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Genetic Aspects of Implantation Failure

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Abstract

Implantation failure refers to the inability of a fertilized egg, or embryo, to successfully implant itself in the endometrial lining of the uterus, leading to pregnancy loss. The repeated failure of good quality embryo implantation is referred to as recurrent implantation failure (RIF). This can occur for a variety of reasons, including chromosomal abnormalities in the embryo, problems with the endometrium, or issues with the immune system. Factors such as advanced maternal age, obesity, smoking, and certain medical conditions can also increase the risk of implantation failure. While treatment such as in vitro fertilization (IVF) can help to improve the chances of successful implantation, there is currently no definite way to prevent or treat implantation failure. Patients and healthcare professionals have substantial diagnostic and treatment hurdles as a result of many etiological factors and lack of knowledge about RIF. A number of studies have indicated a correlation between irregular hormone levels, disruptions in angiogenic and immunomodulatory factors, specific genetic polymorphisms, and the prevalence of RIF. Nonetheless, the precise and intricate underlying pathophysiology of RIF remains elusive. However, many studies are ongoing in this field to understand the underlying causes and to find new ways to help couples achieve pregnancy. This review article extensively explores diverse molecular and genetic facets aimed at enhancing the diagnosis and management of implantation failure.

Keywords: *Implantation failure; IVF; RIF; Genetic factors; Genetic testing; Treatment.*

1. Introduction

In mammals, implantation is a critical stage of pregnancy, implying not only the success of the pregnancy but also the health of the progeny [1]. Implantation can only take place in a receptive uterus [2]. Hoozemans et al., [3] defined implantation as "a coordination event that involves both embryonic and maternal active participation". Makrigiannakis and Minas V [4] also described that "implantation is the stage in an embryonic development, in which the blastocyst apposes, attaches and finally invades the underlying endometrial surface of the female's uterus". Sharkey & Smith [5] defined implantation as "the process by which the free-floating blastocyst attaches to the endometrium, invades into the stroma and establishes the placenta". Hoozemans et al., [3] explained that, "the implantation process contains three stages, apposition, attachment and invasion into the endometrium".

Ashary et al., [6] noticed that, "implantation is the first stage of gestation, the endometrium is to implant the embryo and nourish it to ensure pregnancy". The process involves coordination between an

implanted embryo and an endometrium. Santos et al., [7] estimated that, “in humans, reproductive efficiency has been shown to be rather low, with a probability to achieve pregnancy estimated to 20–30%”. Moreover, Fleming et al., [8] added that, “apart from endogenous factors (such as genetic mutations) that could be detrimental for pregnancy development, various environmental insults (nutrition, pollution and endocrine disruptors, infections stress) have been identified as factors that may affect gamete quality and fertilization, journey of the early embryo through the oviduct, cellular interactions between endometrium and hatched blastocyst or conceptus, foeto-placental development and parturition”. When chromosomal euploidy is absent, the effects of gene mutations and changes in methylation on Recurrent Implantation Failure (RIF) become ambiguous. Research conducted on mice has indicated a correlation between specific gene abnormalities and unsuccessful embryo implantation. This correlation is primarily attributed to the inadequate presence of crucial endometrial factors, such as cytokines and transcription factors [9, 10]. The endometrium becomes receptive for a limited period of time under the influence of steroid hormones and paracrine signals from the developing embryo [5]. Murphy [11] noted that “the endometrium is receptive to implantation during the window of implantation (WOI), a spatially and temporally restricted phase that is complex and multifactorial, during which changes occur at the molecular, cellular and tissue levels”.

From a clinical perspective, Recurrent Implantation Failure (RIF) is characterized by the repetitive inability of well-developed embryos to successfully implant [12]. According to Garneau & Young [13], “RIF is the unsuccessful implantation after repeated transfers of morphologically good quality embryos into a normal uterus”. Cimadomo et al., [14] refers RIF to the failure of the embryo to reach a stage when an intrauterine gestational sac is recognized by ultrasonography. In a study done by Maesawa et al., [15], “biochemical pregnancy is actually not uncommon, and its reported incidence varies from 8 to 33% in the general population, including those who spontaneously conceived”. Hoozemans et al., [3] stated that, “for successful implantation, embryo maturation and uterine receptivity must occur in concert such that a window of implantation is open for 48 hours, 7–10 days after ovulation’’. In the research conducted by Coughlan et al., [16], the term "implantation failure" encompasses two distinct scenarios: individuals without any observable signs of implantation and those who exhibit indications of implantation. Notably, both of these situations are linked to the detection of Human chorionic gonadotropin (hCG). The determination of RIF (Recurrent Implantation Failure) commonly relies on evaluating two criteria: the quantity of well-developed embryos that have been placed, and the number of procedures involving the transfer of these high-quality embryos, as detailed by Rinehart [17].

The occurrence of implantation failure arises from a multitude of factors, encompassing both maternal elements and causes related to the embryo's development. According to Simon & Laufer [18], these maternal factors encompass abnormalities in uterine anatomy, thrombophilia, non-receptive endometrium, and immunological aspects. Franasiak et al., [19] mentioned that, “embryonic causes include either genetic abnormalities or other factors essential to the embryo that impair its ability to develop in the uterus, to hatch and to implant”. Margalioth et al., [20] denoted that “chromosomal abnormalities in embryos are one of the possible causes of implantation failure”. Franasiak et al., [19] added that, “chromosomal abnormalities, such as aneuploidy or chromosome rearrangements affect the implantation. In the year 1999, Stern also noted that “an increased prevalence of chromosomal structural abnormalities has been documented in RIF patients”. The most common fetal chromosomal abnormalities are caused by meiotic nondisjunction like trisomy and monosomy, and structural chromosomal abnormalities (balanced translocation or inversions). According to Brosens [21], “maternal age is the main risk factor for embryonic aneuploidy”.

Hoozemans et al., [3] observed that, “the immunological action against the embryo is the maternal restraint, it may cause implantation failure or failure of adequate placentation. Hence immunomodulation is necessary to prevent the maternal immune system rejecting the embryonic transplant”. Maternal age plays a crucial role in the quality of the embryos that are used for IVF [16]. Salumets et al., [22] discovered that when utilizing the Intracytoplasmic Sperm Injection (ICSI) technique in frozen embryo transfer, the foremost predictive determinant affecting pregnancy outcome was the maternal age. Increased boby mass intex (BMI) (> 25 kg/m^2) has also been shown to impact implantation rate [23].

When compared to non-smoking individuals receiving artificial reproductive technology (ART), smoking has been demonstrated to dramatically increase the probability of miscarriage (time undefined) for each pregnancy [24]. Cigarette toxins may have a role in disrupting both corpus luteum formation and embryo implantation, according to findings by Bashiri et al., [25]. Maternal smoking has shown a higher association with spontaneous miscarriages involving normal fetal karyotypes rather than those with abnormal fetal karyotypes. This pattern suggests that the primary sources of harm are likely the toxic effects of carbon monoxide and nicotine, as highlighted in the research by Anblagan et al., [26]. Elevated cortisol production within the body is a response to psychological, immunological, and diverse stresses. This physiological reaction serves as a warning signal to the female body, suggesting potential suboptimal reproductive conditions, as discussed in Nepomnaschy et al.,'s study [27]. The achievement of successful implantation relies heavily on the presence of robust embryos and a well-functioning endometrium. The cross-talk between the embryo and the endometrium, which is essential for successful implantation, can be negatively impacted by issues arising from the host environment, such as aberrant uterine anatomy, non-receptive endometrium, the mother's health, and other genetic variables. Recurring instances of implantation failure pose a formidable challenge to IVF clinics. Infertile couples who face unsuccessful IVF/ET treatments endure considerable psychological, emotional, and financial stress, while medical professionals working to assist them also experience frustration. This study aims to categorize the multifaceted causes of RIF into specific RIF types, with the aspiration of providing couples who encounter implantation failure after embryo transfer with the appropriate and targeted care.

Implantation failure & genetics

Genetic factors are vital in successful implantation to occur. The presence of abnormal genetic material in the embryo or/and endometrium will cause the implantation to fail. There is also growing evidence that genetic factors regulating invasion and endometrial angiogenesis is essential for embryo implantation [28]. Chromosomal abnormalities, such as aneuploidy or chromosome rearrangements, are well known to cause early pregnancy failure and recurrent pregnancy loss (RPL) [19]. For successful implantation, embryo maturation and uterine receptivity must occur in concert such that a “WOI” is open for 48 hours, 7–10 days after ovulation [3].

Oocyte quality

When there is a poor response to ovarian stimulation with fewer oocytes retrieved, a large proportion of immature oocytes, a lowered fertilisation rate, and a low embryo utilisation rate, compromised oocyte quality is frequently suggested as a cause of RIF [29]. Age-related decline in oocyte quality is associated with increased chromosomal nondisjunction resulting in aneuploid embryos, decrease in mitochondrial membrane potential and increase of mitochondrial DNA damage [2]. Hernandez-Gonzalez et al., [30] recognized that “not only the oocyte but the cumulus cells play an important role in the implantation process. The cumulus oophorus is a mass of granulosa cells associated with the oocyte from the antral follicle stage to fertilization and until early embryo development”.

Sperm quality

Poor-quality spermatozoa may also result in the generation of poor-quality embryos. It is commonly acknowledged that standard sperm analysis criteria do not adequately indicate sperm quality. Cigarette smoking, genital tract infection, and past chemotherapy or radiation are all factors that lead to sperm DNA damage.

The embryo in implantation failure

Global gene analysis of the dormant *versus* active blastocysts demonstrates that heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF) encoded by *Hbegf* gene is significantly up-regulated during blastocyst activation [31]. One of the most important factors is the embryo's quality. Following the transfer of 2, 3, 4, 5, 6, and 7 embryos, the odds of all embryos failing to implant are 0.81, 0.73, 0.66, 0.59, 0.53, and 0.48, respectively, assuming that the likelihood of successful implantation is decreased to 0.10. In other words, all seven embryos have a 48% probability of failing to implant. As a result, in order to arrive at a therapeutically meaningful definition, several researchers specified that good-quality embryos had been transplanted [19]. Poor embryo quality is considered to

be the major cause of implantation failure [32]. Proteomic studies indicated that the embryonic secretome may differ between those that implant and those that fail, although prospective validation studies are as yet lacking [33].

The mother in implantation failure

Maternal age plays a crucial role in pregnancy rates as well as the quality of embryos used for IVF. Many difficulties that emerge clinically in the first trimester, such as miscarriage, or in the second half of pregnancy, such as preeclampsia, preterm birth (PTB), foetal growth restriction (FGR), and gestational diabetes (GDM), have their origins in implantation and placentation disorders [34]. Gellersen et al.,) [35] stated that the endometrium is a multi-layered, dynamic mucosa that overlays the myometrium of the uterus. It comprises a variety of cells, including luminal and glandular epithelial cells, stromal fibroblasts, and vascular and immune cells. During a menstrual cycle, dramatic changes occur in both the phenotype and abundance of many of these cells, especially in the superficial endometrial layer. Takano et al., [36] observed that, "endometrial growth is dependent on estrogen stimulation whereas the postovulatory rise in progesterone levels triggers a coordinated programme of differentiation, characterized by proliferative arrest and secretory transformation of the epithelial cells, transient oedema, in- flux of uterine natural cells (uNK), vascular remodeling, and differentiation of stromal fibroblasts into specialized decidual cells".

Molecular aspects of implantation failure

Dey & colleagues [37] reported that, "molecular and genetic evidence indicates that ovarian hormones together with locally produced signaling molecules, including cytokines, growth factors, homeobox transcription factors, lipid mediators and morphogen genes, function through autocrine, paracrine and juxtacrine interactions to specify the complex process of implantation". However, more studies were done by Zhang et al., [38] on the hierarchical structure of the molecular signaling pathways that control interactions between the uterus and the embryo in the first trimester of pregnancy. Canfield et al., [39] explained that, "implantation is considered to occur when a blastocyst breaches the luminal endometrial epithelium. However, determining precisely when this occurs in the human being is complicated. The only established clinical marker of implantation is hCG". Progesterone is widely acknowledged to be necessary for embryo implantation in almost all of the species investigated, but the significance of the two estrogen surges that occur during the proestrous and luteal phases prior to embryo implantation is still controversial [37, 40, 2). IL-6 is minimally expressed in human endometrium throughout the proliferative phase but has significant immunoreactivity during the mid-secretory phase, primarily in glandular and luminal epithelial cells [41,42]. Hence, a potential involvement in human implantation might similarly be inferred for this cytokine, similar to the roles of leukemia inhibitory factor (LIF) and interleukin (IL)-11. This is owing to the functional overlap between IL-6 and IL-11, as well as LIF. Increasing evidence underscores the substantial contribution of IL-11 to the process of human implantation. Recent studies have shown that the human endometrium contains IL-11 and its receptor (IL-11R) [43, 44]. Koler et al., [45] showed that, "RIF patients show deregulated gene expression during the receptive phase compared to controls".

According to the study conducted by Bashiri et al., [25], they concluded that "implantation failure is marked by the absence of ultrasound signs indicating pregnancy within the uterine cavity." Moreover, in multiple investigations, the definition of recurrent implantation failure (RIF) encompassed the notion of biochemical pregnancy, where an elevation in β-hCG levels was observed without concurrent ultrasound-based confirmation of pregnancy. Moreover, Coughlan et al., [16] pointed out that, "implantation process is complex, the assessment of causes of RIF should be performed on several levels. The most common analyses are chromosomal testing of both parents, the estimation of ovarian function (follicle stimulating hormone (FSH), luteinizing hormone (LH), anti-mullerian hormone (AMH) measurement) in women, and sperm DNA fragmentation in men, as well as assessment of uterine pathologies and fallopian tube permeability (hysterosalpingogram, laparoscopy)".

RIF patients show deregulated gene expression during the receptive phase compared to controls [45]. Studies focusing on p53 tumour suppressor gene, which regulates cell apoptosis, angiogenesis and is a potential mediator of pregnancy show significantly more homozygous genotypes in RIF patients [46]. The human LIF gene, essential for successful implantation, has been identified as a gene regulated by

p53. By means of direct, sequence-specific DNA binding and subsequent transcriptional activation, p53 exerts control over both baseline and inducible LIF transcription, as evidenced by Hu et al., [47]. In their research, Hu et al., [47] delved into LIF as a gene targeted by p53, resulting in heightened expression. The p53 molecule interacts with the p53-binding element within the initial intron, thereby modulating LIF expression in various tissues, including endometrial tissue. The absence of p53 leads to diminished LIF levels, consequently compromising the implantation process.

Polymorphism of genes and implantation failure

Genetic factors play an important role in the success of implantation. The abnormal genetic material in the endometrium can lead to implantation failure [48]. Numerous findings from recent studies suggest that genetic variables controlling angiogenesis and invasion processes play a significant role in embryo implantation. Studies in the literature demonstrate that implantation failure can result from genetic flaws, including genetic polymorphisms of the genes involved in these processes [49]. The genetic variables that cause implantation failure coincide with those that cause recurrent spontaneous abortion and infertility [50].

p53

The p53 gene (17q13) has 11 exons with a single nucleotide polymorphism (SNP) at codon 72 that results in a proline instead of an arginine by changing a G to a C. The p53 protein containing an arginine at codon 72 induces apoptosis, LIF expression, and cellular transformation considerably more efficiently [51]. Through phylogenetic investigation, it has been unveiled that p53 is a gene that has been preserved throughout evolution, and analogous transcriptional factors akin to p53 are present in invertebrates devoid of adult malignancies. These findings propose the likelihood of p53's participation in earlier developmental stages of these species [52]. A genetic polymorphism known as polymorphism of p53 codon 72 is being explored extensively for its significance in reproductive medicine. However, Razieh et al., [53] noted that the results on the correlation between polymorphism and abnormalities, recurrent pregnancy loss and RIF, are still inconclusive. Moreover, recent studies have demonstrated that p53 regulates female reproduction and blastocyst implantation through LIF [47].

MUC-1

MUC-1 (Mucin-1) is a glycoprotein expressed on the epithelial surface of different types of tissues, including the endometrium [54]. One proposal is that in mice MUC-1 mucin forms an anti-adhesive barrier, and its downregulation after ovulation is necessary for embryo attachment. Conversely, in man, rabbits, and baboons, MUC-1 mucin concentrations increase after ovulation and persist during implantation [53]. Women with recurrent pregnancy loss (RPL) were shown to express reduced endometrial MUC-1, as compared with a normal group of patients [55]. Wu et al., [56] demonstrated that MUC-1, a highly glycosylated polymorphic mucin-like protein secreted by the endometrial luminal epithelium is considered a “barrier to implantation”. In humans, MUC-1 is expressed in the luteal and pre-implantation phases in a progesterone-dependent manner.

LIF gene

Steck et al., [57] states that leukaemia inhibitory factor (LIF) is a glycoprotein that plays an important role in reproduction, with particular relevance in the regulation of implantation, but also has a variety of functions in different organ systems”. Cullinan et al., [58] studied that “the expression of LIF, related members of this group of cytokines, oncostatin M and ciliary neurotrophic factor, and the LIF receptor j3 and glycoprotein gpl30 in normal human tissues and in the endometrium of fertile women”. Fenwick et al., [59] explained that “LIF protein and mRNA are detectable in the human endometrial system only during the secretory phase of menstrual cycle”. Le´de´e-Bataille et al., [60] reported that low concentrations of LIF in uterine flushings at day 26 were highly predictive of subsequent implantation.

Hambartsoumian [61] demonstrated that low uterine concentrations of LIF protein in the secretory menstrual phase has been reported to be associated with a high risk of implantation failure after embryo transfer and in unexplained infertility. He also mentions that the secretion of LIF is observed during the proliferative phase of the menstrual cycle, and there exist disparities in LIF secretion within endometrial explant cultures between women who are fertile and those experiencing infertility. In fertile women,

the endometrial LIF secretion was 2.2-fold higher in the secretory than in the proliferative phase, whereas infertile women did not exhibit such an elevation of LIF production in the luteal phase. LIF concentration in uterine flushings of fertile women on days 18–21 of the menstrual cycle was 3.5-fold higher than in infertile women with recurrent IVF failure, and 2.2 times higher than in infertile women without multiple failure of implantation. Mikolajczyk et al., [62] also states that "LIF overexpression in uterine secretions may be used as a potential indicator of uterine receptivity in fertile women". Chen et al., [63] noted that "the majority of unexplained infertile women show significant decrease in LIF expression level, signifying the importance of LIF in implantation". Recently Hu et al., [47] identified that "p53 has a specific binding site on LIF promoter and regulates both basal and inducible transcription of LIF".

MTHFR gene

The human Methylenetetrahydrofolate Reductase (MTHFR) gene, which consists of 11 exons, is found on the short arm of chromosome 1 (1p36.22). The MTHFR enzyme is crucial for cell division, embryo development and early pregnancy. It also plays a crucial function in the metabolism of folate [64]. The MTHFR gene's two most prevalent variants are MTHFR A1298C and MTHFR C677T. Oocyte and embryo development are negatively impacted by decreased MTHFR activity [65,66]. Evidence suggested a connection between MTHFR 677C>T and ovarian reserve, oocyte maturation, and embryo aneuploidy. The MTHFR gene polymorphism might play a role in the etiology of patients with recurrent miscarriage (RM) or RIF [67]. In a study by Choi et al., [68], the findings showed that the combination MTHFR 677/MTHFR 1298 genotype might be linked to an elevated risk of RIF.

Human progesterone receptor (hPR) gene

Kastner et al., [69] present an essential genetic variation within the human progesterone receptor gene, which correlates with the probability of encountering implantation failure. This gene, responsible for the human progesterone receptor (hPR), operates in a dual capacity, encoding two distinct isoforms—hPR-A and hPR-B—with differing transcriptional factor activities. Sartorius et al., [70] states that "the longer isoform, hPR-A, has 165 additional amino acid residues on its amino terminus end, which leads to the change of hPR-B conformation and significant difference between the target genes and physiologic effects of the two isoforms". Cramer et al., [71] noted that "the imbalance between these isoforms' expression leads to severe abnormalities in ovarian and uterine function and defective implantation".

HLA-G gene

The non-classical HLA class Ib protein known as human leukocyte antigen (HLA-G) is essential for the mother to accept the semi-allogenic foetusis located within the major histocompatibility complex (MHC) at 6p21.3 [72, 73]. In contrast to the highly variable conventional HLA Ia genes, the HLA-G gene has limited tissue expression and modest allelic variation. HLA-G is mostly expressed in immunological organs and in the maternal-fetal interface [74]. The suppression of cytolysis by natural killer (NK) cells, enrichment of regulatory T (Treg) cells, and encouragement of a switch from a T-helper (Th)1 to a Th2 cytokine profile are all crucial roles of HLA-G at the fetal-maternal interface [75]. HLA-G is essential for immunological tolerance at the maternal-fetal interface. The crucial component determining embryo implantation is maternal immunological tolerance, which is brought on by interactions between soluble HLA-G and uterine lymphocytes. It is necessary for embryo implantation that HLA-G be soluble. However, research on the function of parental sHLA-G expression before to conception is limited [76, 77]. According to a meta-analysis by Fan et al., [78], the HLA-G 14-bp insertion allele may enhance the incidence of RIF in Caucasians. Implantation failure may be attributed to the high expression of sHLA-G_{tot} and sHLA-G_{EV} as well as the 14-bp deletion allele [79].

GENETIC ASPECTS	DESCRIPTION	REFERENCE
Aneuploidy	Abnormal number of chromosomes in the embryo, often leading to miscarriage or failed implantation.	1. [80] 2. [81] 3. [82]
Chromosomal Translocations	Rearrangement of genetic material between chromosomes, which can disrupt embryo development and implantation.	1. [83] 2. [84] 3. [85]
Genetic Mutations	Inherited mutations or genetic variants that can affect embryo development and implantation.	1. [86] 2. [87] 3. [88]
HLA Matching	Discrepancies in human leukocyte antigen (HLA) compatibility between partners can influence implantation.	1. [89] 2. [90]
Thrombophilic Gene Mutations	Mutations in genes related to blood clotting can impact blood flow to the uterus and embryo implantation.	1. [91] 2. [92] 3. [93]
Immune System Dysregulation	Genetic factors affecting immune response can lead to rejection of the embryo during implantation	1. [94] 2. [95]
Uterine Receptivity Genes	Genetic factors that influence the receptive state of the uterine lining and its interaction with the embryo.	1. [38] 2. [37] 1.
Embryonic Development Genes	Genetic factors controlling early embryonic development can impact embryo viability and implantation.	1. [96] 2. [97]
Uterine Abnormalities	Structural issues in the uterus, such as fibroids or polyps, can hinder proper embryo implantation.	1. [98] 2. [99] 3. [16]
Hormonal Imbalance	Irregularities in hormone levels (estrogen, progesterone) can affect the uterine environment for implantation.	1. [100] 2. [101]

Table 1: Role of Genetic Factors in Implantation Failure

Preimplantation Genetic Testing

Paul R Brezina et al., [102] described the process of Preimplantation genetic (PG) testing, which involves vthe collection of a cellular biopsy sample from a developing human oocyte or embryo, which is obtained through in vitro fertilization (IVF) procedures. This sample's genetic composition is then assessed to determine the most suitable embryos for subsequent uterine transfer. The inception of PG testing dates back was first used to determine the sex of cleavage stage embryos in couples dealing with X-linked genetic conditions [103].

The term PG testing encompasses various forms of genetic testing performed on oocytes or embryos following an IVF cycle [104, 105, 106]. This genetic analysis provides valuable insights that guide the selection of embryos deemed suitable for transfer into the maternal uterus. According to ASRM (2008), PG testing mainly falls under two overarching categories: diagnosis and screening, each serving distinct purposes [107].

Preimplantation genetic diagnosis (PG diagnosis) pertains to the examination of embryos for specific genetic irregularities inherited from one or both parents [105, 106]. This procedure is only feasible when a definite genetic cause has been pinpointed. Since Handyside A H et al., [103] reported the enhancements in methodologies have broadened the spectrum of disorders that can be screened through PG diagnosis. Examples encompass Huntington's disease, haemophilia, and cystic fibrosis. PG diagnosis identifies these anomalies by means like direct DNA sequencing or evaluation of chromosomal imbalances, using techniques such as microarrays and fluorescence in situ hybridisation (FISH) [108, 109, 110, 111].

It's important to underline that while PG diagnosis theoretically has the capacity to uncover specific physical traits such as hair color, actively seeking out this information is widely judged as unsuitable and morally wrong [112, 113]. Additionally, PG diagnosis has the potential to ascertain the gender of embryos. This feature has sparked controversy, particularly when employed for the purpose of family gender balancing. Yet, due to ethical reservations, a substantial number of fertility clinics have chosen

not to provide this service. Furthermore, the legality of utilizing PG diagnosis for gender selection varies across different countries [114. 115, 116].

PG diagnosis also finds utility in selecting embryos that match a sibling's human leukocyte antigen (HLA) for the intention of tissue donation, especially in cases involving medical conditions like leukemia [111, 117]. This application, referred to as HLA matching, is surrounded by intricate ethical and legal considerations. It raises issues concerning informed consent and the potential for exploitation. The permissibility of employing PG diagnosis for HLA matching differs among countries [114, 115, 116].

Genetic Screening for parents

PG screening is a method aimed at identifying numerical chromosome abnormalities (aneuploidy) in embryos produced by parents with presumed normal chromosomal compositions (normal karyotypes). Research shows that chromosomal aneuploidy is a primary contributor to pregnancy failure [118]. Traditionally, PG screening used FISH to examine embryonic cells obtained around three days post-fertilization, focusing on five to 14 chromosomes due to technical limitations. However, FISH-based PG screening [119] has not demonstrated improved pregnancy rates and could potentially worsen outcomes [120, 115, 121, 122].

Recent retrospective studies indicate that utilizing advanced technologies to test all 23 chromosome pairs might benefit certain patient groups compared to FISH. Additionally, a biopsy technique that gathers cells from the trophectoderm (a precursor to the placenta) five or six days after fertilization has shown promise in enhancing pregnancy rates. Despite being widely used, the efficacy of PG screening needs confirmation through large, well-designed randomized trials to establish its value for different patient populations [123]. Disagreement exists within the PG testing community regarding ideal candidates for PG screening. Common reasons for screening include advanced maternal age, repeat implantation failure, and recurrent pregnancy loss [124]. However, these trends primarily stem from reporting centers in Europe, the Middle East, Asia, and South America, with limited data from the United States. In the US, PG screening is often recommended for older patients, and recent data suggest benefits for women older than 35 with a history of recurrent pregnancy loss [102].

Globally, PG screening is most commonly used for advanced maternal age, recurrent pregnancy loss, unsuccessful IVF cycles (repeat implantation failure), and severe male factor. Although prospective randomized trials have not definitively established the benefits for any specific patient group, PG screening is employed to potentially enhance pregnancy rates and decrease miscarriage rates. Its routine use is not universally recommended by professional societies, but it continues to be used worldwide to improve pregnancy outcomes within various patient groups. In some cases, PG screening can be combined with PG diagnosis without the need for additional biopsies.

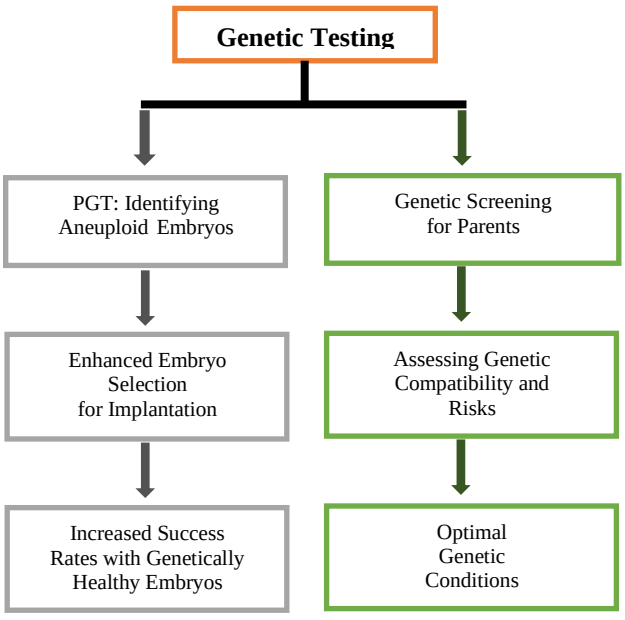

FIGURE 1: Genetic Testing and Diagnosis in Implantation Failure

Treatment Strategie

Once an anomaly related with implantation failure is identified, therapeutic options such as uterine septectomy, intra-uterine adhesion removal, endometrial polypectomy or myomectomy (particularly the submucous variety), and hydrosalpinx excision should be considered [18]. It is believed that intrauterine injection of a patient's own lymphocytes may increase endometrial receptivity and implantation rates while restoring the immunological balance in individuals with RIF, who may be unable to recruit the requisite lymphocytes for successful implantation [125]. New research on intrauterine infusion of platelet-rich plasma has also demonstrated a benefit in IVF transfers for women with thin endometriums [126, 127, 128]. Granulocyte colony-stimulating factor has been investigated as an in vitro fertilization adjunct treatment given locally or systemically to women with a thin endometrial lining, a history of recurrent pregnancy loss (RPL), or RIF [129, 130, 131]. Other immune therapies for RIF under investigation include intrauterine hCG infusion, intravenous immunoglobulin (IVIG), intravenous intralipid therapy and heparin [132]. The above reports signify the various treatment strategies available to achieve a successful pregnancy.

Methods

This review article synthesizes an extensive range of research studies, clinical observations, and scientific literature to provide a comprehensive overview of the molecular and genetic dimensions of implantation failure. A systematic search of databases, including PubMed and Google Scholar, was conducted to identify relevant studies. Out of the 43,699 review articles collected, 137 primary articles closely related to the topic were chosen for inclusion. The collected data were analyzed to highlight key insights into the complex interplay between embryonic and endometrial factors, immune system modulation, and genetic variations that influence implantation success. The methodology also encompassed a critical evaluation of ongoing research endeavors aimed at unraveling the intricate pathophysiology of RIF.

4. Conclusion

It Recurrent implantation failure is the process of failure to attain a pregnancy following 2-6 IVF cycles, in which more than 10 high-grade embryos were transferred to the uterus. There are several factors that cause failure of implantation, especially the genetics of parents and the embryo. There is growing evidence that genetic variables governing invasion and angiogenesis processes are important in embryo implantation. The present review is a pointer of various research studies and genetic factors involved in implantation failure. The review also highlights invasion and angiogenesis as a critical process behind implantation failure. By genotyping RIF suffered couples, the reasons and risk of IVF failure can be predicted in order to provide appropriate therapeutic options. The review also emphasizes further in-depth clinical trials on IVF to overcome the infertility in the near future.

Conflict Of Interest

The Authors declare that there is no conflict of interest.

Author's Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work

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