Review Article

Challenges in Fertilization and Implantation Success

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Abstract:

Assisted reproductive technology (ART) is a medical procedure used to treat infertility that involves manipulating oocytes and sperm in vitro; In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are the most common two techniques used in ART. Male factor infertility, diminished ovarian reserve, ovarian failure, ovulatory dysfunction, uterine malformations, and unexplained infertility are all indications of ART. Although the use of ART has steadily increased, there are a lot of conditions that pose challenges to its success, especially autoimmune diseases like rheumatoid arthritis, inflammatory bowel diseases, multiple sclerosis, and thyroid problems, which result in unfavorable outcomes. Also, diabetes and obesity are obstacles to the success of ART. Despite the fact that ART is a successful method of conception, adverse obstetric and perinatal outcomes such as low birth weight, preterm birth, and genital organ malformations can occur. This review aims to identify the types of challenges that face ART and lead to negative pregnancy outcomes to develop novel approaches and models aimed at successful fertilization and implantation.

Keywords: fertilization; oocyte-sperm interaction; implantation rates; art; miscarriage; rif; ivf; icsi; sperm quality

Introduction:

Assisted reproductive technology (ART) is a medical procedure used to help infertile couples become pregnant [1]. An ART is a fertility-related treatment in which eggs or embryos are manipulated, according to the American Centre for Disease Control [2]. In Vitro fertilization (IVF) and related techniques such as cryopreservation and intracytoplasmic sperm injection (ICSI) are currently used in ART [3]. Procedures that only manipulate sperm, such as intrauterine inseminations, are not included in this definition, nor are ovarian stimulation procedures without an egg retrieval plan [4]. Tubal obstruction, significant endometriosis, severe male factor infertility, ovulatory dysfunction, and unexplained infertility, which is defined as the inability to conceive clinically after 12 months of regular, unprotected sex are all reasons to use ART [5, 6].

Furthermore, ART has been shown to provide significant benefits in achieving a live birth, in addition to other private benefits on the maternal level such as lowering the risk of preeclampsia, caesarean delivery, and severe maternal morbidity [7], and social benefits, particularly on demographic aspects where the proportion of infants born after ART has exceeded 5% in some countries [8]. ART, however, has been linked to

harmful obstetric and perinatal outcomes such as low birth weight, preterm birth, genital organ malformations, and antepartum hemorrhage, despite all of the advancement and progress in the medical field [9]. Although assisted reproductive technology (ART) is widely used worldwide and has helped preserve human fertility, it has faced several challenges. Despite the ability to produce fertilization in a laboratory setting, live birth success rates have not significantly improved due to a variety of factors such as mismatched gametes or embryos [10], especially when kept in vitro for a variable time, as well as oxidative stress, which may harm embryo development [11]. Embryo implantation failure, the impact of chronic diseases and other therapies on gametes, miscarriages, a lack of understanding of biological processes, the optimization of gamete quality data collection, embryo implantation failure, and repeated failed implantation and IVF are all ongoing debates [12, 13].

While assisted reproductive technology (ART) is an important treatment approach for achieving fertility in a couple, its success remains uncertain due to a lack of knowledge, high-quality research, and evidence-based guidelines, as well as high-quality care and preventive measures. As a result, researchers have begun developing novel approaches and new models to achieve successful IVF [14].

Discussion:
Factors affecting the success of IVF:

IVF has four basic stages: superovulation, egg retrieval, fertilization, and embryo transfer [15]. Every IVF depends on successful superovulation, as this stage can predict IVF outcomes before the cycle is complete [16]. It is a drug-induced method of achieving multiple ovulations per cycle in which the patient is first injected with a large amount of FSH to stimulate the follicles, which are then treated with human chorionic gonadotropin (hCG), a hormone normally produced by a fully developed embryo. The hCG stimulates follicle maturation, and the egg is then collected [17]. It is critical at this stage to identify women who are likely to have an excessive response to ovarian stimulation, as this is the primary risk factor for ovarian hyperstimulation syndrome (OHSS), which can result in severe morbidity [18]. The next stage is egg retrieval. Oocyte retrieval is most safely performed under conscious sedation using a transvaginal approach guided by ultrasound and low-pressure aspiration [19]. 34 to 36 hours after hCG administration, mature oocytes are extracted. A vaginal ultrasound probe is used to visualize the ovaries, and an attached needle guide assists the physician in directing the needle into each follicle and aspirating the oocyte and follicular fluid [20]. During the fertilization stage, insemination or ICSI is used to fertilize the oocyte. The extracted eggs are next fertilized with male donor sperm and then examined under a microscope to determine whether fertilization was successful [21]. ICSI has been shown in studies to improve fertilization and the formation of high-quality embryos 48 hours after retrieval [22]. The final stage is embryo transfer. At this stage, healthy embryos are chosen and transferred to the uterus of a woman, who usually begins progesterone treatments 2 weeks before the implantation to develop the endometrium, and a pregnancy test is taken after 2 weeks to confirm the procedure's success [23].

Several factors influence IVF success, including the total number of embryos, the number of injected oocytes, the cause of infertility, the woman's age, and PCOS [24], in addition to the proper injections of the natural hormones FSH and/or LH (gonadotropins) used for this purpose, and other medications used to prevent premature ovulation [25]. Despite technological advances and ongoing research, success rates have not improved significantly in the last decade. While we can completely replicate fertilization in a laboratory setting, we still do not understand all of the biological processes involved in oocyte-sperm interaction. Furthermore, scientists have faced several challenges that have led to repeated failures in implantation, including oocyte-sperm interaction, gamete quality, a lack of knowledge on the critical role of the male partner in the fertility procedure, chronic diseases and therapies on gametes and their fertilization potential, failure of the endometrium to receive the developing embryo, miscarriages, and other factors that may impact the success of IVF such as the age of individual donating oocytes, use of tobacco and other substances, and obesity [26, 27].

To diagnose fertilization failure, we must first understand its aetiology. Total fertilization failure may be caused by asynchrony between the oocyte and the sperm, resulting in a failure of the activation mechanism and fertilization failure [28]. It is well known that sperm defects are the cause of activation failure. Phospholipase C zeta (PLC) has been shown to play an essential role in oocyte activation failure, and any reduced or altered forms of (PLC) have been shown to cause male infertility-related fertilization failure [29]. In mammalian fertilization, sperm-specific phospholipase C zeta is known to be the physiological stimulus that drives egg activation and embryonic development because it generates $Ca2+$ [30]. A phospholipase C zeta deficiency will negatively affect the sperm-egg fusion event [31], as it will elicit atypical and delayed patterns of $Ca2+$ oscillations [32], which are species-specific for a successful fertilization process [33]. According to studies, the parameters of $Ca2+$ oscillations have a significant influence on egg activation because the first $Ca2+$ transient or oscillation occurs in the first few minutes of sperm-egg fusion and lasts for 2 to 3 seconds, resulting in a small rise in cytoplasmic $Ca2+$. This is followed by an inflection point that represents a brief decrease in the rate of $Ca2+$ rise, known as a "shoulder," and then a resumption of a very rapid rate of $Ca2+$ rise [34, 35]. The fertilized egg completes meiosis in response to the increase in intracellular $Ca2+$. The $Ca2+$ signal is delivered in mammalian eggs as a series of long-lasting cytoplasmic $Ca2+$ oscillations that begin shortly after gamete fusion and continue until meiosis is completed. Sperm PLC stimulates $Ca2+$ release from egg intracellular stores by hydrolyzing the membrane lipid PIP2, resulting in activation of the inositol 1,4,5-triphosphate (InsP3) receptor $Ca2+$-signaling pathway and early embryogenesis [36]. Meanwhile, any potential defect in the PLC or PLC-induced $Ca2+$ release has been linked to a variety of male infertility conditions, including abnormal sperm parameters and morphology, sperm DNA fragmentation and oxidation, and abnormal embryogenesis/pregnancies. Such sperm have PLC levels that are absent or reduced, as well as abnormal PLC localization patterns within the sperm head [37]. The remaining question is whether embryo development can occur in the absence of phospholipase C zeta. Although phospholipase C zeta is the physiological agent responsible for $Ca2+$ oscillation

initiation and egg activation, it has been demonstrated that conception in humans can occur in its absence via an alternative route [34]. Dr.Oko and colleagues reported in 2007 an alkaline extracted protein from sperm, the post-acrosomal sheath WW domain binding protein (PAWP), enters the oocyte during fertilization and induces oocyte activation events via the calcium release mechanism [38, 39]. Nonetheless, Wu and colleagues hypothesized that PAWP mediates its effects via other cytoplasmatic proteins, such as the yes-associated protein (YAP), which causes calcium release by activating PLC [40]. In conclusion, oocyte activation is at a crossroads because it is still unknown, while the proposed factors (PLC or PAWP) should be confirmed by additional research. This could provide useful biological sperm markers for ICSI fertilization failure.

Another issue confronting fertilization is gamete quality, where optimizing gamete quality and storage conditions was found to be highly correlated with successful fertilization [41]. To improve ART outcomes and optimize gamete quality, it would be necessary to reduce the accumulation of ROS (reactive oxygen species), which leads to oxidative stress, which has been shown to affect gamete quality [42]. Multiple exogenous factors have been identified as potential sources of ROS, including pH and temperature, exposure to visible light, culture media composition, and ART techniques involving gamete/embryo handling and cryopreservation. One way to improve gamete quality is to boost the antioxidant capacity of the gamete and embryo against the harmful effects of oxidation [43].

The loss of the balance between oxidants and antioxidants is the most basic definition of oxidative stress [44]. ROS can be produced endogenously from gametes or exogenously from environmental factors during the ART procedure [43].

ROS sources in male sources:

1. Immature spermatozoa: immature spermatozoa are functionally defective, with impaired motility and abnormal morphology [45], because their residual cytoplasmic droplets have been linked to the generation of G6PD, which is the major fuel for ROS production [46].
2. Leucocytes: increased sperm leucocytes are strongly associated with ROS generation in vivo, particularly during infection or inflammation, by releasing a large amount of peroxidase [47].
3. Varicocele: the abnormal dilatation of veins in the pampiniform plexus surrounding the spermatic cord is associated with increased ROS and decreased antioxidant concentrations [48].

ROS source in female sources:

1. Oocyte: When ROS levels are high, they can disrupt oocyte function, resulting in chromosomal scattering and aneuploidy and thus negative ART outcomes [49].
2. Cumulus mass cells: Cumulus mass cells are thought to protect the oocyte from damage because they can produce antioxidants such as superoxide dismutase, which if reduced, results in excessive production of 8-OHdG (an oxidative stress by-product), which affects fertilization rates and embryo quality [50].
3. Follicular fluid: High levels of follicular fluid ROS are associated with a negative pregnancy outcome after ICSI, but follicular fluid total antioxidant capacity is associated with a positive pregnancy outcome. In women with tubal factor infertility, endometriosis, and polycystic ovarian syndrome (PCOS), the upper reference limit for viable embryo formation was calculated to be around 107 cps/400 l follicular fluid [51].

Exogenous factors such as pH and temperature, as well as exposure to visible light, culture media, and ART techniques, were discovered to contribute to ROS production in ART. Both pH and temperature have been shown to have a strong influence on cellular haemostasis, as these two parameters can have a significant impact on physiologic properties, protein synthesis, mitochondrial function, and cellular metabolism [52]. Furthermore, pH can obstacle sperm motility. The maturation of oocytes and the development of embryos. As a result, the temperature must be kept at human body temperature, as any variation can cause changes in pH and thus excessive ROS production [52]. Visible light is another factor that can cause ROS release and affect ART outcomes, as it has been shown to cause OS-induced damage to cholesterol and unsaturated lipids contained in cell membranes [53]. The composition of the culture media has a direct impact on embryo development. The presence of metallic ions in the culture medium, such as iron or copper, is especially influential because it can increase ROS generation by activating relevant enzymes or simply by catalysis by Fe^{2+}/Fe^{3+} ions to produce hydroxyl radicals [54]. Although sperm preparation typically involves centrifugation to remove the seminal plasma and other components and cryopreservation to keep gametes and embryos alive, both procedures have the potential to increase ROS levels because longer centrifugation times expose sperm to higher temperatures, which can negatively affect sperm parameters. Additionally, sperm membrane damage from lipid peroxidation and OS-induced DNA fragmentation can occur during cryopreservation, which can also negatively affect sperm parameters [55, 56].

To improve the quality of a good gamete, antioxidant agents such as enzymatic oxidants (Superoxide dismutase, Catalase, Glutathione system) and non-enzymatic oxidants must be used (Vitamins and vitamin-like substances, Hormones, and Other antioxidative substances). In a variety of clinical settings, antioxidants have been used to treat infertility. High levels of ROS, which cause oxidative stress, unquestionably affect assisted reproduction outcomes, resulting in lower rates of fertilization, implantation, and pregnancy. As discussed in this review, in vitro ART procedures provide numerous opportunities for ROS and oxidative stress to develop, reducing gamete/embryo quality and, as a result, ART success.

Furthermore, while gamete storage has become an essential step in optimizing good fertilization, catastrophic incidents such as the death of an employee or the loss of a freezer full of patient embryos or sperm continue to occur frequently enough to concern the industry and highlight the need to make practices significantly safer [57].

ART's challenges:

Chronic diseases are one of ART's challenges in the twenty-first century. Chronic diseases are well known to have an impact on the course of pregnancy as well as fertility rates [58]. Ulcerative colitis, Crohn's disease, rheumatoid arthritis, multiple sclerosis, epilepsy, hyperthyroidism, hypothyroidism, and diabetes mellitus were discovered to be the most common chronic diseases that presented problems with low implantation rates, low fertilization rates, or early embryo development during ART [59].

1. ART efficacy in women with inflammatory bowel disease:

The two most common idiopathic inflammatory bowel diseases (IBDs) are Crohn's disease (CD) and ulcerative colitis (UC) [60]. Symptoms of IBD worsen during the menstrual cycle without being related to disease activity. Endometriosis is more common in women with IBD than in women without IBD. The low fertility rate is due to perianal involvement and ileal pouch anastomosis (IPAA) surgery [61]. Crohn's disease, on the other hand, is a contributor to infertility [62], as it can cause inflammation in the fallopian tubes or ovaries, dyspareunia, decreased libido, depression, and decreased ovarian reserve [63]. IBD can reduce the success rate of IVF. Because the ovaries are usually affected in both organic specific and systemic autoimmune diseases, Honghao Sun et al proposed that IBD can affect the ovarian reserve [64], and because IBD is an autoimmune disease, it can lead to a significant reduction in the levels of AMH secreted by granulosa cells in women of reproductive age [65, 66, 67]. Furthermore, studies showed that drugs used to treat IBD, such as thalidomide, lower AMH and antral follicle counts [68], as well as glucocorticoids and cyclophosphamide, which cause a reduction in the number of primordial follicles, resulting in premature ovarian insufficiency by dormant follicle activation [69, 70]. Moreover, malnutrition was strongly linked to unsuccessful IVF, as IBD was heavily associated with nutrient deficiencies, including low iron levels, Vit B12, and Vit D, which were proven to be associated with a viable pregnancy [71]. Some clinical studies have found that women with IBD have poorer IVF outcomes.

2.ART efficacy in women with rheumatoid arthritis disease:

Women with rheumatoid arthritis already have infertility issues compared to women without rheumatoid arthritis, as they have inflammatory modified settings, limited sexual activity, and adverse drug effects on ovarian function [72], and the efficacy of ART treatment on these women was demonstrated to be severely weakened, with a significantly lower chance of live birth per embryo transfer compared to women receiving ART treatment. Rheumatoid arthritis has been shown to reduce the likelihood of implantation [73]. Autoimmunity may play a significant role in IVF implantation failure. In patients with rheumatoid arthritis, the implantation rate was low, as was endometrial receptivity, both of which are required to maintain the pregnancy throughout the trimesters [74]. These processes, however, are complicated because they involve factors such as the immune system, cytokines, hormones, metabolomics, proteomics, and the quality of the embryo itself [74]. Successful implantation requires the successful establishment of immunologic tolerance towards the

implanting embryo [75], which is accomplished through a cross-talk between the embryo and the maternal immune system, mediated by a variety of biological factors, where implantation is widely recognized as an inflammatory process requiring the regulation of inflammatory pathways [76]. Rheumatoid arthritis is classified as an autoinflammatory disease, in which the innate immune system self-reacts, damaging the surrounding tissue. Based on several studies, a hypothesis suggests that rheumatoid arthritis can cause dysfunction of the innate immune system response, particularly macrophages, natural killer cells, and dendritic cells, which account for most of the leukocytes present in the endometrium during the implantation phase [77, 78]. In patients with rheumatoid arthritis, the treatment can have both beneficial and detrimental effects on ART procedures, depending on the patient's autoimmune profile, risk profile, and thromboprophylaxis during ovarian stimulation [79]. Several anti-inflammatory and immunosuppressive drugs have been assessed to find effective therapies to improve embryo implantation, but it is still debatable whether corticosteroid drugs such as prednisolone can be used with a beneficial effect in ART treatment; appropriate drug therapy administration may be helpful only in a specific group of patients and with specific treatment protocols [80].

3.ART efficacy in women with multiple sclerosis disease:

Several studies comparing the chance of live birth in women with multiple sclerosis receiving ART to women receiving ART without evidence of MS found that women with MS receiving ART have a lower live birth rate [81]. Due to immunological changes induced by hormones, such as an increase in pro-inflammatory cytokines and anti-MGO antibodies, patients with SM appeared to have relapses in ART treatment [82]. Synchronized and coordinated interactions between the embryo and the maternal endometrium are required for successful embryo implantation [75]. Although MS does not preclude the use of assisted reproductive technology, it may impair clinical outcomes and lead to treatment failure by increasing the T-Helper 1 (TH1) response, thereby releasing the interferon-gamma and tumour necrosis factor-alpha associated with MS episodes, as well as increasing the TH2 response related to the circulation of interleukins 4 and 10, which leads to a maternal immune intolerance toward the presence of the fetus [83, 84], as previously reported. In addition, some drugs used in treatment, such as cyclophosphamide and mitoxantrone would have negative effects on oocytes, ovarian reserve depletion, and an increased risk of spontaneous miscarriage [85].

4.ART efficacy in women with epilepsy:

Although epilepsy is not considered an autoimmune disease, it is a chronic disease because of its role in brain inflammation in the pathogenesis of seizures [86]. According to studies, there is a mutual relationship between ART and epilepsy, in which ART treatment can exacerbate epilepsy and epilepsy and anti-epileptic drugs can lead to ART treatment failure [87]. It is well known that assisted reproductive technology involves various techniques aimed at allowing reproduction in infertility, including ovarian stimulation, including the administration of gonadotropins, which lead to a significant increase in estrogens, administered for endometrial preparation [88]. However, most studies have shown

that estrogens increase neuronal excitability, causing glucuronidation of lamotrigine and oxcarbazepine, and thus seizures exacerbations [89]. On the other hand, medications used to treat epilepsy may affect the reproductive functions of the hypothalamus-pituitary-ovary axis, causing an increase in LH hormones, a decrease in progesterone, and an increase in androgen, leading to ovarian hyperstimulation syndrome (OHSS) and thus failure in ART treatment [90]. Exogenous estrogens, according to our knowledge, may worsen seizures in women with epilepsy (WWE) by lowering the seizure threshold and inducing glucuronidation in women taking lamotrigine. Due to the rising prevalence of assisted reproductive technologies and the frequent need for estrogenic and estrogen-raising hormone therapy, adjunctive pre-treatment with benzodiazepines should be considered as part of the therapeutic strategy during hormone treatment that contains estrogens or induces an estrogenic rise in women taking AEDs inactivated by glucuronidation [86, 91].

5. ART efficacy in women with thyroid gland diseases

Thyroid disorders are known to affect female fertility by causing anovulatory cycles, luteal phase defects, high prolactin levels, and sex hormone imbalances, which can lead to adverse ART events [92]. Thyroid hormones have a direct impact on reproductive hormones. Hypothyroidism and hyperthyroidism are common, serious, and often treatable causes of infertility. Hypothyroidism is associated with lower plasma estrogen and androgen concentrations, as well as decreased luteinizing hormone (LH) secretion. Anovulation and decreased libido are possible. In hyperthyroidism, there may be insufficient mid-cycle LH surges, resulting in anovulation. Thyroid function must therefore be tightly controlled for better reproductive outcomes. The medications levothyroxine for hypothyroid women and propylthiouracil for hyperthyroid women are recommended [93]. Thyroid antibodies, thyroid-stimulating hormone, and thyroxine have all been linked to inadequate implantation or early embryo development in the uterus [94]. Thyroid anti-bodies screening should be done in euthyroid women with recurrent IVF failure, and intravenous immunoglobulins can be given in positive cases. During IVF, HCG for ovulation should be extremely helpful in compensating for low LH levels. Following embryo transfer, adequate luteal support should be provided.

6. ART efficacy in women with diabetes mellitus:

Diabetes mellitus reduces fertility in type 1 diabetes patients by interfering with the secretion of essential hypothalamic hormones known as gonadotropin-releasing hormone and luteinizing hormone [95]. Women with type 2 diabetes are more likely to develop polycystic ovarian syndrome (PCOS), a condition marked by obesity, increased testosterone, and infertility. Women with type 1 diabetes had an equal chance of having a live birth per embryo transfer as women with type 2 diabetes had worse glycemic control than women with type 1 diabetes [96]. It is not surprising that women with some autoimmune and chronic inflammatory diseases have a lower chance of implantation or early embryo development. In summary, autoimmune diseases are caused by the dysfunctional activation of the adaptive immune system, which results in tissue destruction by self-reacting B and T lymphocytes,

whereas autoinflammatory diseases are caused by the innate immune system, which damages the surrounding tissues [97]. They play a significant role in the regulation of angiogenesis, vascular remodelling, and trophoblast invasion. Instead, adaptive immune system effector, regulatory, and suppressor T cells participate in immune tolerance toward the semi-allogeneic fetus, and they are partially modulated and activated by the innate immune system. Chronic inflammation caused by a dysfunctional innate immune system may have a greater impact on the implantation process [79, 97].

To clarify, new reproductive technologies, such as in vitro fertilization (IVF), are becoming more common, allowing infertile couples to become parents and start families. However, many medical conditions have been shown to induce endometrial receptivity, changes in endometrial cytokines, abnormal reproductive hormones, or other factors, which can reduce the efficacy of ART.

In recent decades, several studies have compared IVF and ICSI results for oocyte fertilization. Multiple factors, including maternal age and women's parity, have been linked to pregnancy loss during the first IVF cycle [98], and women who conceived during their first IVF cycle and experienced a pregnancy loss were more likely to drop out of their second IVF cycle [99], as the outcomes of the first IVF cycle were as follows: no retrieval, failed fertilization, failed implantation, chemical pregnancy only where the beta-hCG test was positive but no uterine gestational sac was detected on the ultrasound, pregnancy loss including spontaneous abortion, therapeutic abortion, or stillbirth [100]. According to studies, age is a significant factor in IVF failure because it affects ovarian stimulation and oocyte competence. The most common cause of embryonic aneuploidies is maternal age [101]. Ageing impairs certain mechanisms that lead to decreased oocyte/embryo competence and, as a result, IVF cycle failure. These are mitochondrial dysfunction, where mitochondria are considered pivotal, particularly in the delicate first phases of preimplantation development [102], as it covers an essential role in various signalling pathways, such as Ca2+ signalling and regulation of the intracellular redox potential, which is especially important for fertilization and early development [103], and ageing on the mitochondria can cause mitochondrial swelling, vacuolization, and cristae alteration [102]. Telomere shortening has been demonstrated in the oocytes of women who experienced IVF failure or recurrent miscarriage [104], as well as in oocytes that resulted in fragmented or aneuploid embryos [105]. Cohesin dysfunction, which may result in chromosomal missegregation [106], and Spindle Instability, were aberrations in its assembly that appear to contribute to an increased prevalence of aneuploidies in older women [107]. These anomalies may also be attributed to decreased mitochondrial metabolic activity, resulting in a lower amount of ATP due to advanced maternal age [108]. However, even though the ICSI technique resulted in a higher fertilization rate, more embryos developed, and a lower risk of total fertilization failure (TFF), it was proven to be associated with ART cycle failure. The majority of cases are caused by a lack of mature oocytes, a failure of oocyte activation, or a lack of appropriate spermatozoa for injection [109]. Although sperm penetration failures are more commonly blamed on IVF and oocyte activation

and maturation defects in ICSI, the causes of fertilization failures can be multiple and remain poorly understood despite a considerable number of studies [110].

Another difficulty in fertilization treatment is the implantation of human embryos. Bidirectional communication between the blastocyst and the receptive endometrium is required for successful implantation [111]. The causes of repeated implantation failure include delayed endometrial maturation, structural abnormalities, inflammation, and progesterone resistance [112]. Coughlan et al define RIF as "the failure to achieve a clinical pregnancy after transferring at least four good-quality embryos in at least three fresh or frozen cycles in a woman under the age of 40 years [112]." RIF can be caused by two types of disorders: known anatomical disorders and non-anatomical disorders or others [113].

Anatomical disorders:

RIF can be attributed to a variety of anatomical disorders that can distort or damage the endometrial cavity, resulting in repeated fertilization failure, such as fibroids, which are responsible for the modification of HOXA10 [114], a homeobox-containing transcription factor that is required for proper adult endometrial development during each menstrual cycle [115], its expression is required for endometrial receptivity, and LIF (leukaemia inhibitory factor) expression is reduced in women with fibroids during the mid-secretory phase [116]. Other conditions like hydro salpinges, where the inflammatory fluid may harm both the embryo and the endometrium, or endometrial adhesions or infection following surgery [117].

Non-anatomical disorders or others:

a.Chronic: endometritis, identified either by standard histology or, preferably, by immunohistochemically labelling plasma cells with anti-CD163 [118, 119], is characterized by increased plasma cell density in the endometrial stroma. So far, the most common pathogens identified are group B streptococcus, E. coli, Streptococcus Faecalis, and Mycoplasma [120]. According to some studies, chronic endometritis alters endometrial receptivity by creating a dysbiotic environment with dense lymphocyte populations and a shift toward pro-inflammatory cytokine profiles (Th1/Th17) [121].

b.Immunologic disorders:

The literature has extensively discussed the role of differential expression of various cytokines in implantation, where a persistent shift to a Th1 cytokine pro-inflammatory profile causes implantation failure or miscarriage [122]. A change toward a Th2 anti-inflammatory cytokine profile, on the other hand, promotes implantation and early fetal development. It's interesting to note that a T-regulatory (Treg) cell profile is necessary for successful implantation, whereas a shift toward a Th17 phenotype is linked to subpar reproductive outcomes [123].

c.Thin endometrium:

Although its cause is unknown, it is thought that it may be due to defective angiogenesis, which deprives the endometrium of essential nutrients and oxygen [124]. Most experts agree that a thin endometrium is one with an endometrial thickness below 8 mm [125].

For successful fertilization, it is crucial to comprehend the mechanism of endometrial receptivity failure. As a result, multiple techniques, including endometrial biopsy, hysteroscopy, and ultrasonography, have been used to assess endometrial receptivity failure. The best day to transfer the embryo during an IVF cycle can be identified using an endometrial Receptivity Analysis (ERA), a genetic test that can be performed using a small sample of a woman's endometrial lining [126]. When a woman has had two or more unsuccessful embryo transfers after in vitro fertilization (IVF), performing an endometrial receptivity analysis can be quite beneficial [127]. This is because the window of endometrial receptivity can be one of the causes of infertility in these women. Before the IVF cycle, a mock embryo transfer cycle will involve an endometrial biopsy [128]. After that, this sample will be examined to determine the best day for embryo transfer and endometrial receptivity. To decide when to try embryo implantation in a subsequent transfer cycle, the sample will be sent to a lab for molecular analysis. There are three probable outcomes. Pre-receptive means that the endometrium is not ready to receive the embryo and that transfer at this time may not be ideal. Receptive means that the endometrium was ready to receive the embryo at the time the endometrial biopsy was taken, and post-receptive means that the endometrium had reached that stage but has since passed it [129].

It is well known that, compared to a typical pregnancy, pregnancies that use assisted reproductive technology (ART) may have a higher risk of miscarriage [130]. Female age, body mass index, uterine malformation, and prior miscarriages are some of the factors associated with spontaneous miscarriages in ART treatment [131]. The risk of miscarriage varies significantly with maternal age, exhibits a clear recurrence pattern, and is also elevated in the wake of some unfavourable pregnancy outcomes [132]. Maternal age must be considered when analyzing first-trimester pregnancy losses because, according to prior research, aneuploidy rates dramatically rise with maternal age in both the conventional IVF and ICSI groups [133].

Obesity has been linked in studies to a variety of negative health effects [134]. Due to problems with the hypothalamic-pituitary axis, anovulation, and its association with a higher risk of pregnancy complications and miscarriages, women with high BMI are at an increased risk of infertility [135]. The embryo and endometrium must work closely together for implantation to occur and for the pregnancy to progress. Increased BMI is linked to many important endocrines and paracrine changes that may harm oocyte maturation and embryonic competence. Hyperandrogenism [136], insulin resistance, abnormal leptin levels, and LH hypersecretion [134, 137] are a few of these. Additionally, interleukin-6 and tumour necrosis factor levels in the endometrium and intra-follicular tissues are correlated with BMI [138]. These two inflammatory markers have been linked to poor oocyte quality, compromised implantation, and an increased risk of miscarriage, and may therefore mediate the impact of obesity on the success of

IVF.

Congenital uterine abnormalities are typically linked to poor embryological development and unfavourable pregnancy outcomes [139]. Preterm births, miscarriages, and ectopic pregnancies are all more common when the uterus is malformed [140]. In addition to threatening preterm delivery, premature amniotic fluid departure, intrauterine growth restriction, uterine rupture, and caesarean section, uterine malformations impair fertility and cause several obstetric complications [141]. A challenging problem in assisted reproductive technology is recurrent pregnancy loss [142]. Low levels of serum folic acid resulting from mutations in genes related to folate metabolism [143], abnormal maturation and activation of specific subsets of peripheral blood lymphocytes [144, 145], and a deficiency in elements necessary for maintaining placental vascularization and vascular endothelial cell function are just a few possible pathogeneses of recurrent miscarriages in IVF.

Fertilization and implantation are two critical stages in any ART cycle. While we can completely replicate fertilization in the laboratory, we still do not understand all the biological processes involved in oocyte-sperm interaction. Furthermore, data on possible strategies for optimizing gamete quality (including sperm quality, as the critical role of the male partner is all too often overlooked) and the effect of chronic diseases/therapies on gametes and their fertilization potential are required in a clinical setting. Following fertilization, the foundation of a successful pregnancy is a finely tuned synchrony between an appropriately developing embryo and the receptive endometrium. While much has been written about failed implantation and a few methods for testing endometrial receptivity have been proposed, there are still many questions about the subject, beginning with the existence and correct definition of repeated failed implantation (RIF). This special issue aims to shed light on these controversies through collaboration among basic and translational researchers, clinical embryologists, and clinicians, with the ultimate goal of improving clinical practice.

Conclusion:

ART is a medical procedure used to treat infertility in couples attempting to conceive. Male factor infertility, endometriosis, tubular obstruction, uterine malformations, and unexplained infertility are all reasons for ART. Several types of ART procedures use various techniques and reproductive cells, with in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) being the most common. However, ART is facing several challenges that are leading to negative outcomes, such as implantation failure, the effect of chronic diseases and therapies on gametes, a lack of knowledge about the critical role of the male partner, repeated failed implantations, and asynchrony between oocytes and sperm. As a result, patients undergoing ART treatment are at increased risk for several adverse pregnancy outcomes. Patients undergoing ovulation induction do not experience many of these risks, but there are still more negative pregnancy outcomes.

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