JOURNAL OF FERTILITY AND REPRODUCTIVE HEALTH
Jul-Dec 2025, VOL. 3, ISSUE 2, pp. 1-11
https://doi.org/10.61577/jfrh.2025.100006

MINI REVIEW

OPEN ACCESS

Integrin dysfunction key finding to implantation failure

Rajendra Kumar Sahoo

Department of Clinical Embryology, Shridhar University, Odisha, India

ABSTRACT

Integrin dysfunction has emerged as a significant contributor to implantation failure and reproductive disorders, prompting extensive research efforts to elucidate its role in reproductive biology. Integrins, a family of cell adhesion molecules, play crucial roles in mediating embryo-endometrial interactions during implantation. Dysregulated integrin expression or function in the endometrium or the embryo can impair the establishment of pregnancy, leading to recurrent implantation failure and infertility. This paper provides a comprehensive overview of integrin dysfunction and its connection to implantation failure, highlighting key findings regarding integrin expression patterns, mechanisms of dysfunction, clinical implications, and future directions. Through integrative approaches combining omics-based profiling, bioinformatics analysis, and experimental validation, researchers have identified novel integrin isoforms and regulatory elements involved in implantation. Furthermore, therapeutic strategies targeting integrins offer promising avenues for improving implantation success and fertility outcomes in patients undergoing assisted reproductive technologies. However, further research is warranted to deepen our understanding of integrin-related issues in reproductive medicine and develop personalized interventions for patients with implantation disorders. By bridging the gap between basic research and clinical practice, advancements in integrin research hold the potential to enhance fertility outcomes and fulfil the aspirations of individuals seeking to build their families.

KEY WORDS

Endometrium; Cell adhesion molecules; Integrins; Embryo adhesion; Implantation; Endometrium

ARTICLE HISTORY

Received 12 August 2025; Revised 02 September 2025; Accepted 10 September 2025

Introduction

Embryo implantation is a fundamental event in human reproduction and a critical during fertility and pregnancy success. The process functions on coordinated activity between the blastocyst and the receptive endometrium during implantation. Implantation failure remains a leading cause of infertility and unsuccessful assisted reproductive technology (ART) outcomes. At the molecular level, implantation is regulated by a complex network of adhesion molecules, extracellular matrix components, cytokines, and growth factors [1]. Among these, integrins have emerged as key mediators of embryo-endometrial interactions.

Dysregulated expression of integrin subunits, particularly αVβ3 and α4β1, has been reported in the endometrium of women with recurrent implantation failure and unexplained infertility. Similarly, aberrant integrin expression and signalling in trophoblast cells have been linked to defective adhesion and invasion during early pregnancy. Despite these findings, integrin-related mechanisms are not incorporated into clinical protocols [2].

Integrins are heterodimeric transmembrane receptors composed of α and β subunits that mediate cell–cell and cell–extracellular matrix interactions while transmitting bidirectional signals across the plasma membrane. In the endometrium, integrin expression is regulated throughout the menstrual cycle and peaks during the implantation. Integrins expressed by trophoblast cells help blastocyst attachment, migration, and invasion into the maternal decidua. Disruption of integrin expression patterns, ligand-binding capacity, or downstream signalling pathways are reasons for implantation failure. In vitro models using endometrial epithelial cells, stromal cells, and trophoblasts have been used to investigate integrin expression and function under controlled conditions [3]. Functional assays assessing cell adhesion, migration, and invasion have provided insights into integrin-mediated cellular behaviour relevant to implantation.

The current literature on integrin dysfunction is limited by heterogeneity in study populations, variability in experimental designs, and dependence on models. The objective of this review is to critically synthesize existing evidence on integrin dysfunction in implantation failure, integrate findings from clinical, experimental, and molecular studies, and identify key knowledge gaps [4].

Definition of Integrins and Their Role in Cellular Adhesion

Integrins are a family of transmembrane receptors composed of α and β subunits, forming heterodimeric complexes that mediate cell-cell and cell-extracellular matrix (ECM) interactions [5]. These glycoproteins play a crucial role in cellular adhesion, migration, proliferation, and differentiation, thereby influencing various physiological and pathological processes [6]. Integrins are pivotal in linking the cytoskeleton to the ECM, transmitting mechanical signals bidirectionally across the plasma membrane, and regulating intracellular signaling pathways.

Specifically, integrins facilitate cellular adhesion by binding to ECM proteins such as fibronectin, laminin, collagen, and vitronectin, as well as to cell surface ligands like selectins and immunoglobulins. This interaction enables cells to adhere firmly to the ECM or to adjacent cells, allowing for coordinated cellular behaviours essential for tissue development, homeostasis, and repair [7].

***Correspondence:** Mr. Rajendra Kumar Sahoo, Department of Clinical Embryology, Shridhar University, Odisha, India, e-mail: rajendrasahoo998@gmail.com

Moreover, integrins play a dynamic role in modulating cell behaviour through their ability to undergo conformational changes in response to extracellular cues. These conformational alterations regulate integrin affinity and avidity for ligands, thereby influencing cell adhesion strength, migration dynamics, and signalling specificity [8]. Additionally, integrins can form focal adhesion complexes at sites of cell-ECM attachment, facilitating the recruitment of intracellular signalling molecules and cytoskeletal components, which in turn regulate cell spreading, motility, and mechanotransduction [9].

Overall, integrins serve as critical mediators of cellular adhesion, allowing cells to sense and respond to their microenvironment, regulate tissue architecture and function, and participate in various physiological processes such as embryonic development, immune response, wound healing, and angiogenesis. Dysregulation of integrin-mediated adhesion has been implicated in a wide range of pathological conditions, including cancer metastasis, inflammatory diseases, and developmental disorders [10]. Understanding the intricate mechanisms underlying integrin function and dysfunction is therefore essential for elucidating disease pathogenesis and developing targeted therapeutic interventions.

Importance of Integrins in Embryo Implantation

Embryo implantation is a complex process that requires precise molecular interactions between the blastocyst and the receptive endometrium. Integrins play a pivotal role in mediating these interactions, facilitating embryo attachment, invasion, and establishment of a functional placenta [11]. The importance of integrins in embryo implantation can be elucidated through several key mechanisms:

Endometrial receptivity

Integrins expressed on the surface of endometrial epithelial cells and stromal cells undergo dynamic changes throughout the menstrual cycle, culminating in a window of receptivity known as the "implantation window." During this period, integrins such as α4β1, αVβ3, and αVβ6 are upregulated, promoting embryo adhesion and invasion into the endometrial epithelium. Integrin-mediated signalling pathways regulate the expression of adhesion molecules, cytokines, and growth factors necessary for embryo implantation and decidualization [12].

Embryo adhesion and invasion

Embryonic trophoblast cells express specific integrin isoforms, including αVβ3 and αVβ6, which interact with ECM proteins in the endometrial basement membrane such as vitronectin and fibronectin. These interactions facilitate embryo attachment to the endometrial surface and subsequent invasion through the epithelial barrier into the underlying stroma [13]. Integrin-mediated signalling promotes trophoblast proliferation, migration, and differentiation, enabling the formation of syncytiotrophoblasts and extravillous trophoblasts essential for placental development.

Angiogenesis and vascular remodelling

Integrins expressed on trophoblasts and endothelial cells play a critical role in angiogenesis and vascular remodelling within the uterine decidua. Integrin-mediated interactions with ECM components such as fibronectin and laminin regulate endothelial cell migration, tube formation, and vascular permeability, facilitating the establishment of maternal-fetal circulation and nutrient exchange.

Immunomodulation

Integrins contribute to immune cell trafficking and function within the endometrium and decidua, regulating the balance between maternal tolerance and immune defence during implantation. Integrin-mediated interactions between trophoblasts and uterine natural killer (uNK) cells, macrophages, and regulatory T cells modulate cytokine production, phagocytosis, and immune cell recruitment, creating a tolerogenic microenvironment conducive to embryo implantation and fetal development.

Overview of Integrin Dysfunction and Its Connection to Implantation Failure

Integrin dysfunction refers to aberrations in the expression, activation, or signalling of integrin molecules, disrupting their normal cellular functions and physiological processes. In the context of embryo implantation, integrin dysfunction can significantly impair the molecular interactions between the embryo and the endometrium, leading to implantation failure and subsequent reproductive complications. Several key aspects contribute to the connection between integrin dysfunction and implantation failure:

Altered integrin expression patterns

Dysregulated expression of integrin isoforms in the endometrium and/or trophoblasts can disrupt the spatiotemporal coordination necessary for successful embryo implantation. Downregulation or aberrant localization of integrins such as αVβ3, α4β1, and αVβ6 in the endometrial epithelium or trophoblasts may impair embryo adhesion, invasion, or vascular remodeling, compromising the establishment of pregnancy.

Impaired integrin signaling pathways

Integrins transduce signals bidirectionally across the plasma membrane, regulating cell adhesion, migration, proliferation, and differentiation through interactions with intracellular signaling molecules and cytoskeletal components. Dysfunctional integrin signaling pathways, characterized by altered integrin-ligand binding affinity, impaired focal adhesion complex formation, or dysregulated downstream signaling cascades, can disrupt the cellular processes essential for embryo implantation and placental development.

Genetic and epigenetic factors

Genetic mutations or epigenetic modifications affecting integrin genes or regulatory elements can predispose individuals to integrin dysfunction and reproductive disorders. Single nucleotide polymorphisms (SNPs), copy number variations (CNVs), or epigenetic alterations in integrin genes such as ITGA5, ITGB3, or ITGB1 have been implicated in implantation failure, recurrent pregnancy loss, or preeclampsia, highlighting the genetic susceptibility to integrin-related reproductive pathologies [14].

Environmental and lifestyle influences

Environmental factors, including exposure to endocrine disruptors, toxins, pollutants, or lifestyle factors such as diet, stress, and smoking, can impact integrin function and fertility outcomes. Disruptive environmental cues may alter integrin expression levels, disrupt integrin-ligand interactions, or interfere with integrin-mediated signaling pathways, contributing to implantation failure or pregnancy complications.

https://doi.org/10.61577/jfrh.2025.100006

Clinical implications and diagnostic challenges

Integrin dysfunction represents a significant clinical challenge in assisted reproductive technologies (ART), particularly in patients experiencing recurrent implantation failure (RIF) or unexplained infertility. Current diagnostic approaches for assessing integrin function in the endometrium or trophoblasts, such as immunohistochemistry, flow cytometry, or integrin ligand-binding assays, face limitations in sensitivity, specificity, and standardization, hindering the accurate diagnosis and management of integrin-related reproductive disorders.

Integrin Expression Patterns

Endometrial expression of integrins during implantation

The endometrium undergoes dynamic changes in integrin expression and distribution throughout the menstrual cycle, culminating in a receptive state conducive to embryo implantation during the implantation window. Integrins such as αVβ3, α4β1, and αVβ6 are among the key receptors implicated in endometrial receptivity and embryo adhesion. During the mid-secretory phase of the menstrual cycle, coinciding with the implantation window, there is an upregulation of integrin expression in the endometrial epithelium and stroma, facilitating embryo attachment and invasion [15]. This temporally regulated expression of integrins is essential for establishing a receptive endometrial environment capable of supporting embryo implantation and subsequent pregnancy.

Integrin expression in the endometrium

Integrin expression in the endometrium is a finely regulated process essential for the establishment of endometrial receptivity and successful embryo implantation. Throughout the menstrual cycle, endometrial integrins exhibit dynamic changes in expression patterns and localization, reflecting the cyclic nature of endometrial remodeling and preparation for embryo implantation.

During the proliferative phase of the menstrual cycle, integrin expression in the endometrium is relatively low, reflecting the early stages of endometrial regeneration and growth following menstruation. As the menstrual cycle progresses towards the secretory phase, characterized by rising levels of progesterone, there is a gradual increase in integrin expression, particularly of αVβ3, α4β1, and αVβ6 integrin subunits. These integrins play crucial roles in facilitating embryo adhesion to the endometrial epithelium and subsequent invasion into the endometrial stroma [16].

The peak of integrin expression coincides with the mid-secretory phase of the menstrual cycle, corresponding to the implantation window when the endometrium is most receptive to embryo implantation. Integrins such as αVβ3 are prominently expressed on the luminal surface of the endometrial epithelium, providing a molecular platform for embryo attachment and initial adhesion. Additionally, integrins in the endometrial stroma interact with trophoblast integrins, mediating trophoblast invasion and establishment of the placental bed.

The dynamic regulation of integrin expression in the endometrium is orchestrated by ovarian steroid hormones, including estrogen and progesterone, as well as by paracrine and autocrine factors secreted by endometrial cells and the developing embryo. Disruptions in this finely tuned integrin expression pattern can lead to impaired endometrial receptivity and implantation failure, contributing to infertility and recurrent pregnancy loss.

Understanding the spatiotemporal regulation of integrin expression in the endometrium is crucial for diagnosing and managing conditions associated with implantation failure, such as recurrent pregnancy loss and unexplained infertility. Further research into the molecular mechanisms underlying integrin dynamics in the endometrium may uncover novel therapeutic targets for improving fertility outcomes and assisting patients undergoing assisted reproductive technologies.

Integrin expression in the embryo

Integrins play a critical role in embryonic development, particularly during the process of implantation, by facilitating embryo attachment to the endometrial surface and subsequent invasion into the maternal tissue. The expression of integrins in the embryo is tightly regulated and exhibits distinct patterns corresponding to different stages of development and implantation.

During the pre-implantation phase, integrin expression in the embryo is relatively low, reflecting the undifferentiated state of the blastocyst. However, as the blastocyst undergoes differentiation and prepares for implantation, there is a significant upregulation of integrin expression, particularly of αVβ3 and αVβ6 integrin subunits. These integrins are involved in mediating embryo adhesion to the endometrial epithelium and facilitating trophoblast invasion into the endometrial stroma.

The trophectoderm, the outer layer of cells in the blastocyst responsible for implantation, expresses specific integrin isoforms that interact with ECM proteins in the endometrial basement membrane, such as fibronectin and vitronectin. These interactions are essential for establishing firm adhesion between the embryo and the endometrial surface, enabling subsequent invasion and penetration of the trophoblast cells into the maternal tissue.

Furthermore, integrin-mediated signaling pathways in the embryo regulate key cellular processes essential for implantation, including cell adhesion, migration, proliferation, and differentiation. Dysregulation of these signaling pathways can impair trophoblast function and invasive potential, leading to implantation failure and compromised pregnancy outcomes.

The expression of integrins in the embryo is influenced by various factors, including embryonic developmental stage, maternal hormonal cues, and paracrine signaling from the endometrium. Disruptions in these regulatory mechanisms can result in aberrant integrin expression patterns and contribute to implantation failure and infertility.

Understanding the dynamic regulation of integrin expression in the embryo is essential for elucidating the molecular mechanisms underlying implantation and for developing novel therapeutic strategies to improve fertility outcomes in patients undergoing assisted reproductive technologies.

Importance of integrin-mediated interactions for successful implantation

Integrin-mediated interactions play a crucial role in facilitating

https://doi.org/10.61577/jfrh.2025.100006

successful implantation by orchestrating the intricate molecular dialogue between the embryo and the receptive endometrium. These interactions are essential for ensuring firm adhesion, effective invasion, and establishment of a functional placenta, ultimately culminating in the initiation and maintenance of pregnancy.

Integrins serve as key mediators of cell-ECM and cell-cell adhesion, providing the molecular framework necessary for embryo attachment to the endometrial epithelium and subsequent invasion into the underlying stroma. Integrin subunits such as αVβ3, α4β1, and αVβ6 expressed on the surface of both the embryo and the endometrium interact with specific ECM ligands, including fibronectin, laminin, and vitronectin, forming stable adhesion complexes critical for embryo-endometrial interactions. These integrin-ligand interactions not only promote initial embryo attachment but also facilitate trophoblast invasion and vascular remodeling essential for placental development and maternal-fetal nutrient exchange.

Moreover, integrin-mediated signaling pathways regulate a myriad of cellular processes fundamental for successful implantation, including cytoskeletal rearrangements, focal adhesion formation, and intracellular signaling cascades. Activation of integrin-associated kinases such as focal adhesion kinase (FAK) and integrin-linked kinase (ILK) coordinates downstream signaling events that modulate trophoblast migration, proliferation, and differentiation, enabling efficient invasion of the maternal tissue and establishment of the placental interface.

Furthermore, integrin-mediated interactions contribute to the establishment of a tolerogenic microenvironment within the endometrium, promoting immune cell recruitment, immune cell function, and maternal-fetal immune tolerance crucial for successful pregnancy. Integrin engagement with immune cell receptors and ECM components regulates cytokine production, leukocyte trafficking, and uterine natural killer (uNK) cell activity, facilitating maternal immune adaptation to the semi-allogeneic fetus and preventing rejection of the implanting embryo.

Mechanisms of Integrin Dysfunction

Integrin dysfunction can arise from various molecular mechanisms, leading to impaired cellular adhesion, migration, and signaling processes critical for successful implantation. Understanding these mechanisms is essential for elucidating the etiology of implantation failure and developing targeted therapeutic interventions.

Genetic factors

Genetic mutations or polymorphisms affecting integrin genes or regulatory elements can disrupt integrin expression, activation, or signaling, predisposing individuals to integrin dysfunction-related reproductive disorders. For example, mutations in genes encoding integrin subunits, such as ITGA5, ITGB3, or ITGB1, have been associated with recurrent implantation failure, infertility, or pregnancy complications. Additionally, single nucleotide polymorphisms (SNPs) within integrin genes can alter protein structure or function, impairing integrin-ligand interactions or downstream signaling pathways essential for embryo-endometrial interactions.

Epigenetic regulation

Epigenetic modifications, including DNA methylation, histone modifications, and microRNA regulation, can modulate integrin expression and function, contributing to integrin dysfunction-related reproductive disorders. Aberrant DNA methylation patterns within integrin gene promoters or enhancers can silence gene expression or dysregulate integrin isoform switching, impairing endometrial receptivity or trophoblast invasion. Similarly, dysregulated expression of microRNAs targeting integrin transcripts can disrupt integrin signaling pathways, compromising embryo implantation or placentation.

Environmental influences

Environmental factors, including endocrine disruptors, toxins, pollutants, or lifestyle factors such as diet and stress, can impact integrin function and fertility outcomes. Exposure to environmental toxins or pollutants can disrupt integrin-ligand interactions, alter integrin expression levels, or interfere with integrin-mediated signaling pathways, contributing to implantation failure or infertility. Similarly, dietary factors or stress-induced hormonal changes can affect integrin expression and function in the endometrium or trophoblasts, compromising reproductive success.

Hormonal dysregulation

Dysregulation of ovarian steroid hormones, including estrogen and progesterone, can disrupt integrin expression patterns and endometrial receptivity, leading to implantation failure or infertility. Estrogen and progesterone signaling pathways regulate integrin expression in the endometrium, influencing the receptivity of the endometrial epithelium to embryo attachment and invasion. Dysfunctional hormonal signaling, such as estrogen dominance or progesterone resistance, can impair integrin-mediated embryo-endometrial interactions, compromising fertility outcomes.

Genetic factors influencing integrin function

Genetic factors play a significant role in influencing integrin function, with mutations or polymorphisms in integrin genes contributing to aberrant integrin expression, activation, or signaling. These genetic alterations can predispose individuals to integrin dysfunction-related reproductive disorders and implantation failure.

Genetic mutations affecting integrin subunits or regulatory elements can disrupt integrin function and impair cellular adhesion, migration, and signaling processes critical for successful embryo implantation. For example, mutations in genes encoding integrin subunits, such as ITGA5, ITGB3, or ITGB1, have been associated with recurrent implantation failure, infertility, or pregnancy complications. These mutations can alter integrin-ligand binding affinity, impair downstream signaling cascades, or disrupt integrin-mediated cell-ECM interactions essential for embryo-endometrial interactions.

Moreover, single nucleotide polymorphisms (SNPs) within integrin genes can influence integrin function by altering protein structure, expression levels, or post-translational modifications. SNPs within the coding regions or regulatory regions of integrin genes may affect integrin-ligand interactions, integrin clustering, or integrin-associated signaling pathways, thereby impacting cellular behaviors and reproductive outcomes.

Understanding the genetic basis of integrin dysfunction is crucial for identifying individuals at risk of implantation failure and developing personalized therapeutic interventions. Targeted genetic testing and screening for integrin gene

https://doi.org/10.61577/jfrh.2025.100006

mutations or polymorphisms may help identify patients with integrin-related reproductive disorders, enabling tailored treatment strategies to improve fertility outcomes.

Epigenetic regulation of integrin expression

Epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA regulation, play a crucial role in modulating integrin expression and function. These epigenetic modifications can dynamically regulate gene expression patterns, influencing cellular behaviors and reproductive outcomes.

DNA methylation, a reversible epigenetic modification involving the addition of methyl groups to cytosine residues within CpG dinucleotides, can modulate integrin gene expression by silencing or activating gene transcription. Hypermethylation of CpG islands within integrin gene promoters or enhancers can repress gene expression, impairing endometrial receptivity or trophoblast invasion during implantation. Conversely, hypomethylation of integrin gene regulatory regions can enhance gene expression, promoting cell adhesion, migration, and invasion processes critical for embryo-endometrial interactions.

Histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, can also regulate integrin expression by altering chromatin structure and accessibility to transcriptional machinery. Histone acetylation, associated with transcriptional activation, can promote integrin gene expression by loosening chromatin structure and facilitating transcription factor binding. Conversely, histone methylation or deacetylation, associated with transcriptional repression, can silence integrin gene expression, impairing cellular adhesion, migration, and signaling processes essential for embryo implantation.

MicroRNAs (miRNAs), small non-coding RNAs that post-transcriptionally regulate gene expression, can target integrin transcripts and modulate integrin-mediated signaling pathways. Dysregulated expression of miRNAs targeting integrin genes can disrupt integrin function, impairing cell adhesion, migration, and invasion processes crucial for successful implantation. Additionally, miRNAs secreted by endometrial cells or trophoblasts can act as paracrine signaling molecules, regulating integrin expression and function in neighboring cells, thereby influencing embryo-endometrial interactions and pregnancy outcomes.

Environmental factors affecting integrin signaling

Environmental factors can influence integrin signaling pathways, impacting cellular adhesion, migration, and signaling processes essential for successful implantation. Exposure to endocrine disruptors, toxins, pollutants, or lifestyle factors such as diet and stress can disrupt integrin function and compromise fertility outcomes.

Endocrine disruptors, including bisphenol A (BPA), phthalates, and polychlorinated biphenyls (PCBs), can interfere with hormone signaling pathways and disrupt integrin expression or function. These environmental contaminants can alter integrin-ligand interactions, impair integrin-mediated cell adhesion and migration, and compromise embryo-endometrial interactions essential for successful implantation.

Toxins and pollutants present in the environment, such as heavy metals, pesticides, and air pollutants, can also impact integrin signaling pathways and reproductive health. Exposure to heavy metals like lead, mercury, or cadmium can disrupt integrin-mediated cellular processes, impair trophoblast function, and increase the risk of implantation failure or pregnancy complications.

Dietary factors and lifestyle choices can influence integrin signaling pathways and fertility outcomes. Poor dietary habits, including high-fat diets, processed foods, and inadequate nutrient intake, can impair integrin function and endometrial receptivity, affecting embryo implantation and pregnancy establishmentss. Similarly, chronic stress, smoking, and alcohol consumption can dysregulate hormonal signaling pathways, disrupt integrin expression or function, and compromise reproductive success.

Consequences of Aberrant Integrin Expression and Signaling

Aberrant integrin expression and signaling can have profound consequences on cellular behaviors, reproductive processes, and fertility outcomes. Dysregulation of integrin-mediated interactions can impair embryo implantation, placental development, and maternal-fetal immune regulation, leading to reproductive disorders and pregnancy complications.

Implantation failure

Dysfunctional integrin expression or signaling pathways can compromise embryo-endometrial interactions, impairing embryo attachment, invasion, and establishment of pregnancy. Aberrant integrin-ligand interactions or downstream signaling cascades can result in implantation failure, recurrent pregnancy loss, or infertility.

Placental abnormalities

Integrin dysfunction can disrupt trophoblast invasion and vascular remodeling processes essential for placental development. Impaired integrin-mediated interactions between trophoblasts and the maternal decidua can lead to placental abnormalities, such as placenta accreta, placenta previa, or intrauterine growth restriction (IUGR), compromising fetal growth and development.

Maternal-Fetal immune dysregulation

Integrins play a crucial role in modulating maternal-fetal immune interactions and establishing immune tolerance at the maternal-fetal interface. Dysfunctional integrin signaling can disrupt immune cell trafficking, cytokine production, and immune cell function, leading to immune dysregulation, inflammation, and pregnancy complications such as preeclampsia or spontaneous abortion.

Reproductive disorders

Aberrant integrin expression or function has been implicated in various reproductive disorders, including endometriosis, adenomyosis, and polycystic ovary syndrome (PCOS). Dysregulated integrin-mediated interactions within the endometrium or ovarian follicles can impair fertility outcomes and increase the risk of reproductive pathologies.

Assisted reproductive technology (ART) failure

Integrin dysfunction represents a significant clinical challenge in ART procedures, particularly in patients experiencing recurrent implantation failure (RIF) or unexplained infertility. Disrupted integrin-mediated embryo-endometrial interactions can result in repeated unsuccessful attempts at embryo transfer, reducing the success rates of ART treatments.

https://doi.org/10.61577/jfrh.2025.100006

Clinical Implications

Clinical implications of integrin dysfunction extend across various aspects of reproductive medicine, influencing diagnosis, treatment strategies, and patient outcomes. Understanding these implications is essential for improving the management of reproductive disorders and optimizing fertility outcomes for patients.

Diagnostic challenges

Integrin dysfunction poses diagnostic challenges in the assessment of endometrial receptivity and embryo implantation. Current diagnostic approaches, including endometrial biopsy and immunohistochemical analysis of integrin expression, face limitations in sensitivity, specificity, and standardization. Identifying reliable biomarkers or molecular signatures of endometrial receptivity may improve the accuracy of diagnostic tests and facilitate personalized treatment approaches for patients with implantation failure or recurrent pregnancy loss.

Assisted reproductive technologies (ART)

Integrin dysfunction represents a significant clinical challenge in ART procedures, particularly in patients with recurrent implantation failure (RIF) or unexplained infertility. Integrin-based endometrial receptivity assays (ERA) have been developed to assess the window of implantation and guide the timing of embryo transfer in ART cycles. Integrin-targeted therapies, such as integrin agonists or antagonists, may enhance endometrial receptivity and improve implantation rates in patients undergoing ART treatments.

Reproductive counseling and management

Integrin dysfunction can impact reproductive counseling and management strategies for patients experiencing infertility or recurrent pregnancy loss. Identifying genetic or epigenetic factors contributing to integrin dysfunction may inform personalized treatment plans, including lifestyle modifications, pharmacological interventions, or assisted reproductive technologies. Integrating integrin testing into routine clinical practice may help identify patients at risk of implantation failure or pregnancy complications, enabling proactive management strategies to optimize fertility outcomes.

Therapeutic interventions

Targeted therapeutic interventions aimed at restoring integrin function or modulating integrin-mediated signaling pathways hold promise for improving fertility outcomes in patients with integrin-related reproductive disorders. Novel pharmacological agents targeting integrin-ligand interactions, integrin-associated kinases, or downstream signaling effectors may enhance endometrial receptivity, promote embryo implantation, and reduce the incidence of implantation failure or pregnancy loss.

Association between integrin dysfunction and recurrent implantation failure

Recurrent implantation failure (RIF) represents a challenging clinical scenario in assisted reproductive medicine, often attributed to multifactorial etiologies, including embryonic, endometrial, and immunological factors. Integrin dysfunction has emerged as a significant contributing factor to RIF, influencing embryo-endometrial interactions and impairing the establishment of pregnancy.

Endometrial receptivity

Integrins play a crucial role in regulating endometrial receptivity and facilitating embryo implantation. Dysregulated expression or function of endometrial integrins, such as αVβ3, α4β1, and αVβ6, has been associated with impaired endometrial receptivity and RIF. Aberrant integrin expression patterns in the mid-secretory phase of the menstrual cycle, indicative of defective endometrial receptivity, have been observed in patients experiencing RIF.

Embryo-endometrial interactions

Integrin-mediated interactions between the embryo and the endometrium are essential for successful implantation. Dysfunctional integrin-ligand interactions or impaired integrin signaling pathways can disrupt embryo attachment, invasion, and establishment of pregnancy. Altered expression of embryonic integrins, as well as endometrial integrins, has been reported in patients with RIF, indicating compromised embryo-endometrial crosstalk and impaired implantation potential.

Genetic and epigenetic factors

Genetic mutations or epigenetic modifications affecting integrin genes or regulatory elements may predispose individuals to integrin dysfunction-related RIF. Single nucleotide polymorphisms (SNPs) within integrin genes, as well as aberrant DNA methylation patterns within integrin gene promoters, have been implicated in RIF pathogenesis. These genetic and epigenetic alterations can disrupt integrin expression, function, or signaling, contributing to implantation failure and recurrent pregnancy loss.

Diagnostic and therapeutic implications

Integrin-based diagnostic tests, such as integrin expression profiling or endometrial receptivity assays (ERA), may aid in identifying patients at risk of RIF and guiding personalized treatment strategies. Integrin-targeted therapies, including integrin agonists or antagonists, may enhance endometrial receptivity and improve implantation rates in patients with RIF undergoing assisted reproductive technologies.

Diagnostic approaches for assessing integrin function

Diagnostic approaches for assessing integrin function encompass a range of techniques aimed at evaluating endometrial receptivity and embryo-endometrial interactions. These methods are instrumental in identifying patients at risk of implantation failure and guiding personalized treatment strategies in assisted reproductive medicine.

One commonly utilized diagnostic approach is the analysis of integrin expression patterns in the endometrium, typically performed via endometrial biopsy followed by immunohistochemical staining. Immunohistochemical assessment allows for the visualization and quantification of integrin subunit expression, such as αVβ3, α4β1, and αVβ6, in endometrial tissue samples collected during the mid-secretory phase of the menstrual cycle. Abnormalities in integrin expression patterns, including reduced expression or altered localization, may indicate defective endometrial receptivity and increase the risk of implantation failure or recurrent pregnancy loss.

In addition to immunohistochemical analysis, integrin-based

https://doi.org/10.61577/jfrh.2025.100006

endometrial receptivity assays (ERA) have been developed to assess the timing of the window of implantation and guide the timing of embryo transfer in assisted reproductive technology (ART) cycles. ERA involves endometrial sampling followed by molecular analysis of gene expression patterns associated with endometrial receptivity, including integrins and other biomarkers. By identifying the optimal timing for embryo transfer based on endometrial receptivity profiles, ERA aims to improve implantation rates and pregnancy outcomes in patients undergoing ART treatments.

Therapeutic strategies targeting integrins to improve implantation success

Therapeutic strategies targeting integrins offer promising avenues for improving implantation success and fertility outcomes in patients experiencing recurrent implantation failure (RIF) or infertility. By modulating integrin expression, function, or signaling pathways, these therapeutic interventions aim to enhance endometrial receptivity, promote embryo implantation, and mitigate the risk of implantation failure.

One therapeutic approach involves the administration of integrin agonists or antagonists to regulate integrin-mediated interactions between the embryo and the endometrium. Integrin agonists, such as synthetic ligands or peptides mimicking endogenous integrin ligands, may enhance integrin activation and promote cell adhesion, migration, and invasion processes crucial for successful implantation. Conversely, integrin antagonists may selectively block integrin-ligand interactions, preventing inappropriate adhesion or invasion of the embryo and reducing the risk of implantation failure.

Another therapeutic strategy involves the modulation of integrin-associated signaling pathways implicated in endometrial receptivity and embryo implantation. Small molecule inhibitors targeting integrin-associated kinases, such as focal adhesion kinase (FAK) or integrin-linked kinase (ILK), may disrupt downstream signaling cascades involved in cell adhesion, migration, and proliferation, thereby impairing embryo implantation. Conversely, activators of integrin signaling pathways or downstream effectors may enhance endometrial receptivity and promote successful implantation in patients with RIF or infertility.

Furthermore, integrin-based therapeutic interventions may be combined with other assisted reproductive technologies (ART) to optimize treatment outcomes in patients undergoing in vitro fertilization (IVF) or embryo transfer procedures. Integrin-targeted therapies may be integrated into personalized treatment protocols based on individual patient characteristics, including endometrial receptivity profiles, genetic factors, and reproductive history. By addressing integrin dysfunction and enhancing embryo-endometrial interactions, these therapeutic strategies hold promise for improving implantation success rates and pregnancy outcomes in patients undergoing ART treatments.

Experimental Models and Assays

Experimental models and assays play a pivotal role in elucidating the molecular mechanisms underlying integrin function and dysfunction in reproductive biology. These models provide valuable insights into integrin-mediated processes such as endometrial receptivity, embryo implantation, and placental development, facilitating the discovery of novel therapeutic targets and treatment strategies for reproductive disorders.

In vitro cell culture models

In vitro cell culture models utilizing endometrial epithelial cells, stromal cells, or trophoblasts provide a tractable system for studying integrin expression, function, and signaling in reproductive tissues (Aplin, 2010) (Figure 1). These models allow researchers to manipulate integrin expression levels, assess integrin-ligand interactions, and investigate downstream signaling pathways involved in embryo-endometrial interactions and placental development. Additionally, co-culture systems incorporating both maternal and embryonic cell types enable the study of complex cellular interactions underlying successful implantation and pregnancy establishment.

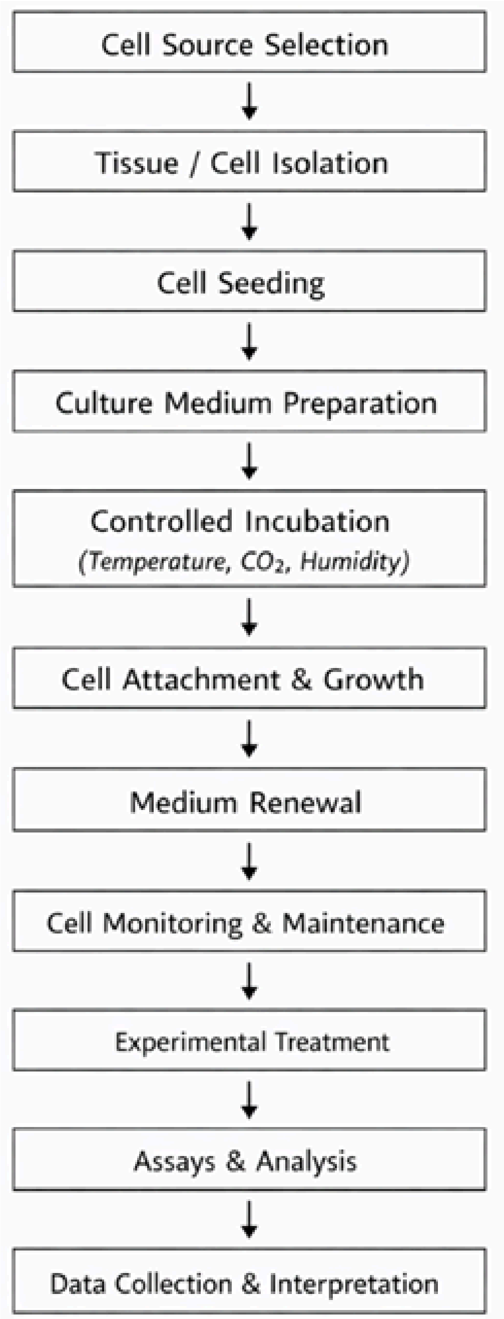

Figure 1. Schematic representation of in vitro cell culture model.

https://doi.org/10.61577/jfrh.2025.100006

Animal models

Animal models, including mice, rats, and non-human primates, have been instrumental in studying integrin function and reproductive physiology in vivo. Transgenic animal models with targeted deletions or mutations in integrin genes allow researchers to investigate the consequences of integrin dysfunction on fertility outcomes, embryo implantation, and placental development. These models enable the manipulation of integrin expression or function in a controlled manner, facilitating the study of integrin-mediated processes in reproductive tissues under physiological and pathological conditions.

Functional assays

Functional assays, such as cell adhesion assays, migration assays, and invasion assays, provide quantitative measures of integrin-mediated cellular behaviors critical for embryo implantation and placental development. These assays assess the adhesive properties of cells, their ability to migrate through ECM substrates, and their capacity to invade maternal tissues, reflecting key aspects of integrin function in reproductive biology. By characterizing integrin-mediated cellular behaviors in vitro, researchers can identify potential therapeutic targets for modulating integrin function and improving fertility outcomes [17].

Molecular profiling techniques

Molecular profiling techniques, including gene expression analysis, proteomics, and high-throughput screening assays, enable comprehensive characterization of integrin expression patterns, signalling pathways, and regulatory mechanisms in reproductive tissues. These techniques provide insights into the molecular signature of endometrial receptivity, embryo-endometrial interactions, and placental development, facilitating the identification of biomarkers and therapeutic targets for reproductive disorders (Figure 2).

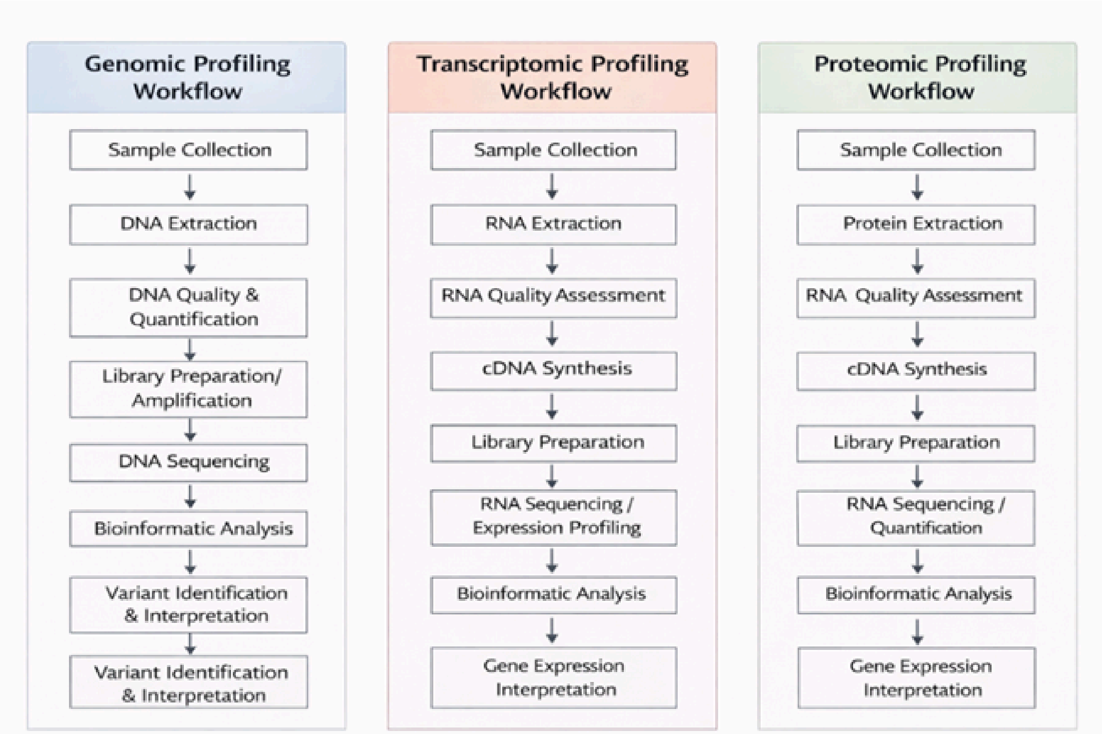

Figure 2. Schematic representation of genomic, transcriptomic, and proteomic molecular profiling.

Animal models for studying integrin function in implantation

Animal models have been instrumental in advancing our understanding of integrin function in implantation processes, providing valuable insights into the molecular mechanisms underlying successful embryo implantation and pregnancy establishment. These models offer opportunities to manipulate integrin expression, function, and signalling pathways in a controlled manner, facilitating the investigation of integrin-mediated events in reproductive tissues.

Mice, in particular, have served as a prominent animal model for studying integrin function in implantation due to their physiological similarities to humans and the availability of genetic manipulation techniques. Transgenic mouse models with targeted deletions or mutations in integrin genes, such as ITGA5 or ITGB3, have been utilized to elucidate the role of specific integrin subunits in embryo attachment, trophoblast invasion, and placental development [18]. These models allow researchers to assess the consequences of integrin dysfunction on fertility outcomes and reproductive physiology in vivo.

Additionally, non-human primate models, such as rhesus macaques, provide valuable insights into integrin function in a species closely related to humans. Non-human primates offer advantages for studying integrin-mediated processes in reproductive tissues, including endometrial receptivity, embryo-endometrial interactions, and placental development, with greater translational relevance to human reproduction.

These models enable researchers to investigate integrin function under physiological conditions and in response to

https://doi.org/10.61577/jfrh.2025.100006

experimental interventions, providing important preclinical data for the development of novel therapeutic strategies.

In vitro assays to evaluate integrin-mediated processes

In vitro assays provide valuable tools for evaluating integrin-mediated processes involved in embryo implantation and reproductive physiology. These assays enable researchers to assess various aspects of integrin function, including cell adhesion, migration, invasion, and signalling, in a controlled laboratory setting. By recapitulating key events of implantation in vitro, these assays facilitate the study of integrin-mediated interactions between the embryo and the endometrium, as well as other aspects of reproductive biology.

Cell adhesion assays, such as static adhesion assays or dynamic flow-based assays, allow researchers to investigate the adhesive properties of cells to extracellular matrix (ECM) proteins or endothelial cells, mimicking the initial steps of embryo attachment to the endometrium. These assays measure the ability of cells expressing specific integrin subunits to adhere to immobilized ligands under defined flow conditions, providing insights into the role of integrins in cell-ECM interactions and embryo implantation.

Migration assays, such as scratch assays or transwell migration assays, assess the migratory capacity of cells in response to integrin-mediated signaling cues. These assays measure the ability of cells to migrate through ECM substrates or porous membranes toward chemotactic stimuli, reflecting the invasive behavior of trophoblasts during embryo implantation. By modulating integrin expression or function, researchers can investigate the impact of integrin-mediated cell migration on implantation success and reproductive outcomes.

Invasion assays, such as Matrigel invasion assays or three-dimensional (3D) organotypic culture models, simulate the invasive behavior of trophoblasts during embryo implantation. These assays assess the ability of cells to penetrate basement membrane barriers and invade into surrounding tissues, reflecting the critical role of integrins in trophoblast invasion and placental development. By examining the effects of integrin dysregulation on cell invasion dynamics, researchers can elucidate the mechanisms underlying implantation failure and pregnancy complications.

Advantages and limitations of experimental approaches

Experimental approaches in studying integrin function in implantation offer several advantages but also come with inherent limitations. Understanding these aspects is crucial for interpreting research findings accurately and advancing our knowledge in reproductive biology.

Advantages

Controlled experimental conditions

In vitro assays and animal models allow researchers to control experimental conditions, including cell culture parameters, genetic backgrounds, and environmental factors, facilitating the investigation of specific aspects of integrin function in implantation.

Mechanistic insights

Experimental approaches provide mechanistic insights into integrin-mediated processes, such as cell adhesion, migration, invasion, and signaling, elucidating the molecular mechanisms underlying embryo implantation and placental development.

Translational relevance

Animal models, particularly non-human primates, offer translational relevance to human reproduction, enabling researchers to study integrin function in a species closely related to humans and validate experimental findings in clinically relevant settings.

Therapeutic target identification

Experimental models and assays facilitate the identification of potential therapeutic targets for improving fertility outcomes in patients with implantation disorders, guiding the development of novel treatment strategies and personalized interventions.

Limitations

Simplified models

In vitro assays and animal models may oversimplify the complex physiological environment of the reproductive tract, potentially limiting the relevance of experimental findings to human reproduction.

Species differences

Variations in integrin expression patterns, signaling pathways, and reproductive physiology between species may impact the translational relevance of animal models to human implantation processes.

Ethical considerations

The use of animal models in research raises ethical considerations regarding animal welfare and the appropriateness of experimental procedures, necessitating careful consideration of ethical guidelines and regulations.

Clinical correlation

While experimental approaches provide valuable insights into integrin function in implantation, translating research findings to clinical practice requires rigorous validation in human populations and correlation with clinical outcomes.

Future Directions

Future directions in the study of integrin function in implantation hold significant promise for advancing our understanding of reproductive biology and improving fertility outcomes. Emerging research avenues aim to address key knowledge gaps, leverage technological advancements, and develop innovative therapeutic strategies to enhance embryo implantation and pregnancy success.

Integrinomics and systems biology

Integrative omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, offer opportunities to comprehensively profile integrin-mediated processes in implantation. By integrating multi-omic datasets and applying systems biology approaches, researchers can unravel complex regulatory networks and identify novel biomarkers and therapeutic targets for reproductive disorders.

Single-cell profiling

Single-cell technologies, such as single-cell RNA sequencing and spatial transcriptomics, enable the characterization of cellular heterogeneity and spatial organization within reproductive tissues during implantation. These high-resolution techniques

https://doi.org/10.61577/jfrh.2025.100006

provide insights into cell-type-specific gene expression patterns, signalling pathways, and interactions, elucidating the dynamics of embryo-endometrial crosstalk and placental development.

Integrin engineering and therapeutics

Advances in integrin engineering and therapeutic development hold promise for developing novel treatment modalities for implantation disorders. Engineered integrin ligands, antibodies, or small molecule agonists/antagonists targeting specific integrin subunits or signaling pathways may enhance endometrial receptivity, promote embryo implantation, and mitigate the risk of implantation failure.

Precision medicine and personalized interventions

The application of precision medicine approaches, including genomic profiling, molecular phenotyping, and predictive modelling, enables the identification of patient-specific factors influencing integrin function and reproductive outcomes. Personalized interventions tailored to individual patient characteristics, such as integrin expression profiles, genetic variants, and epigenetic modifications, may optimize fertility treatments and improve pregnancy success rates.

Identification of novel integrin isoforms involved in implantation

Identification of novel integrin isoforms involved in implantation represents a promising avenue for advancing our understanding of the molecular mechanisms underlying embryo-endometrial interactions and pregnancy establishment. Integrins are a diverse family of cell adhesion molecules composed of α and β subunits, with multiple isoforms expressed in reproductive tissues. While several integrin isoforms, such as αVβ3 and α4β1, have been extensively studied in the context of implantation, emerging evidence suggests the existence of novel integrin isoforms with potential roles in reproductive biology.

Recent studies have employed high-throughput sequencing techniques, such as RNA sequencing (RNA-seq) and proteomics, to systematically profile integrin expression patterns in endometrial tissues, trophoblasts, and embryonic cells during implantation. These omics-based approaches have revealed the presence of previously unrecognized integrin isoforms and alternative splicing variants in reproductive tissues, providing valuable insights into their potential functions in implantation.

Furthermore, advances in bioinformatics and computational biology have enabled the prediction and characterization of integrin isoforms based on sequence homology, domain structure, and functional annotations. Integrative analysis of genomic and transcriptomic data from human and animal models has facilitated the identification of evolutionarily conserved integrin isoforms and regulatory elements involved in implantation.

Experimental validation of novel integrin isoforms using molecular biology techniques, such as quantitative real-time PCR (qPCR), immunohistochemistry, and functional assays, is essential for confirming their expression patterns and elucidating their biological functions in implantation. Targeted disruption or overexpression of specific integrin isoforms in animal models may provide further insights into their roles in embryo-endometrial interactions, trophoblast invasion, and placental development.

Exploration of integrin crosstalk with other signalling pathways

Exploring integrin crosstalk with other signalling pathways represents a crucial aspect of understanding the complex regulatory networks underlying embryo implantation and reproductive physiology. Integrins interact dynamically with various signalling molecules, receptors, and pathways to coordinate cellular behaviours essential for successful implantation, including cell adhesion, migration, invasion, and differentiation.

One area of exploration involves the interplay between integrins and growth factor signaling pathways, such as the transforming growth factor-beta (TGF-β) pathway, the epidermal growth factor (EGF) pathway, and the fibroblast growth factor (FGF) pathway. Integrins can modulate the activation and downstream signalling of growth factor receptors, while growth factors can reciprocally regulate integrin expression, localization, and function, influencing cell behaviour during implantation.

Additionally, integrins collaborate with cytokine signalling pathways, such as the interleukin (IL) pathway and the tumour necrosis factor-alpha (TNF-α) pathway, to regulate immune cell recruitment, inflammation, and tissue remodelling processes in the endometrium during implantation. Integrin-mediated interactions between immune cells, stromal cells, and epithelial cells play critical roles in establishing endometrial receptivity and modulating the local immune microenvironment.

Furthermore, integrins crosstalk with hormonal signalling pathways, including estrogen signalling and progesterone signalling, to coordinate endometrial remodelling and receptivity throughout the menstrual cycle. Estrogen and progesterone receptors can regulate integrin expression and activity in endometrial cells, influencing cell adhesion, proliferation, and differentiation processes required for embryo implantation.

Moreover, integrin crosstalk with intracellular signalling pathways, such as the focal adhesion kinase (FAK) pathway, the mitogen-activated protein kinase (MAPK) pathway, and the phosphatidylinositol 3-kinase (PI3K) pathway, regulates cytoskeletal dynamics, cell motility, and survival in response to extracellular cues during implantation. Integrin-mediated activation of these signalling pathways orchestrates cytoskeletal rearrangements and intracellular signalling cascades essential for cell adhesion, migration, and invasion events.

Conclusion

Integrin dysfunction has emerged as a central factor in understanding why implantation sometimes fails despite otherwise promising reproductive conditions. As key mediators of communication between the embryo and the endometrium, integrins help guide essential processes such as adhesion, invasion, and the early stages of placental development. When these molecules are dysregulated, whether through altered expression, impaired signalling, or disrupted receptor–ligand interactions, the intricate dialogue required for implantation can be weakened. This disruption may manifest as recurrent implantation failure, infertility, or early pregnancy complications, underscoring the sensitivity of implantation to even subtle molecular disturbances.

https://doi.org/10.61577/jfrh.2025.100006

Research continues to demonstrate that integrin-related abnormalities may arise from genetic variations, epigenetic modifications, hormonal influences, or environmental stressors. Each of these factors has the potential to alter the microenvironment in which implantation occurs. Such findings highlight why integrins have become an important focus for both diagnostic evaluation and therapeutic innovation, especially within assisted reproductive technologies.

Looking ahead, advancing our knowledge of integrin function will require deeper exploration of how these molecules interact with broader signalling networks including growth factors, cytokines, and hormonal pathways. Emerging tools such as high-throughput omics, single-cell profiling, and integrative bioinformatics offer promising avenues for identifying previously unrecognized integrin isoforms and regulatory mechanisms that contribute to reproductive success.

Translating these scientific insights into clinical practice holds significant promise. Integrin-based diagnostic assessments, targeted therapies, and personalized treatment strategies may provide more precise and effective approaches for individuals experiencing implantation failure. Ultimately, enhancing our understanding of integrin biology not only contributes to the scientific foundation of reproductive medicine but also supports the broader goal of improving fertility outcomes and helping individuals and families achieve successful pregnancies.

References

1. Davidson LM, Coward K. Molecular mechanisms of membrane interaction at implantation. Birth Defects Res. C Embryo Today. 2016;108(1):19-32. https://doi.org/10.1002/bdrc.21122
2. Elnaggar A, Farag AH, Gaber ME, Hafeez MA, Ali MS, Atef AM. AlphaVBeta3 Integrin expression within uterine endometrium in unexplained infertility: a prospective cohort study. BMC Womens Health. 2017;17(1):90. https://doi.org/10.1186/s12905-017-0438-3
3. Reddy KV, Mangale SS. Integrin receptors: the dynamic modulators of endometrial function. Tissue and Cell. 2003;35(4):260-273. https://doi.org/10.1016/S0040-8166(03)00039-9
4. Kumar P, Philip CE, Eskandar K, Marron K, Harrity C. Effect of intravenous immunoglobulin therapy in recurrent implantation failure: A Systematic review and meta-analysis. J Reprod Immunol. 2024;166:104323. https://doi.org/10.1016/j.jri.2024.104323
5. Pan L, Zhao Y, Yuan Z, Qin G. Research advances on structure and biological functions of integrins. Springerplus. 2016;5(1):1094. https://doi.org/10.1186/s40064-016-2502-0
6. Niu G, Chen X. Why integrin as a primary target for imaging and therapy. Theranostics. 2011;1:30. https://doi.org/10.7150/THNO/V01P0030
7. Humphries MJ, Travis MA, Clark K, Mould AP. Mechanisms of integration of cells and extracellular matrices by integrins. Biochem Soc Trans. 2004;32(5):822-825. https://doi.org/10.1042/BST0320822
8. Kolasangiani R, Bidone TC, Schwartz MA. Integrin conformational dynamics and mechanotransduction. Cells. 2022;11(22):3584. https://doi.org/10.3390/cells11223584
9. Wolfenson H, Lavelin I, Geiger B. Dynamic regulation of the structure and functions of integrin adhesions. Dev Cell. 2013;24(5):447-458. https://doi.org/10.1016/j.devcel.2013.02.012
10. Hamidi H, Ivaska J. Every step of the way: integrins in cancer progression and metastasis. Nat Rev Cancer. 2018;18(9):533-548. https://doi.org/10.1038/s41568-018-0038-z
11. Massimiani M, Lacconi V, La Civita F, Ticconi C, Rago R, Campagnolo L. Molecular signaling regulating endometrium–blastocyst crosstalk. Int J Mol Sci. 2019;21(1):23. https://doi.org/10.3390/ijms21010023
12. Sehring J, Beltsos A, Jeelani R. Human implantation: The complex interplay between endometrial receptivity, inflammation, and the microbiome. Placenta. 2022;117:179-186. https://doi.org/10.1016/j.placenta.2021.12.015
13. Harris LK. Trophoblast-vascular cell interactions in early pregnancy: how to remodel a vessel. Placenta. 2010;31:S93-S98. https://doi.org/10.1016/j.placenta.2009.12.012
14. Xu HX, Liu SN, Xiang XY, Lei Y, Li YX, Tang XJ, et al. Repeated implantation failures and infertility in patients are strongly associated with elevated integrin B3 caused by endometrial copy number variation. Reproduction and Fertility. 2025;6(1). https://doi.org/10.1530/RAF-24-0088
15. Donaghay M, Lessey BA. Uterine receptivity: alterations associated with benign gynecological disease. InSeminars in reproductive medicine. © Thieme Medical Publishers. 2007;25(6):461-475. https://doi.org/10.1055/s-2007-991044
16. Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. Endocr Rev. 2014;35(6):851-905. https://doi.org/10.1210/er.2014-1045
17. Weimar CH, Macklon NS, Post Uiterweer ED, Brosens JJ, Gellersen B. The motile and invasive capacity of human endometrial stromal cells: implications for normal and impaired reproductive function. Hum Reprod Update. 2013;19(5):542-557. https://doi.org/10.1093/humupd/dmt025
18. Wang H, Dey SK. Roadmap to embryo implantation: clues from mouse models. Nat Rev Genet. 2006;7(3):185-199. https://doi.org/10.1038/nrg1808

https://doi.org/10.61577/jfrh.2025.100006