A Mini Review on Stage-Specific Autophagy Dynamics and Immune Regulation in the Reproductive System

Sinthia Mondal[1*]

[1]Max Society of Medical Academics Innovation and Research (MSMAIR), Max Healthcare & RCB Faridabad

Correspondence:

Sinthia Mondal

E-mail: sm16112020@gmail.com

DOI: https://doi.org/10.62830/mmj3-01-4

Abstract:

Autophagy is a conserved intracellular degradation mechanism critical for cellular homeostasis, differentiation, and adaptation to stress. Within the reproductive system, autophagy plays a dynamic, stage-specific role in gametogenesis, implantation, placentation, and parturition, aligning cellular metabolism and immune regulation to reproductive demands. Dysregulation of autophagic pathways contributes to reproductive pathology, including infertility, pre-eclampsia, and polycystic ovary syndrome (PCOS), underscoring its significance in reproductive health. This review aims to synthesise current understanding of stage-specific autophagy regulation in reproductive tissues, with a focus on its intersection with immune dynamics at the maternal–foetal interface. It highlights mechanistic pathways, immune cell modulation, and pathological outcomes associated with altered autophagy. Data were drawn from recent peer-reviewed publications indexed in PubMed, Frontiers, and ScienceDirect, focusing on studies published between 2018 and 2025 that investigated autophagy-related gene expression, signalling pathways, and immune modulation in reproductive tissues. Comparative analyses integrated molecular, cellular, and physiological findings across mammalian models and human studies. Autophagy acts as an integrative regulatory mechanism bridging cellular metabolism and immune adaptation in the reproductive system. Understanding its temporal and spatial regulation provides essential insight into fertility, pregnancy maintenance, and the pathogenesis of gestational disorders. Future research should explore therapeutic strategies that target autophagy to restore immune homeostasis and improve reproductive outcomes.

Key words: Autophagy, Reproductive Immunology, Maternal–Foetal Interface, Pregnancy, Reproductive Ageing.

Introduction

Autophagy, a highly conserved catabolic process, orchestrates intracellular degradation and recycling of proteins and organelles to preserve cellular homeostasis.[1,2] First characterised in yeast and later defined across eukaryotic organisms, autophagy ensures cell survival under conditions of nutrient deprivation, oxidative stress, or infection by mobilising lysosomal degradation pathways.[1,2] In mammalian reproduction, autophagy performs roles that extend far beyond basic metabolic housekeeping — it serves as a critical determinant of cellular fate, tissue remodelling, and immune equilibrium across multiple reproductive stages.

The reproductive system presents a unique biological environment characterised by cyclic tissue remodelling, immune modulation, and cellular differentiation. From gametogenesis to parturition, reproductive success relies on the precise coordination of cellular turnover and immune adaptation. Autophagy acts at the core of this coordination, integrating metabolic cues with immune and endocrine signalling to ensure functional competence of germ cells, embryos, and maternal tissues.[1] Dysregulation of autophagy has

been implicated in infertility, implantation failure, pre-eclampsia, recurrent pregnancy loss, and other gynaecological disorders.[3]

Historical and conceptual framework

The conceptual link between autophagy and reproduction has evolved significantly over the past two decades. Early studies identified autophagic vacuoles in ovarian follicles and preimplantation embryos, suggesting a role in developmental remodelling. Subsequent molecular investigations revealed the involvement of autophagy-related genes (ATG family), Unc-51-like kinase (ULK) complexes, and mammalian target of rapamycin complex 1 (mTORC1) signalling in regulating these processes.[2] Modern approaches, including conditional gene knockout models, live-cell imaging, and omics-based profiling, have deepened understanding of how autophagy coordinates reproductive function in a temporally and spatially specific manner.

Autophagy's physiological importance extends to the maternal–foetal interface, a site where the immune system must balance tolerance and defence. Decidual cells, trophoblasts, and infiltrating immune populations rely on autophagy to adapt to hypoxic, oxidative, and inflammatory microenvironments characteristic of early pregnancy.[1] Autophagic regulation determines trophoblast invasion depth, uterine natural killer (uNK) cell cytotoxicity, macrophage polarisation, and T-cell tolerance, thereby collectively shaping pregnancy outcomes.

Mechanistic overview of autophagy in reproductive biology

Macroautophagy, the most extensively studied subtype, involves sequestration of cytoplasmic components into double-membraned autophagosomes, which subsequently fuse with lysosomes for degradation. Key molecular mediators include the ULK1 complex (ULK1, ATG13, FIP200, and ATG101), the class III phosphatidylinositol 3-kinase (PI3P) complex (Beclin-1, vacuolar protein sorting 34 [VPS34], VPS15, and ATG14), and the ATG5–ATG12–ATG16L1 conjugation system.[1] mTORC1 serves as a master regulator, inhibiting autophagy under nutrient-rich conditions and relieving repression during energy stress or hypoxia—states frequently encountered in reproductive tissues, especially during implantation and placentation.

In reproductive contexts, autophagy provides energy substrates during oocyte maturation, prevents accumulation of damaged organelles in embryos, and enables trophoblast differentiation under limited oxygen supply.[2] Conversely, excessive or insufficient autophagy disturbs these finely tuned processes, leading to embryonic lethality or developmental arrest.

Integration of autophagy and immune function

Pregnancy imposes an immunological paradox: the maternal immune system must tolerate the semi-allogeneic foetus while maintaining defence against pathogens. Autophagy plays a pivotal role in maintaining this balance. In immune cells such as uNK cells and macrophages, autophagy regulates metabolic fitness and survival, modulates cytokine release, and determines the degree of cytotoxicity toward trophoblasts.[1] Autophagic flux within trophoblasts, in turn, shapes local immune responses by altering antigen presentation, cytokine secretion, and apoptotic signalling.

Recent studies have identified reciprocal signalling between autophagy-related transcription factors, such as transcription factor EB (TFEB), microphthalmia-associated transcription factor (MITF), and forkhead box O3 (FOXO3), and immune regulators, including tumour necrosis factor receptor superfamily member 14 (TNFRSF14), also known as herpesvirus entry mediator (HVEM), and nuclear factor kappa B (NF-κB).[2] These molecular circuits contribute to the maintenance of decidual homeostasis[2] and ensure stage-specific immune adaptation during implantation, gestation, and parturition.

Scope of this review

This review synthesises recent findings on stage-specific autophagy dynamics and their immunological implications across reproductive stages. By integrating evidence from molecular, cellular, and clinical studies, it delineates how autophagy governs immune tolerance, stress adaptation, and reproductive success. Emphasis is placed on:Mechanistic regulation of autophagy in reproductive cells and tissues

1. Immunomodulatory effects of autophagy at the maternal–foetal interface

2. Consequences of autophagy dysregulation in pregnancy complications and reproductive disorders
3. Environmental, endocrine, and metabolic influences on autophagic function

Through this synthesis, the review aims to clarify the multifaceted roles of autophagy in reproductive immunology and identify emerging therapeutic opportunities for enhancing fertility and maternal health.

Literature Review — Mechanistic Basis of Autophagy in Reproductive Tissues

Overview of autophagic pathways in reproductive physiology

Autophagy is not a static process but a tightly modulated, multistep cascade comprising initiation, nucleation, elongation, fusion, and degradation. In reproductive tissues, the activation of autophagy reflects a dynamic adaptation to fluctuating hormonal, metabolic, and immune environments. Macroautophagy — mediated through autophagosomes — serves as the principal form of autophagy, with its regulation centred on nutrient-sensing pathways and stress-response kinases.[1,2]

At the molecular level, autophagy initiation is governed by the ULK1 complex (ULK1–ATG13–focal adhesion kinase family-interacting protein of 200 kDa [FIP200]–ATG101), which integrates upstream signals from mTORC1 and adenosine monophosphate-activated protein kinase (AMPK). Under nutrient sufficiency, active mTORC1 phosphorylates ULK1 and ATG13, preventing autophagosome formation. Conversely, energy depletion or oxidative stress activates AMPK, which inhibits mTORC1 and directly phosphorylates ULK1 to trigger autophagy.[1] Once initiated, membrane nucleation proceeds via the Beclin-1–VPS34–ATG14 complex, generating PI3P to recruit additional ATG proteins. Autophagosome elongation depends on two ubiquitin-like conjugation systems involving ATG12–ATG5–ATG16L1 and microtubule-associated protein 1 light chain 3 (LC3, also known as ATG8), which facilitate membrane curvature and cargo sequestration. Finally, autophagosomes fuse with lysosomes to form autolysosomes, enabling the degradation and recycling of macromolecules.[2]

In reproductive physiology, these pathways are not merely cytoprotective but fundamentally developmental. Autophagy mediates follicular atresia, oocyte maturation, sperm capacitation, and implantation[3] — all processes requiring coordinated turnover of cellular components. For instance, autophagic activation ensures removal of defective mitochondria and endoplasmic reticulum in gametes, maintaining genomic integrity and energy efficiency essential for fertilisation.[4]

Autophagy during gametogenesis

Oogenesis and follicular development

Autophagy contributes to both survival and quality control of oocytes. In primordial follicles, basal autophagy maintains quiescence by balancing nutrient supply and oxidative stress. During follicular recruitment, increased autophagic flux supports cytoplasmic remodelling and organelle biogenesis. Studies in murine models have shown that deletion of Atg7 or Beclin-1 within oocytes leads to premature ovarian insufficiency (POI), characterised by accelerated follicular loss and impaired meiotic progression.[1]

Moreover, autophagy interacts with hormonal signalling cascades. Follicle-stimulating hormone (FSH) and luteinising hormone (LH) stimulation upregulate autophagy-related gene expression, while oestrogen suppresses excessive autophagic activity, thereby maintaining optimal oocyte viability.[3] The mTOR–AMPK balance serves as a metabolic switch: activation of mTORC1 inhibits autophagy to support oocyte growth, while its inhibition promotes autophagic clearance during atresia.

In granulosa cells, autophagy prevents apoptosis by regulating mitochondrial function and lipid turnover. However, excessive autophagy under oxidative stress leads to granulosa cell death, contributing to follicular atresia. This dual role underlines the importance of fine-tuned autophagic regulation in ovarian physiology.[1]

Spermatogenesis and male reproductive function

While female reproductive autophagy has been extensively characterised, evidence also supports essential functions in spermatogenesis and sperm maturation. Autophagy facilitates the removal of cytoplasmic droplets and defective organelles during spermiogenesis, ensuring the streamlined morphology of mature spermatozoa.[5]

Autophagy-related gene expression is particularly high in spermatogonia and spermatocytes, with ATG5, ATG7, and LC3B localised to developing germ cells.

Conditional deletion of ATG7 in Sertoli cells results in abnormal sperm morphology, reduced motility, and subfertility, indicating that somatic cell autophagy indirectly supports germ cell maturation.[5]

Moreover, autophagy interacts with androgen receptor (AR) signalling, which is critical for spermatogenic progression. Inhibition of AR signalling downregulates autophagic gene expression and disrupts spermatid differentiation, linking hormonal control to cellular quality assurance mechanisms. Emerging evidence also implicates autophagy in protection against oxidative damage in spermatozoa, a factor crucial for maintaining deoxyribonucleic acid (DNA) integrity and fertilisation capacity.[2]

Autophagy in early embryogenesis and implantation

Zygotic activation and embryonic development

Immediately following fertilisation, the embryo transitions from maternal to zygotic control of gene expression — a process accompanied by extensive cytoplasmic remodelling. Autophagy eliminates residual maternal proteins and damaged mitochondria, ensuring developmental competence. Mouse embryos lacking Atg5 or Atg7 fail to progress beyond the 4- to 8-cell stage, underscoring autophagy's indispensable role in preimplantation development.[2]

During compaction and blastocyst formation, autophagy maintains energy homeostasis under fluctuating oxygen and nutrient conditions. The mTOR–TFEB axis governs this adaptive response, promoting lysosomal biogenesis and degradation of cytoplasmic components to meet bioenergetic demands.[1]

Implantation and decidualisation

Implantation represents one of the most metabolically demanding events in reproduction. Endometrial stromal cells undergo decidualisation, transforming into specialised secretory cells that support embryo implantation. Autophagy modulates this transformation by regulating intracellular lipid metabolism, endoplasmic reticulum (ER) stress, and cytokine release.

Inhibition of autophagy through mTORC1 activation impairs decidualisation, while pharmacological activation of autophagy via rapamycin enhances endometrial receptivity.[1] At the molecular level, ATG5 and ATG16L1 facilitate progesterone-induced differentiation, linking autophagy to hormonal signalling networks. In addition, autophagic degradation of lipid droplets provides fatty acids for prostaglandin synthesis, which is essential for implantation and vascular remodelling.[3]

Autophagy in placentation and trophoblast function

The placenta is a unique organ requiring precise cellular turnover and immune regulation. Trophoblast cells, which mediate maternal–foetal exchange, rely on autophagy for survival under hypoxia and nutrient limitation. Hypoxia-inducible factors (HIF1α) and AMPK upregulate autophagy in early placental development, promoting trophoblast invasion and vascularisation.[1]

Autophagy also mitigates ER stress during syncytiotrophoblast formation. Dysregulated autophagy, particularly reduced Beclin-1 or ATG16L1 expression, leads to excessive ER stress, contributing to pre-eclampsia pathogenesis.[2] Furthermore, autophagy influences trophoblast–immune cell interactions by modulating the secretion of interleukin-10 (IL-10) and transforming growth factor beta (TGF-β), cytokines essential for maintaining immune tolerance.

Interestingly, trophoblast autophagy exhibits temporal specificity: high during early invasion phases to support cellular migration and attenuated during mid-gestation when placental architecture stabilises. Late in pregnancy, autophagic reactivation accompanies parturition-associated inflammation, illustrating cyclic regulation across gestation.[1]

Molecular crosstalk with endocrine and metabolic pathways

Autophagy in reproductive tissues is closely intertwined with hormonal and metabolic cues. Oestrogen and progesterone exert differential effects — oestrogen generally suppresses autophagic activity, whereas progesterone enhances autophagic readiness, consistent with their roles in tissue proliferation and differentiation, respectively.[3]

Metabolic regulators such as AMPK, sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor gamma (PPARγ) link nutrient sensing with reproductive signalling. SIRT1 activation promotes autophagy through deacetylation of ATG proteins and transcriptional regulation of forkhead box O3 (FOXO3) and TFEB, thereby ensuring adequate metabolic adaptation during pregnancy.[2] Dysregulation of these pathways in metabolic syndromes like obesity or diabetes reduces autophagic flux, predisposing to implantation failure and placental insufficiency.

Summary

Autophagy's mechanistic framework in reproductive physiology is multifactorial, encompassing nutrient-sensing networks, hormonal regulation, and immune modulation. Across gametogenesis, embryogenesis, and placentation, autophagy acts as a molecular switch that maintains cellular quality, metabolic equilibrium, and immune readiness. Stage-specific fluctuations in autophagic flux ensure appropriate transitions between proliferation, differentiation, and degeneration — core processes underpinning reproductive success.

The next section will explore how these autophagic mechanisms intersect with immune regulation at the maternal–foetal interface, highlighting the bidirectional signalling between autophagy and immune cells in sustaining pregnancy.

Immune Regulation and the Maternal–Foetal Interface

Immunological paradox of pregnancy

Pregnancy presents a unique immunological paradox: the maternal immune system must tolerate the semi-allogeneic foetus derived from paternal antigens while simultaneously maintaining robust antimicrobial defence. This equilibrium is achieved through precise temporal modulation of immune activation and suppression across gestation. The maternal–foetal interface — comprising decidual stromal cells, trophoblasts, and infiltrating immune populations — functions as a dynamic immunological hub.[1]

Autophagy has emerged as a key regulator of this immunological balance. Acting as both a metabolic and immunological switch, autophagy modulates cytokine production, antigen presentation, and cell survival in the uterine microenvironment.[2] Dysregulation of autophagic signalling disrupts this equilibrium, predisposing to implantation failure, recurrent miscarriage, or pre-eclampsia.[2]

Immune cell composition of the decidua

The decidua, the modified endometrium during pregnancy, harbours a specialised population of immune cells distinct from peripheral immune compartments. The main cell types include:

- uNK cells (40%–70% of decidual leukocytes)
- Macrophages (10%–20%)
- T lymphocytes, including $CD4^+$, $CD8^+$, and regulatory T cells (Tregs) (~10%–20%)
- Dendritic cells (DCs), along with smaller subsets of B lymphocytes and innate lymphoid cells[1]

Each population performs stage-specific functions. In early pregnancy, immune cells promote controlled inflammation to support implantation and vascular remodelling; during mid-gestation, tolerance mechanisms dominate; and near parturition, inflammatory pathways reactivate to facilitate labour.[3]

Autophagy orchestrates these phase transitions by regulating immune cell metabolism, survival, and effector functions. For instance, ATG5-dependent autophagy maintains mitochondrial integrity in immune cells, preventing excessive reactive oxygen species (ROS) production and apoptosis.[2]

Uterine natural killer cells

Development and function

uNK cells, the predominant immune population in the decidua, differ functionally from peripheral natural killer (NK) cells. Rather than exerting cytotoxic effects, they contribute to vascular remodelling, trophoblast invasion, and cytokine-mediated tolerance. Their activity depends heavily on autophagic regulation.

Loss of Atg5 in NK cells results in mitochondrial dysfunction, ROS accumulation, and premature cell death, leading to reduced uNK cell numbers and impaired spiral artery remodelling.[1] Experimental enhancement of autophagy through rapamycin or other activators promotes uNK cell survival and functional maturation, while pharmacological inhibition increases cytotoxicity and embryonic resorption in murine models.[2]

Molecular signalling mechanisms

The MITF–TNFRSF14, also known as HVEM, signalling axis has been identified as a critical pathway through which autophagy in decidual stromal cells (DSCs) promotes uNK cell retention.[1] MITF, a transcription factor responsive to autophagic activity, induces expression of TNFRSF14, which mediates stromal–NK cell adhesion and immune crosstalk.

Additionally, autophagic control of mTORC1 activity in uNK cells influences cytokine production. Suppressed autophagy elevates interferon gamma (IFN-γ) and tumour necrosis factor alpha (TNF-α), driving a pro-

inflammatory phenotype associated with implantation failure, whereas enhanced autophagy supports anti-inflammatory cytokines such as IL-10 and vascular endothelial growth factor A (VEGF-A), promoting vascular stability and foetal tolerance.[2]

Macrophages

Autophagy-dependent polarisation

Decidual macrophages exhibit remarkable plasticity, capable of adopting M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes depending on gestational stage. Autophagy modulates this polarisation through metabolic and signalling control.

Activation of Beclin-1 and LC3B facilitates transition toward an M2-like phenotype, characterised by high IL-10 and TGF-β secretion, essential for tissue remodelling and immune tolerance.[1] Conversely, inhibition of autophagy or excessive mTORC1 activation skews macrophages toward an M1-like profile, elevating pro-inflammatory cytokines such as IL-6 and TNF-α, which can lead to placental inflammation and foetal growth restriction.[2]

Autophagy in phagocytic clearance and tissue remodelling

Autophagy also supports macrophage-mediated clearance of apoptotic cells (efferocytosis) at the maternal–foetal interface. Efficient removal of apoptotic trophoblasts prevents release of damage-associated molecular patterns (DAMPs), maintaining immune quiescence. Impaired autophagic flux in macrophages leads to the accumulation of cellular debris and chronic inflammation.[2]

Furthermore, autophagy-dependent lysosomal degradation provides amino acids and lipids that fuel macrophage biosynthesis during placental vascular remodelling, linking cellular metabolism with immune function.[1]

Dendritic cells and antigen presentation

Dendritic cells bridge innate and adaptive immunity, shaping T-cell responses through antigen presentation. In the decidua, DCs exhibit a tolerogenic phenotype characterised by low expression of co-stimulatory molecules and high IL-10 production.

Autophagy enhances antigen presentation via major histocompatibility complex (MHC) class II loading but paradoxically contributes to immune tolerance during pregnancy. Studies demonstrate that autophagic degradation of endosomal content reduces surface presentation of paternal antigens, limiting maternal T-cell activation.[2]

Additionally, TFEB and FOXO3 — key transcription factors regulating lysosomal biogenesis and autophagy — are upregulated in decidual DCs, promoting cellular adaptation to hypoxia and nutrient stress. This autophagic conditioning maintains DC viability and prevents inflammatory activation.[1]

T lymphocytes and regulatory networks

Effector and Tregs

Autophagy is indispensable for the homeostasis and function of both effector T cells (Teffs) and Tregs.

In $CD4^+$ and $CD8^+$ T cells, autophagy maintains mitochondrial quality control, preventing excessive ROS and apoptosis. Loss of Atg7 or Atg5 in T cells leads to metabolic exhaustion and reduced proliferative capacity.[2]

In Tregs, autophagy sustains FOXP3 expression and suppressive function by modulating intracellular acetyl-CoA levels and mTORC1 signalling.[1] Impaired autophagy reduces Treg frequency in the decidua, resulting in breakdown of maternal–foetal tolerance and increased risk of miscarriage.

Cytokine crosstalk

Autophagy influences the cytokine milieu that shapes T-cell differentiation. By regulating IL-2, TGF-β, and IL-10 signalling pathways, autophagy promotes expansion of tolerogenic Tregs and restrains T helper 1 (Th1) and T helper 17 (Th17) polarisation. Conversely, defective autophagy elevates IL-6 and IFN-γ, reinforcing pro-inflammatory loops detrimental to implantation.[3]

At the molecular level, autophagy interacts with NF-κB, a key inflammatory transcription factor. Under physiological conditions, autophagy restrains NF-κB activation through degradation of IκB kinase (IKK) complexes. Under pathological stress, autophagic suppression leads to uncontrolled NF-κB activation, amplifying cytokine release and tissue inflammation.[1]

Trophoblast–immune cell interactions

Trophoblast cells, which form the foetal component of the placenta, directly communicate with maternal immune cells to establish tolerance. Autophagy within

trophoblasts modulates secretion of chemokines and cytokines that guide immune recruitment.

Enhanced autophagic activity in trophoblasts promotes the secretion of C-X-C motif chemokine ligand 12 (CXCL12) and IL-10, thereby recruiting Tregs and suppressing cytotoxic T-cell activity.[2] In contrast, inhibition of autophagy increases C-X-C motif chemokine ligands 9 and 10 (CXCL9/CXCL10) and IFN-γ expression, fostering a pro-inflammatory environment.

Autophagic flux also regulates expression of programmed death-ligand 1 (PD-L1), a critical immune checkpoint molecule that suppresses T-cell activation. Reduced autophagy diminishes PD-L1 expression, impairing local tolerance and increasing the risk of immune-mediated pregnancy loss.[1]

Temporal regulation of immune autophagy across gestation

Autophagic activity and immune responses vary dynamically throughout pregnancy:

- **Peri-implantation (Days 1–7):** Pro-inflammatory autophagy supports tissue remodelling and trophoblast invasion.
- **Mid-gestation:** Anti-inflammatory autophagy predominates, maintaining immune quiescence and tolerance.
- **Late gestation and parturition:** Re-activation of autophagy accompanies sterile inflammation and labour.[1]

This cyclical modulation reflects a coordinated adaptation to developmental cues and metabolic demands. Misalignment of autophagic timing — either excessive activation or inadequate suppression — disrupts immune balance, contributing to pregnancy disorders such as pre-eclampsia and preterm birth.[3]

Summary

Autophagy serves as a central homeostatic mechanism governing immune equilibrium at the maternal–foetal interface.[6] By orchestrating immune cell survival, differentiation, and cytokine production, autophagy ensures appropriate transitions between inflammatory and tolerant states necessary for successful pregnancy.

Key insights from current research highlight that:

1. Autophagy sustains uNK and macrophage viability while modulating their effector functions.
2. It preserves tolerogenic profiles of DCs and Tregs, maintaining maternal–foetal immune harmony.
3. Autophagic flux within trophoblasts integrates metabolic stress signalling with immune checkpoint regulation.
4. Temporal shifts in autophagy mirror evolving immunological demands across gestation.

Collectively, these mechanisms underscore autophagy's role as a molecular integrator of reproductive immunology, coordinating cellular metabolism, immune adaptation, and foetal tolerance.[1,2]

Autophagy Dysregulation in Pregnancy Complications and Reproductive Disorders

Overview: From homeostasis to pathology

Autophagy is fundamentally a homeostatic process; when appropriately regulated, it supports cellular quality control, metabolic flexibility, and immune adaptation. Conversely, failure to maintain appropriate autophagic flux — whether due to genetic perturbation, metabolic stress, endocrine disruption, or environmental toxicants — can precipitate maladaptive inflammation, defective tissue remodelling, and impaired cellular survival at the maternal–foetal interface. A growing body of preclinical and clinical evidence implicates autophagic dysregulation in major pregnancy complications, including spontaneous abortion, pre-eclampsia, preterm birth, as well as in chronic reproductive disorders such as polycystic ovary syndrome (PCOS), POI, and endometriosis.[1,2,3]

Below, we review mechanistic links between defective autophagy and pathology, summarise relevant experimental and clinical findings, and evaluate therapeutic implications and remaining knowledge gaps.

Spontaneous abortion and recurrent pregnancy loss

Mechanistic links

Spontaneous abortion (miscarriage) and recurrent pregnancy loss (RPL) frequently arise from failures in implantation, trophoblast invasion, or immune tolerance. Several mechanistic pathways connect autophagic

insufficiency to these failures. Loss-of-function in core autophagy genes (e.g., Atg5, Atg7) compromises trophoblast survival and differentiation, increases oxidative stress and mitochondrial dysfunction, and amplifies pro-inflammatory signalling through NF-κB activation.[2] At the immune level, defective autophagy reduces the numbers and tolerance-promoting capacity of decidual Tregs and uNK cells, increasing cytotoxic responses against trophoblasts.[1]

Autophagy also participates in controlled apoptotic cell clearance (efferocytosis) by decidual macrophages; impaired flux results in accumulation of apoptotic debris and DAMP release, which propagate local inflammation and may trigger foetal rejection.[3]

Evidence

Animal models provide compelling causal evidence: conditional knockout of Atg5 or Atg7 in trophoblast or immune compartments leads to increased embryonic resorption and miscarriage-like phenotypes in mice.[2] Human studies of RPL patients report alterations in autophagy markers (reduced LC3-II/LC3-I ratio, altered Beclin-1, and variable ATG16L1 expression) in endometrial and placental tissues, though human data remain more associative than definitively causal.[1,3]

Pre-eclampsia and placental insufficiency

Pathophysiology and autophagy

Pre-eclampsia is characterised by defective trophoblast invasion, inadequate spiral artery remodelling, placental hypoxia, and a maternal systemic inflammatory state. Autophagy is tightly implicated at multiple nodes of this pathophysiology:

- **Hypoxia response and trophoblast survival:** Early placental hypoxia would ordinarily induce protective autophagy (HIF-1α/AMPK-mediated) to permit trophoblast invasion. Blunted autophagic responses compromise trophoblast adaptation to low-oxygen microenvironments, promoting cell death and limiting invasion.[1]
- **ER stress and unfolded protein response (UPR):** Reduced autophagy exacerbates ER stress in syncytiotrophoblasts; unresolved UPR contributes to the release of anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), which drive maternal endothelial dysfunction.[2]
- **Inflammation amplification:** Autophagic failure augments NF-κB signalling and cyclooxygenase-2 (COX-2) expression, escalating pro-inflammatory cytokine production and systemic inflammation implicated in maternal hypertension and endothelial injury.[2,3]

Experimental and clinical observations

Human placentas from pre-eclamptic pregnancies often show altered autophagy marker patterns (variable Beclin-1, decreased ATG16L1, dysregulated LC3 processing) and evidence of heightened ER stress and oxidative damage.[2] Mouse models in which autophagy is impaired in trophoblast lineages recapitulate features of pre-eclampsia, including poor spiral artery remodelling and foetal growth restriction.[1] While human studies are complicated by heterogeneity in disease severity and sampling timing, the convergence of mechanistic and model evidence supports a contributory role for autophagy dysfunction in pre-eclampsia pathogenesis.

Preterm birth and inflammatory premature labour

Preterm birth (PTB) frequently follows intrauterine inflammation, infection, or sterile inflammatory triggers. Autophagy influences the inflammatory tone of decidual and placental tissues through regulation of cytokine release, inflammasome activation, and leukocyte survival.

Inflammasome regulation: Autophagy restrains the nucleotide-binding oligomerisation domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain-containing protein 3 (NLRP3) inflammasome activation by degrading damaged mitochondria and cytosolic DAMPs. Autophagic insufficiency increases IL-1β maturation and release, favouring preterm labour cascades.[3]

Susceptibility to infection: Reduced ATG16L1 activity has been linked to increased susceptibility to intrauterine infection and accelerated labour progression in both human tissues and knockout mouse models, suggesting a dual role in antimicrobial defence and inflammatory regulation.[1]

Clinically, increased markers of inflammasome activation and decreased autophagy-related protein expression have been observed in placentas from PTB cases; experimental restoration of autophagy in murine models attenuates inflammation and lowers rates of preterm delivery.[2]

Polycystic ovary syndrome, premature ovarian insufficiency and endometriosis

Polycystic ovary syndrome

PCOS is a metabolic–endocrine disorder marked by hyperandrogenism, anovulation, and insulin resistance. Autophagy intersects with PCOS pathogenesis at several points:

- **Metabolic dysfunction:** Insulin resistance and chronic low-grade inflammation seen in PCOS modulate AMPK/mTOR signalling, often yielding altered autophagic flux. Reduced autophagy in ovarian granulosa cells is linked to impaired follicular development and anovulation.[3]
- **Steroidogenic dysregulation:** Autophagy influences lipid droplet turnover and cholesterol availability for steroidogenesis; dysregulated autophagy can therefore perturb androgen biosynthesis.[1]

Human studies report variable autophagy marker expression in ovarian tissue from PCOS patients. Mechanistic studies implicate high-mobility group box 1 (HMGB1) and Wnt family member 5A (Wnt5a) signalling as modulators linking autophagy to local inflammation and aberrant folliculogenesis.[3]

Premature ovarian insufficiency

POI involves early depletion of ovarian reserve. Genetic and environmental insults that impair autophagy in oocytes (e.g., defective Atg gene expression or chronic oxidative stress) accelerate follicular atresia via mitochondrial dysfunction and apoptosis.[1] Murine oocyte-specific deletion of autophagy genes results in POI phenotypes, supporting a causal role. In humans, associations between decreased autophagy markers and diminished ovarian reserve are reported but require larger, longitudinal studies to establish causality.[2]

Endometriosis

Endometriosis is characterised by ectopic growth of endometrial tissue, chronic inflammation, and altered immune surveillance. Autophagy appears to be dysregulated in ectopic lesions, with conflicting reports of both increased and decreased autophagic activity depending on lesion site and disease stage. Mechanistically, aberrant autophagy may promote survival of ectopic endometrial cells under oxidative and hypoxic stress, contribute to altered antigen presentation, and modulate macrophage polarisation in peritoneal fluid.[3] Molecules such as HMGB1 and Wnt5a have been implicated in linking autophagy to lesion survival and inflammation.[3]

Molecular mediators and genetic contributors to pathology

Several specific molecular factors have been directly associated with adverse outcomes when autophagy is dysregulated:

- **ATG16L1:** Reduced ATG16L1 expression associates with labour progression anomalies and heightened infection susceptibility; animal models with deficient ATG16L1 demonstrate exacerbated inflammation during gestation.[1]
- **mTORC1 hyperactivation:** Persistent mTORC1 signalling inhibits adaptive autophagy responses, promoting inflammatory signalling (NF-κB), impaired decidualisation, and defective trophoblast function.[2]
- **COX2 and NF-κB upregulation:** Autophagy deficiency often accompanies elevated COX2 and NF-κB signalling, shifting tissues toward pro-labour and pro-inflammatory states linked to preterm birth.[2]
- **HMGB1 and Wnt5a:** These mediators are reported in PCOS and endometriosis contexts, where they may sustain inflammation and aberrant autophagy that support disease progression.[3]

Genetic polymorphisms in autophagy genes and transcriptional regulators (e.g., TFEB, FOXO3) are plausible contributors to individual susceptibility, though human genetic data are still sparse and require rigorous association studies.

Environmental, metabolic, and endocrine triggers of dysregulation

External and systemic factors compound genetic vulnerability to autophagy dysfunction:

- **Obesity and diabetes:** Nutrient excess and insulin resistance disrupt AMPK/mTOR signalling, often suppressing beneficial autophagic responses in reproductive tissues. These metabolic states

are associated clinically with higher rates of miscarriage, pre-eclampsia, and embryopathy.[1,3]

- **Endocrine disruptors:** Environmental chemicals (phthalates, bisphenols) alter hormonal signalling and can disrupt autophagy-related gene expression in reproductive cells, potentially contributing to infertility and placental dysfunction.[2]
- **Ageing:** Age-associated decline in autophagic capacity promotes accumulation of mitochondrial damage and genomic instability in gametes and placenta, aligning with increased reproductive pathology in older individuals.[2]

Therapeutic perspectives and challenges

Given autophagy's centrality to reproductive homeostasis, modulating autophagy is an attractive therapeutic avenue. Potential strategies include:

- **mTOR inhibitors (e.g., rapamycin analogues):** These agents can enhance autophagic flux and have shown efficacy in experimental models to improve decidualisation and reduce inflammation. However, systemic mTOR inhibition carries risks (immunosuppression, metabolic effects) and may adversely affect foetal growth if not targeted precisely.
- **AMPK activators and SIRT1 modulators:** Agents that restore metabolic sensing and autophagic competence (e.g., metformin) may confer reproductive benefit, as suggested by clinical improvements in PCOS patients treated with metformin; mechanistic links to autophagy warrant further study.
- **Antioxidants and mitochondrial protectants:** By reducing mitochondrial damage and ROS, these agents can indirectly restore autophagic balance and reduce inflammasome activation.
- **Targeted delivery systems:** Nanoparticle-based or tissue-specific delivery of autophagy modulators to the decidua or placenta would theoretically minimise systemic side effects but remains largely experimental.

Crucially, the dualistic nature of autophagy — protective at physiological levels but potentially deleterious when excessive — necessitates precision in any interventional approach. Timing is critical: enhancing autophagy during early implantation may be beneficial, whereas late-gestation modulation could precipitate adverse inflammatory responses.

Outstanding questions and research directions

Several key gaps remain:

1. **Causality in humans:** Most mechanistic evidence derives from animal knockouts and in vitro models; longitudinal human studies linking autophagy markers to pregnancy outcomes are needed.
2. **Biomarkers of functional flux:** Reliable, non-invasive biomarkers that reflect autophagic flux in reproductive tissues (rather than static protein levels) are lacking.
3. **Temporal specificity:** Greater resolution is required to define when and where to modulate autophagy for therapeutic benefit.
4. **Interplay with microbiome and infection:** The influence of systemic and local microbiota on autophagy–immune interactions at the maternal–foetal interface remains an emerging research area.
5. **Individual genetic susceptibility:** Large-scale genomic and epigenomic studies could identify polymorphisms in autophagy pathways that predispose to reproductive disorders.

Summary

Dysregulation of autophagy represents a convergent mechanism in several pregnancy complications and chronic reproductive disorders. Experimental models provide strong mechanistic links — loss of core Atg genes leads to trophoblast dysfunction, impaired immune tolerance, and pregnancy loss — while human tissue studies support associations between altered autophagy markers and clinical pathology. Therapeutic modulation of autophagy is promising but requires nuanced, stage-specific strategies and improved biomarkers to ensure efficacy and safety.

Autophagy, Immune Regulation, and Female Reproductive Ageing

Transition from reproductive homeostasis to senescence

Reproductive ageing marks a progressive decline in ovarian reserve, oocyte quality, and uterine receptivity, culminating in menopause. At the cellular level, this transition reflects cumulative oxidative damage, mitochondrial dysfunction, genomic instability, and

altered hormonal signalling — all processes under tight autophagic control. With advancing age, the efficiency of autophagic flux diminishes across ovarian and uterine tissues, impairing clearance of damaged organelles and macromolecules).[5] This decline disturbs the metabolic and immune equilibrium necessary for fertility and healthy gestation.

Autophagy's role in maintaining gamete integrity and tissue remodelling situates it at the nexus between cellular ageing and reproductive capacity. Age-related attenuation of autophagy in oocytes, granulosa cells, and endometrial stromal cells fosters a pro-inflammatory microenvironment and heightens susceptibility to oxidative stress, leading to poor oocyte competence, implantation failure, and pregnancy complications.[2]

Molecular mechanisms of autophagy decline with age

Mitochondrial quality control

Mitochondrial autophagy (mitophagy) declines with age, resulting in accumulation of dysfunctional mitochondria and ROS in ovarian cells. The phosphatase and tensin homolog-induced kinase 1 (PINK1)–Parkin pathway, critical for recognising and recycling depolarised mitochondria, exhibits reduced activity in aged oocytes and granulosa cells.[1] Excess ROS not only damages mitochondrial DNA but also oxidises lipids and proteins, further impairing energy production and signalling. Diminished mitophagy limits adenosine triphosphate (ATP) availability for meiotic spindle formation and chromosomal segregation, contributing to the aneuploidy and embryonic loss frequently observed in advanced maternal age.

Lysosomal inefficiency and proteostasis imbalance

Lysosomal acidity and enzymatic capacity wane with age, reducing the degradation efficiency of autophagosomes. This results in the accumulation of lipofuscin and misfolded proteins in ovarian and uterine tissues.[2] The impairment feeds forward to suppress new autophagosome formation, aggravating proteostasis imbalance. In decidual and placental cells, lysosomal dysfunction impairs antigen processing and cytokine turnover, promoting chronic sterile inflammation.

mTORC1 hyperactivation and AMPK decline

Nutrient-sensing pathways modulate autophagy through reciprocal regulation of mTORC1 and AMPK. Ageing, often accompanied by insulin resistance and metabolic inflexibility, favours chronic mTORC1 activation and reduced AMPK signalling. This shift suppresses autophagy initiation via ULK1 inhibition and diminishes the cell's ability to adapt to energetic stress.[1,2] Pharmacologic or dietary interventions that restore AMPK activity (e.g., metformin, caloric restriction mimetics) partially rescue autophagic responsiveness in aged ovaries.

Hormonal regulation of autophagy during ageing

Sex steroids directly modulate autophagy gene expression and flux. Oestrogen up-regulates Beclin-1 and LC3 transcription through oestrogen receptor alpha (ERα)-dependent signalling, whereas progesterone exerts context-dependent inhibitory effects.[3] The perimenopausal decline in oestrogen therefore removes a key stimulatory input to autophagy, compounding oxidative stress and metabolic imbalance. In the post-reproductive uterus, hypoestrogenism correlates with reduced autophagy and heightened inflammatory infiltration, consistent with accelerated tissue senescence.

FSH and LH also influence autophagic turnover in granulosa cells via cyclic adenosine monophosphate/protein kinase A (cAMP/PKA)-mediated regulation of mTORC1.[2] Dysregulated gonadotropin signalling with age may thus further disrupt autophagy-dependent folliculogenesis.

Immune remodelling and "inflammageing" in the reproductive tract

Chronic low-grade inflammation

Systemic ageing is accompanied by "inflammageing", defined as persistent, low-level activation of innate immunity characterised by elevated IL-6, TNF-α, and IL-1β. In reproductive tissues, decreased autophagic clearance of damaged mitochondria and cytosolic DNA activates pattern-recognition receptors, including NLRP3, cyclic guanosine monophosphate (GMP)–adenosine monophosphate (AMP) synthase (cGAS)–stimulator of interferon genes (STING) pathway, thereby sustaining cytokine release.[1] This inflammatory milieu disrupts endometrial receptivity and may impair blastocyst implantation, even in assisted reproduction settings.

Altered immune cell composition

Declining autophagy modifies the phenotype and function of local immune populations. In aged decidua, macrophages show reduced LC3 lipidation and

defective efferocytosis, leading to accumulation of apoptotic debris and secondary inflammation.[2] uNK cells exhibit impaired mitochondrial metabolism and decreased survival when autophagy is inhibited, limiting their capacity for vascular remodelling during early pregnancy. Reduced autophagy in stromal cells further disrupts MITF-TNFRSF14/HVEM signalling required for NK cell retention, mirroring defects seen in pregnancy loss models.[1]

Adaptive immunity and tolerance erosion

Tregs rely on autophagy to maintain metabolic quiescence and suppressive function. Age-related autophagy impairment in Tregs diminishes their stability and tolerance-inducing capacity, predisposing to autoimmune-like endometrial inflammation and implantation failure.[2] Collectively, these immune alterations reflect a collapse of the autophagy-mediated immune balance that supports successful gestation.

Impact on oocyte quality, fertilisation, and implantation

Oocyte competence

Autophagy participates in oocyte maturation by eliminating damaged mitochondria and ribosomes during germinal vesicle breakdown. With age, autophagic responsiveness to hormonal cues declines, resulting in cytoplasmic inclusions, spindle abnormalities, and reduced fertilisation potential.[2] Experimental induction of autophagy via AMPK or SIRT1 activators improves oocyte mitochondrial function and developmental competence in aged animal models, underscoring its functional significance.

Embryo–endometrium crosstalk

Successful implantation depends on synchronised autophagy between the embryo and endometrium. In aged uteri, reduced endometrial autophagy alters cytokine gradients, including IL-15 and leukaemia inhibitory factor (LIF), as well as extracellular matrix remodelling, creating a hostile environment for blastocyst adhesion.[1] Mouse studies show that pharmacologic activation of autophagy during the peri-implantation window restores receptivity and implantation rates.

Placental development

Although few human data exist, animal evidence indicates that maternal age compromises placental autophagy, resulting in increased oxidative stress and inflammatory signalling. The combination of impaired trophoblast autophagy and maternal immune dysregulation contributes to higher incidence of pre-eclampsia and foetal growth restriction in advanced-age pregnancies.[3]

Interventions to preserve autophagic capacity in ageing reproduction

1. **Caloric restriction and mimetics:** Nutrient limitation activates AMPK and SIRT1 while inhibiting mTORC1, thereby enhancing autophagy. Lifelong or mid-life caloric restriction delays reproductive senescence in animal models, preserving ovarian reserve and improving oocyte quality.[1]
2. **Pharmacological activators:** Agents such as metformin, resveratrol, and spermidine stimulate autophagic pathways and demonstrate reproductive benefits in preclinical studies; however, optimal dosing, timing, and long-term safety during pregnancy require careful evaluation.
3. **Hormone replacement strategies:** Physiological oestrogen replacement may partially restore autophagy and mitochondrial integrity in post-menopausal uterine tissue, though systemic risks necessitate individualised approaches.[3]
4. **Antioxidant and mitochondrial protectants:** Agents such as coenzyme Q10 and melatonin reduce oxidative load and indirectly sustain autophagy; small trials suggest improved oocyte parameters in older women undergoing in vitro fertilisation (IVF).
5. **Lifestyle modulation:** Physical activity and optimised metabolic control attenuate mTORC1 hyperactivity, reinforcing autophagic adaptability and immune homeostasis.

Future directions

Key research priorities include:

- Longitudinal profiling of autophagic markers in human ovarian and uterine tissues across reproductive lifespan
- Integration of multi-omics (transcriptomic, proteomic, metabolomic) to define signatures of autophagy decline

- Investigation of how age-related epigenetic changes in autophagy genes (e.g., methylation of ATG5, Beclin 1) contribute to reproductive senescence
- Development of targeted therapeutics that enhance autophagy specifically within reproductive tissues without systemic adverse effects

Summary

Female reproductive ageing exemplifies the systemic interplay between metabolic, hormonal, and immune senescence. Autophagy, by sustaining mitochondrial quality, restraining inflammation, and supporting hormonal responsiveness, acts as a central defence against reproductive decline. Its age-related attenuation accelerates ovarian depletion, impairs uterine receptivity, and increases susceptibility to pregnancy complications. Therapeutic strategies aimed at restoring autophagic competence offer promise for extending reproductive health span, although robust translational validation in humans remains essential.

Discussion

Integrative discussion

Autophagy has emerged as a fundamental regulator of reproductive health, governing cellular adaptation, immune balance, and tissue remodelling across the reproductive lifespan. Cumulative evidence from molecular, cellular, and physiological studies underscores that this evolutionarily conserved process is neither static nor uniform; it operates in a stage-specific and tissue-specific manner, responding dynamically to developmental and environmental cues. Across gametogenesis, implantation, decidualisation, and placentation, autophagic flux facilitates the removal of damaged organelles, supports cellular differentiation, and maintains immune tolerance at the maternal–foetal interface.[1,2]

A consistent theme across reproductive biology is that autophagic balance, rather than simple activation or inhibition, is critical for physiological function. Both insufficient and excessive autophagy can be deleterious, highlighting its role as a finely tuned homeostatic mechanism. During early pregnancy, autophagy sustains trophoblast invasion and immune tolerance; late in gestation, its regulated reactivation contributes to parturition. These dynamic oscillations align with distinct immunological states, from inflammation at implantation, to immune quiescence during foetal development, and subsequent reactivation during labour — indicating that autophagy synchronises immune and metabolic programmes within reproductive tissues.[1]

When autophagy is compromised, its consequences manifest across multiple biological levels. At the cellular level, defective autophagy results in oxidative stress, mitochondrial dysfunction, and protein aggregation, thereby impairing cell viability and differentiation. At the tissue level, it disrupts immune equilibrium, leading to excessive cytotoxicity or inadequate tolerance. At the systemic level, it amplifies inflammatory signalling and perturbs endocrine feedback loops. These disruptions collectively contribute to reproductive pathologies ranging from early miscarriage to pre-eclampsia and preterm birth.[2,3]

Evidence examining immune modulation at the maternal–foetal interface further highlights autophagy as integral to immune cell homeostasis. In uNK cells, macrophages, and Tregs, autophagy supports mitochondrial integrity, regulates cytokine secretion, and ensures controlled immune activation. Experimental inhibition of autophagy increases NK cell cytotoxicity and embryo resorption, whereas pharmacological induction promotes immune tolerance and foetal survival.[1] This immune–autophagy crosstalk thus represents a central node in the maintenance of successful pregnancy.

Pathological implications

Defective autophagy contributes to a spectrum of reproductive disorders. In spontaneous abortion and recurrent pregnancy loss, impaired autophagic flux in trophoblasts and immune cells triggers oxidative stress and unrestrained inflammation, compromising implantation and placental development. In pre-eclampsia, reduced autophagy exacerbates ER stress and inflammasome activation, promoting the release of anti-angiogenic factors and endothelial dysfunction. In preterm birth, autophagy deficiency enhances inflammasome activity and susceptibility to infection, accelerating premature labour.[2,3]

Beyond gestation, chronic disorders such as PCOS, POI, and endometriosis exhibit distinct patterns of autophagy dysregulation. In PCOS, reduced autophagy impairs granulosa cell metabolism and follicular maturation, linking metabolic stress to infertility. In endometriosis, autophagy appears paradoxically upregulated in certain lesion types, facilitating ectopic cell survival under

stress. These divergent patterns reinforce the notion that autophagy must be contextually regulated; both deficiency and excess can drive pathology depending on the reproductive stage and tissue environment.[3]

Ageing and the temporal dimension of autophagy

Female reproductive ageing intensifies these vulnerabilities. Progressive loss of autophagic efficiency in oocytes, endometrium, and placenta contributes to diminished fertility, increased aneuploidy, and greater risk of gestational complications in advanced maternal age.[1] Mechanistically, age-related hyperactivation of mTORC1, reduced AMPK signalling, and lysosomal inefficiency limit adaptive autophagic responses. The resultant accumulation of damaged mitochondria and heightened oxidative stress fuels "inflammageing," undermining endometrial receptivity and immune tolerance.[2]

The interplay between autophagy decline, hormonal changes, and immune remodelling encapsulates a broader biological truth: reproductive ageing is not merely a hormonal phenomenon but a cellular homeostasis failure. Targeting autophagy-related pathways offers a compelling avenue to mitigate reproductive senescence, but translation to clinical application requires precise temporal and tissue targeting to avoid systemic side effects.

Therapeutic and translational perspectives

Emerging therapeutic strategies aim to modulate autophagy pharmacologically or through lifestyle interventions. mTOR inhibitors (e.g., rapamycin analogues) and AMPK activators (e.g., metformin, resveratrol) have demonstrated the ability to restore autophagic flux and improve reproductive outcomes in experimental settings. SIRT1 modulators, antioxidants, and caloric restriction mimetics further illustrate the potential to rejuvenate reproductive function via autophagy enhancement.[1]

However, the double-edged nature of autophagy poses translational challenges. Overactivation may induce cell death or disrupt developmental signalling. Therefore, future therapies must calibrate autophagic activity to specific reproductive windows — supporting implantation, maintaining tolerance, and preventing premature labour — while safeguarding foetal development.

Advances in biomarker development (e.g., circulating LC3 or Beclin-1 fragments) and targeted delivery systems could enable non-invasive monitoring and tissue-specific modulation of autophagy. These innovations will be pivotal for integrating autophagy modulation into fertility preservation and pregnancy management.

Limitations and future directions

Despite substantial progress, several key gaps persist:

- Human data remain primarily correlative; robust longitudinal and interventional studies are needed to define causal relationships between autophagy dynamics and reproductive outcomes.
- The lack of standardised assays to measure autophagic flux in clinical samples limits comparability across studies.
- The integration of omics-based approaches (transcriptomics, proteomics, metabolomics) promises a systems-level understanding but demands harmonised frameworks.
- Finally, the field requires a deeper exploration of epigenetic regulation of autophagy genes during reproductive ageing and stress adaptation.
- Collaborations across reproductive biology, immunology, and systems medicine will be essential to translate autophagy knowledge into therapeutic benefit.

Disclosures

The author declares that no conflicts of interest exist. Artificial intelligence (AI) assistance (ChatGPT by OpenAI) was used for grammar correction, language enhancement, and formatting improvements during manuscript preparation. The study design, data collection, analysis, interpretation, and conclusions are entirely original and solely authored by the listed contributors.

Conclusion

Autophagy stands at the intersection of cellular survival, immune tolerance, and reproductive success. Its precise regulation orchestrates the complex transitions from gametogenesis to implantation, gestation, and parturition. Disruption of this balance — by genetic, metabolic, inflammatory, or age-related factors — compromises fertility and maternal–foetal health. Evidence from molecular to clinical studies converges on a unified concept: autophagy is a dynamic integrator of reproductive and immune homeostasis.

Future research must progress beyond descriptive associations towards temporal and mechanistic precision, defining when, where, and how autophagy can be safely modulated in human reproduction. Targeted modulation of this pathway holds promise not only for addressing infertility and pregnancy complications but also for extending reproductive health span through cellular rejuvenation and immune recalibration.

Sinthia Mondal. A Mini Review on Stage-Specific Autophagy Dynamics and Immune Regulation in the Reproductive System. MMJ. 2026. March. Vol 3 (1).
DOI: https://doi.org/10.62830/mmj3-01-4

References

1. Wang J, Tu S. Stage-specific autophagy dynamics in reproductive processes and associated disorders. *Front Cell Dev Biol*. 2025;13:1639691.
2. Komijani E, Parhizkar F, Abdolmohammadi-Vahid S, *et al.* Autophagy-mediated immune system regulation in reproductive system and pregnancy-associated complications. *J Reprod Immunol.* 2023;158:103973.
3. Singh A, Perez ML, Kirsanov O, *et al.* Autophagy in reproduction and pregnancy-associated diseases. *iScience.* 2024;27(12):111268.
4. Ma Y, Yu X, Liu YF, *et al.* Immunoregulation and male reproductive function: Impacts and mechanistic insights into inflammation. *Andrology*. 2025;13(6):1302–21.
5. Nakashima A, Furuta A, Yamada K, *et al.* The role of autophagy in the female reproduction system: for beginners to experts in this field. *Biology.* 2023;12(3):373.
6. Wang J, Han T, Zhu X. Role of maternal–fetal immune tolerance in the establishment and maintenance of pregnancy. *Chin Med J.* 2024;137(12):1399–406.