

Reviews

Endometrial aging and female fertility: Molecular mechanisms, clinical consequences and therapeutic opportunities

Tamar Alkon^{1a}, Jorge Suarez², Ricardo H. Asch Schuff³¹ Reproductive Medicine Associates International, México-Ciudad de México, México, ² Instituto Tecnológico de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina, ³ Instituto Mexicano de Alta Tecnología Reproductiva, Ciudad de México

Keywords: endometrial aging, uterine receptivity, donor oocyte, implantation failure, senescence, advanced maternal age

<https://doi.org/10.46989/001c.171806>

Journal of IVF-Worldwide

Vol. 4, Issue 4, 2026

Endometrial aging encompasses progressive structural, vascular, hormonal, cellular, and epigenetic changes that impair uterine receptivity and embryo implantation in both natural conception and assisted reproductive technology (ART). Although ovarian aging has historically been considered the principal determinant of female fertility decline, mounting clinical and molecular evidence demonstrates that the uterus itself is not age-invariant. This review summarizes the historical paradigm of the “ageless uterus,” the demographic and social context that has made endometrial aging a clinically urgent question, the cellular and molecular mechanisms underlying endometrial aging (including senescence, decidualization failure, transcriptomic remodeling, vascular decline, and epigenetic drift), the clinical evidence demonstrating its impact on implantation, pregnancy loss, live birth, and obstetric outcomes, the contemporary public narrative around late motherhood, the emerging regenerative strategies aimed at restoring endometrial function, and future directions including artificial intelligence-based endometrial assessment. A central clinical message is that although reproductive outcomes decline with age, they remain non-zero even into the fifth decade and beyond, supporting calibrated rather than dichotomous counseling.

INTRODUCTION

For more than three decades, the prevailing view in reproductive medicine has been that the uterus does not age. This paradigm originated from the preliminary oocyte-donation report by Sauer and colleagues, in which seven women aged 40–44 years with ovarian failure who received oocytes from young donors achieved pregnancies at rates comparable to those reported in younger recipients. These findings led to the conclusion that maternal age primarily affects oocyte quality rather than uterine receptivity.¹

Subsequent landmark studies appeared to reinforce this concept. Navot and colleagues, sharing oocytes from the same donors between younger and older recipients, reported preserved implantation in recipients up to the mid-forties and attributed the age-related decline in fertility to oocyte quality rather than to a diminished capacity of the uterus to sustain implantation.^{2,3} Notably, Borini and colleagues demonstrated that successful pregnancies could be achieved in postmenopausal women over 50 years of age through oocyte donation, reporting clinical pregnancies in

this age group and confirming that hormonal preparation of the endometrium could support implantation even beyond natural reproductive age.⁴ Abdalla and colleagues found no significant association between recipient age and pregnancy outcomes in donor cycles,⁵ while Noci and colleagues, in a morphological and immunohistochemical study, found no significant differences between the endometria of women under 30 and over 40 years of age and concluded that the human endometrium does not appear to age as long as cyclic hormonal stimulation and menstruation persist.⁶ Together, these reports established the concept of the “ageless uterus,” which for decades served as a clinical reassurance for women delaying motherhood ([Table 1](#)).

However, early signals challenging this paradigm emerged shortly thereafter. Flamigni et al. reported reduced pregnancy and implantation rates in older oocyte-donation recipients, with pregnancy rates declining from 45% in women aged 21–35 years to 23% in those aged 41–49 years, and implantation rates from 23% to 10%.⁷ The same dataset was subsequently discussed by Borini and Asch in

^a Corresponding Author. Tamar Alkon, email: tamara.alkon@rmamexico.com
Reproductive Medicine Associates International, México

Prolongación Paseo de la Reforma 2673, torre B, piso 10. Colonia Lomas de Bezares, delegación Miguel Hidalgo, CP. 11910, CDMX

Table 1. Historical and Contemporary Landmark Studies on Endometrial Aging: Insights from Donor-Oocyte Cycles and Histological Evidence

Author(s) (Year)	Key Contribution	Position on the paradigm
Sauer, Paulson & Lobo (1990)	Report of oocyte donation in seven women aged 40–44 years with ovarian failure, extending reproductive potential beyond age 40	Supports
Navot et al. (1991, 1994)	Shared-donor design: implantation preserved in recipients up to the mid-forties; age-related decline attributed to oocyte quality rather than to uterine capacity	Supports
Noci et al. (1995)	Morphological and immunohistochemical study: no significant differences between the endometria of women <30 and >40 years; concluded that the endometrium does not appear to age while cyclic hormonal stimulation and menstruation persist	Supports
Abdalla et al. (1997)	Found no significant association between recipient age and pregnancy outcome in donor-oocyte cycles in a UK series	Supports
Flamigni, Borini et al. (1993)	Oocyte donation in women aged 21–49 years: pregnancy rate 45% in ages 21–35 vs. 23% in ages 41–49; implantation rate 23% vs. 10% — among the first evidence of age-related endometrial contribution	Questions
Borini et al. (1996)	Confirmed age-related differences in pregnancy and implantation rates across age groups sharing oocytes from a single donor	Questions
Glasser (1998)	Provocative editorial questioning whether the uterus truly remains functionally intact with aging: “The Uterus: Idiot Savant or Rosetta Stone?” — among the first to formally challenge the ageless-uterus paradigm	Questions
Yeh et al. (2014)	Analysis of >27,000 donor-oocyte cycles from SART registry demonstrating graded live-birth decline with recipient age, largest drop after age 44	Demonstrates aging
Williams et al. (2022)	SART registry analysis of 40,485 donor-oocyte cycles (2016–2018): odds of live birth after single embryo transfer fall with recipient age (OR 0.80 at 40–44, 0.77 at 45–49, 0.65 at >49 years)	Demonstrates aging
Sebastian-Leon et al. (2025)	Largest donor-oocyte cohort to date (33,141 transfers): live birth rate declines from 45.8% at age 40 to 32.7% at age 50; implantation failure +4.2%/year and pregnancy loss +3.2%/year beyond age 40	Demonstrates aging

Position on the paradigm: Supports = studies supporting the “ageless uterus” paradigm; Questions = studies beginning to question the paradigm; Demonstrates aging = studies demonstrating endometrial aging.

a contemporaneous book chapter on factors affecting implantation in the human⁸; these two publications therefore represent a single body of evidence rather than independent confirmation. These observations were later corroborated by Borini et al. in a 1996 cohort study of recipients sharing oocytes from a single donor.⁹

In a provocative 1998 *JARG* editorial titled “*The Uterus: Idiot Savant or Rosetta Stone?*”, Glasser formally questioned whether the uterus itself undergoes aging,¹⁰ marking an important conceptual shift.

Since then, accumulating evidence has increasingly challenged the notion of an “ageless uterus.” Large donor-oocyte cohort studies, along with transcriptomic and single-cell analyses and mechanistic investigations of cellular senescence, now converge to demonstrate that the endometrium ages independently of oocyte quality. This aging process is associated with impaired implantation, increased pregnancy loss, and reduced live birth rates after age 40.

More recent donor-oocyte studies incorporating larger cohorts, detailed outcomes, and embryos of known ploidy provide the strongest support for this shift. Yeh and colleagues, analyzing 27,959 first fresh donor cycles in the United States, demonstrated a graded decline in live birth rates with increasing recipient age.¹¹ A subsequent SART

registry analysis of 40,485 donor-oocyte cycles (2016–2018) confirmed a reduction in live birth with increasing recipient age after single embryo transfer, with adjusted odds ratios of 0.80 for ages 40–44, 0.77 for ages 45–49 and 0.65 for recipients over 49 years.¹² Most notably, the largest cohort to date by Sebastian-Leon and colleagues showed a decline in live birth rate from 45.8% at age 40 to 32.7% at age 50, accompanied by significant annual increases in implantation failure (4.2% per year) and pregnancy loss (3.2% per year) beyond age 40.¹³

Collectively, these data provide compelling evidence that endometrial aging independently contributes to reproductive outcomes (Table 1).

DEMOGRAPHIC CONTEXT: WHY ENDOMETRIAL AGING MATTERS NOW

The average age at first birth has risen across high-income countries over the past four decades. In the European Union, the mean age at first childbirth reached 29.7 years in 2022.¹⁴ In the United States, the proportion of first births to women aged 35 and older has more than tripled since 1990, and first births to women aged 40 and older have quadrupled.¹⁵ This demographic shift collides with biolog-

ical reality. Fecundability begins to decline measurably in the early thirties and accelerates after age 35; natural conception rates fall to single digits per month after age 40.

Particularly noteworthy is the growing number of gestational surrogacy cycles undertaken by women of advanced age; including grandmothers, mothers, and other older relatives carrying pregnancies on behalf of family members. As surrogacy becomes more legally available across jurisdictions, gestational carriers of advanced reproductive age represent a distinct clinical population whose uterine biology warrants dedicated attention. The available literature on reproductive outcomes as a function of gestational carrier age is unfortunately very limited, and direct comparisons between age groups of proven carriers are sparse. This gap represents an important and underexplored area, as the uterine biology of a 45- or 50-year-old gestational carrier who has previously carried successful pregnancies may differ meaningfully from a nulliparous woman of similar age, yet current evidence is insufficient to guide age-specific counseling in this population.

Beyond demographics, egg freezing, oocyte donation, and gestational surrogacy have created a more flexible reproductive map, but they have not eliminated the underlying biology of uterine aging, and they have introduced new questions about how best to counsel women across the entire reproductive lifespan.

PATHOPHYSIOLOGY OF ENDOMETRIAL AGING

Endometrial aging is driven by the same fundamental biological mechanisms that underlie aging in other tissues, expressed in a uterus-specific context. The classical hallmarks of aging, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, dysbiosis, and impaired macroautophagy are now recognized to operate within the endometrium.¹⁶ (Table 2)

OXIDATIVE STRESS, MITOCHONDRIAL DYSFUNCTION, AND TELOMERE ATTRITION

Cellular aging in the endometrium is initiated by the convergence of three upstream stressors that progressively accumulate across menstrual cycles. Oxidative stress arises from the imbalance between reactive oxygen species (ROS) generation and antioxidant capacity. The cycling endometrium experiences repeated bursts of ROS during ovulation, menstrual shedding, and re-vascularization, and with age both ROS production rises and antioxidant defenses decline. Mitochondrial dysfunction is closely coupled to oxidative stress: with age, mitochondrial copy number declines, membrane potential is reduced, electron transport chain efficiency drops, and mitochondrial DNA acquires deletions and point mutations. Telomere attrition provides a third upstream driver; telomere shortening triggers the DNA damage response and irreversibly commits cells to senescence.^{16,17}

CELLULAR SENESENCE AND THE SASP

Cellular senescence is the irreversible cell-cycle arrest of cells that have accumulated unsustainable damage, enforced through the p16⁺INK4a-Rb and p21⁺Cip1-p53 pathways. In the endometrium, senescence has a dual nature: transient, controlled senescence is required for the inflammatory burst supporting embryo invasion, but when clearance by uterine natural killer cells becomes incomplete, as occurs with chronological aging and immunosenescence, the accumulated senescence-associated secretory phenotype (SASP) sustains chronic inflammation that disrupts cyclic remodeling and impairs angiogenesis. Lucas and colleagues demonstrated that women with recurrent pregnancy loss show a pro-senescent decidual response during the peri-implantation window,¹⁸ and analogous profiles have been described in older endometria without overt pathology.

DECIDUALIZATION FAILURE AND PROGESTERONE SIGNALING

Decidualization is impaired with age: aged stromal cells show reduced expression of decidualization markers (prolactin, IGFBP-1), attenuated morphological transformation, and diminished capacity to mount the controlled pro-inflammatory response required for embryo invasion. Wang and colleagues demonstrated that aged endometrium loses histone H3 lysine 27 acetylation at progesterone-receptor target genes, with consequent downregulation of progesterone-receptor expression and impaired decidual response.¹⁹ An influential conceptual advance is the recognition that the decidualized endometrium functions as a biosensor of embryo quality: Teklenburg, Brosens, Macklon and colleagues demonstrated that decidualized stromal cells differentially modulate their cytokine secretion in response to competent versus chromosomally abnormal embryos.²⁰⁻²² Aged endometrium with its decidualization defects may lose some of this discriminatory capacity, contributing to higher early pregnancy loss observed in older women.

TRANSCRIPTOMIC REMODELING, EPIGENETIC DRIFT, AND EXTRACELLULAR VESICLES

Genome-wide transcriptomic analysis of the endometrium of women over 35 years identified 5,778 dysregulated genes, with ciliary processes as the primary dysregulated function, together with altered expression of genes required for receptivity (PAEP, MMP26), cell-cycle arrest (FGF2), telomere maintenance (TINF2) and genomic stability (SIRT1).²³ Loid and colleagues described an age-related expansion of multi-ciliated epithelial cells together with miR-34/449-mediated dysregulation that may interfere with trophoblast invasion.²⁴ Beyond histone modifications, DNA-methylation-based epigenetic clocks indicate that the endometrium ages epigenetically, and the age-related dysregulation of telomere-maintenance and genomic-stability genes described above suggests a broader epigenetic drift in the aging endometrium.²⁵ Extracellular vesicles

Table 2. Key Pathophysiological Mechanisms of Endometrial Aging

Mechanism	Key Features	Clinical Consequence
Oxidative Stress & Mitochondrial Dysfunction	Elevated ROS; reduced antioxidant defenses (SOD, catalase, GPx); mitochondrial DNA deletions; impaired ATP synthesis; higher 8-OHdG levels	Impaired decidualization; accelerated stromal senescence; compromised secretory gland function
Telomere Attrition	Progressive shortening across menstrual cycles; declining telomerase activity in secretory phase; cumulative DNA damage response activation	Irreversible senescence commitment; reduced basal is regenerative capacity; impaired cyclic tissue reconstitution
Cellular Senescence & SASP	p16/p21 pathway activation; SASP (IL-6, IL-8, TNF- α , MMPs); incomplete uNK clearance; persistent β -galactosidase and γ -H2AX foci	Chronic pro-inflammatory microenvironment; disrupted cyclic remodeling; impaired angiogenesis; higher pregnancy loss risk
Decidualization Failure & Progesterone Resistance	Reduced PRL and IGFBP-1; loss of H3K27ac at PGR target genes; downregulated PGR; blunted morphological transformation	Suboptimal response to exogenous progesterone; impaired embryonic biosensing; increased implantation failure and pregnancy loss
Epigenetic Drift & Transcriptomic Remodeling	Genome-wide CpG methylation changes; miR-34/449 upregulation; multi-ciliated cell expansion; 5,778 dysregulated genes in women >35 years; ciliary processes as primary dysregulated function	Disrupted implantation window timing; excess cilia at embryo apposition site; less plastic transcriptional landscape; measurable biological age divergence
Vascular Decline & Structural Changes	Reduced microvascular density; impaired spiral artery remodeling; stromal fibrosis; vascular calcification; variable thickness response to estrogen	Placental insufficiency; fetal growth restriction; hypertensive disorders; elevated preeclampsia risk in donor-oocyte pregnancies
Stem Cell Exhaustion	Reduced eMSC numbers and clonogenic activity; attenuated proliferative/differentiation potential; slower post-menstrual regeneration	Thin endometrium; reduced injury recovery; impaired receptivity; rationale for PRP and bone marrow-derived cell therapies
Immune Dysregulation	Declining uNK cell numbers/function; attenuated Treg activity; pro-inflammatory cytokine shift; altered CXCL12/CXCL14/IL17RB signaling	Reduced senescent-cell clearance; blunted trophoblast invasion support; increased immune-mediated implantation failure; higher preeclampsia rates

8-OHdG: 8-hydroxy-2'-deoxyguanosine; ATP: adenosine triphosphate; CpG: cytosine-phosphate-guanine; CXCL12/CXCL14: C-X-C motif chemokine ligand 12/14; DNA: deoxyribonucleic acid; eMSC: endometrial mesenchymal stem cell; γ -H2AX: phosphorylated histone H2AX (Ser139); GPx: glutathione peroxidase; H3K27ac: histone H3 lysine 27 acetylation; IGFBP-1: insulin-like growth factor binding protein 1; IL-6: interleukin-6; IL-8: interleukin-8; IL17RB: interleukin-17 receptor B; miR: microRNA; MMPs: matrix metalloproteinases; PGR: progesterone receptor; PRL: prolactin; PRP: platelet-rich plasma; ROS: reactive oxygen species; SASP: senescence-associated secretory phenotype; SOD: superoxide dismutase; TNF- α : tumor necrosis factor α ; Treg: regulatory T cell; uNK: uterine natural killer cell.

(EVs) secreted by endometrial cells participate in nearly every step of implantation, and aging may alter EV secretion, cargo composition, and uptake efficiency, representing a substantially under-investigated dimension of endometrial aging.²⁶

VASCULAR DECLINE, STRUCTURAL CHANGES, AND IMMUNE DYSREGULATION

With age, endometrial microvascular density declines, spiral artery remodeling becomes less efficient, and stromal fibrosis increases, contributing to higher rates of pregnancy loss, placental insufficiency, and hypertensive disorders in older mothers.²⁷ A systematic review of age-related uterine changes documented progressive loss of spiral arteriole volume from age 35, mineral deposition in uterine arteries, and a thinner endometrium in women over 35–40 years, changes that reinforce the importance of careful uterine evaluation prior to embryo transfer.²⁵ The maternal immune compartment shifts in parallel with systemic immunosenescence: uterine natural killer cell numbers and functional activity decline, regulatory T cell function is attenuated, and the pro-inflammatory/tolerogenic balance tilts toward inflammation, increasing the risk of immune-

mediated implantation failure and the elevated preeclampsia rates observed in donor-oocyte pregnancies.²⁸

CLINICAL EVIDENCE OF ENDOMETRIAL AGING

PREGNANCY AND LIVE BIRTH IN DONOR-OOCYTE CYCLES

Donor-oocyte cycles isolate the endometrial contribution to reproductive outcome by holding oocyte quality constant. Yeh and colleagues, analyzing more than 27,000 first-fresh-donor cycles from the SART registry, demonstrated a graded decline in live birth rate with increasing recipient age.¹¹ Williams and colleagues confirmed this trend in a SART registry analysis of 40,485 donor-oocyte cycles from 2016–2018, in which the odds of live birth after single embryo transfer fell progressively with recipient age (OR 0.80 at 40–44 years, 0.77 at 45–49 years and 0.65 above 49 years).¹² The Sebastian-Leon cohort represents the most granular analysis to date, documenting a live birth rate decline from 45.8% at age 40 to 32.7% at age 50, with significant annual increases in implantation failure (4.2% per year) and pregnancy loss (3.2% per year) beyond age

Table 3. Selected Recent Publications on Endometrial Aging (2020–2026)

Reference	Topic	Key Finding
Rafael et al. (2026)	Natural vs. artificial cycle in donor-oocyte recipients; impact of recipient age	Multicentre cohort of 67,048 donor-oocyte single blastocyst transfers: natural cycles associated with higher live birth (aOR 1.38) and lower miscarriage (aOR 0.68) than artificial cycles; the advantage was not modified by recipient age (non-significant interaction)
Wang et al. (2025)	Epigenetic basis of endometrial aging	Age-related loss of H3K27 acetylation at PGR target genes drives decidualization failure; identifies epigenetic restoration as therapeutic target
Sebastian-Leon et al. (2025)	Donor-oocyte outcomes by recipient age	LBR declines from 45.8% at age 40 to 32.7% at age 50; implantation failure +4.2%/year and pregnancy loss +3.2%/year beyond 40 in the largest donor-oocyte cohort to date
Chemerinski et al. (2024)	Mechanisms of endometrial aging in natural and ART cycles	Integrative review confirming LBR decline in euploid-transfer cycles (~8–9% drop between <35 and >42); highlights stem cell exhaustion, oxidative damage, and senescence as convergent drivers
Marti-Garcia et al. (2024)	Age-related uterine and endometrial changes and reproductive outcomes	Systematic review of 142 studies and meta-analysis: women >35–40 years have thinner endometrium (MD 0.52 mm); in donor-oocyte cycles, lower odds of implantation (OR 0.73) and clinical pregnancy (OR 0.80) and higher odds of pregnancy loss (OR 1.44)
Loid et al. (2024)	Senescent and multi-ciliated cells in aging endometrium	Age promotes accumulation of senescent cells and multi-ciliated epithelium; miR-34/449 upregulation drives ciliary expansion potentially interfering with trophoblast invasion
López-Otín et al. (2023)	Hallmarks of aging framework	Expanded hallmarks of aging (12 hallmarks including dysbiosis and macroautophagy impairment) providing conceptual scaffold for classifying endometrial aging mechanisms
Pathare et al. (2023)	Endometrial receptivity in advanced age	Comprehensive review integrating oxidative stress, senescence, and transcriptomic aging; links higher 8-OHdG and antioxidant decline to aging phenotype; advocates for senolytic interventions
Devesa-Peiro et al. (2022)	Transcriptomic aging across female reproductive tissues	Genome-wide functional analysis identifying 5,778 dysregulated genes in the endometrium of women >35 years; ciliary processes as the primary dysregulated function; altered receptivity (PAEP, MMP26), cell-cycle (FGF2), telomere (TINF2) and genomic-stability (SIRT1) genes
Lucas et al. (2020)	Senescence and recurrent pregnancy loss	Pro-senescent decidual response during peri-implantation window associated with RPL; links persistent senescence to clinical reproductive failure independent of embryo quality

8-OHdG: 8-hydroxy-2'-deoxyguanosine; aOR: adjusted odds ratio; ART: assisted reproductive technology; FGF2: fibroblast growth factor 2; H3K27: histone H3 lysine 27; LBR: live birth rate; MD: mean difference; miR: microRNA; MMP26: matrix metalloproteinase 26; OR: odds ratio; PAEP: progesterone-associated endometrial protein (glycodelin); PGR: progesterone receptor; RPL: recurrent pregnancy loss; SIRT1: sirtuin 1; TINF2: TERF1-interacting nuclear factor 2.

40.¹³ Three principles emerge from this literature: the endometrium contributes independently to outcome; the contribution is graded across age; and absolute outcomes remain clinically meaningful into the fifth decade. (Table 3)

IMPLANTATION FAILURE AND PREGNANCY LOSS WITH EUPLOID EMBRYOS

Even after transfer of a single euploid blastocyst, live birth declines progressively with maternal age. Reig and colleagues, analyzing 8,175 single euploid embryo transfers, found that implantation rates were negatively correlated with age: after adjustment for confounders, women aged 38 years or older had significantly lower implantation rates than those under 35 (OR 0.85 for 38–40 years, 0.69 for 41–42 years and 0.69 for >42 years), with parallel differences in clinical pregnancy and live birth rates, whereas the rates of progression from implantation to clinical pregnancy and from clinical pregnancy to live birth did not differ significantly by age group.²⁹ Consistently, a systematic review and meta-analysis of 11,335 euploid embryo trans-

fers, together with an analysis of PGT-A cycles recorded in the SART registry, documented a progressive decline in cumulative live birth per euploid transfer from 54.8% in women under 35 to 46.2% in women over 42 years, a difference of nearly nine percentage points that cannot be attributed to aneuploidy.³⁰ These findings support endometrial aging as an independent factor operating beyond oocyte aneuploidy. Endometrial preparation may also matter: Rafael and colleagues, in a multicentre cohort of 67,048 donor-oocyte single blastocyst transfers, found that natural cycles were associated with a higher live birth rate (adjusted OR 1.38) and a lower miscarriage rate (adjusted OR 0.68) than artificial cycles, and that this advantage was not modified by recipient age (non-significant interaction), suggesting that the preparation protocol is a modifiable factor to be considered alongside recipient age.³¹ Together, these findings underscore the need for age-stratified, protocol-controlled prospective studies.

DIAGNOSTIC TOOLS AND ENDOMETRIAL BIOMARKERS

Identifying the aging endometrium in clinical practice has historically relied on endometrial thickness and morphological pattern, which correlate only loosely with implantation success. In a systematic review of 142 studies with meta-analysis, Marti-Garcia and colleagues found that women over 35–40 years have a thinner endometrium (mean difference 0.52 mm) and, in donor-oocyte cycles, lower odds of implantation (OR 0.73) and clinical pregnancy (OR 0.80) and higher odds of pregnancy loss (OR 1.44), while no validated biomarker of biological endometrial age is yet available.²⁵ Candidate markers under investigation include p16-positive senescent cells and multiciliated cell accumulation, DNA-methylation (epigenetic clock) estimates of endometrial age, and transcriptomic aging signatures, but these have not been combined into a clinically validated panel for stratifying women by biological rather than chronological age.

OBSTETRIC AND PERINATAL OUTCOMES

Even when pregnancy is achieved, older mothers face increased risks of hypertensive disorders, gestational diabetes, placental insufficiency, intrauterine growth restriction, preterm birth, and stillbirth.^{27,32,33} Donor-oocyte pregnancies show particularly elevated rates of preeclampsia, attributed to immunological mismatch and age-related vascular and decidual dysfunction.²⁸ The magnitude increases markedly after age 40 and again after age 45, though absolute risk remains acceptable in carefully monitored patients.

PREGNANCY AT ADVANCED MATERNAL AGE: THE REAL NUMBERS AND THE PUBLIC NARRATIVE

The social and media landscape surrounding reproduction at advanced maternal age has undergone a marked transformation. Widely publicized pregnancies and births among public figures in their late forties and fifties rarely specify the underlying reproductive strategy, yet they undeniably influence how women perceive their own reproductive options. A central message for clinical counseling is that although reproductive outcomes decline progressively with age, they are not zero. In donor-oocyte cycles, live birth rates remain above 30% per transfer at age 50.¹³ The accurate framing is not “it is impossible” but “the odds decrease and the risks rise, but a successful pregnancy remains a realistic goal for many women.”

The celebrity visibility of late motherhood has the unintended consequence of underrepresenting the role of egg donation and gestational surrogacy. Transparent counseling that addresses all available options: own oocytes, frozen oocytes from earlier years, donor oocytes, donor embryos, and gestational surrogacy where legally available supports informed decision-making aligned with individual values and goals.

EMERGING THERAPEUTIC STRATEGIES

No single therapeutic target addresses the multifactorial nature of endometrial aging; strategies addressing multiple mechanisms or upstream regulatory nodes are therefore likely to be most clinically effective. The proposed therapies are summarized in [Table 4](#).

SENOLYTICS AND SENOMORPHICS

Pharmacological elimination of senescent cells (senolytics, such as dasatinib plus quercetin) and inhibition of the SASP (senomorphics) are under active investigation for age-related diseases.³⁶ In endometrial models, senolytic strategies have restored decidualization and reduced inflammatory cytokine release.²⁶ Clinical translation to reproductive medicine remains preclinical, and safety in the reproductive context requires careful evaluation before clinical adoption.

EPIGENETIC AND HORMONAL MODULATORS

Strategies aimed at restoring progesterone-receptor signaling, including epigenetic modifiers targeting H3K27 acetylation, have shown promise in preclinical models.¹⁹ Sonic Hedgehog pathway agonists may rejuvenate endometrial mesenchymal stem cells. Whether tailored estrogen-progesterone regimens can compensate for the diminished progesterone responsiveness of aged endometrium remains an open question.

STEM CELL-BASED APPROACHES

Autologous endometrial stem cell therapies, including intrauterine instillation of bone marrow-derived mesenchymal stem cells, have been studied in small series of women with refractory thin endometrium and Asherman syndrome. Application specifically to age-related endometrial decline remains exploratory.

PLATELET-RICH PLASMA: THE MOST CLINICALLY ADVANCED OPTION

Autologous platelet-rich plasma (PRP) is a centrifuged platelet concentrate releasing growth factors (PDGF, TGF- β , VEGF, EGF, IGF, bFGF) that target the vascular, proliferative, and anti-inflammatory deficits characteristic of the aged endometrium.^{37–39} A 2024 meta-analysis of eight randomized controlled trials including 678 patients reported that intrauterine PRP significantly increased endometrial thickness (mean difference 1.23 mm), clinical pregnancy rate (RR 2.04), live birth rate (RR 2.46), and implantation rate (RR 2.71), without significant adverse events.³⁴ Lad and colleagues demonstrated improved endometrial thickness specifically in older women who had failed conventional hormone replacement therapy.³⁵ An important limitation is that not all PRP preparations are equivalent: biological potency depends critically on platelet concentration, preparation method, and activation protocol.^{40,41} Because none of these is standardized, quality and effec-

Table 4. Proposed Therapeutic Strategies for Endometrial Aging

Intervention	Mechanism of Action	Current Evidence	Limitations / Status
Senolytics (dasatinib + quercetin)	Pharmacological elimination of senescent cells via p16/p21 pathways	Preclinical endometrial models: restored decidualization, reduced SASP and inflammatory cytokine release	Reproductive safety unestablished; no clinical trials in fertility; offspring effects require evaluation before adoption
Senomorphics (rapamycin, navitoclax)	Suppression of SASP without cell elimination; mTOR inhibition	Reduced pro-inflammatory secretome in aging tissue models; preserved tissue architecture	Clinical data in reproductive context absent; dose-finding and safety work required
Epigenetic modulators (H3K27ac restoration)	Restore progesterone-receptor target gene accessibility via histone acetyltransferase modulation	Preclinical models: improved PGR expression and decidualization markers; identified by Wang et al. 2025 as key aging mechanism	Translation to clinical reproductive medicine nascent; epigenetic off-target effects must be characterized
Platelet-Rich Plasma (PRP)	Autologous growth-factor concentrate (PDGF, TGF- β , VEGF, EGF, IGF, bFGF) targeting vascular, proliferative, and anti-inflammatory deficits	Meta-analysis of 8 RCTs (n=678): $\uparrow$ endometrial thickness +1.23 mm, CPR RR 2.04, LBR RR 2.46, implantation RR 2.71. ³⁴ Improved thickness in older women failing HRT ³⁵	Preparation protocols heterogeneous; no RCT specifically targeting chronological aging; Cochrane 2024 rates evidence as low-to-moderate
Stem Cell Therapies (bone marrow-derived MSC; autologous endometrial cells)	Intrauterine instillation to replenish endometrial mesenchymal stem cell compartment and stimulate regeneration	Small series in thin endometrium and Asherman syndrome: improved thickness and clinical pregnancies reported	Standardization, cell source, regulatory pathway, and rigorous outcome assessment remain unresolved; not yet evaluated specifically for age-related decline
Sonic Hedgehog (SHH) pathway agonists	Rejuvenation of endometrial mesenchymal stem cells via SHH signaling modulation	Preclinical evidence of eMSC renewal; conceptual extension from stem cell biology	Human endometrial data absent; purely exploratory at present
Growth Hormone adjuvant	Systemic or local GH supplementation to enhance endometrial proliferation and IGF-1 signaling	Mixed results in IVF trials; some improvement in thin endometrium subgroups	No consistent benefit established in older women; requires age-stratified RCT
Extracellular Vesicle (EV)-based therapies	Engineered MSC- or platelet-derived EVs delivering growth factors, regulatory RNAs, and pro-implantation cargo	Emerging concept with biological plausibility; superior immunogenicity and standardization profile vs. whole-cell therapies	No human reproductive clinical data; efficacy in age-defined endometrial populations undemonstrated

bFGF: basic fibroblast growth factor; CPR: clinical pregnancy rate; EGF: epidermal growth factor; eMSC: endometrial mesenchymal stem cell; EV: extracellular vesicle; GH: growth hormone; H3K27ac: histone H3 lysine 27 acetylation; HRT: hormone replacement therapy; IGF/IGF-1: insulin-like growth factor (1); IVF: in vitro fertilization; LBR: live birth rate; MSC: mesenchymal stem cell; mTOR: mechanistic target of rapamycin; PDGF: platelet-derived growth factor; PGR: progesterone receptor; PRP: platelet-rich plasma; RCT: randomized controlled trial; RR: risk ratio; SASP: senescence-associated secretory phenotype; SHH: Sonic Hedgehog; TGF- β : transforming growth factor beta; VEGF: vascular endothelial growth factor.

tiveness vary widely between centers, making broadly applicable recommendations premature. Additional limitations include absence of RCTs specifically targeting chronological endometrial aging. The 2024 Cochrane review, which included 12 randomized controlled trials (1,069 women), rated the certainty of evidence as very low for almost all outcomes, including live birth and clinical pregnancy, and found no significant benefit of intrauterine PRP when the analysis was restricted to trials at low risk of bias.⁴²

EXTRACELLULAR VESICLES AND EXOSOMES

Extracellular vesicles (EVs), particularly exosomes, small membrane-bound vesicles of endosomal origin — have emerged as potent mediators of intercellular communication at the embryo-endometrial interface. Endometrial-de-

rived exosomes carry a cargo of proteins, lipids, and regulatory RNAs that modulate trophoblast adhesion, invasion, and immune tolerance.⁴³⁻⁴⁵ In the aging uterus, mesenchymal stem cell-derived exosomes promote angiogenesis, exert anti-fibrotic effects by suppressing TGF- β -mediated myofibroblast differentiation, support endometrial proliferation and regeneration, and modulate immune responses by expanding regulatory T cells mechanisms directly relevant to the aged endometrium. Acting simultaneously on angiogenesis, anti-fibrosis, remodeling, proliferation, and immunomodulation, EV-based therapies may eventually represent one of the most mechanistically precise interventions for the aging uterus. No clinical data yet exist for age-related endometrial decline specifically, but the biological rationale is strong.⁴³⁻⁴⁵

DISCUSSION

Endometrial aging reflects the cumulative impact of cellular senescence, epigenetic drift, vascular decline, and immune dysregulation, creating a uterine environment less supportive of implantation even with euploid embryos. Clinically, implantation and live birth rates decline with advancing age, including in donor-oocyte cycles confirming the endometrium as an independent determinant of reproductive outcomes.^{13,17} Emerging therapies, including senolytics, epigenetic modulation, and regenerative approaches such as PRP, aim to restore endometrial function.

Despite the rapid growth of the endometrial-aging literature, several methodological limitations should be acknowledged. Women of advanced reproductive age represent a self-selected population; most studies are retrospective; transcriptomic analyses are limited by small samples and cross-sectional designs; the biosensor function has not been systematically investigated across age strata; and the therapeutic literature suffers from substantial heterogeneity. The gestational surrogacy literature is particularly sparse with respect to gestational carrier age differences, and dedicated prospective studies in this population are a priority.

One area that merits explicit discussion is the comparison of reproductive outcomes between proven gestational carriers of different ages. Although gestational surrogacy represents a growing reproductive pathway including for older family members willing to carry pregnancies for relatives the literature on how gestational carrier age affects outcomes remains unfortunately limited. Current evidence is insufficient to establish age-specific thresholds for gestational carriers based on endometrial biology alone, and this gap represents an important unresolved clinical question.

FUTURE DIRECTIONS

Several priority areas emerge from this review. First, age-stratified prospective studies with standardized endometrial endpoints are needed to characterize the contribution of chronological versus biological endometrial age to reproductive outcome. Second, dedicated randomized trials of regenerative therapies: PRP, senolytics, and epigenetic modulators should be conducted in age-defined populations rather than extrapolated from thin-endometrium or recurrent-implantation-failure cohorts.

Third, and of particular emerging importance, artificial intelligence (AI) represents a promising tool for the identification and classification of the aging endometrium.⁴⁶ Machine-learning and deep-learning models applied to endometrial imaging, histological, and molecular data may enable automated, reproducible, and non-invasive estimation of biological endometrial age with greater precision than any single biomarker.

Fourth, the role of gestational carrier age in surrogacy outcomes warrants dedicated investigation. As surrogacy becomes more common; including intrafamilial arrangements where mothers, grandmothers, and other older relatives serve as gestational carriers, the question of how

carrier age affects endometrial receptivity and pregnancy outcomes becomes clinically urgent. A particularly valuable research design would be to compare outcomes in gestational carrier cycles stratified by carrier age among proven carriers; women who have demonstrated prior successful pregnancies thereby isolating the effect of chronological endometrial aging from confounding variables such as nulliparity or unknown reproductive history. Unfortunately, the current literature is very limited in age differences among gestational carriers, and prospective registries capturing carrier age, endometrial biological markers, and pregnancy outcomes are needed to fill this gap.

Fifth, validated biomarker panels integrating p16 expression, telomere length, epigenetic clock data, and transcriptomic age estimators should be prospectively validated against clinical outcomes in independent cohorts, with clear clinical decision thresholds established for use in reproductive medicine practice.

CONCLUSION

The longstanding view that the uterus does not age is no longer tenable. Convergent clinical, transcriptomic, mechanistic, and epigenetic evidence demonstrates that endometrial aging is an independent biological process that contributes to implantation failure, pregnancy loss, and reduced live birth rates in women of advanced reproductive age. Recognizing endometrial aging as a distinct therapeutic target represents an important frontier in contemporary reproductive medicine.

Reproductive outcomes decline with age, but they are not zero. Among emerging therapies, intrauterine platelet-rich plasma is currently the most clinically advanced option, although dedicated trials in age-defined populations are still required. Future progress will depend on integrating molecular profiling; including AI-based tools for endometrial classification, regenerative interventions, and individualized counseling into the reproductive care of women across the entire reproductive lifespan, recognizing that the endometrium is not a passive vessel but an actively aging, biologically informative, and therapeutically actionable organ.

AUTHORS' CONTRIBUTION - CREDIT

Conceptualization: Tamar Alkon (Equal), Ricardo H. Asch Schuff (Equal). Investigation: Tamar Alkon (Equal), Jorge Suarez (Equal), Ricardo H. Asch Schuff (Equal). Writing – original draft: Tamar Alkon (Equal), Jorge Suarez (Equal), Ricardo H. Asch Schuff (Equal). Writing – review & editing: Tamar Alkon (Equal), Jorge Suarez (Equal), Ricardo H. Asch Schuff (Equal). Supervision: Ricardo H. Asch Schuff (Lead).

Submitted: August 05, 2026 CDT. Accepted: September 15, 2026 CDT. Published: October 08, 2026 CDT.



This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-4.0). View this license's legal deed at <http://creativecommons.org/licenses/by/4.0> and legal code at <http://creativecommons.org/licenses/by/4.0/legalcode> for more information.

REFERENCES

1. Sauer MV, Paulson RJ, Lobo RA. A preliminary report on oocyte donation extending reproductive potential to women over 40. *N Engl J Med*. 1990;323(17):1157-1160. doi:[10.1056/NEJM199010253231702](https://doi.org/10.1056/NEJM199010253231702)
2. Navot D, Bergh PA, Williams MA, Garrisi GJ, Guzman I, Sandler B, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. *Lancet*. 1991;337(8754):1375-1377. doi:[10.1016/0140-6736\(91\)93060-m](https://doi.org/10.1016/0140-6736(91)93060-m)
3. Navot D, Drews MR, Bergh PA, Guzman I, Karstaedt A, Scott RT Jr, et al. Age-related decline in female fertility is not due to diminished capacity of the uterus to sustain embryo implantation. *Fertil Steril*. 1994;61(1):97-101. doi:[10.1016/S0015-0282\(16\)56459-0](https://doi.org/10.1016/S0015-0282(16)56459-0)
4. Borini A, Bafaro G, Violini F, Bianchi L, Casadio V, Flamigni C. Pregnancies in postmenopausal women over 50 years old in an oocyte donation program. *Fertil Steril*. 1995;63(2):258-261. doi:[10.1016/S0015-0282\(16\)57351-8](https://doi.org/10.1016/S0015-0282(16)57351-8)
5. Abdalla HI, Wren ME, Thomas A, Korea L. Age of the uterus does not affect pregnancy or implantation rates; a study of egg donation in women of different ages sharing oocytes from the same donor. *Hum Reprod*. 1997;12(4):827-829. doi:[10.1093/humrep/12.4.827](https://doi.org/10.1093/humrep/12.4.827)
6. Noci I, Borri P, Chieffi O, Scarselli G, Biagiotti R, Moncini D, et al. I. Aging of the human endometrium: a basic morphological and immunohistochemical study. *Eur J Obstet Gynecol Reprod Biol*. 1995;63(2):181-185. doi:[10.1016/0301-2115\(95\)02244-9](https://doi.org/10.1016/0301-2115(95)02244-9)
7. Flamigni C, Borini A, Violini F, Bianchi L, Serrao L. Oocyte donation: comparison between recipients from different age groups. *Hum Reprod*. 1993;8(12):2088-2092. doi:[10.1093/oxfordjournals.humrep.a137986](https://doi.org/10.1093/oxfordjournals.humrep.a137986)
8. Borini A, Asch RH. Factors that affect implantation in the human. In: Asch RH, Studd JWW, eds. *Annual Progress in Reproductive Medicine 1993*. Parthenon Publishing; 1993:19-26.
9. Borini A, Bianchi L, Violini F, Maccolini A, Cattoli M, Flamigni C. Oocyte donation program: pregnancy and implantation rates in women of different ages sharing oocytes from single donor. *Fertil Steril*. 1996;65(1):94-97. doi:[10.1016/S0015-0282\(16\)58033-9](https://doi.org/10.1016/S0015-0282(16)58033-9)
10. Glasser SR. The uterus: idiot savant or Rosetta Stone? *J Assist Reprod Genet*. 1998;15(4):168-173. doi:[10.1023/a:1023035915993](https://doi.org/10.1023/a:1023035915993)
11. Yeh JS, Steward RG, Dude AM, Shah AA, Goldfarb JM, Muasher SJ. Pregnancy outcomes decline in recipients over age 44: an analysis of 27,959 fresh donor oocyte in vitro fertilization cycles from the Society for Assisted Reproductive Technology. *Fertil Steril*. 2014;101(5):1331-1336. doi:[10.1016/j.fertnstert.2014.01.056](https://doi.org/10.1016/j.fertnstert.2014.01.056)
12. Williams RS, Ellis DD, Wilkinson EA, Kramer JM, Datta S, Guzick DS. Factors affecting live birth rates in donor oocytes from commercial egg banks vs. program egg donors: an analysis of 40,485 cycles from the Society for Assisted Reproductive Technology registry in 2016-2018. *Fertil Steril*. 2022;117(2):339-348. doi:[10.1016/j.fertnstert.2021.10.006](https://doi.org/10.1016/j.fertnstert.2021.10.006)
13. Sebastian-Leon P, Sanz FJ, Molinaro P, Pellicer A, Diaz-Gimeno P. Advanced maternal age was associated with an annual decline in reproductive success despite use of donor oocytes: a retrospective study. *Fertil Steril*. 2025;124(4):635-644. doi:[10.1016/j.fertnstert.2025.05.150](https://doi.org/10.1016/j.fertnstert.2025.05.150)
14. Eurostat. *Mean Age of Women at Childbirth and at First Child*. European Statistical System; 2022.
15. Mathews TJ, Hamilton BE. Mean age of mothers is on the rise: United States, 2000-2014. *NCHS Data Brief*. 2016;(232):1-8.
16. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell*. 2023;186(2):243-278. doi:[10.1016/j.cell.2022.11.001](https://doi.org/10.1016/j.cell.2022.11.001)
17. Chemerinski A, Garcia de Paredes J, Blackledge K, Douglas NC, Morelli SS. Mechanisms of endometrial aging: lessons from natural conceptions and assisted reproductive technology cycles. *Front Physiol*. 2024;15:1332946. doi:[10.3389/fphys.2024.1332946](https://doi.org/10.3389/fphys.2024.1332946)
18. Lucas ES, Vrljicak P, Muter J, Diniz-da-Costa MM, Brighton PJ, Kong CS, et al. Recurrent pregnancy loss is associated with a pro-senescent decidual response during the peri-implantation window. *Commun Biol*. 2020;3(1):37. doi:[10.1038/s42003-020-0763-1](https://doi.org/10.1038/s42003-020-0763-1)
19. Wang Y, Zhou P, Shan H, Liu X, Cheng M, Ye Z, et al. Endometrial aging is accompanied by H3K27ac and PGR loss. *Nat Aging*. 2025;5(5):816-830. doi:[10.1038/s43587-025-00859-5](https://doi.org/10.1038/s43587-025-00859-5)

20. Teklenburg G, Salker M, Molokhia M, Lavery S, Trew G, Aojanepong T, et al. Natural selection of human embryos: decidualizing endometrial stromal cells serve as sensors of embryo quality upon implantation. *PLoS One*. 2010;5(4):e10258. doi:[10.1371/journal.pone.0010258](https://doi.org/10.1371/journal.pone.0010258)
21. Salker M, Teklenburg G, Molokhia M, Lavery S, Trew G, Aojanepong T, et al. Natural selection of human embryos: impaired decidualization of endometrium disables embryo-maternal interactions and causes recurrent pregnancy loss. *PLoS One*. 2010;5(4):e10287. doi:[10.1371/journal.pone.0010287](https://doi.org/10.1371/journal.pone.0010287)
22. Brosens JJ, Gellersen B. Something new about early pregnancy: decidual biosensing and natural embryo selection. *Ultrasound Obstet Gynecol*. 2010;36(1):1-5. doi:[10.1002/uog.7714](https://doi.org/10.1002/uog.7714)
23. Devesa-Peiro A, Sebastian-Leon P, Parraga-Leon A, Pellicer A, Diaz-Gimeno P. Breaking the ageing paradigm in endometrium: endometrial gene expression related to cilia and ageing hallmarks in women over 35 years. *Hum Reprod*. 2022;37(4):762-776. doi:[10.1093/humrep/deac010](https://doi.org/10.1093/humrep/deac010)
24. Loid M, Obukhova D, Kask K, Apostolov A, Meltsov A, Tserpelis D, et al. Aging promotes accumulation of senescent and multiciliated cells in human endometrial epithelium. *Hum Reprod Open*. 2024;2024(3):hoae048. doi:[10.1093/hropen/hoae048](https://doi.org/10.1093/hropen/hoae048)
25. Marti-Garcia D, Martinez-Martinez A, Sanz FJ, Devesa-Peiro A, Sebastian-Leon P, Del Aguila N, et al. Age-related uterine changes and its association with poor reproductive outcomes: a systematic review and meta-analysis. *Reprod Biol Endocrinol*. 2024;22(1):152. doi:[10.1186/s12958-024-01323-6](https://doi.org/10.1186/s12958-024-01323-6)
26. Pathare ADS, Loid M, Saare M, Gidlöf SB, Zamani Esteki M, Acharya G, et al. Endometrial receptivity in women of advanced age: an underrated factor in infertility. *Hum Reprod Update*. 2023;29(6):773-793. doi:[10.1093/humupd/dmad019](https://doi.org/10.1093/humupd/dmad019)
27. Lean SC, Derricott H, Jones RL, Heazell AEP. Advanced maternal age and adverse pregnancy outcomes: a systematic review and meta-analysis. *PLoS One*. 2017;12(10):e0186287. doi:[10.1371/journal.pone.0186287](https://doi.org/10.1371/journal.pone.0186287)
28. Storgaard M, Loft A, Bergh C, Wennerholm UB, Söderström-Anttila V, Romundstad LB, et al. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. *BJOG*. 2017;124(4):561-572. doi:[10.1111/1471-0528.14257](https://doi.org/10.1111/1471-0528.14257)
29. Reig A, Franasiak J, Scott RT Jr, Seli E. The impact of age beyond ploidy: outcome data from 8175 euploid single embryo transfers. *J Assist Reprod Genet*. 2020;37(3):595-602. doi:[10.1007/s10815-020-01739-0](https://doi.org/10.1007/s10815-020-01739-0)
30. Vitagliano A, Paffoni A, Viganò P. Does maternal age affect assisted reproduction technology success rates after euploid embryo transfer? A systematic review and meta-analysis. *Fertil Steril*. 2023;120(2):251-265. doi:[10.1016/j.fertnstert.2023.02.036](https://doi.org/10.1016/j.fertnstert.2023.02.036)
31. Rafael F, David BN, Mascarós JM, Neves A, Labarta E, Garrido N, et al. Live birth rates after natural cycle versus artificial cycle in women receiving donated oocytes and the impact of female age. *Hum Reprod*. 2026;41(6):918-928. doi:[10.1093/humrep/deag058](https://doi.org/10.1093/humrep/deag058)
32. Frick AP. Advanced maternal age and adverse pregnancy outcomes. *Best Pract Res Clin Obstet Gynaecol*. 2021;70:92-100. doi:[10.1016/j.bpobgyn.2020.07.005](https://doi.org/10.1016/j.bpobgyn.2020.07.005)
33. Bouzaglou A, Aubenas I, Abbou H, Rouanet S, Carbonnel M, Pirtea P, et al. Pregnancy at 40 years old and above: obstetrical, fetal, and neonatal outcomes. Is age an independent risk factor for those complications? *Front Med (Lausanne)*. 2020;7:208. doi:[10.3389/fmed.2020.00208](https://doi.org/10.3389/fmed.2020.00208)
34. Liu X, Qian C, Jiang X, Zhou Y, Feng X, Ding Y, et al. Efficacy of platelet-rich plasma in the treatment of thin endometrium: a meta-analysis of randomized controlled trials. *BMC Pregnancy Childbirth*. 2024;24(1):567. doi:[10.1186/s12884-024-06741-3](https://doi.org/10.1186/s12884-024-06741-3)
35. Lad NL, Lad NN, Limaye RA. Platelet-rich plasma in managing a thin endometrium. *Int J Infertil Fetal Med*. 2024;15(2):115-119. doi:[10.5005/jp-journals-10016-1342](https://doi.org/10.5005/jp-journals-10016-1342)
36. Kirkland JL, Tchkonina T. Senolytic drugs: from discovery to translation. *J Intern Med*. 2020;288(5):518-536. doi:[10.1111/joim.13141](https://doi.org/10.1111/joim.13141)
37. Coksuer H, Akdemir Y, Ulas Barut M. Improved in vitro fertilization success and pregnancy outcome with autologous platelet-rich plasma treatment in unexplained infertility patients that had repeated implantation failure history. *Gynecol Endocrinol*. 2019;35(9):815-818. doi:[10.1080/09513590.2019.1597344](https://doi.org/10.1080/09513590.2019.1597344)
38. Lin Y, Qi J, Sun Y. Platelet-rich plasma as a potential new strategy in the endometrium treatment in assisted reproductive technology. *Front Endocrinol (Lausanne)*. 2021;12:707584. doi:[10.3389/fendo.2021.707584](https://doi.org/10.3389/fendo.2021.707584)

39. Karadbhaine P, Dzoagbe HY, More A. Platelet-rich plasma (PRP) for endometrial treatment efficacy and safety in assisted reproductive technology: a comprehensive review. *Cureus*. 2024;16(5):e59728. doi:[10.7759/cureus.59728](https://doi.org/10.7759/cureus.59728)
40. Tandulwadkar SR, Naralkar MV, Surana AD, Selvakarthick M, Kharat AH. Autologous intrauterine platelet-rich plasma instillation for suboptimal endometrium in frozen embryo transfer cycles: a pilot study. *J Hum Reprod Sci*. 2017;10(3):208-212. doi:[10.4103/jhrs.JHRS_28_17](https://doi.org/10.4103/jhrs.JHRS_28_17)
41. Wang X, Wang Y, Li J, Han Y, Wei M, Xu A, et al. Effects of intrauterine infusion of autologous platelet-rich plasma gel on endometrial thickness and outcomes of frozen-thawed embryo transfer in women with thin endometrium. *J Assist Reprod Genet*. 2024;41(10):2635-2647. doi:[10.1007/s10815-024-03254-y](https://doi.org/10.1007/s10815-024-03254-y)
42. Vaidakis D, Papapanou M, Siristatidis CS. Autologous platelet-rich plasma for assisted reproduction. *Cochrane Database Syst Rev*. 2024;4(4):CD013875. doi:[10.1002/14651858.CD013875.pub2](https://doi.org/10.1002/14651858.CD013875.pub2)
43. Greening DW, Nguyen HP, Elgass K, Simpson RJ, Salamonsen LA. Human endometrial exosomes contain hormone-specific cargo modulating trophoblast adhesive capacity: insights into endometrial-embryo interactions. *Biol Reprod*. 2016;94(2):38. doi:[10.1095/biolreprod.115.134890](https://doi.org/10.1095/biolreprod.115.134890)
44. Mishra A, Ashary N, Sharma R, Modi D. Extracellular vesicles in embryo implantation and disorders of the endometrium. *Am J Reprod Immunol*. 2021;85(2):e13360. doi:[10.1111/aji.13360](https://doi.org/10.1111/aji.13360)
45. Poh QH, Rai A, Salamonsen LA, Greening DW. Omics insights into extracellular vesicles in embryo implantation and their therapeutic utility. *Proteomics*. 2023;23(6):e2200107. doi:[10.1002/pmic.202200107](https://doi.org/10.1002/pmic.202200107)
46. Asch Schuff RH, Suarez J, Laugas N, Zamora Ramirez ML, Alkon T. Artificial intelligence model utilizing endometrial analysis to contribute as a predictor of assisted reproductive technology success. *J IVF Worldwide*. 2024;2(2). doi:[10.46989/001c.115893](https://doi.org/10.46989/001c.115893)