WOMEN WITH IMPLANTATION FAILURE: A NARRATIVE REVIEW ON ENDOMETRIAL BIOMARKERS

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ABSTRACT

Because women postpone parenthood, reproductive failure is a major social and economic issue. Unfortunately, natural fertilisation and pregnancy maintenance decrease with age. Many need ART. Recurrent implantation failure (RIF) occurs in 10% of IVF-embryo transfer patients. Oocyte and sperm quality, parental chromosomal anomalies, embryo genetic or metabolic abnormalities, poor uterine receptivity, immunological disturbances in the implantation site, and some gynecologic pathologies like endometriosis, uterine fibroids, hydrosalpinx, and endometrial polyps can cause RIF. In vitro fertilisation may also harm implantation. Because NK cells dominate the endometrium and interact with allogeneic extravillous trophoblast cells in early pregnancy decidua, several research are examining their involvement in normal and pathologic pregnancy. CD56bright cells predominate. These cells can express killer immunoglobulin-like receptors (KIRs), which recognise HLA class I molecules (HLA-C and HLA-G) on trophoblasts and stimulate or inhibit NK cells to produce soluble factors and display low cytotoxicity needed to maintain the allogeneic embryo and foetus in later pregnancy stages. The human placenta also contains ILT (immunoglobulin-like transcript) and leukocyte immunoglobulin-like receptor (LILR) family members. LILRB1 (ILT2) was identified on stromal cells, whereas LILRB2 (ILT4) was detected surrounding arteries in the smooth muscle layer. This review discusses the prospective relevance of polymorphism of KIR, LILRB, and their ligands (HLA-C, HLA-G) in vulnerability to recurrent implantation failure, which might be diagnostic biomarkers.

Keywords: Endometrium, Blastocyst, Trophoblast, hCG, Endometrial markers, Recurrent implantation failure,

1. INTRODUCTION

After implantation, the superficial (compact) layer of the endometrium becomes known as the decidua. Implantation is described as the blastocyst's penetration of this layer. Beginning on day six following fertilisation, implantation is complete by day eleven. Hatching, apposition, adhesion, and invasion are the stages of implantation. Embryo implantation, decidualization, and placentation all need to go well for a pregnancy to end in a healthy baby. Pregnancy development is a delicate balancing act that requires a number of molecular and physiological mechanisms. A healthy endometrium and active contact between the endometrium and the blastocyst are both necessary for implantation to occur. The implantation phase is the most

crucial, and it consists of many steps including blastocyst adhesion stability, trophoblast cell invasion, and immunological regulation **(Figure 1)** [1].

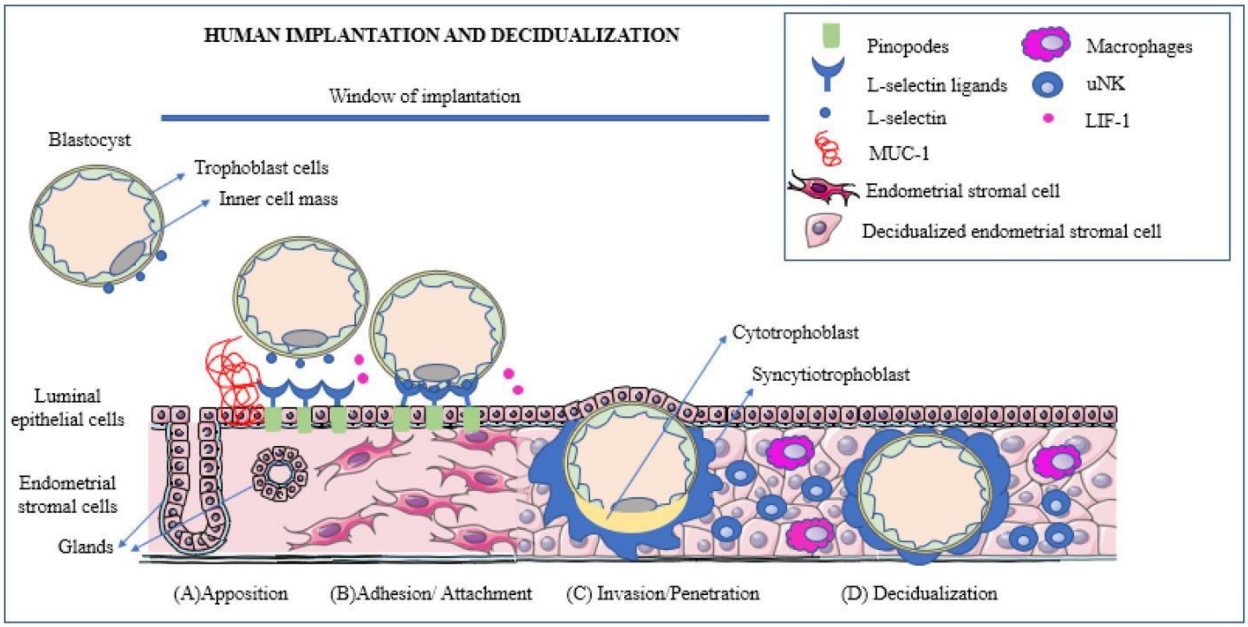

Figure 1. Human implantation and Decidualization.

The endometrium's shape and receptivity are crucial factors in successful implantation. High responsiveness of the endometrium determines the precise period of the greater rate of successful implantation, known as the window of implantation (WOI; days 20-24 of the cycle, during the secretory phase). There may be no clinical indication of pregnancy at all if implantation fails during the adhesion stage, when no hCG is being produced. Biochemical pregnancy is also possible at a later stage, when hCG production has been initiated by the implanting embryo but before the creation of an intrauterine gestational sac detectable by ultrasonography. Embryo and/or maternal variables have been linked to unsuccessful implantation. Poor oocyte quality or fatherhood considerations may both contribute to embryonic problems.However, implantation issues in women may arise from a number of different conditions, including uterine, tubal, immunological, endometriosis, and thrombophilia [2].

Many couples go through many IVF failures since only around one-quarter of IVF cycles result in live newborns in non-oocyte donation cycles, despite breakthroughs in IVF technology. Pregnancy rates drop dramatically with each succeeding IVF cycle after a failed effort, falling dramatically by the third cycle after an unsuccessful attempt. More than 20 years ago, it was shown that RIF occurred when a total of eight embryos at the cleavage stage or four blastocysts

transferred 14 days following egg pick-up (OPU) did not result in a positive pregnancy test. However, according to the ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium, RIF is defined as the inability to produce a clinical pregnancy despite the transfer of at least three high-quality embryos or ten embryos in total over many transfers [3].

More recently, RIF has been defined as the inability to obtain a pregnancy despite the transfer of at least four healthy embryos over at least three separate fresh or frozen cycles. RIF occurs at a rate of roughly 10%-15% in ART facilities. It affects women under the age of 40. Variables such as the number of embryos transplanted, the number of IVF tries, the quality of the embryos, and the age of the mother have all been used to define RIF. Several definitions of RIF have been offered using these variables in varying permutations, but there is currently no consensus on a single definition. As a result, it's hard to get an accurate count of the number of people that have RIF. The endometrium is fertile for implantation of a blastocyst from day 6 following ovulation until day 96 (cycle days 20-24) [4].

Birth control use, obesity, smoking, and alcohol use, and a previous diagnosis of endometriosis are all known to enhance the likelihood of RIF. Factors affecting either the embryo or the uterus may contribute to the need for RIF. The role of both male and female variables in RIF's prevalence, however, has also been established. This article attempts to provide a concise summary of the components involved in RIF development; nonetheless, the precise multifactorial aetiology of RIF remains unknown. The functions of adjuvants in ART are multifaceted. Their functions are distinct, but they have the ability to significantly speed up cell division, encourage angiogenesis and endothelial cell chemotaxis, and stimulate the growth of bone and cartilage. Protein signals on the cell membrane are activated when growth factors released by platelets bind to certain receptors. Wound healing is aided by cytokines, which then produce plenty of procollagen.Autologous platelet rich plasma (PRP), intralipid emulsions, injectable G-CSF, growth hormones, letrozole, and endometrial scratching are some of the adjuvants utilised in patients with implantation difficulties [5].

Anti-inflammatory and pro-regenerative substances are abundant in autologous platelet-rich plasma. Within 10 minutes of clotting, platelets in PRP actively produce and change into their bioactive form’s growth factors as VEGF, TGF, PDGF, and EGF. The treatment of G-CSF predicts a successful pregnancy every time.Women with a history of RIF may benefit from immunotherapy since it has the potential to improve endometrial receptivity, hence increasing the likelihood of a healthy pregnancy. Several clinical trials have looked into the efficacy of

intravenous intralipid (IVI), an emulsion of fats including soybean oil, glycerine, phospholipids, egg, and polyunsaturated fatty acids, in downregulating uNK cells and macrophages and inhibiting pro-inflammatory mediators like T1 helper cells. Nonetheless, there is a need for more research on the available data. The idea behind endometrial scratching is that the body's inflammatory response is triggered when the uterine lining is damaged, and that the healing process results in the production of growth factors, hormones, and proinflammatory cytokines. When given during early placentation, glucocorticoids protect against miscarriage. The CPR, LBR, and TTHR were all improved by the addition of growth hormone. When the implantation window is interrupted, V3 integrin expression decreases. This WOI is enhanced by letrozole [6].

1.1. Endometrial markers

Various endometrial markers **(Figure 2)** have been identified which directly correlate to the receptivity.

1. Integrin α5ß3:
    a. Integrins are cell surface glycoproteins that bind to extracellular matrix proteins and regulate cell-cell and cell-matrix interactions.
    b. It has been shown to be associated with the initial attachment of the embryo to the endometrium, and reduced expression has been associated with an adverse effect on blastocyst implantation.
    c. Conditions associated with subfertility such as endometriosis, hydrosalpinges and luteal phase defects.
2. MUC1:
    a. It is a member-associated protein, highly expressed in luminal and glandular epithelium on day 21 of a regular cycle.
    b. Fertile women show higher levels of MUC1 expression than infertile women.
3. Glycodelin A:
    a. It is an abundant secretory glycoprotein in the first trimester decidua, and takes part in maintenance of feto-maternal immunotolerance.
    b. GdA is dominated in the mid-secretory phase and has six different glycosylated forms.

c. In proper implantation, GdA stimulates endometrial proliferation and regulates attachment of trophoblast cells.
d. It affects cell proliferation, differentiation, adhesion and motility.
e. It also modulates immunosuppression responses and reduces cytotoxic effects of NK cells and shifts balance to Th2 cytokines. Moreover, GdA inhibits T cell proliferation and stimulates its apoptosis to modulate immune response of B cells [7,8].

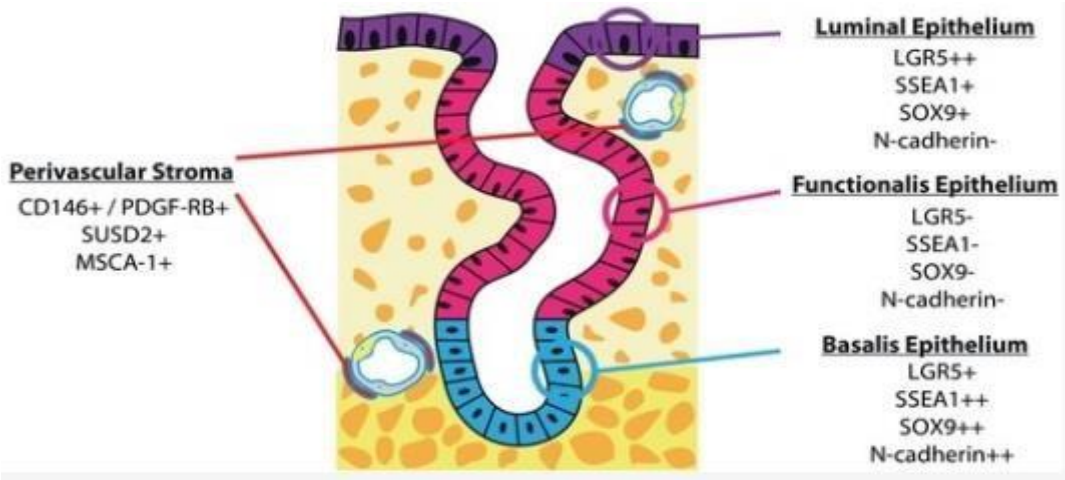

Figure 2. Endometrial markers.

1.2. Other biomarkers

Other biomarkers **(Figure 3)** which are expressed for endometrial receptivity are:

1. Genetic factors such as inherited thrombophilia, presence of factor-V leiden mutation, MTHFR mutation and p53 genetic polymorphism.
2. Interleukins such as IL-6
3. Leukemia inhibitor factor (LIF)
4. Matrix metalloproteinase 7 (MMP-7)
5. Placental growth factor (PlGF)
6. Progesterone, estrogen and their hormone receptors
7. Vaginal and endometrial microbiota disturbances
8. Vascular endothelial growth factor (VEGF) [9]

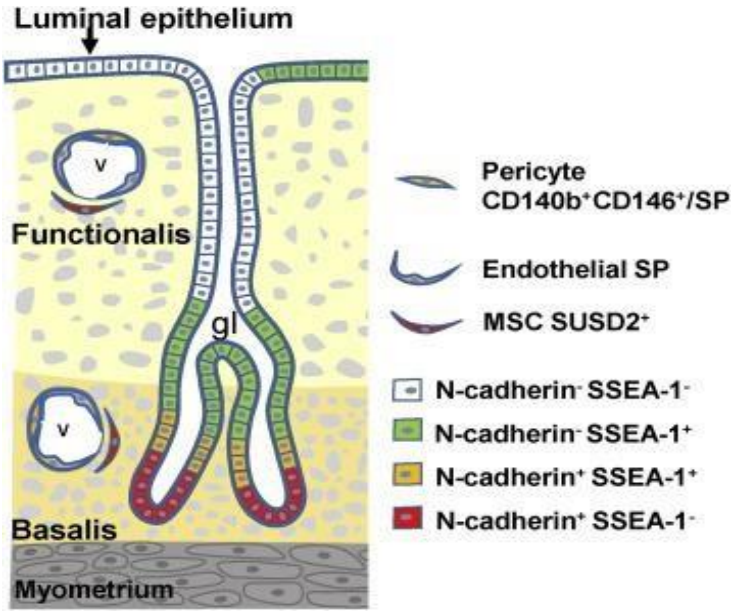

Figure 3. Miscellaneous biomarkers.

The implantation rate per embryo transfer in assisted reproductive technology (ART) is approximately 30%, while the incidence of recurrent implantation failure (RIF) (universally applied definition is 'three or more failed treatment cycles') *in vitro* fertilization (IVF) patients is as high as 10%.

Causes of recurrent implantation failure can be due to various etiologies like

1. Gamete and Embryo factors such as decreased embryo quality or compromised ovarian and sperm parameters. Various causes are found for the above-mentioned condition like advanced maternal age, high FSH, low AFC and AMH, increased DNA fragmentation index in sperm, chromosomal disjunction and mitochondrial damage.
2. Factors affecting endometrial receptivity include anatomical abnormalities which can be congenital (mullerian duct abnormalities) or acquired (myomas, polyps, adhesions, endometritis, polyps and hyperplasia); thin endometrium, altered expression of adhesive molecules (such as dysregulated interleukins, change in pinopodes expressions, increased MMP's)
3. Immunological disturbances like decreased secretion of TH2 cytokines like IL-4 and 6, increased quantity of TH1 cytokines like IL-2 and 12 and dysregulated NK cells.
4. Faulty endometrial microbiota.
5. Multifactorial effectors like PCOS, endometriosis and hydrosalpinx [10].

2. SPECIFIC STUDIES

Feng et al., 2018 establish an lncRNA-mRNA network associated with implantation failure and to isolate the main lncRNAs as potential predictors of endometrial receptivity. Predicted lncRNA-miRNA and miRNA-mRNA pairings retrieved from lncRNASNP and miRTarBase were used to build the global background network. Using the information from GSE26787, we determined which genes were differentially expressed in IF and re-annotated them as DEMs and lncRNAs. The IFLMN was built using a hypergeometric test, and it contains 10 lncRNAs, 212 mRNAs, and 255 lncRNA-mRNA pairings. Important lncRNAs were identified as having the highest centroid by means of topological analysis. Unsupervised clustering, Gene Ontology classification, the Kegg pathway, and co-expression module analyses were used to perform functional enrichment analyses, yielding six key lncRNAs and their ceRNA sub-networks that facilitated immunological activity, growth factor binding, vascular proliferation, apoptosis, and steroid biosynthesis in the uterus and primed the endometrium for embryo implantation. Midway during the luteal phase, the endometrium from 16 women was collected; 8 of these women had experienced either recurrent implantation failure or recurrent miscarriage (RM), while the other 8 had conceived normally. When the expression of the aforementioned six lncRNAs was compared using quantitative real-time PCR, it was confirmed that the expression of all six lncRNAs was considerably increased in the endometrium of RIF/RM patients. There is a need for further research into the mechanism at play, and the lncRNAs show promise as potential predictive biomarkers for endometrial receptivity [11].

Wu et al., 2018 performed endometrial biopsies on 14 women with RIF, 25 women with RM, and 20 fertile controls on day LH + 7 (the beginning of the implantation window). By using semi-quantitative immunohistochemistry, we were able to examine the expression of MUC1, LIF, and Integrin 3 across many time points and locations. Expression levels of MUC1, LIF, and integrin 3 were analysed in relation to demographic and clinical factors. The expression of MUC1 in luminal and glandular epithelium was considerably lower in women with RIF compared to women with RM and fertile controls. Endometrial epithelium LIF and Integrin 3 expression were similar across the board. Age, body mass index, number of children, duration of pregnancy cycles, progesterone levels, or history of miscarriage were not linked with lower

MUC1 expression. Reproductive incompetent (RIF) women have been shown to have reduced expression of MUC1, an independent diagnostic for endometrial receptivity [12].

Nowak et al., 2017 supposes that a mother's immune system's ability to accept a foetus is crucial to a successful pregnancy. Embryo implantation may be affected by how well activating and inhibitory signals are balanced between NK cells in the decidua and trophoblast. Genetic studies of the KIR, LILRB, HLA-C, and HLA-G receptors thought to play a role in this mechanism may aid with RIF diagnosis, therapeutic outcome prediction, and understanding illness pathophysiology. More patients and healthy controls from the same demographic should be included in future research. Both naturally fertile couples who conceive without history of spontaneous abortion or other immunological and gynaecological problems, and IVF success stories with healthy pregnancies and deliveries should serve as controls in this research. Since the distribution of KIR, LILRB, and HLA alleles varies greatly between ethnic groups, it has been suggested that additional IVF clinics in various parts of the globe collaborate on studying the causes of repeated implantation failure [13].

Ledee et al., 2016 emphasised that the low success rate (20%) of assisted reproductive technology is due mostly to difficulties with embryo implantation. Three hundred ninety-four women with a history of recurrent embryo implantation failures (RIF) underwent an endometrial immune profile. Biomarkers of angiogenesis and the Th1/Th2 balance were recorded by the endometrial immune profile, as was the ratio of IL-15/Fn-14 mRNA as a biomarker of uNK cell activation/maturation. The analysis of the live birth rate (LBR) for the subsequent embryo transfer allowed us to evaluate the efficacy of the individualised treatment we suggested to prevent the observed dysregulation. Eighty-one percent of RIF patients had dysregulated endometrial immune profiles compared to controls. There were 56.6% cases of overactivation and 25% cases of inadequate activation. At the time of the first consecutive embryo transfer, the LBR among these dysregulated/treated individuals was 39.8%. Immune profile of the endometrium has the potential to provide light on RIF and, if treated, its sequelae (LBR) [14].

Coughlan et al., 2013 evaluated the potential predictive relevance of integrin 1, 4, and V3 expression in the glandular and luminal epithelium, stroma, and blood vessel wall cells of the endometrium from women with recurrent implantation failure (RIF). Forty-five RIF patients and six fertile women without the condition were enlisted. Recurrent infertility (RIF) was described as a woman's inability to conceive after attempting to conceive with four healthy embryo

transfers throughout three or more fresh or frozen cycles. On cycle days LH+7 through LH+9, endometrial biopsies were taken from women with RIF and from controls. Immunohistochemistry was used to examine the expression of integrin alpha 1, alpha 4, and alpha V beta 3. H-score analysis provided a semiquantitative estimate of integrin protein expression in the luminal and glandular epithelium, stroma, and vascular endothelial cells. Luminal and glandular epithelial cells, as well as blood vessel wall cells, showed the highest levels of integrin 1 and 4 expression, with a higher level of integrin 1 and 4 expression in the glandular epithelium than in the luminal epithelium (H-scores: 1 293 15 and 180 12, and 4 287 14 and 191 11, respectively). No significant difference in V3 expression was found between glandular and luminal epithelium, while expression of V3 was higher in the epithelium and blood vessels than in the stroma. Tissue from women with RIF and controls showed no significant difference in H-scores for 1, 4, and V3 expression in any of the endometrial compartments. There was no discernible change in 1, 4, and V3 expression between women who became pregnant after receiving assisted conception therapy and those who did not. Failure to produce a clinical pregnancy following the transfer of at least four good-quality embryos throughout at least three transfer cycles, which is the definition of RIF, is not linked to aberrant endometrial integrin expression. Furthermore, it seems that there is little predictive utility in using integrin 1, 4, and V3 expression in future IVF therapy [15].

Teh et al., 2016 examined the present understanding of embryo-endometrial synchrony's role in assisted reproductive technology. The 'window of implantation' is generally agreed upon to be the period of time during which the blastocyst initially adheres to and invades the endometrium. It's important to avoid using the word "window of implantation" in a way that suggests there's just one window of opportunity that matters for a successful implantation. Endometrial development and embryo maturation are two separate but concurrent processes. When these two tissues join during implantation, a pregnancy is created. Understanding the idea of developmental'synchrony,' which occurs when the early embryo and the uterus grow at the same pace and are therefore ready to initiate and maintain implantation at the same moment, is crucial to grasping this phenomenon. There are a number of things that might throw off embryo-endometrial synchronisation, including the controlled ovarian hyperstimulation that is often utilised in in vitro fertilisation. Embryo-endometrial development asynchrony of more than 3 days is associated with a considerable decrease in implantation rates in humans. Synchronisation

between the embryo and the endometrium is essential for implantation. To better align the embryo and endometrium in preparation for implantation, there is a need for more accurate assessment of endometrial development [16].

Bastu et al., 2015 collected endometrial biopsies and blood samples at the same time and date from women with recurrent implantation failure and women with established fertility to assess the levels of Mucin 1 (MUC-1) and Glycodelin A (GdA). Using enzyme-linked immunosorbent assay, researchers analysed MUC-1 and GdA expression in the human endometrium and blood throughout the implantation window. During this time, western blotting was also used to examine tissue levels of MUC-1 and GdA. Measurements of MUC-1 and GdA in the blood and tissues of women with recurrent implantation failure were considerably lower than those of fertile women during the implantation window. Furthermore, we discovered a very substantial association between MUC-1 and GdA levels in the blood and levels in tissue. The current research shows that MUC-1 and GdA levels in RIF women's blood and tissues are much lower than those in fertile women. Since there is a correlation between blood and tissue measurements of MUC-1 and GdA, receptivity may be tested using blood sample rather than the more intrusive endometrial sampling [17].

Lessey et al., 2011 given an in-depth analysis of the research done on receptive endometrium. Although there is general agreement that there is a certain time frame in which implantation may take place, acceptable and reliable techniques to evaluate "receptivity" have yet to be developed. Endometrial receptivity seems to be reduced, resulting to infertility and pregnancy loss, in women with specific gynecologic illnesses such as endometriosis, tubal disease, and polycystic ovarian syndrome. The development of effective biomarkers for the diagnosis of endometrial receptivity abnormalities has been a long-sought but unrealized objective. Recognising that endometrial receptivity abnormalities are not uniformly distributed in women with endometriosis or these other disorders is crucial for the development of research that can validate endometrial biomarkers. New biomarkers with the potential to shed light on the intricacies of the implantation process are entering clinical practice as technology advances at a breakneck pace [18].

Wei et al., 2009 Comparison of implantation biomarker expression between women with and without endometriosis in eutopic endometrium was performed using glycodelin A, osteopontin, lysophosphatidic acid receptor 3, and HOXA10. After day 22 of a cycle, patients

showed a dramatic decrease in endometrial GdA expression. Women with endometriosis had lower levels of expression of OPN in the late secretory phase, as well as lower levels of expression of LPA3 and HOXA10 in the midsecretory and late secretory phases, respectively, in their endometrium. Patients with endometriosis may have poor endometrial receptivity, which might explain why subfertility is present even in women with a small number of pelvic implants due to the reduced expression of these four indicators of implantation. These results are significant because they may indicate less endometrial P action in this cohort, since P is required for the expression of several of these markers [19].

Aghajanova et al., 2008 explained that a receptive endometrium and a developmentally competent blastocyst are necessary for the implantation process, which is a dynamic process involving paracrine interactions between the maternal compartment and the conceptus. In order to better diagnose and treat implantation-related disorders like miscarriage, foetal growth restriction, pre-eclampsia, and infertility, we take a look at histology, clinical approaches, and the promise of transcriptomics in elucidating mechanisms underlying implantation and developing biomarkers of uterine receptivity [20].

Horne et al., 2005 investigated biomarkers of endometrial receptivity by comparing the results of hematoxylin and eosin staining, SEM and TEM, and the expression of MUC1 glycoform, sex steroid receptor, and interleukin receptor among well-defined clinically fertile and infertile groups of women. Endometrial pinopodes have been related with embryo adhesion, and scanning immunoelectron microscopy confirms that MUC1 mucin is not associated with these structures. Abnormal endometrial expression of MUC1 mucin and nuclear progesterone receptor (PR) retention, especially in epithelial cells, were also linked to a lack of successful embryo implantation. Interleukin receptor immunohistochemistry, TEM, and SEM alone have not been validated as meaningful indicators. Endometrial receptivity seems to be determined in large part by progesterone's ability to regulate MUC1 [21].

Cavagna and Mantese, 2003 explained that the embryo and the maternal endometrium interact to cause the occurrence known as implantation. During the menstrual cycle, the relationship between the mother and the embryo is at its peak, leading to the adherence and invasion of the blastocyst into the secretory endometrium stimulated by progesterone. Nidation refers to this time frame, also known as the implantation window. Changes in endometrial epithelial morphology occur during the implantation window, and are characterised by the development of

membrane projections termed pinopodes. Pinopodes, which are apical cellular protrusions reliant on progesterone, emerge on days 20 and 21 of a normal menstrual cycle. Multiple variables control the onset of the pinopodes and the narrowing of the implantation window. Growth factors and cytokines, calcitonin, HOX genes, and cell adhesion molecules may all play important roles in the implantation process, as may the production of these molecules by the embryo and the mother. In addition to their chemical messenger role, cytokines may also be used as indicators of uterine receptivity. Better diagnosis and treatment of infertility will be possible if it is learned that how these indicators work and what role they play in defining the implantation window in women [22].

3. CONCLUSION

Mother-fetus immunological tolerance determines reproductive success. The decidua's NK cells and trophoblast's signal balance may affect embryo implantation. We hope that studying the genetic history of receptors engaged in this process—KIR, LILRB, HLA-C, and HLA-G—may aid RIF diagnosis, treatment prediction, and illness causation. However, bigger homogenic patient and control groups should be studied. These studies should also include two suitable control groups: fertile couples who spontaneously conceive with no prior spontaneous abortion or immunological and gynaecological problems, and couples who had IVF, got pregnant, and had a healthy child. We recommend that additional IVF centres worldwide explore recurrent implantation failure since ethnicity affects KIR, LILRB, and HLA allele distribution.

CONFLICT OF INTEREST

No conflict of interest is declared.

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