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REVIEW

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MicroRNAs, endometrial receptivity and molecular pathways

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Abstract

MicroRNAs (miRNAs) are a type of specific molecules that control the activities of the uterus, such as the process of cellular maturing and evolution. A lot of substances like growth factors, cytokines, and transcription factors play a role in embryo-endometrial interaction. MiRNAs could regulate various these factors by attaching to the 3' UTR of their mRNAs. Moreover, current research show that miRNAs participate in formation of blood vessels in endometrium (miR-206, miR-17-5p, miR-16-5p…), decidualization (miR-154, miR-181, miR-9…), epithelial-mesenchymal transition (miR-30a-3p), immune response (miR-888, miR-376a, miR-300…) embryo attachment (miR-145, miR-27a,451…) and pinopod formation (mir-223-3p, mir-449a, mir-200c). In this study, the focus is on the role of miRNAs in managing the uterus' receptivity to an embryo and its ability to facilitate attachment. More specifically, we are exploring the mechanisms by which miRNAs regulate the presence of specific molecules involved in this crucial physiological process.

Keywords MicroRNA, Endometrium, Uterus, Embryo research

Introduction

MiRNAs are short types of RNAs which do not code any proteins. They are consist of from 19 to 25 nucleotides that are retained in various organisms [1]. These molecules in addition to expression in tissues, are detectable in different biological fluids [2] .

The process of creating miRNAs involves the replication of specific genes by RNA polymerase II, resulting in the formation of a primary miRNA molecule known as Pri-miRNA [3]. Drosha, an RNase III enzyme located in the nucleus, functions by excising segments of the primiR in order to generate the precursor microRNA (pre-miRNA) [4]. Pre-miRNA is moved by exportin-5 to the cytoplasm. In the cytoplasm, it is changed by another molecule called Dicer to become double-strand miRNA [5]. The duplex structure of miRNA/miRNA* is transported to the RISC (RNA-induced silencing complex) in order to identify regulatory mRNAs, thereby facilitating their degradation or translation inhibition [6].

miRNAs control expression of genes after transcription by attaching to the 3' UTR of certain mRNAs [6]. Bioinformatics investigates show that miRNAs mainly control many specific mRNAs, and numerous miRNAs can target each mRNA [7].

miRNAs contribute in many genetic procedures for example aging, cell growth, changing into specialized

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cells, cell division, cell death, metabolism, and creation of blood vessels, stem cell maintenance, inflammatory, and immune responses [8]. Moreover, miRNAs have crucial role in controlling reproductive processes such as steroidogenesis, oogenesis, corpus luteum function, spermatogenesis, fertilization, early embryonic development, endometrial receptivity, implantation, and placentation [9–15].

So far, 29 miRNAs have been documented in humans and 15 in mice, located in different areas of the endometrium, that could potentially affect its receptivity. Both species share miRNAs that influence Wnt signalling and belong to the let-7, miR-23, miR-30, miR-200, and miR-183 families. Further research is needed to explore the use of these miRNAs as indicators or therapeutic targets for identifying and enhancing endometrial receptivity in fertility treatments for humans [16].

Aberrant expression of miRNA has been implicated in a multitude of conditions, including cancer, cardiovascular diseases, inflammatory conditions, as well as gynecological disorders such as infertility, abortion, endometriosis, and hypertension during pregnancy [17, 18]. The endometrium, generates and discharges multiple miRNAs. These molecules are associated with the uterus' capacity to receive and integrate an embryo, as well as the embryo's ability to adhere to the uterine wall [19]. This article delves into the significance of miRNAs in regulating the uterus' receptiveness towards an embryo and its role in promoting attachment. The specific focus is on understanding how miRNAs control the expression of certain molecules that play a vital role in this essential physiological process. This study involved conducting a comprehensive analysis of previously published research. As a result, all of the information was gathered directly from these original sources. The statistical significance of the data in each study was assessed using either Student's t-test or ANOVA, and was reported as a P value. Any P values that fell below 0.05 were deemed to be statistically significant.

Search strategies and data extraction

A comprehensive search was conducted in three databases, namely, PubMed, Scopus, and ScienceDirect, in order to identify literature pertaining to miRNAs and their role in endometrial receptivity. Numerous search terms were utilized, including variations of "endometrio," "microRNAs," "miRNA," and "miR-" which were searched as Mesh or Entree headings when applicable, or as free-text terms in the title, abstract, or topic fields. The search spanned from the beginning to the year 2024, and all languages were considered. After assessing all available full texts or abstracts (in case full texts were unavailable), data on the mechanisms and pathways by which miRNAs influence endometrial receptivity were extracted.

Embryo implantation

Successful gravidity is a complicated procedure that encompasses the embryo attaching to the uterus, the formation of the placenta, and giving birth [20]. Implantation is a very important stage in reproduction. The failure of embryo attaching to the uterus sets up approximately 75% of cases of infertility [20, 21]. For this process to be successful, it requires a suitable and responsive endometrium, a healthy and operational blastocyst, and a synchronized interaction between the embryonic and maternal tissues [22]. Implantation is a complicated and extremely controlled procedure that has three steps: apposition, adhesion, and invasion [23]. Different endocrine, paracrine, autocrine, and modulators participate in synchronization between the luminal epithelium of receptive endometrial and the blastocyst [24]. However, further elaboration is needed on how are the exact effects of these stages.

Microarray analysis demonstrated that the expression levels of 149 specific miRNAs were significantly altered in human endometrial cells following treatment with IFN-λ. Specifically, there was a notable decrease in miR-124-3p expression after IFN-λ treatment (with a p-value less than 0.05). In a mouse model of pregnancy, overexpression of miR-124-3p resulted in a decrease in embryo implantation rate and caused abnormal changes in the epithelial phenotype. Additionally, miR-124-3p negatively affected the migration and proliferation of endometrial cells, and impaired the developmental competence of embryos in terms of blastocyst formation and global DNA re-methylation. Subsequent analysis revealed that potential target genes for miR-124-3p included LIF, MUC1, and BCL2, which was confirmed through western blotting and immunofluorescence assays. In conclusion, the downregulation of miR-124-3p during embryo implantation, driven by IFN-λ, plays a role in modulating uterine receptivity [25].

Endometrial receptivity

The endometrium is a complex and ever-changing tissue that responds to hormones and experiences recurring transformations [26]. Endometrial sensitivity to blastocyst implantation has three steps: refractory, receptive, and pre-receptive [27]. During the pre-receptive stage, for implantation the endometrium is not an appropriate environment. Receptive endometrium can begin to implant when a viable blastocyst exists. In the refractory step, the blastocyst cannot implant into the endometrium [27].

The endometrium has the ability to accept blastocysts for a brief period of time in their monthly cycle, referred to as the implantation window (WOI) [28]. This period occurs while the mid-luteal stage of (20–24 days = 6–12 post fertilization days) normal menstrual cycle in women [10, 27] and, 3.5–4.5 post coitus days in mouse [27]. The receptivity of endometrium defect is a main reason (approximately 60%) of the unsuccessful implantations [29, 30]. The enhancement of knowledge regarding endometrial receptivity can not only aid in the assessment and treatment of infertility, but also offer potential for the creation of new methods of birth control that focus on the endometrium [31]. The endometrium's capacity to receive and support a pregnancy involves different kinds of changes, like chemical, physical, genetic, and molecular changes [32]. A vast molecular array has been proposed to participate in the initial involvement between the developing embryo and the mother's body, encompassing growth factors, cytokines, transcription factors, cell adhesion molecules, lipids, and hormones. Several molecular mediators that affect endometrial receptivity are listed in Table 1.

Many genes involve in endometrial maturation and embryo implantation [37]. Different studies on animal and humans models confirmed that miRNAs have significant function in physiology of endometrium by controlling gene expression (Figs. 1 and 2) [38–40]. Here we review association between miRNAs with IGF1, cytokines, HOX class homeobox, cell adhesion molecules, and pinopodes formation.

Table 1 Endometrial receptivity mediators

Molecular mediators	Examples	References
Growth factors	Heparin-binding EGF-like growth factor (HB-EGF) Epithelial growth factor (EGF) Insulin like growth factor$_1$ (IGF$_1$) family Vascular endothelial growth factor (VEGF) Transforming growth factor beta (TGF-β) family	[33, 34]
Cytokines	Leukemia inhibitory factor (LIF) IL-1 IL-6 IL-11 Colony stimulating factor-1 (Csf1)	[33, 34]
Transcription factors	HAXA9 HAXA10 HAXA11 Hmx3 FOXO1	[33, 34]
Adhesion molecules	Integrins Mucins Selectins Selectin-L ligands Cadherins β-catenin Osteopontin (OPN)	[33–35]
Lipids	PGE2 PGF2alpha	[33, 36]
Hormones	Estrogen Progesterone Calcitonin	[33, 37]
Other molecules	Cyclooxygenase2 (COX2) Stathmin1 Annexin A2 Matrix metalloproteases	[33, 34]

Insulin-like growth factor (IGF)

IGF group has two parts, IGF1 and IGF2, which have receptors called IGF1R and IGF2R. Insulin-like growth factor binding protein, also known as IGFBP1-6, comprises a total of six binding proteins [21]. IGFs exhibit a degree of structural similarity of approximately 50% to pro-insulin, thus bestowing upon them the designation of insulin-like growth. The complexity of the IGF system is notable and its functionalities extend across various physiological and pathological scenarios in a wide range of tissue types [21]. IGF family participate in endometrial development, differentiation, and formation of the endometrium, apoptosis, and receptivity [41]. Experimental findings have been obtained that substantiate the function of IGF1 in orchestrating the capability of blastocyst implantation in conjunction with the receptiveness of the endometrium [42]. IGF1 helps the biological functions through IGF1R [42]. During the early stage of pregnancy, a lot of IGF1R was seen in the lining of the uterus. This could help the fertilized egg stick to the uterus [43, 44]. IGF$_1$ regulates endothelial cell migration and promote angiogenic process in human endometrium by prompting expression of VEGF [45]. Bioinformatics studies reveals that the genes which are target of several miRNAs play a role in angiogenesis-related pathways. IGF$_1$ protein is direct target gen of miR-206 and this miRNA targets 3′-UTR of IGF$_1$ and inhibited protein expression [46]. This information proposes that the miR-206downregulation in endometrium can help the angiogenesis of endometrium while the implantation is happening [46].

Once the endometrium has developed to receptive stage and the embryo has developed to the blastocyst phase, the embryo will begin to cooperate with the uterine luminal epithelium [47]. After that a number of molecular and physiological procedures is activated, resulting in the creation of a steady maternal–conceptus connection [48]. The IGF1R receptor plays a crucial role in the receptivity of the endometrium. When it is elevated on the endometrial surface during the phase of receptivity, it may play a role in establishing connections with the embryo [38].

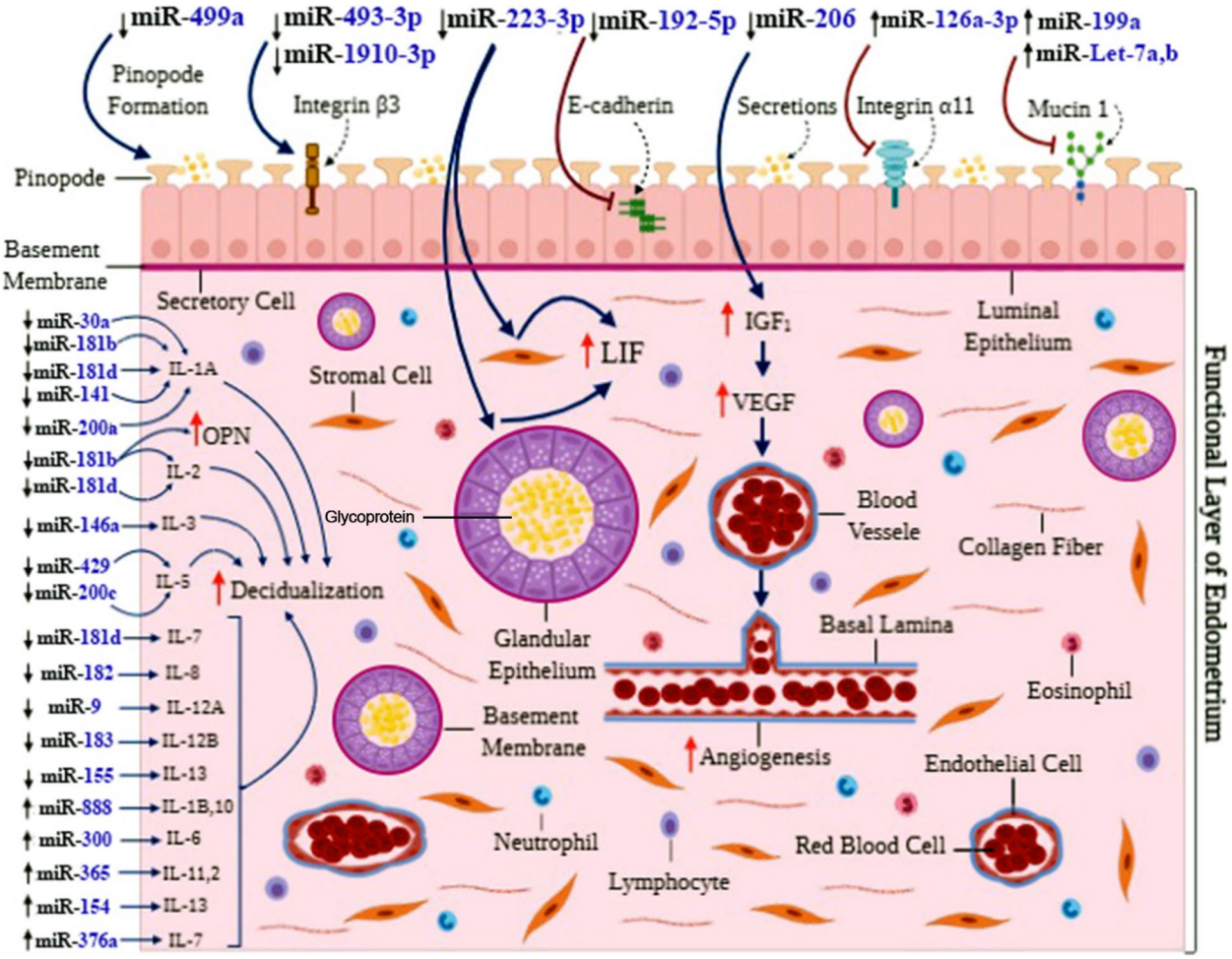

Fig. 1 Schematic illustration of miRNAs functions in improving the endometrial receptivity. MiRNA works as a regulator of gene expression and is actively involved in regulating embryo development, endometrial functions, and embryo-maternal communications. The verification of functional extracellular miRNAs brings new opportunities for improving implantation outcomes mainly from two aspects: first, intercellular communication through extracellular miRNAs provides a new dimension for understanding the mechanism of implantation; second, extracellular miRNAs have the potential for being effective biomarkers in IVF-ET for detection and prognosis of embryo quality and endometrium receptivity

Via a co-culture embryo attachment model, it was recommended that high expression of miR-145 decreases the steadiness of connections between embryo and epithelium by negatively regulating IGF1R which results in failure of implantation in vitro [49]. The researchers thoroughly evaluated the significance of miR-145 and its target, IGF1R, during the initial stages of implantation. They succeeded in increasing the levels of miR-145 and decreasing the expression of IGF1R in Ishikawa endometrial cells. Through quantitative PCR, western blotting, and 3'UTR luciferase reporter assays, it was confirmed that miR-145 directly targets IGF1R in the endometrium. To study the impact of altered miR-145 and/or IGF1R expression on early implantation events, the researchers conducted experiments involving the attachment of mouse embryos or IGF1-coated beads to endometrial epithelial cells. In both cases, the overexpression of miR-145 or specific reduction of IGF1R hindered the attachment process. However, by using an IGF1R target protector, the miR-145-induced decrease in IGF1R levels was prevented, and the negative effect of miR-145 overexpression on attachment was reversed. In the endometrium of individuals with RIF, stimulation of mir-145 happens [49]. Another research presented that up-regulation of miR-140 fallowing to use ormeloxifen (the non-steroidal SERM contraceptive) reduces IGF_1R in stromal cells and endometrial epithelial [50]. The use of miRNA sequencing analysis identified 168 different miRNAs that were expressed differently in uterine tissue of rats treated with ormeloxifene on day 5 (10:00 h) of pregnancy, also

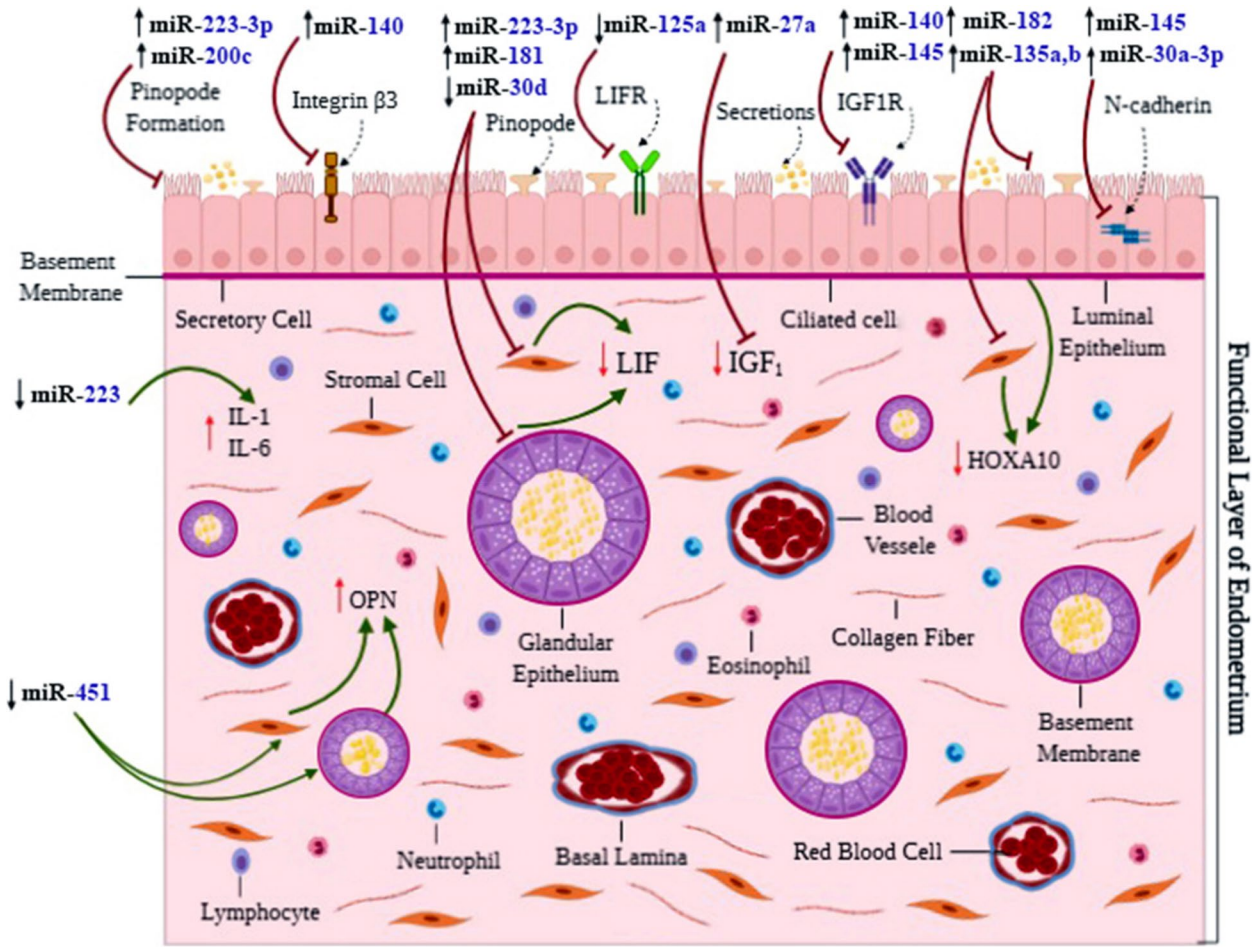

Fig. 2 Schematic illustration of miRNAs functions in reducing the endometrial receptivity. The aberrant expression of endometriumor embryo-derived miRNAs can cause early pregnancy and gestational disorders, including repeated implantation failure, recurrent miscarriage, and pathological conditions such as endometriosis

known as the peri-implantation period. Of these miRNAs, increased levels of miR-140 were observed in the ormeloxifene-treated groups, leading to further examination of its role. Manipulating the levels of miR-140 in vivo showed a considerable decrease in implantation sites, indicating its involvement in embryo implantation. Additional research using a delayed implantation model revealed that estradiol down-regulated miR-140 and inhibited the attachment and outgrowth of BeWo spheroids to RL95-2 endometrial cells. Furthermore, experiments using transwell migration assays demonstrated that miR-140 was responsible for suppressing the migration and invasion of endometrial epithelial cells. Treatment with ormeloxifene caused an increase in miR-140 expression and a decrease in its target, IGF1R, in endometrial epithelial and stromal cells. This resulted in the suppression of downstream effectors integrin β3 and FAK. In groups that received a mimic of miR-140, a reduction in IGF1R expression and suppression of downstream integrin β3 and FAK were observed, similar to what was seen in uterine tissue of ormeloxifene-treated rats. These results led to reduce the embryo attachment and implantation in rat endometrium [50]. miR-27a targets IGF1, and its upregulation has an inverse influence on IGF1 expression and impaired endometrial receptivity in woman with endometriosis [51]. Through the use of miRNA sequencing analysis, researchers discovered that the uterine tissue of ormeloxifene-treated rats during the peri-implantation period (day 5 at 10:00 am) exhibited differential expression of 168 miRNAs. In order to further investigate this finding, a group of 15 women with CE and 15 healthy women were studied using RT-qPCR single assays targeting specific miRNAs that affect the expression of IL11, CCL4, IGF1, and IGFBP1 in the endometrium. Additionally, the expression of IGF1 and IL11, which are targeted by the deregulated miRNAs, was analyzed in the same endometrium samples. Further validation of these miRNAs as potential biomarkers was

achieved through their expression profiles in the serum of the same patients and subsequent statistical analysis. The miRNAs related to IGF family regulation are listed in Table 2.

Cytokines

The implantation process has been described as a provocative reaction and cytokines have a significant impact in this process [53]. Cytokines are a group of proteins that work together to assist in the connection and bonding between the embryo and the luminal epithelium, oversee proper immune response, and support the growth of the placenta [53, 54]. It has been emphasized that several cytokines, such as IL-6, IL-1, and LIF, play an essential role in creating the ideal communication between the endometrium and the embryo [55, 56].

IL-1

IL-1 is a very important signal that is able to change how embryos and endometrium reaction which leads to the next surge of cytokines [53] .In endometrium, IL-1 produced in the epithelium and stromal cells [41, 53]. Studies have shown that there is a remarkable increase in IL-1 expression during the implantation window [57].

IL-6

The IL-6 group encompasses the cytokines IL-6 and LIF, which are widely recognized for their role in embryonic development. IL-6, with its multifaceted functions, plays a significant part in the body's immediate response to inflammation [58]. Besides of its function in immune system, IL-6 plays a role in procedures associated to reproductive capability [59]. This particular cytokine is synthesized by various cells, encompassing placental trophoblasts, macrophages, epithelial cells, and fibroblasts [60]. IL-6, a pro-inflammatory cytokine, is predominantly synthesized by the stromal cells and epithelium of endometrium in the context of implantation [61].

It is made in the lining of the uterus and its amounts are highest throughout the middle of the menstrual cycle, when the uterus is ready for a fertilized egg, and during menstruation [62]. The endometrium undergoes alterations in its expression as a result of hormonal stimuli. Specifically, an increase has been noted in the middle to end phase of the secretory process, which is followed by a gradual decrease in the subsequent late phase of secretion [53]. IL-6 is generated in the developing tissues of the fetus as well as within the reproductive system of females.

Throughout the menstrual cycle, the endometrial glandular and luminal epithelial cells secrete IL-6, with higher levels released during the mid-secretory phase and early pregnancy. This cytokine acts through the activation of gp130 and its specific receptor IL-6R, similar to LIF. The signaling pathways of IL-6 involve STAT3 and MAPKs. Its receptors are present in both human endometrium and trophoblast cells, highlighting its importance in implantation and communication between the embryo and mother [63]. This cytokine plays a vital role in facilitating the implantation of the embryo and promoting the growth of the placenta, and it is also critical for maintaining pregnancy [62]. The production of IL-6 during the implantation process within the endometrium and blastocyst draws attention to the role of IL-6 in the period before implantation [64].

Research has demonstrated that the presence of elevated levels of inflammatory components among people with metabolic syndrome is widely recognized as a contributing factor to the occurrence of recurrent implantation failure (RIF). Serum level of IL-1β and IL-6 were increased and miR-223 expression was downregulated meaningfully in PBMCs (Peripheral blood mononuclear cell) of RIF-MS individuals [65].These outcomes indicate that reduction of miR-223 may cause of IL-6 and IL-1β overexpression and implantation failure [65].

Decidualization refers to the process by which endometrial stromal fibroblasts undergo a significant transformation, both in terms of morphology and biochemistry, resulting in their differentiation into decidual cells. This procedure is absolutely critical for achieving a successful implantation of the embryo and ultimately establishing a pregnancy. In the context of decidualized human embryonic stem cells (hESCs), a comprehensive analysis revealed that a total of 26 microRNAs were observed to be upregulated, while 17 microRNAs It was noted that they showed a significant decrease in expression levels comparing to non-decidualized hESCs. This observation was made during the isolation of endometrial stromal

Table 2 miRNAs related to IGF family regulation

miRNAs	Sample	Specie	Target	Function	References
miR-206 Downregulation	Endometrium	Pig	⬆ IGF_1	⬆ Angiogenesis	[46]
miR-145 Upregulation	Endometrium	Human	⬇ IGF_1 R	⬇ Embryo attachment	[49]
miR-140 Upregulation	Endometrium	Rat	⬇ IGF_1 R	⬇ Embryo attachment	[50]
miR-27a Upregulation	Endometrium	Human	⬇ IGF_1	⬇ Endometrial receptivity	[52]

cells, followed by their culture and subsequent in vitro decidualization [66].

Leukemia inhibitory factor

Leukemia inhibitory factor (LIF) is a multifunctional cytokine belonging to the IL6 group, which exerts its effects via the LIF cell-surface receptor (LIFR) and stimulates various biological processes through various signaling pathways [67, 68]. LIF is mainly found in the cells of the uterus and has a pattern of being released during the menstrual cycle. It is lowest before ovulation, increases after ovulation, and stays high during the middle of the cycle [69]. LIF has a critical role in successful implantation by aiding trophoblast invasion, affects immune tolerance, and embryo survival [67, 70, 71]. Research has demonstrated that pinopodes release payloads containing LIF within the uterine lumen, and the development of pinopodes is connected to the presence of LIFR in women who are able to conceive [72, 73]. Also, This molecule is majorly generated within the tissue lining the embryo in healthy people, but its levels are reduced in individuals who experience continuous struggles with implantation [74]. Online sequence alignment (http://www.targetscan.org/) revealed that miR-223-3p regulate LIF expression (http://www.targetscan.org/) and a study showed that miR-223-3p upregulation diminished the LIF expression and implantation in mice [72].

Studies have confirmed that maintaining a low but essential level of miR-181 expression in the endometrium is necessary for the successful attachment of the embryo. The production of miR-181 through both temporary and long-lasting genetic modification resulted in hindered implantation. The underlying mechanism involves miR-181 directly targeting LIF and suppressing its expression, thus, impeding the process of implantation of embryo. In order to obtain mouse endometrial epithelium cells, the uterus of a 4-day pregnant mouse was cut into 1–2 mm pieces lengthwise and then treated with collagenase for enzymatic digestion. In an effort to discover novel miRNA molecules involved in the process of embryo implantation, researchers conducted a microarray analysis and utilized real-time PCR to compare miRNA expression in the uterus of non-pregnant mice and 4-day pregnant mice. To investigate whether miR-181a and miR-181b directly targeted and decreased the levels of LIF in cells, the 3'-untranslated region (3'UTR) of the LIF mRNA was examined and found to contain a site (nucleotides UGAAUGU) that could be recognized by these miRNAs. To uncover the factors influencing the regulation of miR-181a/b during early pregnancy, the genomic sequence upstream of the genes encoding miR-181a1/b1 and miR-181a2/b2 was analyzed using the genomatix suite of sequence analysis tools. These results reveal a previously unknown function of miR-181 in the process of embryo implantation by controlling LIF, and indicate a potential link between aberrant miR-181 expression and issues with human embryo attachment [75].

The findings of a study examining the influence of calcitonin on the receptiveness of the endometrium revealed that administering calcitonin after stimulating the ovaries resulted in a considerable increase in the expression of LIF by inhibiting miR-223-3p in the endometrium of mice. 64 female BALB/c mice were divided into two main groups: one consisting of mice with a normal ovarian cycle and the other consisting of mice with a stimulated ovarian cycle. Within each group, there were four subgroups: control (Ctrl), calcitonin (CT), pp242, and CT + pp242. The mice received injections of calcitonin and pp242 on days 3, 4, and 5 of their pregnancy. On day 5 of gestation, all of the mice were euthanized and their uterine tissue was collected for analysis of morphology, gene expression, and protein levels. As a result, calcitonin has the potential to improve the ability of the endometrium to respond during the process of ovarian stimulation [76]. Dexamethasone has been shown to be utilized as an immunosuppressant in the management of certain heath conditions, as well as in individuals experiencing supported reproductive methods [77]. At the time of implantation, the administration of Dexamethasone leads to a decrease in receptivity of uterine. The cause of this decline can be attributed to an upsurge in the levels of miRNA223-3p and a decline in the levels of LIF [78].

Numerous research efforts reveal a strong correlation between variations in genetic sequence, known as single-nucleotide polymorphisms (SNPs), and recurrent miscarriages. It has been suggested that differences in pre-miR-125a can play a role in the genetic tendency to recurrent pregnancy loss by affecting the production of miR-125a and how its target genes like LIFR are expressed and function. They established the connection by confirming significant variations in the distribution of the genetic markers rs41275794 ($P = 0.0005$) and rs12976445 ($P = 0.001$) within the pri-miR-125a among 217 Han Chinese patients with RPL compared to 431 control participants. Based on this finding, they constructed two-locus haplotypes and discovered that the A-T haplotype was linked with a higher likelihood of developing RPL (OR = 2.84, 95% Confidence Interval 1.98–4.07, $P = 0.0000000057$). Further analysis revealed that the levels of both pre-miR-125a and mature miR-125a were decreased in cells transfected with the A-T haplotype, consistent with their in vivo observations of lower mature miR-125a levels in 30 pregnant women with the A-T haplotype compared to those with the G-C haplotype. Through in vitro RNA processing experiments, the researchers also observed a decrease in the

amount of pre-miR-125a and a decline in the binding capacity of nuclear factors to pri-miR-125a with the A-T haplotype. Most significantly, the reduction in miR-125a caused by the A-T haplotype led to a less effective inhibition of target genes, LIFR and ERBB2, which are crucial for embryo implantation and decidualization [79]. An in vivo study showed that miR-30d presence found to be correlated with hurts the early stages of pregnancy and the growth of the baby by reducing the levels of LIF [80].

An analysis of the levels of miRNA in the endometrium during menstruation and the decidua during initial pregnancy stages revealed a decrease in several miRNAs, including miR-146b-5p, miR-532, miR-424, miR-181b-5p, and miR-199a-3p, as well as LIF and IL6, when compared to the levels in the decidua. Conversely, there was an increase in miR-1, miR-423, let-7i-5p, and miR-22-3p in the decidua. The technique of quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was utilized to measure the levels of expression of a set of specific microRNAs, namely miR-146b-5p, miR-181b-5p, miR-424, miR-532, miR-199a-3p, miR-423, miR-22-3p, let-7i-5p, and miR-1, as well as the predicted target genes IGF2R, LEPR, SGK1, MMP2, MMP10, LIF, IL6, and STAT3 in both menstrual endometria and the decidua during early pregnancy. These findings offer novel visions into the production patterns of miRNAs that play a role in the controlling the genes that function in decidualization and the maintaining pregnancy in first steps [81]. The miRNAs related to cytokines regulation are listed in Table 3.

HOX class homeobox

HOX category homeobox genes are top choices for controlling how the endometrium changes to get ready for a fertilized embryo to attach [82]. A few HOX genes including HOXA9, HOXD10HOXA10, HOXA11, HOXC11, HOXC10, and HOXD11 expressed cyclically in endometrium during the menstrual stage under the impact of steroid hormones [83–85]. HOXA9, HOXA10, and HOXA11 increased expression during the mid-secretory phase of the menstrual cycle and participate in endometrial receptivity [83] .

During the period of cell growth, the proliferative phase, HOXC10, HOXD11, HOXC11, and HOXD10 exhibit significant levels of expression, but their levels decrease in the secretory phase [84].

Table 3 miRNAs related to cytokines expression

miRNAs	Sample	Specie	Target	Function	References
miR-223 Downregulation	Plasma and serum	Human	⬆ IL-1 ⬆ IL-6	⬇ Embryo implantation	[65]
miR-30a, miR-181b, miR-181d miR-141, miR-200a Downregulation	Endometrium	Human	IL-1 A	⬆ Decidualization	[66]
miR-181b, miR-181d Downregulation	Endometrium	Human	IL-2		
miR-146a Downregulation	Endometrium	Human	IL-3		
miR-429, miR-200c Downregulation	Endometrium	Human	IL-5		
miR-181d Downregulation	Endometrium	Human	IL-7		
miR-182 Downregulation	Endometrium	Human	IL-8		
miR-9 Downregulation	Endometrium	Human	IL-12 A		
miR-183 Downregulation	Endometrium	Human	IL-12B		
miR-155 Downregulation	Endometrium	Human	IL-13		
miR-888 upregulation	Endometrium	Human	IL-1B		
miR-154 upregulation	Endometrium	Human	IL-2		
miR-365, miR-371-5p, miR-369-3p upregulation	Endometrium	Human	IL-6		
miR-376a upregulation	Endometrium	Human	IL-7		
miR-888 upregulation	Endometrium	Human	IL-10		
miR-154 upregulation	Endometrium	Human	IL-11		
miR-300 upregulation	Endometrium	Human	IL-13		
miR-223-3p Upregulation	Endometrium	Mouse	⬇ LIF	⬇ Embryo implantation	[72, 78]
miR-181 Upregulation	Endometrium	Mouse	⬇ LIF	⬇ Embryo implantation	[75]
miR-223-3p Downregulation	Endometrium	Mouse	⬆ LIF	⬆ Endometrial receptivity	[76]
miR-30d Downregulation	Endometrium	Mouse	⬇ LIF	⬇ Endometrial receptivity	[80]
miR-125a Downregulation	Blood	Human	⬇ LIFR	⬇ Endometrial receptivity	[79]

HOXA10 has been identified as a molecular indicator of endometrial readiness for having an embaryo, displaying diverse impacts on various elements of mature endometrial progression [86]. HOXA10 has the ability to affect the expression of factors related to the readiness of the endometrium, such as the production of integrins, pinopodes, the estrogen receptor, prostaglandin receptors, and insulin growth factor binding protein 1 (IGFBP-1) [87, 88].This transcription factor regulate the endometrial proliferation, differentiation, leukocyte infiltration, decidualization, and pinopode development [86, 89]. Multiple investigations have consistently shown that interfering with the expression of the HOXA10 gene targets results in disruption of the procedure for endometrial receptivity [88]. HAXA9 and HOXA11 also involve in the endometrial receptivity and loss of them leads to discordant implantation [83].

HOXA10 gene has a vital function in the expansion of pinopodes [32]. It was described that HOXA10 downregulation leads to fewer pinopodes and more HOXA10, which causes more pinopodes to form [90]. The potential association between miRNAs and the HOXA10 gene is thought to have a considerable impact on the formation of pinopodes. Research suggests that HOXA10 is targeted by a number of miRNAs, including miR-16, miR-494, miR-29b, miR-320a, miR-29c, miR-218, miR-204, miR-182, miR-16, miR-27a, and miR-705. For instance, the upregulation of miR-29b, miR-494, miR-204, miR-320a, miR-27a, miR-218, miR-182, and miR-705 leads to a decrease in HOXA10 expression [32, 91, 92].

The use of miR-182 simulations has shown a reduction in HOXA10 levels in gEECs. Inhibiting the HOXA10 gene caused gEECs to undergo programmed cell death and a decrease in estrogen receptor a (ERa), IGF1R, VEGF, OPN, PRLR prolactin receptor (PRLR), cyclooxygenase-2 COX-2, and PRb progesterone receptor B (PRb) in vitro. This research validated that the expression of HOXA10 was controlled by miR-182 through binding to its 3'UTR, which selectively decreased HOXA10 levels in goat endometrial epithelium cells (gEECs) but not in stromal cells (gESCs) in laboratory conditions. However, at gestational day 15 (D15) compared to gestational day 5 (D5), both HOXA10 and miR-182 were upregulated in the goat endometrium, indicating the presence of additional factors that regulate HOXA10 expression during the development of goat endometrium in vivo. Interestingly, silencing HOXA10 gene (using HOXA10-siRNA) led to apoptosis in gEECs in vitro, and had an impact on the protein levels of important molecules such as estrogen receptor a (ERa), progesterone receptor B (PRb), insulin-like growth factor 1 receptor (IGF1R), BCL-2, pleiotrophin (PTN), AKT and p-JNK in gEECs. Moreover, HOXA10 might also be involved in controlling the protein levels of endometrial receptivity markers, including vascular endothelial growth factor (VEGF), osteopontin (OPN), cyclooxygenase-2 (COX-2) and prolactin receptor (PRLR) in gEECs. These findings suggest that increasing miR-182 repairs endometrial receptivity by targeting the HOXA10 gene [91].

Studying miRNA has given us a novel way to find out why some women who have trouble getting pregnant may keep having problems with embryo implantation [39]. The examination of miRNA levels in the endometrium of females with infertility has exposed that the heightened expression of miRNA-135b may have adverse effects on the ability of the endometrium to receive and support a fertilized egg. The harmful impact is thought to result from the inhibition of crucial genes necessary for a successful implantation process, such as HOXA-10 [39]. Endometriosis is a condition in which the endometrial lining of the uterus expands and develops outside of its usual location within the uterus [93]. Increased miR135a or miR135b downregulated HOXA10 and reduce endometrial receptivity in women with endometriosis [85]. The miRNAs related to HOXA10 regulation are listed in Table 4.

Cell adhesion molecules

The group of cell adhesion molecules (CAM) is composed of four separate categories, which are selectins, integrins, cadherins, and immunoglobulins. The surface ligands within this family serve various essential roles including the facilitation of wound healing, preservation of tissue integration, promotion of morphogenic movements, facilitation of tumor metastasis, and facilitation of cell migration [94]. The luminal epithelium is important for the mother and embryo to connect and for the uterus to be ready for the embryo [95]. Endometrial epithelial

Table 4 miRNAs related to HOXA10 expression

miRNAs	Sample	Specie	Target	Function	References
miR-182 Upregulation	Endometrium	Goat	⬇ HOXA10	⬇ Endometrial receptivity	[91]
miR- 135b Upregulation	Endometrium	Human	⬇ HOXA10	⬇ Endometrial receptivity	[39]
miR-135a Upregulation miR-135b Upregulation	Endometrium	Human	⬇ HOXA10	⬇ Endometrial receptivity	[85]

cells that are not open to receiving signals show polarized features like other usual cells, with clear top and bottom sections. Cells are connected together with different kinds of junctions and make a flat layer [96]. The microvilli covering the top part of non-receptive EECs lack adhesive possessions [97]. These characteristics of epithelium create a blockade that prevents blastocysts from sticking and entering the tissue [97].

However, when the cells are receiving signals, they lose their shape and stickiness to each other decreases. Also, the cells undergo a transformation from their initial tall and rectangular form to a more square-like shape, resulting in a decrease in the number of microvilli present. This decrease in microvilli then leads to the fusing together and formation of the top of the remaining microvilli [98, 99]. Aggressive trophoblasts produce CAMs on their apical part, which cooperate with ligands produced by the decidua ECM to regulate binding and attack [94].

Cadherins

Cadherins are proteins that play a vital role in cell adhesion and require calcium as a key component for their function. E-cadherin, a specific type of cadherin found in various regions of the body, plays a crucial role prior to the implantation process [100].

$Arhgap_{19}$, a part of the RhoGAP group, involves in controlling the structure of epithelium [101]. It is found in the side membrane and helps cells stick together in epithelial cells that are polarized [102]. Arhgap19 is able to induce structural modifications in EECs by managing the remodeling of junctional complexes and the cytoskeleton of the membrane [103]. It was reported that $Arhgap_{19}$ is a direct target of miR-192-5p, and increasing of miR-192-5p improved $Arhgap_{19}$ expression in receptive endometrium. The levels of ARHGAP19 were assessed in mouse uteri during early pregnancy and in human EEC lines. To better understand its function, the expression of ARHGAP19 was altered in EECs. The influence of ARHGAP19 on junctional proteins in EECs was analyzed through western blotting and immunofluorescence. The impact of ARHGAP19 on microvilli was observed using scanning electron microscopy. Through online databases, the potential upstream miRNA was predicted and later verified through a dual-luciferase assay. To further investigate its effects, both in vivo and in vitro experiments were conducted by injecting miRNA agomirs into the uterus and transfecting EECs with miRNA mimics or inhibitors, respectively, to observe the effects on endogenous ARHGAP19. Then of $Arhgap_{19}$ more expression significantly decreased production of E-cadherin in EECs and improved endometrial receptivity [103].

Defects in attachment of blastocyst to the endometrium result in failure of embryo attaching to the uterus wall and not being able to have a baby [55]. During the period of implantation, people who experience repeated implantation failure (RIF) in in vitro fertilization (IVF) demonstrate a unique genetic profile expression in the lining of the uterus (Revel et al., 2011).Comparison of endometrium between normal women and RIF-IVF shows that, overexpression of miR-45 reduces N-cadherin mRNA in RIF-IVF patients during the secretory phase. In order to compare the secretory endometrium of RIF-IVF patients with fertile women, they employed TaqMan miRNA array cards to detect differentially expressed miRNAs. They then utilized bioinformatics techniques to determine the potential targets of these miRNAs and the molecular pathways that may be impacted by them [104].

Epithelial-mesenchymal transition (EMT) is a process that lets cells to change from one type to another and become more mobile and aggressive [105, 106]. The key features of EMT consist of decreased adhesion between cells, attainment of mesenchymal factors like N-cadherin and Vimentin, and lack of epithelial factor like E-cadherin [107]. This machinery helps blastocysts stick to the lining of the uterus quickly. and improves embryo implantation [108].Experiments carried out on both cells and mice have proven that the administration of agomir and mimics, which facilitate the transfer of miR-30a-3p, to human endothelial cells (HECs) resulted in a reduction of N-cadherin expression and implantation rate of embryo. The researchers established various mouse models, including normal pregnancy, pseudopregnancy, delayed implantation, and artificial decidualization, in order to study the role of miR-30a-3p in embryo implantation. Through real-time reverse transcription PCR (qRT-PCR), they analyzed the expression of miR-30a-3p in these models and identified potential target genes using a dual-luciferase assay. Furthermore, they confirmed the co-location of miR-30a-3p and its target genes through immunofluorescence-fluorescence in situ hybridization. The team also investigated the impact of miR-30a-3p on embryo implantation both in vivo and in vitro. They utilized wound healing and transwell assays to examine the potential effects of miR-30a-3p on epithelial-mesenchymal transition (EMT) and used qRT-PCR to analyze molecules involved in this process [109]. Another research presented that upregulation of miR-429 in mice endometrium led to a major decrease of the amount of implantation by suppression of Pcdh8 (member of cadherin gene family) and Cdh2 (EMT marker) during implantation period. The expression pattern of miR-429 was thoroughly investigated across several models, and its target gene was verified. The impact of miR-429 on embryo implantation was assessed both in vivo and in vitro. In order to achieve pregnancy, female C57BL6/J mice were naturally bred with male mice, and a range of models

were established, including pseudopregnancy, delayed implantation, and artificial decidualization. Through these models, the expression pattern of miR-429 during the embryo implantation period was elucidated. Using bioinformatic analysis, potential target genes of miR-429 were identified and then confirmed through luciferase activity assays. Additionally, the effects of miR-429 on embryo implantation were investigated in vivo. The in vitro effects of miR-429 on EMT were also evaluated by analyzing migratory and invasive abilities through transwell assays, and assessing the expression levels of cadherin family members using western blotting and qRT-PCR [110].

Integrins

A group of transmembrane proteins are Integrins that as a heterodimeric adhesion molecules regulate different biological process such as cell - matrix interactions, intracellular signaling, inflammatory responses, immunoresponses, angiogenesis, cellular proliferation, adhesion, migration, phagocytosis, and tumorigenesis [67, 111, 112].

The αβ integrin subunits are protein structures that span across the cell membrane. These subunits consist of a large and complex extracellular portion, a transmembrane helix, and a brief cytoplasmic tail. The main role of the extracellular region is to interact with extracellular matrix (ECM) ligands, and in the α subunit, it is made up of approximately 1104 residues (with a range of 700–1100), while the β subunit has 778 residues. The cytoplasmic tail, on the other hand, is shorter and usually made up of 30–50 amino acids. It is responsible for mediating interactions with proteins involved in the cytoskeleton and signaling pathways within the cell. The activation of integrins is triggered by internal or external stimuli, which can occur through ligand binding or modifications in the cytoplasmic domains. This activation leads to the elongation and separation of the integrin "legs." Normally, integrins exist in a "closed" or bent conformation on inactive cells, which results in a lower affinity for ligand binding and less efficient signaling. However, upon activation, the integrins shift into an open conformation, allowing for a stronger affinity with ligands and increased potential for signaling. In the closed conformation, the bent shape of the α and β subunits keeps the ligand-binding site approximately 5 nm away from the cell surface. However, in the open conformation, the two subunits straighten, resulting in a closer proximity to the bound ligand. When extracellular ligands initially bind to integrins, they cause the cytoplasmic domains to separate, enabling interaction with signaling molecules and the cytoskeleton during "outside-in" signaling. In contrast, talin and other activators work to separate the cytoplasmic domains and activate the head, making it possible for ligand binding during "inside-out" signaling [113].

18 α and 8 β subunits can be combined to form 24 αβ integrin complexes, which are a organizationally and functionally varied group of adhesion molecules [114]. Various cellular molecules including glycoproteins, carbohydrate ligands, and receptors are important for way an embryo attaches to the uterus wall, and having too many or too few of them might be connected to not being able to have a baby for no clear reason [32, 115]. Several integrins with varying capacities in successful implantation are biomarkers of fertility [32, 116]. As the embryo attaches, it is possible to detect the presence of αvβ5, α5β1, αvβ6, and αvβ3 integrins in the developing embryo. Following this, α6β1, α7β1, and α1β1 integrins are subsequently important in invasion [117]. Osteopontin, a substance from cells in the body, helps stick to integrin αvβ3 on the surface that is related to the mother's body. This helps with sticking to each other [118]. The integrins display dynamic behavior, as the α5β1 integrin takes on its role in the development of the inner cell mass during the early stages of embryo formation. It then moves to the trophoblast cells, which invade the endometrium during the process of implantation [119].

Some cell proteins, like α1β1, αvβ5, α3β1, αvβ1, α4β1, αvβ3, α4β3, and α6β1, upsurge when the baby attaches to the uterus. They each do diverse things to help with early pregnancy. Integrin α3β1 and α6β1 bind to galectin-8 and mediate interaction between cells [120]. The levels of αv, α5, α7, and β3 integrin subunits in the myometrium during pregnancy are higher, and these subunits all align with the proteins in the IAC during labor. This indicates that the combination of α3β1, α5β1, and α7β1 integrins may play a role in the myometrium at term [121]. Integrin α4β3 and α4β1 play a vital role in aiding the blastocyst's attachment, whereas integrin α4β1 also plays a role in facilitating decidualization [122]. Galectin-8 is a protein that belongs to the galectin family and is present in most cells. It consists of two similar parts, known as carbohydrate recognition domains (CRDs), that are connected by a short peptide made of around 26 amino acids. Once it is released from the cell, galectin-8 attaches to specific glycoproteins on the surface of cells, namely integrins α3β1 and α6β1, but not α4β1. This interaction between galectin-8 and integrins is believed to be responsible for its ability to hinder the adhesion of cells [123, 124].

Numerous studies have demonstrated the crucial role of a specific protein, known as integrin αvβ3, in the decidualization process. This protein appears to serve as a critical receptor for embryo attachment to

the uterus, thus facilitating the initial step of adhering to the uterine lining [125].

Throughout the implantation window, the integrin αvβ1 exerts a restraining effect on invasion, with its highest level of activity. This integrin serves as a receptor for collagen and fibronectin and interrelates with the basal membrane rich in laminin. Additionally, this protein makes a signal for cell endurance and facilitates embryonic connection. Integrin αvβ5, on the other hand, participates in the primary connections between cells, attaching to vitronectin, fibronectin, and fibrinogen, thus contributing to invasion of the trophoblast [117]. Throughout the time when an embryo attaches to the uterus, αvβ3 is usually higher in level. But in women with endometriosis, this protein has been seen to be lower or not there at all [126]. Although numerous integrin are now recognized to be controlled by miRNAs [127, 128].

It has been noted that there is a higher presence of miR-126a-3p in the areas where the mouse embryo implants itself in the mouse. Through the use of bioinformatics, it was discovered that miR-126a-3p targets the gene Itga11. ITGA11, also known as Integrin alpha 11, is a specific subunit of integrin that plays a crucial role in tissue fibrosis in the liver, lungs, and kidneys by specifically binding to type I collagen. In fibrotic diseases, it has shown great potential as a target due to its selective overexpression in myofibroblasts and ability to control their differentiation and important characteristics [129]. To confirm this, a luciferase activity test was conducted, which revealed that this specific miRNA binds to the 3' untranslated region of Itga11, hindering the translation of mRNA. As a result, when miR-126a-3p was upregulated, it led to a decrease in Itga11 expression in the endometrium, ultimately resulting in an increase in embryo implantation [130].

In a study that examined the mechanism of ormeloxifene, the non-steroidal contraceptive ormeloxifene was found to prevent the endometrium from being ready for pregnancy and to stop the embryo from attaching. This happens because ormeloxifene treatment increases the levels of miR-140 and integrin β3 in the lining of the uterus in rats. In a mimic of miR-140, there was less integrin ß3 being produced. All of this information recommends that ormeloxifene stops embryos from attaching by causing miR-140 to increase and suppressing integrin ß3 in rat uterus [50].

It has shown that metformin affects the coat of the uterus in women with PCOS by decreasing miR-491-3p and miR-1910-3p molecules and stimulating the Itg β3 production [131].

Osteopontin

Osteopontin (OPN) belongs to the extracellular matrix group [132]. This glycoprotein is involved in many normal and illness-related procedures in the body. It helps cells stick together, communicate with their environment, grow, change into different cell types, form new blood vessels, and spread to other parts of the body by binding to receptors on the cell surface [132, 133].

OPN is expressed in the endometrial glandular epithelium and stromal cells [134, 135]. OPN attaches to integrins receptors of cells, CD44 to anchor cells to the ECM and IGF_1R, FGFR, and EGFR for regulating mechanisms in the cellular [136]. Some scientists propose that OPN is made in the glands and then released into the uterus, where it attaches to the surface of the uterus [137]. Microarray screening test found that OPN is more active in the lining of the uterus during begging to middle of secretory stage [138]. According to reports, the level of OPN expression in stromal cells increases following the secretory phase, coinciding with the transformation of perivascular stromal cells [139]. OPN is stimulated in vivo and human endometrium by progesterone (P4) [140, 141]. Based on findings, osteopontin serves as an indicator of the readiness of the endometrium for implantation and plays a crucial role in promoting successful implantation and fertility [142, 143].

The protein Osteopontin, also known as early T-lymphocyte activation 1 protein, is produced by the SPP1 gene and belongs to the SIBLING family. It is a glycosylated phosphoprotein that is found in various tissues and is involved in a range of biological processes such as vascularization, cell growth, calcification, and immune and neurologic disorders. This glycoprotein is created by different types of cells like osteoclasts, osteoblasts, epithelial, endothelial, neuronal, and immune cells (T cells, NK cells, macrophages, and Kupffer cells) and is continuously expressed in multiple tissues (kidney, breast, brain, skin, bone, bone marrow, and bladder) and biological fluids like plasma, urine, milk, and bile. Most of its functions at the cellular level are a result of its extracellular activities after it is secreted, binding to receptors and causing specific signaling pathways to activate. These receptors include αv (β1, β3, or β5) and (α4, α5, α8, or α9) β1-integrins, variants 6 and 7 of CD44, a receptor for hyaluronan, and the epidermal growth factor receptor (EGFR) [144].

OPN plays noteworthy functions in implantation through many pathways.1- OPN of endometrial epithelial cells (component of histotroph) attaches to the receptor ITG avb3 at the endometrial part to help attaching and signal transduction at the crossing point of mother and embryo [118, 137, 142]. 2- The process of decidualization involves the production of this glycoprotein by

endometrial stromal cells, triggered by the invasion of the blastocyst. Therefore, the glycoprotein plays a crucial role in this process [145]. 3- As a component of the immune cells present within the endometrium, Mucin-1 serves as a regulator of the behavior of immune cells and the production of cytokines [146].

It was demonstrated that the OPN production was increased in endometrial cells during the part of the cycle when implantation occurs, and in lab-grown cells that mimic the lining. At the same time, the production of miR181b diminished. More research showed that OPN levels increase with C/EBPβ and cAMP signaling pathway, but decrease with miR181b. Higher OPN production can help increase the expression of genes related to the formation of the lining of the uterus and the development of new blood vessels [145].

In a study that examined the associated between miRNAs and endometrial receptivity showed that the OPN level was increased in miR-26a mimic-treated EECs. It was suggested that miR-26a can be an significant element to control the OPN production and endometrial receptivity in goat [147].

The process of ovarian stimulation has an impact on the microRNA profile of the endometrium, which in turn affects the receptivity of the endometrium [148]. Previous studies showed that when women undergo ovarian stimulation, it causes their estrogen [149] and P4 amounts to become higher than normal during the late follicular stage [150] .

The increased levels of steroids have the potential to bring about changes in all aspects related to uterine receptivity, including physical, molecular, chemical, and gene expression [150], such as miRNA expression [151]. The study looked at tiny pieces of genetic material and how they affect the lining of the uterus in women with high progesterone levels. It was showed that downregulation of hsa-miR-451 increased osteopontin expression and decreased embryonic attachment [152].

L-Selectin

L-Selectins and their oligosaccharide receptors have a critical role in enabling communication between the embryo and the maternal tissue [99, 153]. L-Selectin ligands are found on the superficial part of the uterus lining in large quantities during the fertile stage of a woman's menstrual cycle. They may help with the movement of a fertilized egg in the uterus [89]. No article was found on miRNAs association with L-selectin expression. The miRNAs related to Cell adhesion molecules expression are listed in Table 5.

Mucin

Ensuring that the receptive endometrium and functional blastocyst are able to effectively interact with each other is crucial for the successful implantation of an embryo [154]. Endometrial luminal epithelial surface is covered with the mucinous layer (the glycocalyx layer) that affect embryo - endometrial crosstalk [155, 156]. It has been proved that, Mucin-13 (Muc13), Mucin-1 (Muc1), Mucin-4 (Muc4), Mucin-15 (Muc15), Mucin-16 (Muc16) are cell-surface glycoprotein that mediate embryo binding to the endometrium [155, 157].

Mucin-1, Mucin-16, Mucin-15, and Mucin-4 are anti adhesion molecules that are missing from utmost pinopodes and create the right place for the embryo to attach [157, 158]. Muc13, while, stays within the cells of the uterine luminal epithelium and plays a specific function in either adhesion or cell signaling during the specific time frame for implantation [32, 159]. Mucin-16 helps to make the outside of our body wet, smooth, and safe from germs and other harmful things [160]. Findings from three different studies focusing on the presence of

Table 5 miRNAs related to cell adhesion molecules expression

miRNAs	Sample	Specie	Target	Function	References
miR-145 Upregulation	Endometrium	Human	⬇ N-cadherin	⬆ Implantation failure	[104]
miR-192-5p Downregulation	Endometrium	Human	⬇ E-cadherin	⬆ Endometrial receptivity	[103]
miR-30a-3p Upregulation	Endometrium	Mouse	⬇ N-cadherin	⬇ Embryo implantation	[109]
miR-429 Upregulation	Endometrium	Mouse	⬇ Pcdh8	⬇ Embryo implantation	[110]
miR-126a-3p Upregulation	Endometrium	Mouse	⬇ Itga11	⬆ Implantation sites	[130]
miR-140 Upregulation	Endometrium	Rat	⬇ Itg β3	⬆ Implantation failure	[50]
miR-491-3p Downregulation miR-1910-3p Downregulation	Endometrium	Human	⬆ Itg β3	⬆ Endometrial receptivity	[131]
miR-181b Downregulation	Endometrium	Human	⬆ OPN	⬆ Decidualization	[145]
miR-26a Upregulation	Endometrium	Goat	⬆ OPN	⬆ Endometrial receptivity	[147]
miR-451 Downregulation	Endometrium	Human	⬆ OPN	⬇ Embryo attachment	[152]

MUC16 during the period of implantation indicate that it acts as a deterrent for successful implantation [161]. Mucin-1, an intrinsic glycoprotein that spans the cell membrane, displays a plentiful presence on the uppermost layer of most epithelial cells in different body parts, such as the female reproductive system, mammary gland, stomach, lung, pancreas, and kidney [162]. Mucin-1 does diverse jobs in the body. It supports cell surfaces, helps cells stick together, breaks down other substances, avoids infections, acts as a lubricant, and helps with fetal development [163].

This protein is found a lot on the inside surface of the uterus and can stop cells from sticking together. It's most common when the uterus isn't ready for pregnancy [164, 165]. Mucin-1 helps embryos attach to the uterus in many animals [166]. So loss of Mucin-1 is a requirement for the receptivity of endometrium [167].

It has been shown that let-7b and let-7a control the Mucin-1 production in the cells of the endometrium [168]. In the initial stages of pregnancy, Mucin-1 levels are at their peak on day 1 and gradually decrease until day 4. However, on day 4, there is a significant increase in the expression of let-7a and let-7b in mice. This indicates that the heightened levels of let-7a and let-7b cause a decrease in Mucin-1 expression, resulting in a more receptive endometrium. These results suggest upregulation of let-7a and let-7b decreases Mucin-1 expression and improves endometrial receptivity [168]. According to another research, it has been demonstrated that Mucin-1 is direct target of miR-199a in luminal epithelium of endometrium [169]. miR-199a upregulation reduced Mucin-1expression and increased embryo attachment [169]. The miRNAs related to mucin expression are listed in Table 6.

Pinopode

One of the morphological changes that occurs during endometrial receptivity is ultrastructural alterations on the upper part of epithelium of lumen that are recognized as pinopodes [32, 170]. The pinopodes (Translated from drinking foot, also known uterodomes) [171] The cellular bumps on the top of uterine cells during the secretory phase [172]. The structure of pinopodes varies among diverse species, exhibiting shapes resembling a balloon, flower, mushroom, or bleb-like projections [99]. At the start of the time when an embryo can attach to the uterus, small structures called pinopodes form by joining together a group of tiny finger-like projections on the cell surface [173]. In humans, pinopodes emerge soon following ovulation and persevere throughout the initial pregnancy trimester [174].

The natural role of pinopodes is not completely understood [175]. To investigate the role of pinopodes, transmission electron microscopy (TEM) can be employed. TEM analysis has demonstrated that pinopodes have specialized vacuoles that extend into the lumen. These vesicles contain essential nutrients for the developing embryo and play a crucial role in establishing its connection to the uterine endometrium [176]. The pinopod serves multiple functions, including the absorption of fluids and larger molecules from the uterus and the prevention of cilia movement. This leads to significant swelling of the lining and ultimately closes the uterus, facilitating attachment.

It is proposed that pinopodes are promising clinical markers of implantation window and receptivity of endometrium [90, 177]. Research has found that the quantity of these markers is connected to the ability of the uterus to accept and support a fertilized egg in humans [53]. The existence of completely formed pinopodes shows that the endometrium is ready for a fertilized egg to attach and start growing [178]. The clinical usefulness of pinopodes on predicting receptivity of endometrium as a structural factor is yet to be fully understood [179].

There multiple molecular factors that are associated with the existence of pinopodes. These markers encompass glycodelinA, integrins, HOXA10, latrotoxin, leukemia inhibiting factor (LIF, L-selectin, mucins, heparin-binding epidermal growth factor (HB-EGF), and miRNAs [32]. Several pieces of evidence show that miRNAs impact the creation of pinopodes during the time when implantation occurs [32].

The act of administering miR-223-3p agomir has been well-documented as a hindrance to the development of pinopodes, ultimately leading to the continued presence of microvilli on the upper layer of luminal epithelial cells in mice who have received treatment with miR-223-3p. The inhibitory effect of miR-223-3p on the creation of pinopodes is believed to have significant implications for the process of embryo implantation [72].

Table 6 miRNAs related to mucin expression

miRNAs	Sample	Specie	Target	Function	References
miR- let-7a Upregulation miR- let-7b Upregulation	Endometrium	Mouse	⬇ Mucin1	⬆ Embryo adhesion	[168]
miR-199a Upregulation	Endometrium	Mouse	⬇ Mucin1	⬆ Embryo adhesion	[169]

According to research, the level of miR-449a in the endometrium prior to the receptive phase was lower than in the receptive stage. In vivo observation showed that the miR-449a agomir group had a higher presence of complete pinopodes on the endometrial surface compared to the miR-449a antagomir group. This implies that miR-449a promotes the development of pinopodes and enhances the receptivity of the endometrium [180].

The members of miR-200 group were upregulated in the blood of unproductive individuals in comparison to the normal individuals that are not pregnant [181]. Moreover, it was showed that following miR-200c mimics injection, pinopodes were reduced in the mouse endometrium [181]. miR-200c upregulation reduces endometrial receptivity and subsequent implantation by negatively affecting pinopodes formation [181]. The miRNAs that participate in the formation of pinopodes are listed in Table 7.

Limitations of miRNAs studies

Presently, a variety of therapeutics aimed at inhibiting specific miRNAs have advanced to the clinical development stage. For instance, a drug that mimics the behavior of the tumor suppressor miR-34 is currently being tested in Phase I clinical trials as a potential cancer treatment. Additionally, antimiRs that target miR-122 have progressed to Phase II trials for treating hepatitis C by interfering with the virus' RNA replication process. The detection of circulating miRNAs in bodily fluids, such as serum and plasma, prompted their investigation as potential non-invasive diagnostic and prognostic markers for various diseases, with a particular focus on cancer. However, the accurate measurement of these circulating miRNAs has proven to be more challenging than previously anticipated, despite initial promising findings [182].

Various techniques have been utilized to assess miRNAs, but each has its own drawbacks. The original approach of cloning was employed for miRNA discovery, which was later confirmed using Northern blotting. Though cloning remains a primary method for detecting new miRNAs, it is time-consuming, has limited throughput, and is biased towards identifying highly abundant miRNAs. Other techniques for profiling miRNAs also have advantages and limitations. For instance, in situ hybridization has low throughput, and its sensitivity and specificity are restricted, but it provides valuable information on the cellular localization of miRNAs, aiding in their biological characterization. Generally, direct miRNA detection techniques also suffer from low sensitivity due to the short length and low abundance of miRNAs, necessitating a larger input of total RNA. On the other hand, amplification-based methods can be prone to errors due to the brief and inflexible nature of miRNA templates, as well as the similarity in sequences among miRNA families. Amplified samples are also more susceptible to handling errors [183].

The small concentration of miRNA in circulating blood presents a challenge, necessitating the use of kits that can efficiently extract miRNA from small amounts of serum or plasma. Furthermore, the sensitivity of miRNA downstream assays can be significantly impacted by contaminants from the extraction process, specifically residual salts from the use of denaturing and wash buffers. As a result, specialized kits are needed for the isolation of specific miRNA from plasma. Many research studies have identified the RNA extraction step as the main source of errors and inaccuracies in the miRNA isolation process, rather than the reverse transcription or PCR reactions. The variability in this process may be attributed to differences in the overall yield of miRNA [184].

Standard techniques used for assessing miRNA expression include qRT-PCR, droplet digital PCR (ddPCR), microarrays, and miRNA sequencing. Absolute or relative quantification methods can be used for miRNA expression analysis by qRT-PCR. However, the lack of a universally invariant calibrator has posed a significant challenge for relative quantification of miRNA in plasma or serum. In the past, small nuclear (e.g., U6) or small nucleolar RNAs (e.g., SNORD44) have been commonly used as normalizers for the relative expression of miRNAs. However, a study by Masè et al. has shown that frequently used normalizers such as U6 do not perform well [185]. Interestingly, various validated miRNA reference genes, including miR-16, miRs-10b, miR-30a, miR-30d, miR-103, miR-148b, miR-191, and miR-192, have been found to be differentially regulated in breast cancer patient's serum or plasma in multiple publications [186].

Research on miRNA is a highly appealing and hopeful area of study. Better understanding and identification of the role of miRNA is a crucial step in the advancement

Table 7 miRNAs involved in the formation of pinopode

miRNAs	Sample	Specie	Effect on Pinopode	References
miR-223-3p Upregulation	Endometrium	Mouse	Negative	[72]
miR-449a Downregulation	Endometrium	Mouse	Positive	[180]
miR-200c Upregulation	Endometrium	Mouse	Negative	[181]

of new treatment and diagnostic techniques. As key elements in arrhythmia, miRNA has become a new target for addressing diseases. The promising outcomes of miRNA trials in experimental settings and minimal harmful effects on healthy tissues indicate that these molecules have significant potential for therapy. Despite the potential of miRNA-based diagnostics, such as non-invasive biomarkers, various challenges, including errors in miRNA sequence databases, inadequate RNA extraction methods, variability in detection assays, numerous online resources for bioinformatics analyses, and a lack of standardized statistical analyses for clinical testing, complicate or impede their translation into routine use in clinical practice [187].

Discussion and conclusion

MiRNAs showed novel perceptions on the multifaceted molecular machineries of endometrial receptivity and implantation. These molecules alter the expression of endometrial receptivity mediators by affecting intracellular pathways. Therefore, miRNAs can be considered as effective markers to detect and prognosis endometrial maturation in normal pregnancy and assisted reproductive technology.

Currently, the majority of trials for miRNA therapeutics primarily involve miRNA inhibitors rather than miRNA mimics. However, patent applications have been filed for both forms and tend to focus on cancer treatment. While not yet on the market, a few miRNAs have been tested in clinical trials, such as Miravirsen which targets miR-122 to combat hepatitis C. Although there is some interest in developing therapeutics for the endometrium, there are currently no miRNA treatments in clinical trials. While the technology necessary for effective delivery of miRNAs is still being heavily researched, most methods rely on nanoparticles to protect the miRNAs or miRNA inhibitors from degradation. Previous studies have shown that natural extracellular vesicles do exist in the uterine space and can safely transfer miRNAs between tissues. The use of artificially created external vesicles may facilitate the delivery of miRNA therapeutics to the endometrium while avoiding unnecessary off-target sites. However, this is a new and evolving field, and the nanoparticles used and their surface properties vary among studies. The endometrium is a highly complex and ever-changing tissue. It is crucial to understand the molecular mechanisms that govern endometrial receptivity in order to improve fertility treatments. This article reviewed the current knowledge on miRNAs that have been identified as potential regulators of endometrial receptivity in mice and humans. It is important to note that due to significant differences in basic biology, findings in mice may not directly apply to humans. However, there are a few miRNAs that have been found to have potential roles in regulating endometrial receptivity in both species. These include miRNAs involved in the Wnt pathway, as well as members of the let-7, miR-23, miR-30, miR-200, and miR-183 families. Further research is needed to understand the clinical implications of these miRNAs. The problem of repeated implantation failure is increasingly prevalent in the field of reproductive medicine and has significant consequences for patients, both financially and in terms of their physical and mental well-being. A promising approach to address this issue is identifying the expression of miRNAs and key genes in the endometrium, as it has the potential to predict the success of implantation. The striking feature of miRNAs is their ability to target multiple signaling pathways and alter cell fate, making them a potential tool in preventing or treating implant failure in those with repeated implantation failure. However, there is currently a lack of research on using miRNA-targeting strategies to treat repeated implantation failure. Additionally, specific endometrial miRNAs show promise as effective biomarkers for diagnosing and treating repeated implantation failure. MiRNAs have been identified as crucial regulators involved in the developmental processes of all eukaryotes. Due to their ability to control cell growth and differentiation, they have been proposed as promising candidates for regulating endometrial receptivity. Disruptions or excesses of microRNAs have been linked to various disorders in endometrial receptivity. This can occur through mutations in the microRNA itself or its target, or through epigenetic mechanisms that silence the transcription of microRNA. Recent advancements in microRNAs have offered hope that they may be used for diagnosing and treating endometrial receptivity disorders in the near future. Further studies, particularly in vitro and in vivo, could uncover more unknown uses of microRNAs in this field. Clinical research, in particular, may identify specific microRNAs as effective therapeutic tools for managing endometrial receptivity disorders. It is believed that comprehending the function of miRNAs in endometrium while implantation will make allowance for identification of targets in management of infertility and assist to make new contraceptives. Thoroughly comprehending the function of miRNAs during the process of embryo implantation in the endometrium has the potential to unveil specific pathways that can be targeted in the management of infertility. Furthermore, it is necessary to conduct a more comprehensive prospective study with a larger number of participants in order to validate the findings of previous studies. Moreover, focusing on particular miRNA biomarkers for examination instead of conducting whole-genome sequencing analysis could also decrease testing expenses, alleviating the

financial burden for patients in the future. More research is needed in clinical trials to understand effectiveness of miRNAs to endometrial receptivity and development of implantation.

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