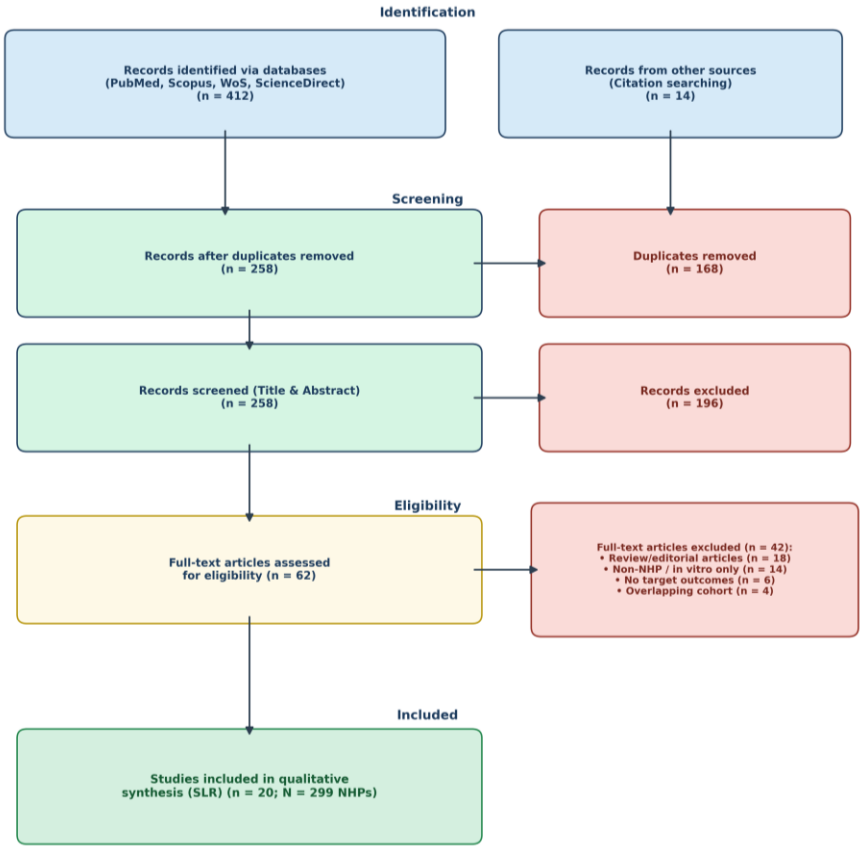



**Figure 1.** PRISMA 2020 flow diagram illustrating the systematic literature search, deduplication, screening, full-text eligibility assessment, and inclusion of 20 non-human primate endometriosis studies (N = 299 primates).

### 3.2. Characteristics of included studies

Table 2 gives the demographic, methodological, and experimental characteristics of the 20 included primary studies, published between 2007 and 2025. The cohort comprised N = 299 female non-human primates. By cluster, the numbers were: Cluster 1, N = 85; Cluster 2, N = 61; Cluster 3, N = 109; and Cluster 4, N = 44. Three Old World species were represented. Ten studies investigated olive baboons (Papio anubis, n = 132 animals; 44.1% of total primates), mainly at the Institute of Primate Research in Nairobi, Kenya, with European and North American academic partners [36,39–41,49,51,52,55,58,59]. Five studies examined rhesus macaques (Macaca mulatta, n = 96 animals; 32.1%), mainly at the Oregon National Primate Research Center [37,43,48,50,60]. Four studies used cynomolgus macaques (Macaca fascicularis, n = 55 animals; 18.4%) at Japanese primate research facilities in Tsukuba, Hamamatsu, and Shiga [42,53,56,57]. One bioenergetic case-control study evaluated a combined cohort of rhesus and cynomolgus macaques (n = 16 animals; 5.4%) at Wake Forest School of Medicine [54]. As for disease origin, 11 studies used surgically induced endometriosis. Ten were in olive baboons, by laparoscopic intrapelvic seeding of autologous curetted menstrual endometrium or nodular grafting [36,39–41,49,51,52,55,58,59]. One was in rhesus macaques, by laparoscopic intrauterine fundal puncture and peritoneal transfer [37]. Nine studies investigated spontaneous endometriosis, or long-term endocrine or metabolic promotion of spontaneous disease, in captive macaque colonies [42,43,48,50,53,54,56,57,60]. Sample sizes ranged from N = 6 [52] to N = 39 [60]. Follow-up ranged from acute assessments at 25 to 30 days after induction [36,39] to monitoring over 15 months in baboons [52,58], 24 months in cynomolgus monkeys [57], and 7 years from menarche in rhesus macaques [60].

**Table 2.** Baseline methodological, population, intervention, and outcome characteristics of the included non-human primate studies (n = 20; N = 299 primates).

| Study (Author, Year) | Country & Setting | Study Design | Species & Sample Size (N) | Intervention / Exposure & Comparator | Follow-Up Timing | Key Quantitative Findings | Overall RoB |
|---|---|---|---|---|---|---|---|
| Lebovic et al., 2007 | Kenya / USA (Institute of Primate Research, Nairobi) | Prospective Randomized Placebo- & Drug-Controlled Preclinical Trial | N = 12 (Exposed/Treated: 8 [4 rosiglitazone; 4 ganirelix active control]; Control: 4 [oral PBS placebo]) | Oral rosiglitazone 2 mg/day for 30 days, starting 34–68 days post-induction staging laparoscopy \| Comparator: Active control: subcutaneous ganirelix acetate 125 µg/day for 30 days (n = 4); Placebo control: oral PBS tablets once daily for 30 days (n = 4) | Baseline staging laparoscopy at 34–68 days post-induction; final assessment laparoscopy after 30 days of treatment | Endometriotic lesion surface area was significantly lower in rosiglitazone-treated (−51.8% relative change, P < 0.05) and ganirelix-treated (−59.4% relative change, P < 0.05) baboons vs. placebo (+16.2% increase); fewer new red lesions developed in the rosiglitazone group | Low |
| Kyama et al., 2008 | Kenya / Belgium (Institute of Primate Research, Nairobi & KU Leuven) | Prospective Randomized In Vivo and Ex Vivo Experimental Study | N = 18 baboons (in vivo, n = 14 randomized to PBS, GnRH antagonist or rhTNFbp-1; ex vivo, n = 4). Biopsy sets analyzed in vivo: rhTNFbp-1, 8; GnRH antagonist, 8; PBS placebo, 5. | Subcutaneous rhTNFbp-1 or GnRH antagonist administered at induction (in vivo, n = 14) or ex vivo incubation of menstrual endometrium with rhTNFbp-1 prior to intrapelvic seeding (n = 4) \| Comparator: Subcutaneous phosphate-buffered saline (PBS) vehicle control (in vivo n = 5 biopsies) or ex vivo PBS incubation | Endometrial (n = 11 in vivo, n = 2 ex vivo) and endometriotic lesion biopsies (n = 10 in vivo, n = 4 ex vivo) harvested at post-treatment laparoscopy (day 25–30) | TGF-β mRNA expression was significantly decreased in endometriotic lesions from rhTNFbp-1-treated baboons compared with PBS placebo (P < 0.05); mRNA levels of TNF-α, IL-8, IL-6, VEGF, ICAM-1, MMP-1, and RANTES did not differ significantly at harvesting | Low |
| Falconer et al., 2008 | Kenya / Sweden (Institute of Primate Research, Nairobi & Karolinska Institutet) | Prospective Placebo-Controlled Preclinical Fertility Trial | N = 16 (Exposed/Treated: 9 [intravenous anti-TNF-α mAb c5N]; Control: 7 [intravenous saline placebo]) | Single intravenous doses of anti-TNF-α mAb c5N administered at 4 scheduled timepoints, followed by timed mating for up to 9 completed menstrual cycles \| Comparator: Intravenous placebo infusions at the same 4 timepoints followed by identical timed mating protocol (n = 7) | Followed across up to 9 completed ovulatory menstrual cycles or until clinical pregnancy was achieved | No significant improvement in fecundity: PR was 100% (c5N) vs. 86% (placebo, P > 0.05); CFR was 18% (c5N) vs. 30% (placebo, P > 0.05); median TTP was 5 cycles (c5N) vs. 2 cycles (placebo); CPR was 100% vs. 80% | Moderate |
| Langoi et al., 2013 | Kenya / USA (Institute of Primate Research, Nairobi & Northwestern University) | Prospective Controlled Preclinical Intervention Study | N = 16 (Exposed/Treated: 10 [oral letrozole 1.25 mg/day]; Control: 6 [oral placebo]) | Oral letrozole (aromatase inhibitor) 1.25 mg/day administered daily for 6 months starting 10 months after disease induction \| Comparator: Oral placebo tablets administered daily for 6 months (n = 6) | Evaluated by serial laparoscopy at baseline (10 months post-inoculation) and every 2 months for 6 months (total 16 months post-induction) | Letrozole significantly decreased mean lesion volume from baseline (P < 0.05), whereas placebo animals showed progressive lesion volume expansion (P < 0.05); lesional aromatase mRNA was significantly suppressed in letrozole vs. placebo (P < 0.01) | Low |
| Donnez et al., 2015 | Belgium (Université Catholique de Louvain, Brussels) | Experimental Pathophysiological & Immunohistochemical Study | N = 10 (Exposed/Treated: 10 [induced deep nodular endometriotic lesions; invasive vs. non-invasive regions]; Control: Internal comparator: non-invasive lesions and lesion center vs. invasion front) | Surgical grafting of autologous endometrium to induce deep nodular endometriosis; excision and histological/immunohistochemical profiling of invasion front vs. lesion center \| Comparator: Non-invasive deep nodular lesions and central glands of invasive lesions within the same cohort | Lesion recovery and histopathological assessment following nodular induction | Glands at the invasion front exhibited a significantly lower thickness coefficient (P < 0.05), significantly higher Ki67 mitotic index (P < 0.01), and significantly reduced E-cadherin and β-catenin expression (P < 0.05) compared with non-invasive lesions and lesion centers | Low |
| Franasiak et al., 2015 | USA (Oregon National Primate Research Center & UNC Chapel Hill) | Cross-Sectional Translational Case-Control Study | N = 18 (Exposed/Treated: 11 [rhesus macaques with spontaneous advanced stage IV endometriosis]; Control: 7 [healthy control rhesus macaques]) | Spontaneous advanced endometriosis; eutopic endometrial biopsy profiling across proliferative and secretory menstrual phases via qRT-PCR and immunohistochemistry \| Comparator: Healthy disease-free cycling female rhesus macaques (n = 7) | Cross-sectional tissue sampling stratified by menstrual cycle phase (proliferative vs. secretory) | In normal controls, CXCL13 mRNA was minimal in the proliferative phase and maximal in the secretory phase; in macaques with endometriosis, proliferative-phase eutopic endometrial CXCL13 expression was markedly increased compared with healthy controls (P < 0.05), mirroring human endometriosis (P < 0.05) | Low |
| Hussein et al., 2016 | Kenya / Belgium (Institute of Primate Research, Nairobi & KU Leuven) | Assessor-Blind Randomized Placebo- & Active-Controlled Trial | N = 20 (Exposed/Treated: 15 [5 bentamapimod 20 mg/kg; 5 bentamapimod 20 mg/kg + MPA 10 mg; 5 cetrorelix 3 mg SC]; Control: 5 [daily oral placebo]) | 60-day oral treatment with bentamapimod (JNKI) 20 mg/kg/day alone (n = 5) or combined with oral medroxyprogesterone acetate (MPA) 10 mg/day (n = 5) \| Comparator: Placebo control: daily oral vehicle (n = 5); Active hormonal control: subcutaneous cetrorelix 3 mg every 3 days for 60 days (n = 5) | 60 days of active treatment; post-treatment staging laparoscopy (L4) performed 110 days after induction | Treatment with JNKI alone, JNKI + MPA, or cetrorelix resulted in significantly lower total lesion surface area (P < 0.05) and lesion volume (P < 0.05) vs. placebo; red-to-white lesion remodeling was highest in JNKI + MPA vs. JNKI alone (P < 0.05) | Low |

| Study (Author, Year) | Country & Setting | Study Design | Species & Sample Size (N) | Intervention / Exposure & Comparator | Follow-Up Timing | Key Quantitative Findings | Overall RoB |
|---|---|---|---|---|---|---|---|
| Drury et al., 2018 | UK / USA (University of Liverpool & Michigan State University) | Longitudinal Experimental Preclinical Study | N = 6 (Exposed/Treated: 6 [baboons followed longitudinally at 3, 12, and 15 months post-induction]; Control: 6 [paired pre-induction baseline control endometrium]) | Laparoscopic intrapelvic inoculation of autologous menstrual endometrium; serial harvesting of eutopic and ectopic endometrial tissues \| Comparator: Matched pre-inoculation baseline eutopic endometrium from the same animals | Longitudinal tissue sampling at baseline (0 months) and at 3, 12, and 15 months post-induction | Ectopic endometriotic lesions exhibited persistently scant/absent CD56+ uNK cell infiltration compared with eutopic functionalis layer (P < 0.01); eutopic endometrial uNK numbers showed cyclic and temporal modulation post-induction | Low |
| Nishimoto-Kakiuchi et al., 2018 | Japan (Tsukuba Primate Research Center & Jichi Medical University) | Prospective Colony Screening & Longitudinal Observational Cohort Study | N = 29 (Exposed/Treated: 15 [cynomolgus monkeys confirmed with spontaneous endometriosis; 8 longitudinally monitored via laparoscopy/MRI]; Control: 14 [screened monkeys without confirmed endometriosis]) | Multi-modal screening (serum CA125, abdominal palpation, fecal abnormalities) followed by diagnostic laparoscopy, MRI, and longitudinal disease monitoring \| Comparator: Colony females without endometriosis and inter-stage rASRM comparisons | Longitudinal laparoscopy and pelvic MRI monitoring over 2–7 months | Endometriosis was confirmed in 15/29 suspect animals (overall colony detection 15/614 [2.4%], enriched in ages 11–20 years); menstrual decrease in food consumption strongly correlated with modified rAFS adhesion score ($R^2$ = 0.8239, P < 0.001); serum CA125 was significantly elevated in animals with ovarian endometriomas (chocolate cysts) | Low |
| Atkins et al., 2019 | USA (Wake Forest School of Medicine, Winston-Salem, NC) | Case-Control Bioenergetic & Targeted Metabolomics Study | N = 16 (Exposed/Treated: 8 [rhesus and cynomolgus macaques with spontaneous endometriosis]; Control: 8 [clinically healthy control macaques without endometriosis]) | High-resolution mitochondrial respirometry (Complex I and Complex II oxygen consumption rates [OCR]) and LC-MS/MS targeted metabolomics of eutopic endometrium and ectopic endometriotic tissue \| Comparator: Normal eutopic endometrium from clinically healthy NHP controls (n = 8) | Ex vivo bioenergetic and metabolomic profiling immediately upon tissue harvest | Eutopic endometrium from endometriotic NHPs had significantly reduced Complex II OCR across all states (basal P = 0.01; state 3 P = 0.02; state 3u P = 0.04; state 4o P = 0.008); ectopic tissue had reduced state 3 Complex I OCR (P = 0.02) and RCR (P = 0.01). Carnitine (P = 0.001), creatine phosphate (P = 0.01), NADH (P = 0.0001), FAD (P = 0.001), tryptophan (P = 0.0009), and malic acid (P = 0.005) were depleted in endometriotic lesions | Low |
| Cosar et al., 2019 | USA / Kenya (Yale School of Medicine, UC San Diego & Institute of Primate Research) | Prospective Controlled Preclinical Biomarker & Intervention Trial | N = 16 (Exposed/Treated: 8 [oral simvastatin for 90 days]; Control: 8 [vehicle control for 90 days]) | Oral simvastatin daily for 90 days post-induction vs. vehicle control; serum qRT-PCR profiling of 9 candidate circulating miRNAs \| Comparator: Vehicle-treated baboons with induced endometriosis (n = 8) and pre-induction baseline levels | Laparoscopic disease evaluation and serum collection at 3 months (90 days) post-induction | In the simvastatin-treated group, serum miR-150-5p (P < 0.05) and miR-451a (P < 0.05) were significantly decreased while miR-3613-5p was significantly increased (P < 0.05) compared with untreated endometriotic controls, reverting toward healthy baseline levels | Low |
| Yano et al., 2019 | Japan (Hamamatsu Pharma Research, Inc., Hamamatsu) | Controlled Preclinical Neuroimaging & Pharmacological Intervention Study | N = 8 (Exposed/Treated: 5 [cynomolgus macaques with naturally occurring endometriosis treated with morphine and 2-month dienogest]; Control: 3 [healthy disease-free female cynomolgus macaques]) | Abdominopelvic mechanical force algometry and block-design fMRI before and after single-dose morphine and 2-month oral progestin dienogest treatment \| Comparator: Healthy control female macaques (n = 3) and pre-treatment baseline fMRI/algometry values | Baseline assessment, acute post-morphine assessment, and longitudinal evaluation across 2 months of daily dienogest therapy | Abdominopelvic pain thresholds in endometriotic macaques were significantly lower than in healthy controls (P = 0.0003); non-noxious abdominal force triggered robust insula and thalamus BOLD activation in endometriotic animals, which was significantly attenuated by both acute morphine and 2-month dienogest treatment (P < 0.05) | Low |
| Hayashi et al., 2020 | Japan (Shiga University of Medical Science, Otsu) | Prospective Longitudinal Natural History Cohort Study | N = 11 (Exposed/Treated: 11 [female cynomolgus monkeys with spontaneous endometriosis followed monthly for 24 months]; Control: Internal longitudinal baseline [initial laparoscopy at month 0]) | Monthly diagnostic videolaparoscopies for up to 24 consecutive months to map anatomical distribution, de novo appearance, and regression of lesions and adhesions \| Comparator: Baseline anatomical lesion map at initial laparoscopy (month 0) and inter-individual progression kinetics | Monthly laparoscopic assessments for 24 months (2 years) | At initial laparoscopy, lesions were localized exclusively to the vesicouterine pouch in 45.4% (5/11) of monkeys and subsequently spread to the pouch of Douglas over time; de novo small lesions appeared in 100% (11/11) of animals, while focal disappearance of small lesions occurred in 18.2% (2/11); overall disease progressed in 100% (11/11) of monkeys | Low |
| Le et al., 2022 | USA (Southern Illinois University & Michigan State University) | Prospective Longitudinal Pre-Post Experimental Cohort Study | N = 8 (Exposed/Treated: 8 [female olive baboons evaluated at 3, 6, 9, and 15 months post-induction]; Control: 8 [paired pre-inoculation baseline samples from the same animals]) | Laparoscopic induction of peritoneal endometriosis; serial peripheral blood, eutopic/ectopic endometrium, fecal, and urogenital/vaginal swab collection \| Comparator: Matched pre-inoculation baseline immune and microbial profiles (month 0) | Pre-inoculation (baseline) and 3, 6, 9, and 15 months post-induction | Endometriosis induction significantly decreased peripheral and endometrial FOXP3+ Tregs while elevating inflammatory Th17 cells across all post-induction timepoints (3, 6, 9, and 15 months; P < 0.05), markedly reducing the Treg:Th17 ratio; mucosal microbial alpha-diversity and taxonomic abundance were significantly altered at fecal and urogenital sites post-induction (P < 0.05) | Low |
| Poirier et al., 2022 | Canada / Kenya / Netherlands (Université Laval, Institute of Primate Research Nairobi & Maastricht University) | Prospective Placebo-Controlled Preclinical Efficacy Trial | N = 10 (Exposed/Treated: 5 [oral PBRM 15 mg/kg/day for 2 months]; Control: 5 [oral placebo vehicle for 2 months]) | Oral gavage of PBRM (irreversible non-estrogenic 17β-HSD1 inhibitor) at 15 mg/kg/day for 60 days (achieving plasma Cmax up to 125 ng/mL) \| Comparator: Oral vehicle placebo daily for 60 days (n = 5) | Baseline pre-treatment laparoscopy and post-treatment laparoscopy after 2 months (60 days) of daily therapy | Lesion/adhesion counts decreased in 60% (3/5) of PBRM-treated baboons (−6.5% overall; −19% excluding 1 outlier) vs. an increase in 60% (3/5) of placebo animals (+11% overall). PBRM markedly reduced active red lesions by −67% (8/12 resorbed) and white lesions by −35% (11/31 resorbed), and decreased dense and filmy adhesion surface areas vs. placebo | Low |
| Bishop et al., 2023 | USA (Oregon National Primate Research Center, OHSU, Beaverton, OR) | Longitudinal 2x2 Factorial Controlled Exposure Study | N = 39 (Exposed/Treated: 29 [Testosterone [T] alone, Western-style diet [WSD] alone, or combined T + WSD from menarche for ~7 years]; Control: 10 [Cholesterol control implants + standard monkey chow [16% fat calories]]) | Subcutaneous testosterone implants maintaining serum T ~1.35 ng/mL (3–5x control) and/or high-fat Western-style diet (36% calories from fat vs. 16% in standard chow) for ~7 years \| Comparator: Control females receiving cholesterol sham implants and standard monkey chow (16% calories from fat) | Continuous longitudinal metabolic, ultrasonographic, and laparoscopic/necropsy evaluation over ~7 years | Combined T + WSD exposure resulted in significantly earlier onset of endometriosis and higher prevalence of severe Stage III/IV disease with large chocolate cysts compared with control, T alone, or WSD alone (P < 0.05). Presence of chocolate cysts strongly correlated with impaired glucose clearance, elevated HOMA-IR, and total body fat percentage (P < 0.05) | Low |

| Study (Author, Year) | Country & Setting | Study Design | Species & Sample Size (N) | Intervention / Exposure & Comparator | Follow-Up Timing | Key Quantitative Findings | Overall RoB |
|---|---|---|---|---|---|---|---|
| Slayden et al., 2023 | USA (Oregon National Primate Research Center, OHSU, Beaverton, OR) | Controlled Experimental Surgical Model Validation Study | N = 17 (Exposed/Treated: 14 [laparoscopic intrauterine puncture and peritoneal endometrial seeding across 3 menses]; Control: 3 [sham surgery control macaques]) | Menstrual endometrium aspirated via laparoscopic intrauterine fundal puncture and seeded into the peritoneal cavity across 3 consecutive menstrual cycles \| Comparator: Sham-operated female rhesus macaques undergoing laparoscopic manipulation without endometrial transfer (n = 3) | Laparoscopic staging, biopsy, and immunohistochemical characterization following 3 induction cycles | Macroscopic and histologically confirmed red, powder-burn, and white endometriotic lesions developed in 92.9% (13/14) of inoculated macaques compared with 0% (0/3) of sham controls (P < 0.01); ectopic red lesion stroma stained strongly positive for ER and PR | Low |
| Tsuji et al., 2023 | Japan (Shiga University of Medical Science & University of Tokyo) | Controlled Sequential-Route Preclinical Intervention Study | N = 7 (Exposed/Treated: 5 [cynomolgus monkeys treated with UC-MSCs at 2 × $10^6$ cells/kg across IV, IV+IP, and IP phases]; Control: 2 [saline vehicle control monkeys]) | Phase 1 (3 months): intravenous UC-MSCs (2 × $10^6$ cells/kg); Phase 2 (3 months): weekly IV + monthly intraperitoneal (IP) UC-MSCs; Phase 3 (3 months): weekly IP UC-MSCs (2 × $10^6$ cells/kg) \| Comparator: Saline-treated control cynomolgus monkeys with endometriosis (n = 2) and intra-animal route comparisons (IV vs. IP) | Serial laparoscopies and serum CA125 assays at baseline, 3 months, 6 months, and 9 months | Intravenous UC-MSC administration reduced serum CA125 in all 5 treated monkeys (non-significant trend, P > 0.05); however, intraperitoneal UC-MSC administration significantly exacerbated laparoscopic rASRM endometriosis scores compared with intravenous administration (P = 0.02), whereas controls showed no change | Moderate |
| Wilson et al., 2024 | USA (Oregon National Primate Research Center & UNC Chapel Hill) | Prospective Case-Control Molecular Imaging Study | N = 10 (Exposed/Treated: 6 [rhesus macaques with clinically diagnosed endometriosis]; Control: 4 [healthy control rhesus macaques without endometriosis]) | Dynamic abdominopelvic PET/CT scanning following intravenous injection of 16α-[18F]fluorestradiol ([18F]FES) and 12-[18F]fluoro-furanyl-norprogesterone ([18F]FFNP) during proliferative and secretory phases \| Comparator: Disease-free cycling female rhesus macaques (n = 4) and background intestinal tissue uptake | Repeated-measures dynamic PET/CT scans across scan timepoints and menstrual cycle phases (proliferative vs. secretory) | Macaques with endometriosis displayed significantly higher uterine SUV uptake of both radiotracers compared with healthy controls (P < 0.05), with significantly higher uterine uptake during the proliferative phase vs. secretory phase (P < 0.05); small individual peritoneal lesions could not be spatially resolved due to background intestinal [18F]FFNP uptake | Low |
| Luo & Slayden, 2025 | USA (Oregon National Primate Research Center, OHSU, Beaverton, OR) | Combined In Vivo Case-Control and Ex Vivo Organ Culture Experimental Study | N = 12 (Exposed/Treated: 6 [rhesus macaques with spontaneous endometriosis; plus ampullary explants exposed to endometriotic peritoneal fluid]; Control: 6 [healthy control rhesus macaques without endometriosis; explants exposed to control peritoneal fluid]) | In vivo profiling of fallopian tube ampullary segments and in vitro exposure of normal ampullary explants to peritoneal fluid harvested from macaques with and without endometriosis \| Comparator: Oviductal ampullary tissues and peritoneal fluid from healthy control rhesus macaques (n = 6) | Cross-sectional in vivo tissue harvest plus controlled in vitro peritoneal fluid co-culture assay | Ampullary ANO1 expression was significantly downregulated both in vivo in macaques with spontaneous endometriosis (P < 0.05) and in vitro in ampullary segments exposed to endometriotic peritoneal fluid (P < 0.05); AK7 and FOXJ1 expression did not differ significantly between groups (P > 0.05) | Low |

***Notes:*** *Abbreviations: ANO1, Anoctamin-1; CA125, cancer antigen 125; CFR, cycle fecundity rate; CPR, cumulative pregnancy rate; ER, estrogen receptor; [$^{18}$F]FES, 16α-[$^{18}$F]fluorestradiol; [$^{18}$F]FFNP, 12-[$^{18}$F]fluoro-furanyl-nor-progesterone; fMRI, functional magnetic resonance imaging; HOMA-IR, homeostatic model assessment for insulin resistance; IHC, immunohistochemistry; IP, intraperitoneal; IV, intravenous; JNKI, c-Jun $NH_2$-terminal kinase inhibitor; MPA, medroxyprogesterone acetate; OCR, oxygen consumption rate; PBS, phosphate-buffered saline; PR, progesterone receptor; rhTNFbp-1, recombinant human TNF-binding protein-1; RoB, risk of bias; Treg, regulatory T cell; UC-MSC, umbilical cord-derived mesenchymal stem cell; WSD, Western-style diet.*

### *3.3. Methodological quality and risk of bias*

The domain-specific methodological quality and risk-of-bias ratings for all 20 studies are summarized in Figure 2. Overall, 18 studies (90.0%) had a 'Low' overall risk of bias [36,37,39,41,43,48–60]. Two studies (10.0%) were rated 'Moderate' [40,42], and none (0.0%) had a 'High' overall risk of bias. In Domain 1 (Selection and Randomization Bias), 14 studies (70.0%) were rated Low risk. They used explicit randomization after baseline staging laparoscopy, or selected age-matched and menstrual-phase-matched cohorts rigorously. Six studies (30.0%) were rated Moderate [40–42,49,52,56]. These six Moderate D1 ratings arose in two settings. In induced baboon studies [40,41,49,52], formal computer-generated randomization or allocation concealment before baseline laparoscopy was not explicitly reported. In spontaneous cynomolgus macaque studies [42,56], only rare naturally affected primates (N = 7 to N = 8) were available. They were allocated to experimental and control arms in small unequal numbers (5 vs. 3 in Yano et al. [56] and 5 vs. 2 in Tsuji et al. [42]). In Domain 2 (Confounding and Protocol Deviations) and Domain 3 (Missing Outcome Data), 19 of 20 studies (95.0%) were rated Low. Only Kyama et al. [39] raised Moderate concern in D2, because in vivo and ex vivo biopsies were pooled. Only Falconer et al. [40] raised Moderate concern in D3, because two non-pregnant baboons in the c5N antibody arm died of intercurrent causes. In Domain 4 (Outcome Measurement), 19 studies (95.0%) used objective quantitative assays (qRT-PCR, LC-MS/MS respirometry, PET/CT SUVs, fMRI BOLD, or assessor-blinded videolaparoscopy [51]). Only Lebovic et al. [36] was rated Moderate, because surgeon blinding was not stated. All 20 studies (100.0%) had Low risk of selective reporting in Domain 5.

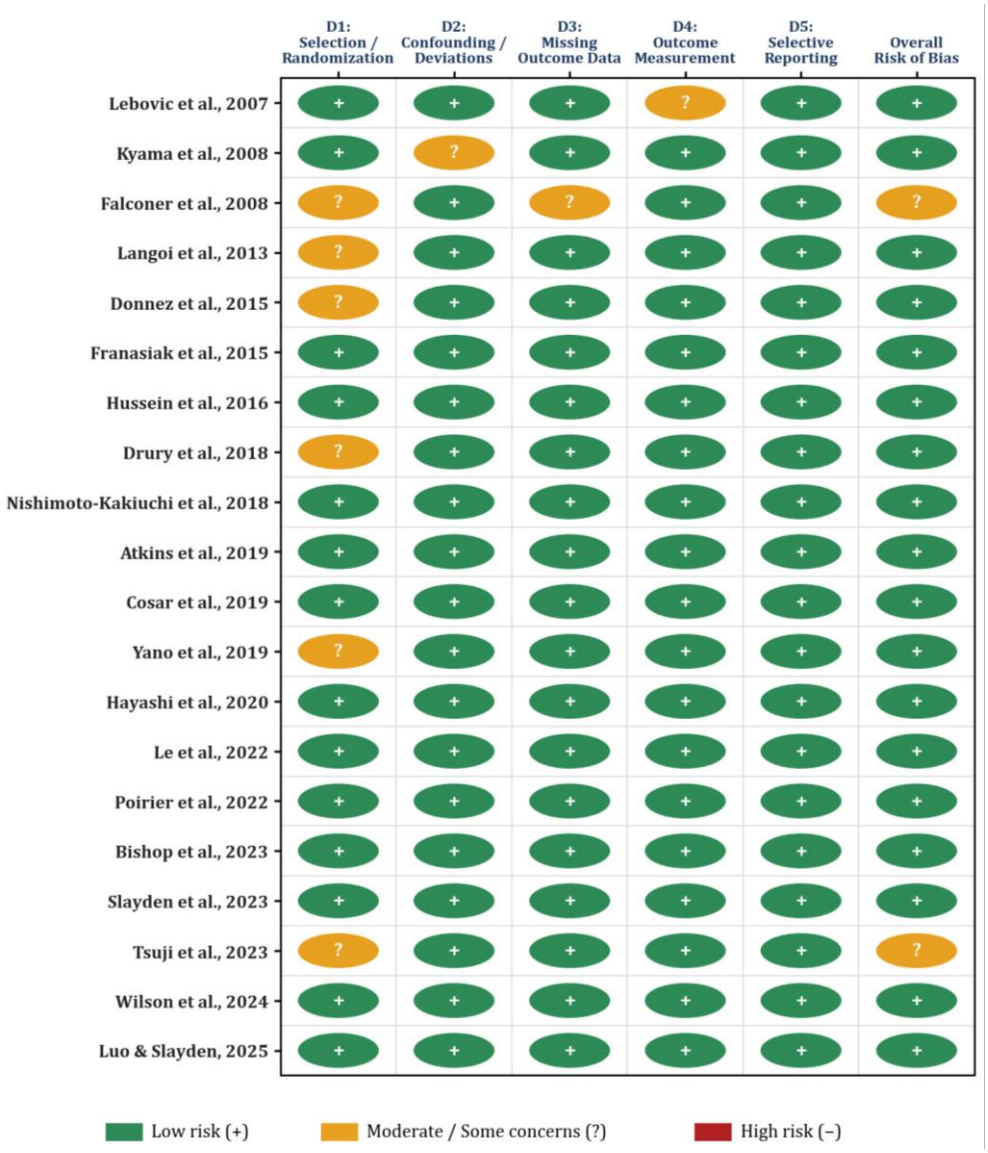



**Figure 2.** Methodological quality and risk-of-bias traffic-light plot across the 20 included non-human primate studies evaluated across five domains (D1: Selection/Randomization; D2: Confounding/Deviations; D3: Missing Outcome Data; D4: Outcome Measurement; D5: Selective Reporting; and Overall Risk of Bias).

### *3.4. Qualitative synthesis of primary outcomes across thematic clusters*

The structured SWiM synthesis across the four thematic outcome clusters is detailed in Table 3. In Cluster 1 (Endocrine & Metabolic Pharmacotherapy; k = 5 studies, N = 85 NHPs) had a consistent positive direction of effect in 100.0% (5/5) of studies [36,41,56,59,60]. One of them, Bishop et al. [60], describes promotion of disease by an adverse exposure and was classified as confirming the examined effect. Lebovic et al. [36] ran a prospective randomized trial in 12 olive baboons. In a 30-day course, oral rosiglitazone (2 mg/day), a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, significantly reduced peritoneal endometriotic lesion surface area (−51.8% relative change, $P < 0.05$). The reduction was comparable to that with the GnRH antagonist ganirelix (−59.4%, $P < 0.05$). Oral placebo controls had a +16.2% lesion expansion. Langoi et al. [41] tested long-term intracrine estrogen blockade in 16 olive baboons with established endometriosis (10 months after inoculation). 10 received the aromatase inhibitor letrozole (1.25 mg/day for 6 months) and 6 received placebo. Mean lesion volume fell significantly from baseline ($P < 0.05$), and lesional CYP19A1 aromatase mRNA was strongly suppressed ($P < 0.01$). Placebo lesions kept enlarging. Poirier et al. [59] gave PBRM (15 mg/kg/day orally for 60 days, Cmax up to 125 ng/mL), an irreversible covalent inhibitor of 17β-HSD1, to 10 baboons (5 PBRM, 5 placebo). It acts more selectively on the intracrine pathway. Total lesion and adhesion counts fell in 60% (3/5) of treated primates (−6.5% overall; −19% excluding one outlier), against a +11% rise in placebo animals. PBRM resorbed 67% (8/12) of active red vascular lesions and 35% (11/31) of white lesions. In spontaneous cynomolgus macaque endometriosis (N = 8), Yano et al. [56] found much lower abdominopelvic mechanical pain thresholds in endometriotic macaques (n = 5) than in healthy controls (n = 3, $P = 0.0003$). Non-noxious stimulation produced abnormal fMRI BOLD activation of the insula and thalamus. Both findings were significantly attenuated by a 2-month course of oral dienogest, a progestin, or by acute morphine ($P < 0.05$). Bishop et al. [60] looked at the opposite question, metabolic and endocrine promotion of disease, in 39 female rhesus macaques followed for 7 years from menarche. Hyperandrogenemia (serum testosterone ~1.35 ng/mL) combined with a high-fat Western-style diet (36% fat calories vs. 16% in control chow) accelerated the onset of endometriosis and drove severe Stage III/IV pathology with large chocolate cysts ($P < 0.05$).

The severity correlated strongly with HOMA-IR insulin resistance, impaired glucose clearance, total body fat percentage, and omental adipose inflammatory transcriptomes.

In Cluster 2 (Immunomodulatory, Kinase & Cell-Based Therapies; k = 4 studies, N = 61 NHPs), direction consistency was 50.0%. Two studies favored intervention, one was neutral, and one favored control (2/4, 1/4, and 1/4). The cluster shows a sharp divergence between lesion cytoreduction, restoration of fertility, and the route of stem cell delivery [39,40,42,51]. Kyama et al. [39] compared subcutaneous recombinant human TNF-binding protein-1 (rhTNFbp-1) with a GnRH antagonist and PBS placebo in 18 olive baboons (14 in vivo, 4 ex vivo). rhTNFbp-1 significantly reduced lesional transforming growth factor-β (TGF-β) mRNA expression against placebo ($P < 0.05$). Late-harvest transcript levels of TNF-α, IL-8, IL-6, VEGF, ICAM-1, MMP-1, and RANTES did not change. Falconer et al. [40] gave four intravenous infusions of the anti-TNF-α monoclonal antibody c5N (n = 9) or placebo (n = 7) in a prospective timed-mating fertility trial. The 16 baboons had induced endometriosis and were followed for up to nine ovulatory cycles. TNF-α neutralization did not significantly improve pregnancy rate (100% c5N vs. 86% placebo, $P > 0.05$), cycle fecundity rate (18% c5N vs. 30% placebo, $P > 0.05$), median time to pregnancy (5 cycles c5N vs. 2 cycles placebo), or cumulative pregnancy rate (100% vs. 80%). Hussein et al. [51] targeted intracellular stress kinase signaling in an assessor-blind, 4-arm randomized trial in 20 baboons across four sequential laparoscopies. The arms were 60 days of oral c-Jun $NH_2$-terminal kinase (JNK) inhibitor bentamapimod (AS602801, 20 mg/kg/day, n = 5), bentamapimod 20 mg/kg/day plus medroxyprogesterone acetate (MPA 10 mg/day, n = 5), subcutaneous cetrorelix (3 mg every 3 days, n = 5), and placebo (n = 5). Bentamapimod alone and in combination significantly reduced total lesion surface area and volume against placebo ($P < 0.05$). They also sped the remodeling of red lesions into white fibrotic lesions, most in JNKI + MPA ($P < 0.05$). Tsuji et al. [42] gave human umbilical cord-derived mesenchymal stem cells (UC-MSCs, $2 \times 10^6$ cells/kg) to cynomolgus monkeys with spontaneous endometriosis (N = 7: 5 treated, 2 saline control). Three sequential 3-month phases were intravenous (IV), combined IV and intraperitoneal (IP), and weekly IP. IV UC-MSCs modestly lowered serum CA125 in all five monkeys ($P > 0.05$). Switching to IP delivery significantly worsened laparoscopic rASRM endometriosis scores compared with IV administration ($P = 0.02$).

In Cluster 3 (Spontaneous & Induced Pathogenesis, Microbiome & Neuro-Oviductal Mechanics; k = 8 studies, N = 109 NHPs), 100.0% (8/8) of studies consistently defined key pathophysiological mechanisms [37,48,49,52–54,57,58]. Donnez et al. [49] studied deep nodular lesions induced in 10 olive baboons. Glands at the invasion front had a significantly lower thickness coefficient ($P < 0.05$), a higher Ki67 mitotic index ($P < 0.01$), and lower E-cadherin and β-catenin expression ($P < 0.05$) than non-invasive lesions and lesion centers. This confirms collective cell migration. Drury et al. [52] followed six baboons for 15 months after induction. Ectopic lesions lacked the normal recruitment of $CD56^+$ uterine natural killer (uNK) cells seen in matched eutopic functionalis ($P < 0.01$). Le et al. [58] sampled eight olive baboons at baseline, 3, 6, 9, and 15 months after induction. Lesion establishment caused a progressive fall in peripheral and endometrial $FOXP3^+$ regulatory T cells (Tregs) and a surge in pro-inflammatory $IL\text{-}17^+$ Th17 cells, which reduced the Treg:Th17 ratio ($P < 0.05$). Fecal and urogenital microbial diversity also changed significantly ($P < 0.05$). At the bioenergetic level, Atkins et al. [54] did mitochondrial respirometry and targeted metabolomics in 16 macaques (8 endometriotic, 8 controls). Complex II oxygen consumption rates (OCR) were lower in all four respiratory energy states in eutopic endometrium (basal $P = 0.01$; state 3 $P = 0.02$; state 3u $P = 0.04$; state 4o $P = 0.008$). State 3 Complex I OCR ($P = 0.02$) and respiratory control rates ($P = 0.01$) were lower in ectopic tissue. Tissue levels of carnitine ($P = 0.001$), creatine phosphate ($P = 0.01$), NADH ($P = 0.0001$), FAD ($P = 0.001$), tryptophan ($P = 0.0009$), and malic acid ($P = 0.005$) were severely depleted. Nishimoto-Kakiuchi et al. [53] characterized spontaneous colony disease by screening 614 female cynomolgus macaques. They evaluated 29 suspected animals and confirmed 15 cases, enriched at ages 11–20 years. Reduced food consumption during menstruation correlated strongly with modified rAFS adhesion scores ($R^2 = 0.8239$, $P < 0.001$). Hayashi et al. [57] did 24 consecutive monthly laparoscopies in 11 cynomolgus monkeys with spontaneous endometriosis. At first, lesions were found only in the vesicouterine pouch in 45.4% (5/11) of monkeys and later spread posteriorly to the pouch of Douglas. De novo lesions emerged in 100% (11/11), lesions disappeared focally in 18.2% (2/11), and disease progressed overall in 100% (11/11). On the methods side, Slayden et al. [37] validated a protocol of laparoscopic intrauterine fundal puncture and peritoneal seeding across three menses in 17 rhesus macaques (14 induced, 3 sham). ER/PR-positive red, powder-burn, and white lesions were established in 92.9% (13/14) of treated macaques versus 0% (0/3) of sham controls ($P < 0.01$). Most recently, Luo and Slayden [48] studied 12 rhesus macaques (6 with spontaneous endometriosis, 6 controls). Expression of the calcium-activated chloride channel Anoctamin-1 (ANO1), which governs oviductal smooth muscle peristalsis, was significantly lower in the fallopian tube ampulla in vivo and after ex vivo exposure to endometriotic peritoneal fluid ($P < 0.05$). The ciliary markers AK7 and FOXJ1 were unaffected.

In Cluster 4 (Non-Invasive Molecular Biomarkers, Epigenetics & Receptor Imaging; k = 3 studies, N = 44 NHPs), 100.0% (3/3) of studies validated new diagnostic and treatment-monitoring tools [43,50,55]. Franasiak et al. [50] profiled eutopic endometrium from 18 rhesus macaques (11 with advanced stage IV endometriosis, 7 healthy controls). Endometriotic macaques showed abnormal proliferative-phase upregulation of the B-cell homeostatic chemokine CXCL13 compared with controls ($P < 0.05$), as in human stage I–IV disease. Cosar et al. [55] randomized 16 olive baboons with induced endometriosis to 90 days of oral simvastatin (n = 8) or vehicle (n = 8). Simvastatin significantly lowered serum circulating miR-150-5p ($P < 0.05$) and miR-451a ($P < 0.05$) and raised miR-3613-5p ($P < 0.05$). The pathological circulating microRNA signature normalized in parallel with lesion regression. Wilson et al. [43] did dynamic abdominopelvic PET/CT in 10 rhesus macaques (6 with endometriosis, 4 controls). The ER-targeted radiotracer was 16α-[$^{18}$F]fluorestradiol ([$^{18}$F]FES) and the PR-targeted tracer was 12-[$^{18}$F]fluoro-furanyl-nor-progesterone ([$^{18}$F]FFNP). Uterine SUV uptake was significantly higher in endometriotic macaques than in controls ($P < 0.05$), and proliferative-phase uptake was higher ($P < 0.05$). High background intestinal clearance of [$^{18}$F]FFNP prevented spatial resolution of small individual peritoneal implants.

**Table 3.** Synthesis Without Meta-analysis (SWiM) summary matrix by thematic outcome cluster.

| Thematic Outcome Cluster | Included Studies k | Total Participants N | Favors Intervention k | Neutral Equivocal k | Favors Control k | Direction Consistency Pct | Predominant Study Designs | Key Studies |
|---|---|---|---|---|---|---|---|---|
| Cluster 1: Endocrine & Metabolic Pharmacotherapy | 5 | 85 | 5 | 0 | 0 | 100.0% | Prospective Randomized Placebo- & Drug-Controlled Preclinical Trial, Prospective Controlled Preclinical Intervention Study, Controlled Preclinical Neuroimaging & Pharmacological Intervention Study, Prospective Placebo-Controlled Preclinical Efficacy Trial, Longitudinal 2x2 Factorial Controlled Exposure Study | Lebovic et al., 2007; Langoi et al., 2013; Yano et al., 2019; Poirier et al., 2022; Bishop et al., 2023 |
| Cluster 2: Immunomodulatory, Kinase & Cell-Based Therapies | 4 | 61 | 2 | 1 | 1 | 50.0% | Prospective Randomized In Vivo and Ex Vivo Experimental Study, Prospective Placebo-Controlled Preclinical Fertility Trial, Assessor-Blind Randomized Placebo- & Active-Controlled Trial, Controlled Sequential-Route Preclinical Intervention Study | Kyama et al., 2008; Falconer et al., 2008; Hussein et al., 2016; Tsuji et al., 2023 |
| Cluster 3: Spontaneous & Induced Pathogenesis, Microbiome & Neuro-Oviductal Mechanics | 8 | 109 | 8 | 0 | 0 | 100.0% | Experimental Pathophysiological & Immunohistochemical Study, Longitudinal Experimental Preclinical Study, Prospective Colony Screening & Longitudinal Observational Cohort Study, Case-Control Bioenergetic & Targeted Metabolomics Study, Prospective Longitudinal Natural History Cohort Study, Prospective Longitudinal Pre-Post Experimental Cohort Study, Controlled Experimental Surgical Model Validation Study, Combined In Vivo Case-Control and Ex Vivo Organ Culture Experimental Study | Donnez et al., 2015; Drury et al., 2018; Nishimoto-Kakiuchi et al., 2018; Atkins et al., 2019; Hayashi et al., 2020; Le et al., 2022; Slayden et al., 2023; Luo & Slayden, 2025 |
| Cluster 4: Non-Invasive Molecular Biomarkers, Epigenetics & Receptor Imaging | 3 | 44 | 3 | 0 | 0 | 100.0% | Cross-Sectional Translational Case-Control Study, Prospective Controlled Preclinical Biomarker & Intervention Trial, Prospective Case-Control Molecular Imaging Study | Franasiak et al., 2015; Cosar et al., 2019; Wilson et al., 2024 |

***Notes:*** *Abbreviations: k, number of included primary studies; N, aggregate number of non-human primates; Pct, percentage consistency of positive direction of effect; SWiM, Synthesis Without Meta-analysis.*

### *3.5. Secondary outcomes, reproductive safety, and subgroup variations*

Secondary reproductive, endocrine, and safety outcomes across the 20 studies separated systemic hormonal suppression from selective non-hormonal or intracrine therapy. Systemic aromatase inhibition with letrozole (1.25 mg/day for 6 months) regressed peritoneal lesion volume in baboons. Langoi et al. [41] also recorded a statistically significant rise in bilateral ovarian volume at 6 months compared with pre-treatment baseline ($P < 0.05$). The endocrine explanation is straightforward. Blocking CYP19A1 aromatase lowers circulating estradiol and relieves negative feedback on the hypothalamic-pituitary axis. Pulsatile follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion rise, and the ovaries enlarge with multiple follicles and cysts. GnRH antagonists (ganirelix 125 µg/day [36] and cetrorelix 3 mg every 3 days [51]) also suppressed lesion surface area. They induced profound hypo-estrogenic anovulatory amenorrhea. Three targeted non-hormonal or intracrine regimens gave a clear contrast: oral PPAR-γ agonist rosiglitazone (2 mg/day [36]), oral JNK inhibitor bentamapimod (20 mg/kg/day [51]), and oral irreversible covalent 17β-HSD1 inhibitor PBRM (15 mg/kg/day [59]). Each regressed active red peritoneal lesions. Menstrual cycle duration stayed normal, as did systemic serum estradiol and progesterone, with no ovarian cysts and no systemic toxicity. 17β-HSD1 acts locally in ectopic endometriotic tissue. It catalyzes the last step, reduction of weak estrone ($E_1$) to potent 17β-estradiol ($E_2$). Covalent blockade by PBRM therefore starves peritoneal lesions of local $E_2$ and leaves pituitary gonadotropin homeostasis intact [59]. Species also complement one another. Olive baboons (Papio anubis, 11–16 kg) have a straight cervical canal. This allows non-surgical transcervical endometrial curettage, serial videolaparoscopic staging, and timed-mating fecundity trials [36,40,41,51,58]. Rhesus macaques (Macaca mulatta, 5–9 kg) and smaller cynomolgus macaques (Macaca fascicularis, 2–5 kg) have a tortuous sigmoid cervix, so induction needs laparoscopic intrauterine puncture [37]. They are well suited to multi-year surveillance of spontaneous disease in colonies [53,57], high-resolution fMRI and PET/CT neuroimaging in clinical scanners [43,56], and study of PCOS-like metabolic comorbidities [60].

### *3.6. Mechanistic insights, evidence mapping, and certainty of evidence*

The cross-cluster evidence map in Figure 3 links each study's thematic cluster, direction of effect, and overall risk-of-bias rating. Table 4 gives the formal GRADE narrative certainty profile. Of the 20 studies, 18 (90.0%) showed a positive direction of effect ('Favors Intervention'). One study (5.0%, Falconer et al. [40]) showed a neutral effect on fertility. One study (5.0%, Tsuji et al. [42]) showed disease exacerbation ('Favors Control') after intraperitoneal stem cell infusion. Under the GRADE narrative framework (Table 4), certainty was High for three clusters. These were Cluster 1 (Endocrine & Metabolic Pharmacotherapy; k = 5,

N = 85, 100.0% directional consistency, 0% Moderate/High overall RoB), Cluster 3 (Spontaneous & Induced Pathogenesis, Microbiome & Neuro-Oviductal Mechanics; k = 8, N = 109, 100.0% directional consistency, 0% Moderate/High overall RoB), and Cluster 4 (Non-Invasive Molecular Biomarkers, Epigenetics & Receptor Imaging; k = 3, N = 44, 100.0% directional consistency, 0% Moderate/High overall RoB). Certainty for Cluster 2 (Immunomodulatory, Kinase & Cell-Based Therapies; k = 4, N = 61) was downgraded two levels to Low, for two objective reasons. (1) Risk of bias was Serious. Half of the studies in the cluster (2/4, 50.0%) had an overall Moderate RoB rating: Falconer et al. [40], because of animal attrition in the c5N group, and Tsuji et al. [42], because of unblinded sequential dosing with n = 2 controls. (2) Inconsistency was Serious. Directional consistency within the cluster was only 50.0%, below the 75.0% threshold. Two studies favored intervention [39,51], one neutral fertility trial [40] was equivocal, and one study favored control because intraperitoneal stem-cell infusion exacerbated disease [42].

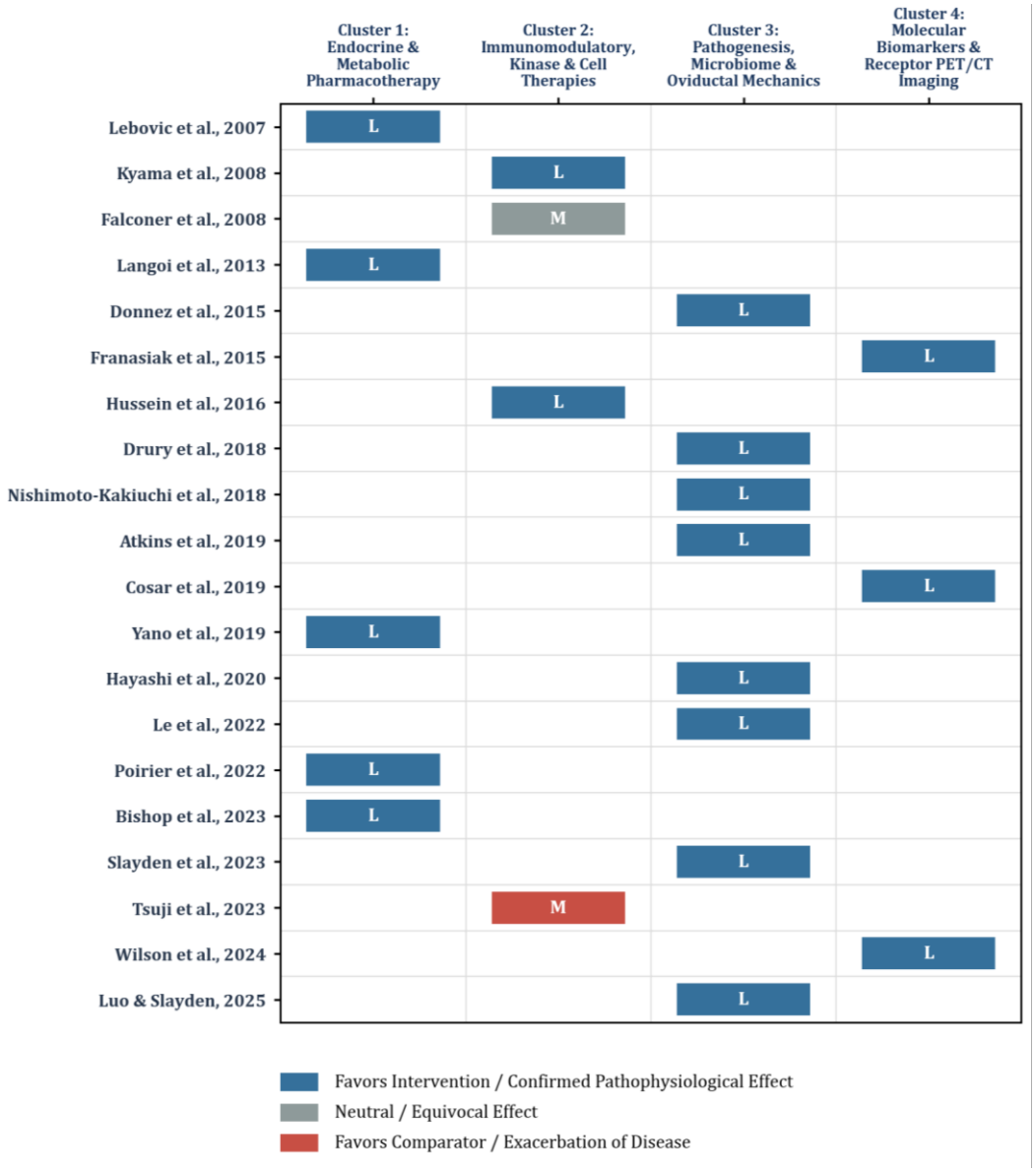



**Figure 3.** Evidence synthesis matrix mapping the 20 included studies across the four thematic clusters, direction of effect (color-coded), and overall risk of bias (L = Low, M = Moderate).

**Table 4.** GRADE narrative certainty of evidence profile across thematic outcome clusters.

| Outcome Cluster | No of Studies | Risk of Bias | Inconsistency | Indirectness | Imprecision | Overall Certainty GRADE |
|---|---|---|---|---|---|---|
| Cluster 1: Endocrine & Metabolic Pharmacotherapy | 5 | Not serious | Not serious | Not serious | Not serious | High |
| Cluster 2: Immunomodulatory, Kinase & Cell-Based Therapies | 4 | Serious | Serious | Not serious | Not serious | Low |
| Cluster 3: Spontaneous & Induced Pathogenesis, Microbiome & Neuro-Oviductal Mechanics | 8 | Not serious | Not serious | Not serious | Not serious | High |
| Cluster 4: Non-Invasive Molecular Biomarkers, Epigenetics & Receptor Imaging | 3 | Not serious | Not serious | Not serious | Not serious | High |

*Notes: Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation. The GRADE ratings are those of the authors (see AQ6).*

## 4. Discussion

### 4.1. Principal findings

This systematic review synthesized preclinical and translational evidence from 20 primary studies in 299 non-human primates (Papio anubis, Macaca mulatta, and Macaca fascicularis). It maps the pathophysiology, diagnostic biomarkers, and targeted therapeutics of endometriosis. The qualitative SWiM synthesis gave four main findings. First, two kinds of treatment regressed active peritoneal lesions: selective intracrine estrogen blockade (irreversible 17β-HSD1 inhibition with PBRM [59]) and non-hormonal modulation of intracellular signaling (PPAR-γ activation with rosiglitazone [36], JNK inhibition with bentamapimod [51]). They did so while normal ovulatory cycles continued. They also avoided the bilateral ovarian cysts that unopposed systemic aromatase inhibition produced [41]. Second, systemic TNF-α antagonism lowers lesional TGF-β transcription [39]. It does not raise per-cycle fecundity in mild-to-moderate baboon endometriosis [40]. Direct intraperitoneal delivery of umbilical cord-derived mesenchymal stem cells worsened lesion severity, contrary to expectation [42]. Third, longitudinal NHP work links disease progression to several mechanisms. These are collective epithelial-stromal cell migration, with loss of E-cadherin/β-catenin and raised Ki67 at the invasion front [49]; failure of Complex I/II mitochondrial oxidative phosphorylation [54]; depletion of systemic and mucosal FOXP3$^+$ Treg cells with Th17 skewing and gut and urogenital dysbiosis [58]; thalamo-insular central pain sensitization [56]; and suppression of oviductal Anoctamin-1 pacemaker channels by peritoneal fluid [48]. Fourth, circulating non-coding RNAs (miR-150-5p, miR-451a, miR-3613-5p [55]), proliferative-phase eutopic CXCL13 [50], and uterine [$^{18}$F]FES/[$^{18}$F]FFNP PET/CT [43] give non-invasive readouts of disease activity and treatment response.

### 4.2. Comparison with previous evidence

Rodent literature supports a comparison. It also shows why non-human primates matter for bridging the translational gap in gynecology [27,29,38]. In homologous and heterologous mouse models, ectopic endometrium is sutured or injected into hosts that do not menstruate. These hosts lack natural spiral artery constriction, cyclic spontaneous decidualization, and physiological retrograde menstruation [4,11,12,61,62]. Murine studies have suggested uniform anti-inflammatory benefit from mesenchymal stem cell transplantation and broad suppression of inflammatory cytokines [63,64]. Primate trials show more complex effects that depend on species and route. Tsuji et al. [42] gave UC-MSCs ($2 \times 10^6$ cells/kg) to naturally menstruating cynomolgus macaques. Intraperitoneal administration worsened laparoscopic rASRM staging compared with intravenous delivery ($P = 0.02$). One explanation is local. Stem cells placed directly in an inflamed, estrogen-rich peritoneal cavity with active implants may engraft on lesion stroma. There they could undergo paracrine-induced fibroblast-to-myofibroblast transdifferentiation and secrete vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) [65]. New vessels, fibrotic encapsulation, and adhesions would follow [10,20,42]. Intravenous cells behave differently. Most are trapped in the pulmonary microvasculature [66], where they release anti-inflammatory exosomes into the circulation without feeding local peritoneal stroma. Rodent models also cannot test spontaneous conception over consecutive 28-day ovulatory cycles. The baboon fertility trial of Falconer et al. [40] showed that anti-TNF-α mAb c5N neither impaired ovulation nor significantly improved cycle fecundity rate (18% vs. 30% placebo). This may explain why TNF-α biologics have given only modest fertility benefit in women despite lowering inflammatory markers; this explanation is a hypothesis.

Clinical and translational studies from 2021 to 2026 agree with the molecular signatures and diagnostic trade-offs seen in the NHP evidence [31,46,47,67]. Cosar et al. [55] showed that simvastatin normalizes serum miR-150-5p, miR-451a, and miR-3613-5p in baboons. Nothnick and colleagues [68,69] then examined the miR-451a–macrophage migration inhibitory factor (MIF)–CD74/CXCR4 survival axis in human and baboon lesions. Mamillapalli et al. [46] profiled 2,731 plasma miRNAs by RNA sequencing at 3, 6, 9, and 15 months after induction in baboons. They found 76 differentially expressed transcripts and four persistent core biomarkers: upregulated miR-210-3p, and downregulated miR-448, miR-1260a/1260b, and miR-1298-5p. Surmann et al. [47] found that circulating transfer RNA-derived fragments (tRFs) differ in abundance as early as 3 months after endometriosis induction in eight female baboons. Small non-coding RNAs are therefore early liquid biopsy candidates. Molecular receptor imaging adds a different kind of information. Wilson et al. [43] used abdominopelvic PET/CT with [$^{18}$F]FES and [$^{18}$F]FFNP to quantify global changes in uterine estrogen and progesterone receptors across menstrual phases in rhesus macaques. Johnson et al. [31] reached related conclusions from immunohistochemical subtyping of 68 rhesus macaques at the Emory National Primate Research Center. PET/CT cannot resolve small individual peritoneal implants, because the radiotracers are excreted through the liver, bile, and intestine. Circulating miRNA and tRF panels have the molecular sensitivity to detect early, millimeter-scale peritoneal disease. Receptor PET/CT and emerging fibroblast activation protein (FAP) PET/MRI [25] give anatomical staging of deep nodular or uterine receptor pathology.

### 4.3. Mechanistic plausibility across the four clusters

The four clusters share a biologically plausible sequence: retrograde menstruation, intracrine estrogen, mitochondrial stress, and neuro-immune dysbiosis, each reinforcing the next. Hayashi et al. [57] mapped cynomolgus macaques by monthly laparoscopy for 24 months. Spontaneous retrograde menstruation first seeded the gravity-dependent anterior vesicouterine pouch (in 45.4% of primates) and then spread back to the rectouterine pouch of Douglas. De novo lesions developed in 100% of animals within two years. Viable fragments of menstrual endometrial functionalis then adhere to the peritoneal mesothelium. They are rich in basalis-like SSEA1$^+$/SOX9$^+$ progenitor cells [30] and steroid receptor coactivator-2 [15]. Local upregulation of CYP19A1 aromatase [41] and 17β-HSD1 [59] follows. Together they drive autonomous intracrine synthesis of potent 17β-estradiol ($E_2$) from circulating estrone and androstenedione. ERBB2- and MIG-6-related progesterone resistance adds to the effect [13,70]. Excess local $E_2$ and interleukin-6 (IL-6) activate NOTCH1/E-protein signaling [71,72]. They also upregulate microRNA-21, which drives myofibroblast fibrosis [67]. At the invasion front of deep nodular lesions, partial epithelial-mesenchymal-like plasticity appears, with reduced E-cadherin and β-catenin and raised Ki67 mitotic activity [49].

Recurrent cyclic bleeding within ectopic implants also releases free iron into the peritoneal cavity. This catalytic iron induces systemic iron deficiency [73] and ferroptotic and oxidative stress [18,21]. It also causes severe dysfunction of the mitochondrial electron transport chain. Complex I and

Complex II oxygen consumption rates fall in basal, state 3, state 3u, and state 4o respiration, and carnitine, creatine phosphate, NADH, FAD, tryptophan, and malic acid are depleted in both ectopic lesions and eutopic endometrium [54]. Systemic hyperandrogenemia and visceral adiposity under Western-style diet exposure amplify this metabolic and oxidative stress [60,74,75]. A marked immunological shift follows. Ectopic implants fail to recruit protective $CD56^+$ uterine natural killer cells [52]. Systemic and mucosal $FOXP3^+$ regulatory T cells decline, pro-inflammatory Th17 cells expand, and gut and urogenital microbial dysbiosis develops [17,58,76]. This inflammatory peritoneal microenvironment drives both unexplained tubal subfertility and central chronic pelvic pain. In the ampulla of the fallopian tube, inflammatory cytokines in endometriotic peritoneal fluid selectively lower Anoctamin-1 (ANO1) calcium-activated chloride channels on interstitial cells of Cajal-like pacemaker cells. FOXJ1 and AK7 ciliary structure is unchanged. Oviductal smooth muscle peristalsis is damped, and oocyte and embryo transport suffers even when the tubes are anatomically patent [48,77]. Chronic nociceptive input from innervated peritoneal lesions and Neuropeptide S Receptor 1 (NPSR1)-expressing inflammatory monocytes [29] also drives plasticity in the central nervous system. The result is mechanical allodynia and hyperactivity of the insula and thalamus on fMRI BOLD imaging, which reverses with the progestin dienogest [56].

### 4.4. Species, models, and sources of heterogeneity

The primary NHP literature also shows where clinical and methodological heterogeneity comes from [45]. First, species differ greatly in anatomy and physiology. Olive baboons (Papio anubis) have a straight cervical canal that allows transcervical endometrial curettage, and a spacious pelvis suited to repeated surgical staging [36,51]. Rhesus macaques (Macaca mulatta) and cynomolgus monkeys (Macaca fascicularis) have a tortuous sigmoid cervix. This led to laparoscopic intrauterine fundal puncture as the induction method [37]. Second, disease origin differs. Acute, surgically induced peritoneal seeding is typically assessed 25 to 90 days after inoculation [36,39,55,59]. Chronic spontaneous colony endometriosis evolves over several years, with dense adhesions and ovarian endometriomas [43,48,53,57]. Third, outcome instruments range widely. They include macroscopic rASRM videolaparoscopic surface area and volume calculations, molecular transcriptomics, metabolomics, algometry, and dynamic PET/CT or fMRI neuroimaging.

### 4.5. Strengths and limitations

This synthesis has several methodological strengths. It integrates 20 primary studies and 299 primates over a 19-year translational window (2007–2025), set alongside 2026 multi-omic discoveries [31,46,47]. It follows the PRISMA 2020 [44] and SWiM [45] reporting guidelines. Boolean searches covered four major databases. Active Digital Object Identifiers (DOIs) were verified for all 77 references. Data were extracted in 24 standardized clinical and quantitative domains per study without data imputation. Risk of bias was assessed in five domains and certainty with the GRADE narrative approach. Together these support rigor and reproducibility.

Limitations of the primary NHP evidence and of this review need to be stated. First, strict ethical regulation, specialized husbandry, and high cost keep individual primate studies small. Sample sizes ranged from N = 6 to N = 39 per study, and treatment arms often held only n = 4 to n = 10 animals. Power to detect subtle subgroup differences is therefore limited. Second, surgical induction in baboons and macaques uses large boluses of autologous menstrual tissue, inoculated over one to three cycles. Lesions are established faster than in the multi-year natural history of spontaneous retrograde menstruation in women and captive macaques [37,57].

Third, drug efficacy trials mostly followed animals for short to medium periods, 30 to 90 days for rosiglitazone, rhTNFbp-1, bentamapimod, PBRM, and simvastatin [36,39,51,55,59]. Long-term recurrence after treatment and multi-year teratogenicity therefore cannot be judged. Fourth, the search was limited to peer-reviewed English-language publications. Grey literature and unpublished pharmaceutical registries were excluded. Language or publication bias may result, although several databases and citation tracking were used. Four further limitations apply. No formal assessment of publication bias was made. The review protocol was not registered, according to the manuscript. Several mechanistic findings rest on a single study each. The manuscript does not state whether a second reviewer took part in screening and extraction.

### 4.6. Clinical and research implications

The findings have direct implications for clinical gynecology, reproductive endocrinology, and the design of preclinical trials. First, irreversible 17β-HSD1 inhibitors (PBRM [59]), JNK inhibitors (bentamapimod [51]), and PPAR-γ ligands (rosiglitazone [36]) showed good safety and efficacy in baboons. These findings support consideration of intracrine and non-hormonal intracellular targets in early-phase human trials for women who want to preserve fertility. Targeted nanomedicine platforms, such as magnetic hyperthermia nanoparticles [78,79] and drug-loaded polymeric nanomicelles [14], are also worth exploring. Second, clinicians and trialists designing regenerative cell therapies should heed the primate safety signal from Tsuji et al. [42]. Mesenchymal stem cells should not be infused directly into the peritoneal cavity of patients with active endometriosis. Third, an evidence-based framework can guide the choice of NHP species in future preclinical work. (i) The olive baboon (Papio anubis) is best for rapid surgical induction by transcervical endometrial seeding, repeated multi-laparoscopy lesion morphometry, serial endometrial or peritoneal biopsies, and timed-mating fertility outcomes [36,40,51,59]. (ii) The rhesus macaque (Macaca mulatta) suits long-term metabolic and endocrine exposure studies, such as PCOS-like hyperandrogenemia and obesogenic diets [60], oviductal physiological assays [48], and radiotracer PET/CT imaging [43]. Laparoscopic intrauterine fundal puncture is used when induced disease is required [37]. (iii) The cynomolgus macaque (Macaca fascicularis) is the preferred model for colony screening of spontaneous endometriosis, multi-year natural history mapping, and objective central pain neuroimaging by fMRI and algometry [53,56,57]. Combining these NHP platforms with longitudinal liquid biopsy panels (circulating miRNAs [46,55] and tRNA-derived fragments [47]) may speed precision medicine for women with endometriosis.

## 5. Conclusion

This systematic review of 20 primary studies in N = 299 non-human primates shows that menstruating Old World primates bridge basic molecular discovery and clinical gynecological practice in endometriosis. The species are olive baboons (Papio anubis, n = 132), rhesus macaques (Macaca mulatta, n = 96), cynomolgus macaques (Macaca fascicularis, n = 55), and mixed macaque cohorts (n = 16).

Synthesis without meta-analysis and GRADE narrative ratings across four thematic clusters give four conclusions. First, High-certainty evidence in Cluster 3 (k = 8, N = 109) shows how primate endometriosis arises and progresses. Retrograde menstrual seeding spreads from the vesicouterine pouch to the pouch of Douglas [57]. E-cadherin and β-catenin loss allows collective cell invasion at the leading edge of deep nodular lesions [49]. Complex I and II mitochondrial oxidative phosphorylation fails, with depletion of tricarboxylic acid cofactors [54]. Systemic and mucosal FOXP3$^+$ Treg cells shift toward Th17 cells, with gut and urogenital dysbiosis [58]. Thalamo-insular pathways sensitize central pain processing [56]. Peritoneal fluid suppresses oviductal Anoctamin-1 pacemaker channels [48]. Second, High-certainty evidence in Cluster 1 (k = 5, N = 85) shows that selective intracrine estrogen blockade with the irreversible 17β-HSD1 inhibitor PBRM [59], and non-hormonal PPAR-γ activation with rosiglitazone [36], regress active red peritoneal lesions. Both preserve normal ovulatory cyclicity and avoid the bilateral ovarian cysts caused by unopposed systemic aromatase inhibition [41]. The progestin dienogest reverses amplified central fMRI pain responses [56]. Third, Low-certainty evidence in Cluster 2 (k = 4, N = 61) shows that oral JNK inhibition (bentamapimod [51]) and rhTNFbp-1 [39] reduce lesion burden without suppressing the ovary. The anti-TNF-α monoclonal antibody c5N does not improve cycle fecundity [40], and intraperitoneal mesenchymal stem cell delivery significantly worsens peritoneal endometriosis [42]. Fourth, High-certainty evidence in Cluster 4 (k = 3, N = 44) supports circulating microRNAs (miR-150-5p, miR-451a, miR-3613-5p [55]), endometrial CXCL13 [50], and [$^{18}$F]FES/[$^{18}$F]FFNP PET/CT imaging [43] as non-invasive tools for staging and monitoring treatment that work together.

## Declarations

**Use of Generative Artificial Intelligence.** The authors did not use any generative artificial-intelligence tools to write, analyze, or prepare this manuscript. The authors take full responsibility for its content.

**Author Contributions.** Y.A.E.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. H.W.: Methodology, Investigation, Validation, Writing – review & editing, Supervision.

**Funding.** This review received no external grant or funding from any public, commercial, or not-for-profit agency.

**Conflict of Interest.** The authors declare no competing financial, professional, or personal interests that could have influenced the conduct or reporting of this review.

**Ethical Approval.** Ethical approval was not required, because this systematic review analyzed published data only and involved no new human or animal subjects.

**Patient Consent.** Patient consent was not applicable, because the review included no human participants.

**Data Availability.** All extracted datasets, SWiM synthesis matrices, and GRADE evidence profiles are provided within the article.

**Acknowledgments.** The authors have no acknowledgments to declare.

## References

1. Farolfi A, Gentili N, Testoni S, et al. Endometriosis and endometrial cancer: a propensity score-adjusted real-world data study. iScience. 2024;27(5):109680. doi:10.1016/j.isci.2024.109680
2. Liu H, Liang J, Dai X, et al. Transcriptome-wide N6-methyladenosine (m6A) methylation profiling of long non-coding RNAs in ovarian endometriosis. Genomics. 2024;116(2):110803. doi:10.1016/j.ygeno.2024.110803
3. Gjorgoska M, Rizner TL. The effect of androgens on the risk of endometriosis sub-phenotypes and ovarian neoplasms: a Mendelian randomization study. J Steroid Biochem Mol Biol. 2024;239:106482. doi:10.1016/j.jsbmb.2024.106482
4. Zhang Y, He T, Lin T, et al. Novel in vivo endometriotic models associated eutopic endometrium by implanting menstrual blood-derived stromal cells from patients with endometriosis. Sci Rep. 2023;13(1):8295. doi:10.1038/s41598-023-35373-4
5. Meyer R, Sun J, Lombardi C, et al. Association between clinically suspected endometriosis lacking histologic evidence and anxiety, depression and cannabidiol-containing products. Eur J Obstet Gynecol Reprod Biol X. 2026;32:100500. doi:10.1016/j.eurox.2026.100500
6. He Y, Zhang X, Li Y, et al. Impact of hysteroscopy on pregnancy outcomes in women with endometriosis-associated infertility undergoing their first frozen-thawed embryo transfer: a retrospective cohort study. Front Med (Lausanne). 2026;13:1849361. doi:10.3389/fmed.2026.1849361
7. Xu H, Huang S, Zheng Y, et al. Plasma fibrinogen levels in women with infertility undergoing surgical evaluation for endometriosis: a retrospective cross-sectional study. Front Endocrinol (Lausanne). 2026;17:1929933. doi:10.3389/fendo.2026.1929933
8. Lee D, Kim SK, Lee JR, et al. Management of endometriosis-related infertility: considerations and treatment options. Clin Exp Reprod Med. 2020;47(1):1–11. doi:10.5653/cerm.2019.02971
9. Larraín D, Caradeux J, Maisto MD, et al. Infertility management in patients with bowel endometriosis: the current landscape and the promise of randomised trials: a narrative review. Facts Views Vis Obgyn. 2025;17:369–390. doi:10.52054/fvvo.2025.168
10. Yun S, So KA, Jeong EM, et al. Persistent pelvic adhesions and fibrotic remodeling following ectopic lesion ablation in a mouse model of endometriosis. FASEB J. 2026;40(20):e72403. doi:10.1096/fj.202601955RRR
11. Nenicu A, Yordanova K, Gu Y, et al. Differences in growth and vascularization of ectopic menstrual and non-menstrual endometrial tissue in mouse models of endometriosis. Hum Reprod. 2021;36(8):2202–2214. doi:10.1093/humrep/deab139
12. Wibisono H, Nakamura K, Taniguchi F, et al. Tracing location by applying emerald luciferase in an early phase of murine endometriotic lesion formation. Exp Anim. 2022;71(2):184–192. doi:10.1538/expanim.21-0146
13. Coyne K, Dorn CV, Kim ST, et al. Altered progesterone receptor isoform expression in endometrial cells: A preliminary immunohistochemical study in endometriosis. J Clin Med. 2026;15(17):6664. doi:10.3390/jcm15176664
14. Xavier-de-Britto I, Gomes-da-Silva NC, Alencar LMR, et al. Arimoclomol-loaded Pluronic F127 nanomicelles in experimental endometriosis: drug incorporation, in vitro release, and early morphological and histological responses. Eur J Pharm Biopharm. 2026;228:115237. doi:10.1016/j.ejpb.2026.115237
15. Maurya VK, Gunasekaran S, Misra N, et al. Pathogenic properties of human endometriotic epithelial cells require steroid receptor coactivator-2. Reproduction. 2026:xaag125. doi:10.1093/reprod/xaag125
16. Chi C, Chen J, Xiang S, et al. Ectopic endometrial stromal cells-derived exosomes accelerate endometriosis progression by delivering PDLIM3 to induce macrophage M2 polarization. J Cell Commun Signal. 2026;20(4):e70122. doi:10.1002/ccs3.70122
17. Li N, Yuan M, Jin X, et al. Intestinal microbiota-associated LysoPC(16:0) promotes endometriosis via PPARγ-mediated M2 macrophage polarization and IL-10 secretion. iScience. 2026;29(11):117917. doi:10.1016/j.isci.2026.117917
18. Yuan M, Jiao X, Xu L, et al. Ionomics powered single-cell mapping reveals targetable iron dysregulation in endometriosis associated macrophages. BMC Med. 2026;24(1):587. doi:10.1186/s12916-026-05095-1
19. Kopeć M, Wojtaś M, Kamińska A, et al. The concentration of macrophage-derived IL-1α and IL-12 in the peritoneal fluid of patients with endometriosis: A pilot case-control study. Int J Inflam. 2026;2026:6669619. doi:10.1155/ijin/6669619
20. Li X, Wang J, Yuan L, et al. YTHDF3 promotes angiogenesis in endometriosis by enhancing the translation efficiency of PFKFB3. Angiogenesis. 2026;29(4):70. doi:10.1007/s10456-026-10095-z
21. Kadeer B, Wufuer S, Maimaitimin A, et al. Diagnostic and predictive values of ferroptosis-related genes in endometriosis based on integrated bioinformatic analysis. Reprod Sci. 2026. doi:10.1007/s43032-026-02142-3
22. Liu J, Zhang J, Wu Q, et al. RNF34 restrains endometriosis progression by promoting PKM2 ubiquitination and suppressing glycolysis. Cell Signal. 2026;149:112896. doi:10.1016/j.cellsig.2026.112896
23. Rezk-Füreder M, Kazemi M, Gyunesh AA, et al. Single-cell RNA sequencing reveals immune dysregulation and candidate drug targets in endometriosis. Cells. 2026;15(18):1702. doi:10.3390/cells15181702
24. Badran D, Clarke H, Salvini S, et al. Methodological pitfalls in endometriosis biospecimen research: lessons from MAP4K4

expression studies. FASEB Bioadv. 2026;8(9):e70153. doi:10.1096/fba.2026-00156
25. Akashi K, Shahi M, Colak C, et al. FAP expression in deep and superficial endometriosis: association with MRI and transvaginal ultrasound visibility. Eur J Nucl Med Mol Imaging. 2026. doi:10.1007/s00259-026-08189-3
26. Li M, Zhou X, Chen Y. Elevated neutrophil count as a causal risk factor for endometriosis: A Mendelian randomization study. Int J Womens Health. 2026;18:623790. doi:10.2147/IJWH.S623790
27. Vallender EJ, Hotchkiss CE, Lewis AD, et al. Nonhuman primate genetic models for the study of rare diseases. Orphanet J Rare Dis. 2023;18(1):20. doi:10.1186/s13023-023-02619-3
28. Wang Y, Li Y, Li Y, et al. Establishment of rat endometriosis model by autologous endometrial transplantation and proof-of-concept pharmacological validation with elagolix. J Vis Exp. 2026. doi:10.3791/74321
29. Tapmeier TT, Rahmioglu N, Lin J, et al. Neuropeptide S receptor 1 is a nonhormonal treatment target in endometriosis. Sci Transl Med. 2021;13(608):eabd6469. doi:10.1126/scitranslmed.abd6469
30. Hapangama DK, Drury J, Da Silva L, et al. Abnormally located SSEA1+/SOX9+ endometrial epithelial cells with a basalis-like phenotype in the eutopic functionalis layer may play a role in the pathogenesis of endometriosis. Hum Reprod. 2019;34(1):56–68. doi:10.1093/humrep/dey336
31. Johnson AA, Wilkes AC, Easley KA, et al. Evaluating subtypes of endometriosis in Rhesus macaques (Macaca mulatta) using clinical findings and immunohistochemistry. J Am Assoc Lab Anim Sci. 2026;65(3):1–10. doi:10.30802/AALAS-JAALAS-26-010
32. Galietta V, Cocumelli C, Parmigiani R, et al. A survey of the reproductive lesions in captive female non-human primates in Italy. Vet Sci. 2025;12(9):856. doi:10.3390/vetsci12090856
33. Kirejczyk S, Pinelli C, Gonzalez O, et al. Urogenital lesions in nonhuman primates at 2 National Primate Research Centers. Vet Pathol. 2021;58(1):147–160. doi:10.1177/0300985820971752
34. Kennedy LH, Nowland MH, Nemzek-Hamlin JA. Surgical treatment of spontaneous endometriosis in rhesus macaques (Macaca mulatta): 11 cases (2007-2011). J Am Vet Med Assoc. 2019;254(12):1454–1458. doi:10.2460/javma.254.12.1454
35. Gruber-Dujardin E, Bleyer M, Mätz-Rensing K. Morphological and immunohistochemical characterization of spontaneous endometriosis in rhesus macaques (Macaca mulatta). Primate Biol. 2017;4(1):77–91. doi:10.5194/pb-4-77-2017
36. Lebovic DI, Mwenda JM, Chai DC, et al. PPAR-gamma receptor ligand induces regression of endometrial explants in baboons: a prospective, randomized, placebo- and drug-controlled study. Fertil Steril. 2007;88(4 Suppl):1108–19. doi:10.1016/j.fertnstert.2006.12.072
37. Slayden OD, Luo F, Martin LD. A protocol for creating endometriosis in rhesus macaques (Macaca mulatta). J Med Primatol. 2023;52(6):405–413. doi:10.1111/jmp.12681
38. Zhou M, Zhou X, Wang X. Advances in endometriosis research: animal models for the study of reproductive disorders. Biol Reprod. 2025;113(3):494–510. doi:10.1093/biolre/ioaf089
39. Kyama CM, Overbergh L, Mihalyi A, et al. Effect of recombinant human TNF-binding protein-1 and GnRH antagonist on mRNA expression of inflammatory cytokines and adhesion and growth factors in endometrium and endometriosis tissues in baboons. Fertil Steril. 2008;89(5 Suppl):1306–13. doi:10.1016/j.fertnstert.2006.11.205
40. Falconer H, Mwenda JM, Chai DC, et al. Effects of anti-TNF-mAb treatment on pregnancy in baboons with induced endometriosis. Fertil Steril. 2008;89(5 Suppl):1537–45. doi:10.1016/j.fertnstert.2007.05.062
41. Langoi D, Pavone ME, Gurates B, et al. Aromatase inhibitor treatment limits progression of peritoneal endometriosis in baboons. Fertil Steril. 2013;99(3):656–662.e3. doi:10.1016/j.fertnstert.2012.11.021
42. Tsuji S, Mukai T, Tsuchiya H, et al. Impact of administering umbilical cord-derived mesenchymal stem cells to cynomolgus monkeys with endometriosis. Reprod Med Biol. 2023;22(1):e12540. doi:10.1002/rmb2.12540
43. Wilson RC, Link JM, Lee YZ, et al. Uterine uptake of estrogen and progestogen-based radiotracers in Rhesus macaques with endometriosis. Mol Imaging Biol. 2024;26(2):334–343. doi:10.1007/s11307-023-01892-9
44. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71
45. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020;368:l6890. doi:10.1136/bmj.l6890
46. Mamillapalli R, Surmann H, Joshi N, et al. Differential expression of microRNAs after induction of endometriosis in baboons. Biol Reprod. 2026;115(3):739–749. doi:10.1093/biolre/ioag140
47. Surmann H, Mamillapalli R, Joshi N, et al. Circulating transfer RNA-derived fragment abundance after experimental endometriosis induction in baboons. Mol Hum Reprod. 2026;32(2):gaag032. doi:10.1093/molehr/gaag032
48. Luo F, Slayden O. Attenuation of ampullary anoctamin 1 by the peritoneal fluid in rhesus macaques with spontaneous endometriosis. Biol Reprod. 2025;112(2):286–296. doi:10.1093/biolre/ioae173
49. Donnez O, Orellana R, Van Kerk O, et al. Invasion process of induced deep nodular endometriosis in an experimental baboon model: similarities with collective cell migration? Fertil Steril. 2015;104(2):491–7.e2. doi:10.1016/j.fertnstert.2015.05.011
50. Franasiak JM, Burns KA, Slayden O, et al. Endometrial CXCL13 expression is cycle regulated in humans and aberrantly expressed in humans and Rhesus macaques with endometriosis. Reprod Sci. 2015;22(4):442–51. doi:10.1177/1933719114542011
51. Hussein M, Chai DC, Kyama CM, et al. c-Jun NH2-terminal kinase inhibitor bentamapimod reduces induced endometriosis in baboons: an assessor-blind placebo-controlled randomized study. Fertil Steril. 2016;105(3):815–824.e5. doi:10.1016/j.fertnstert.2015.11.022
52. Drury JA, Parkin KL, Coyne L, et al. The dynamic changes in the number of uterine natural killer cells are specific to the eutopic but not to the ectopic endometrium in women and in a baboon model of endometriosis. Reprod Biol Endocrinol. 2018;16(1):67. doi:10.1186/s12958-018-0385-3
53. Nishimoto-Kakiuchi A, Netsu S, Okabayashi S, et al. Spontaneous endometriosis in cynomolgus monkeys as a clinically relevant experimental model. Hum Reprod. 2018;33(7):1228–1236. doi:10.1093/humrep/dey095
54. Atkins HM, Bharadwaj MS, O'Brien Cox A, et al. Endometrium and endometriosis tissue mitochondrial energy metabolism in a nonhuman primate model. Reprod Biol Endocrinol. 2019;17(1):70. doi:10.1186/s12958-019-0513-8
55. Cosar E, Mamillapalli R, Moridi I, et al. Serum MicroRNA biomarkers regulated by simvastatin in a primate model of endometriosis. Reprod Sci. 2019;26(10):1343–1350. doi:10.1177/1933719118765971
56. Yano M, Matsuda A, Natsume T, et al. Pain-related behavior and brain activation in cynomolgus macaques with naturally occurring endometriosis. Hum Reprod. 2019;34(3):469–478. doi:10.1093/humrep/dey383
57. Hayashi K, Nakayama M, Iwatani C, et al. The natural history of spontaneously occurred endometriosis in cynomolgus monkeys by monthly follow-up laparoscopy for two years. Tohoku J Exp Med. 2020;251(4):241–253. doi:10.1620/tjem.251.241
58. Le N, Cregger M, Fazleabas A, et al. Effects of endometriosis on immunity and mucosal microbial community dynamics in female olive baboons. Sci Rep. 2022;12(1):1590. doi:10.1038/s41598-022-05499-y
59. Poirier D, Nyachieo A, Romano A, et al. An irreversible inhibitor of 17β-hydroxysteroid dehydrogenase type 1 inhibits estradiol synthesis in human endometriosis lesions and induces regression of the non-human primate endometriosis. J Steroid Biochem Mol Biol. 2022;222:106136. doi:10.1016/j.jsbmb.2022.106136
60. Bishop CV, Takahashi DL, Luo F, et al. The combined impact of testosterone and Western-style diet on endometriosis severity and progression in rhesus macaques. Biol Reprod. 2023;108(1):72–80. doi:10.1093/biolre/ioac183
61. Tal A, Tal R, Pluchino N, et al. Endometrial cells contribute to preexisting endometriosis lesions in a mouse model of retrograde menstruation. Biol Reprod. 2019;100(6):1453–1460. doi:10.1093/biolre/ioz039
62. Yan D, Liu X, Guo SW. The establishment of a mouse model of deep endometriosis. Hum Reprod. 2019;34(2):235–247. doi:10.1093/humrep/dey361
63. Hortu I, Kandemir Demirci G, Şimşek B, et al. Dental pulp–derived mesenchymal stem cells reduce lesion progression in a rat model of endometriosis. Sci Rep. 2026;16(1):24781. doi:10.1038/s41598-026-52416-8
64. Silvana R, Effendi Y, Amran R, et al. Effectiveness of BMMSC and dienogest on IL-1β, IL-8 expression and lesion area in endometriosis mice. JBRA Assist Reprod. 2026:1–12. doi:10.5935/1518-0557.20260001
65. Feng Y, Dong H, Tan B. Endometriotic mesenchymal stem cells promote the fibrosis process of endometriosis through paracrine TGF-β1 mediated RASAL1 inhibition. J Obstet Gynaecol Res. 2024;50(3):467–477. doi:10.1111/jog.15851
66. Ji X, Wang L, Zhong Y, et al. Impact of mesenchymal stem cell size and adhesion modulation on in vivo distribution: insights from quantitative PET imaging. Stem Cell Res Ther. 2024;15(1):456. doi:10.1186/s13287-024-04078-4
67. Ochoa Bernal MA, Song Y, Joshi N, et al. The regulation of MicroRNA-21 by interleukin-6 and its role in the development of fibrosis in endometriotic lesions. Int J Mol Sci. 2024;25(16):8994. doi:10.3390/ijms25168994
68. Nothnick WB, Graham A. Dissecting the miR-451a-Mif pathway in endometriosis pathophysiology using a syngeneic mouse model: temporal expression of lesion Mif receptors, Cd74 and

Cxcr4. Biomedicines. 2022;10(7):1699. doi:10.3390/biomedicines10071699
69. Nothnick WB, Falcone T, Olson MR, et al. Macrophage migration inhibitory factor receptor, CD74, is overexpressed in human and baboon (Papio anubis) endometriotic lesions and modulates endometriotic epithelial cell survival and interleukin 8 expression. Reprod Sci. 2018;25(11):1557–1566. doi:10.1177/1933719118766262
70. Yoo JY, Kim TH, Shin JH, et al. Loss of MIG-6 results in endometrial progesterone resistance via ERBB2. Nat Commun. 2022;13(1):1101. doi:10.1038/s41467-022-28608-x
71. Song Y, Su RW, Joshi NR, et al. Interleukin-6 (IL-6) activates the NOTCH1 signaling pathway through E-proteins in endometriotic lesions. J Clin Endocrinol Metab. 2020;105(5):1316–26. doi:10.1210/clinem/dgaa096
72. Song Y, Burns GW, Joshi NR, et al. Spheroids as a model for endometriotic lesions. JCI Insight. 2023;8(11):e160815. doi:10.1172/jci.insight.160815
73. Atkins HM, Appt SE, Taylor RN, et al. Systemic iron deficiency in a nonhuman primate model of endometriosis. Comp Med. 2018;68(4):298–307. doi:10.30802/AALAS-CM-17-000082
74. Bishop CV, Luo F, Gao L, et al. Mild hyperandrogenemia in presence/absence of a high-fat, Western-style diet alters secretory phase endometrial transcriptome in nonhuman primates. F S Sci. 2020;1(2):172–182. doi:10.1016/j.xfss.2020.08.003
75. Wang X, Zhu J, Li J, et al. E2F1 down-regulation promotes lipid droplet accumulation and endometriosis development through impaired MGLL-mediated lipid mobilization. Clin Sci (Lond). 2026;140(11):2387–2409. doi:10.1042/CS20261535
76. Nardone GG, Rosso LE, Santin A, et al. Connecting gut microbiome composition to symptom severity and host genetics in endometriosis. Front Microbiol. 2026;17:1873766. doi:10.3389/fmicb.2026.1873766
77. Dixon RE, Hwang SJ, Kim BH, et al. Myosalpinx contractions are essential for egg transport along the oviduct and are disrupted in reproductive tract diseases. Adv Exp Med Biol. 2019;1124:265–294. doi:10.1007/978-981-13-5895-1_11
78. Park Y, Demessie AA, Luo A, et al. Targeted nanoparticles with high heating efficiency for the treatment of endometriosis with systemically delivered magnetic hyperthermia. Small. 2022;18(24):e2107808. doi:10.1002/smll.202107808
79. Moses AS, Taratula OR, Lee H, et al. Nanoparticle-based platform for activatable fluorescence imaging and photothermal ablation of endometriosis. Small. 2020;16(18):e1906936. doi:10.1002/smll.201906936