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Opinion Articles

Traumatic potential of Recurrent Implantation Failure in Assisted Reproductive Technology paths for couples experiencing infertility

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Abstract

Heterosexual couples dealing with infertility can seek Assisted Reproductive Technology (ART) treatments to achieve pregnancy. Within these programs, infertile couples can experience Recurrent Implantation Failure (RIF), which is the failure to achieve a clinical pregnancy after three or more transfers of good-quality embryos into the uterus. RIF also refers to cases of biochemical pregnancy in which increased levels of Beta hCG hormone are detected without subsequent signs of clinical pregnancy.

Although the psychological literature has shown that the repetition of ART attempts significantly correlates with negative psychological outcomes for men and women, to date there are no studies regarding the potentially traumatic features of RIF experiences.

Hence, we provide an overview of the extant literature to highlight points of contact between the features of traumatic experiences and those of RIF and infertility, including the specific characteristics that make the population of infertile couples in ART programs potentially more vulnerable to trauma. This article aims to stimulate reflection in this area and emphasize the importance of expanding research to deepen our knowledge of the psychological processes involved in RIF conditions within ART treatments for infertile couples.

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1. Introduction

The present contribution aims to provide a reflection regarding the traumatic potential of repeated reproductive failures in the context of Assisted Reproductive Technology (ART) journeys for infertile heterosexual couples. We will focus on experiences of biochemical pregnancy and recurrent implantation failure (RIF) of the embryo, which are scarcely investigated in the psychological literature. Hence, this article aims to stimulate reflection in this field and emphasize the importance of expanding research and deepening our knowledge around the issues described, hoping to drive more attention to the psychological processes involved in RIF conditions in the context of ART treatments for infertile couples.

1.1 Infertility and Recurrent Implantation Failure in ART programs

The World Health Organization (WHO) International Committee for Monitoring Assisted Reproductive Technologies (ICMART) defines infertility as the "failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse, or due to an impairment of the person's capacity to reproduce either as an individual or with his/her partner" (Zegers-Hochschild et al., 2017, p. 1795). Infertility is estimated to affect between 8 and 12% of reproductive-aged couples worldwide (Vander Borght & Wyns, 2018) and 15% in Italy (ISS, 2022).

On a global scale, only half of the couples who experience reproductive difficulties (Boivin et al., 2007) seek pregnancy through Assisted Reproductive Technology (ART), which is the set of medical, biological, and surgical procedures and technologies that treat different types of fertility problems (Zegers-Hochschild et al., 2017). To date, more than 10 million children have been born worldwide thanks to ART (ESHRE, 2022). In Italy, over 77 thousand couples underwent ART treatments in 2019, and 14162 children were born (www.salute.gov.it).

The most widely employed ART are IntraUterine Insemination (IUI), In Vitro Fertilization Embryo Transfer (IVF), and IntraCytoplasmatic Sperm Injection (ICSI). These procedures differ according to the level of invasiveness and the place where conception occurs. In IUI treatment, conception takes place “in vivo”, that is, inside the woman’s body, while IVF and ICSI rely on “in vitro” fertilization, which is carried out in a culture medium in a controlled environment. In 2017 in Europe, the pregnancy rate by embryo transfer was 39.0% after IVF, 40.2% after ICSI, 33.1% cryopreserved embryo transfer, and 49.2% after egg donation, with higher success rates for patients under 35 years old (ESHRE, 2022).

The application of ART can have a negative outcome if embryo implantation fails after being transferred into the uterus. Specifically, the medical literature defines Recurrent Implantation Failure (RIF) as the failure to achieve clinical pregnancy after three or more transfers of good-quality embryos into the uterus (Orvieto et al., 2015). This condition also refers to cases of biochemical pregnancy, in which increased levels of Beta hCG hormone (indicator of pregnancy) are detected without subsequent signs of clinical pregnancy (Coughlan, Ledger, et al., 2014).

Data regarding the incidence of RIF are scarce within the Italian and international literature, and an accurate representation of the extant prevalence of this phenomenon is not available. However, it is estimated that there is a 30% probability of successful embryo implantation (Coughlan, Ledger, et al., 2014). Furthermore, it has been observed that the rate of embryo implantation after transfer increases according to the stage of embryo development, reaching around 40% for embryos on the fifth or sixth day. Additional factors that appear to affect successful implantation are the mother's age as well as the quality and quantity of the transferred embryos (Coughlan, Ledger, et al., 2014).

Data on biochemical pregnancy show that this condition affects 8 to 33% of the population (Maesawa et al., 2015), including those who conceive naturally. To date, however, it is not possible to estimate the reliability of this data on a general scale since most women who acknowledge having had a biochemical pregnancy are undergoing ART treatments and therefore pay special attention to all stages of the reproductive process (Bashiri et al., 2018).

1.2 Couples' psychological experiences of ART treatments

From a psychological perspective, it has been widely acknowledged that heterosexual couples who face infertility experience an "emotional roller coaster" (Swanson and Braverman, 2021, p. 68), characterized by cyclical shifts of affective states such as hope, disappointment, anger, and mourning after each reproductive failure (Swanson and Braverman, 2021). In addition, ART programs often lead to an emotional experience that has been described as an "emotional short-circuit" strongly contingent on treatment outcomes (Righetti et al., 2016, p. 3) and possibly linked to emotional dysregulation (Calvo et al., 2021).

Indeed, the diagnosis of infertility and subsequent ART programs represent the most psychologically complex and critical event in many couples' lives, resulting in a traumatic experience for some (Bhat & Byatt, 2016; Pasch & Sullivan, 2017).

Burns (2007) identifies five classes of psychological effects of infertility: emotional effects (grief and depression, anger and frustration, guilt, shock and denial, anxiety); feelings of loss of control (over one's own body and health, safety, and future); effects on self-esteem, identity, and worldview; social effects (on relationship with one's partner, sexuality, family and social interactions); loss of the bond with the desired child. Therefore, infertile couples may experience feelings of inadequacy, inferiority toward peers (Cousineau & Domar, 2007), shame, anger, and sadness (Frederiksen et al., 2015), as well as frustration and guilt over life choices that may have led to infertility, including the decision to schedule childbearing for later in life (Dunkel-Schetter & Lobel, 1991). Furthermore, reproductive failure can undermine self-esteem and sense of self, especially in women (El Kissi et al., 2013). Contemporary research has also shown that a reduced sense of control is associated with a higher risk of depression and lower psychological well-being (Myles et al., 2020; Myles et al., 2021; Miles & Merlo, 2022a; Miles & Merlo, 2022b). The overall sense of loss of control brought about by the infertility condition (Greil, 2002) could potentially manifest as the hopelessness of their autonomy, which may result in infertile couples' psychological distress.

In this sense, infertility represents a complex and multifaceted condition, with implications for both the individual and the couple (Calvo et al., 2023; Donarelli et al., 2016; Maroufizadeh et al., 2015). On the one hand, partners may experience increased tensions or crises in the couple (Greil, 1997; Van Der Merwe & Greeff, 2015); on the other hand, this phenomenon concerns a common project shared by both partners. Hence, infertility can be an opportunity to increase intimacy and confrontation within the couple, eventually consolidating and strengthening the bond (Schmidt et al., 2005).

Furthermore, ART programs require a significant psychological, financial, and physical investment for the couple, with treatments primarily targeting the woman's body and including highly invasive procedures, such as daily injections for ovarian stimulation, transvaginal ultrasound scans, egg and sperm retrieval, fertilization of oocytes, and embryo transfer into the uterus (Righetti et al., 2007). Thus, both physical and psychic dimensions are significantly involved in these programs. The American Society for Reproductive Medicine (ASRM) has highlighted how stress related to repeated unsuccessful ART attempts can affect women's hormone levels and, consequently, the response to ovarian stimulation, ultimately decreasing the chances of pregnancy, in addition to affecting the couple's sex life (Andrews et al., 1992; Tao et al., 2011).

Based on these elements, ART couples may perceive a loss of control over their lives and their bodies (Greil, 2002), a sense of helplessness, lower self-esteem as a result of the diagnosis and failed conception attempts (Benyamini et al., 2009; El Kissi et al., 2013), and identity repercussions due to the failure in assuming the parental role (Labadini et al., 2004; Loftus & Andriot, 2012; Park & Wonch Hill, 2014; Manfredi & Tomasi, 2022).

2. Recurrent Implantation Failure in ART

In this context, RIF may significantly affect couples' overall experience of ART treatments. Despite no significant correlations between the experience of treatments and the onset or presence of psychopathology within couples emerge in the psychological literature, it has been observed that repetition of ART attempts significantly correlates with negative psychological experiences both for men and women (Righetti et al., 2016; Zurlo et al., 2018, 2019), such as depressive symptoms, hopelessness, and stress (Gameiro et al., 2016). Furthermore, most women seem to perceive oocyte collection and the waiting period following an embryo transfer as the most stressful phases of ART treatments (Boivin & Takefman, 1995; Yong et al., 2000).

In one study, Coughlan et al. (2014) compared psychological stress among women with RIF within the context of ART treatments, women with recurrent pregnancy loss (three or more consecutive pregnancy losses), and women without reproductive failure as a control group. Results of the study showed that women with RIF and with recurrent pregnancy loss had significantly higher stress levels compared with the control group. The authors suggested that this difference may be related to consecutive ART failures, specifically to sustained uncertainty of the outcome and disappointments that women with RIF and recurrent pregnancy loss repeatedly experience (Coughlan et al., 2014).

A recent study by Ni et al. (2021) explored the quality of life and related factors in a sample of 137 infertile women with RIF in China. The research analyzed the quality of life, anxiety, depression, and perceived social support, focusing on specific factors (distance between the participants' home and medical center, financial difficulties, and absence of family support) that could potentially affect participants' quality of life. Despite the relevance of this contribution in understanding the impact of social factors, the authors emphasized the need to investigate the psychological effects of RIF, given the significant implications of this condition on quality of life and the little psychological literature on the subject.

As a matter of fact, the ones above are the only two available studies that analyzed stress and quality of life in women with RIF: the exploration of additional psychological effects of this condition, such as psychological adjustment to anxiety, depression, and posttraumatic reactions,

appears to be absent in the scientific literature. Similarly, it does not emerge any previous study of this condition from a dyadic perspective. Our knowledge regarding the psychological and social effects of RIF could benefit from an analysis of this condition that takes into account partners' interdependence.

Nevertheless, based on the premises offered by the existing literature, we can hypothesize that RIF may have negative psychological effects on infertile patients undergoing ART treatments. To date, however, this condition does not appear to have been sufficiently investigated.

Although previous research has demonstrated equal levels of stress between women with RIF and those experiencing recurrent pregnancy loss (Coughlan et al., 2014), unlike the latter (Homer et al., 2016; Scott, 2011), RIF has not been recognized yet as a potentially traumatic condition in the field of reproductive trauma.

3. Reproductive trauma

The American Psychological Association defines trauma as "any disturbing experience that results in significant fear, helplessness, dissociation, confusion, or other disruptive feelings intense enough to have a long-lasting negative effect on attitudes, behavior, and other aspects of functioning" (APA, 2022 https://dictionary.apa.org/trauma). More generally, events can be defined as traumatic if they destabilize the balance and stability of experience by disrupting daily routines and by generating a marked perception of impotence (Van Der Kolk, 2015). Moreover, a traumatic experience seems to be the result of the interaction between the characteristics of the event and the person's perception of it, contextualized in a specific socio-cultural setting (Van Der Kolk, 2015). Hence, the psychological literature has been considering different kinds of trauma and several resulting clinical conditions (Straussner & Calnan, 2014), including traumatic stress, acute stress disorder, post-traumatic stress disorder (PTSD), complex trauma, and traumatic bereavement.

Therefore, Bhat and Byatt (2016) suggest that infertility and perinatal loss can represent "reproductive traumas," eventually leading to grief, depression, anxiety, and post-traumatic stress disorder (PTSD). Specifically, it has been observed that distress experienced by both partners after an unsuccessful ART treatment can persist for up to 20 years afterward. This data suggests that experiencing reproductive traumas constitutes an important source of stress that can alter self-perception and – up to 15% of cases – can lead to psychological consequences associated with psychiatric symptoms or disorders (Wirtberg et al., 2006).

Although couples dealing with reproductive failure are at risk for developing trauma-related clinical conditions, this area still appears scarcely studied, especially in the context of ART pathways. A systematic review conducted in 2015 (Daugirdaitė et al., 2015) confirms this lack of literature. The authors aimed to investigate rates of PTSD and post-traumatic stress (SPT) related to reproductive failures, including in vitro procreation failure; surprisingly, they were not able to find any evidence or previous study regarding the prevalence of PTSD and SPT in couples who had experienced ART failure.

4. The traumatic potential of RIF in ART journeys

According to the article's objective, in this section, we will provide an overview of the literature highlighting points of contact between the features of traumatic experiences and those of RIF and infertility, as well as the specific characteristics that make the population of infertile couples in ART programs potentially more vulnerable to trauma.

According to the WHO Mental Health Action Plan 2013-2020 (2013), specific individual characteristics can represent risk factors in the face of exposure to potentially traumatic events. For example, some social groups are considered more vulnerable to the onset of trauma-related disorders or dysfunctional patterns, among which are included people within socially stigmatized groups and those with chronic illnesses. Therefore, couples undergoing ART treatments can be considered vulnerable to the development of traumatic-related psychological symptoms. In fact, because of its psychological effects and its perception as an "invisible disability", infertility is compared to chronic diseases such as HIV or cancer (Greil, 1991, p. 22).

Members of infertile couples are thus exposed to extensive social stigma (Greil, 1991; Slade et al., 2007). The perception of such stigmatization is exacerbated by the non-physically visible nature of infertility, which contributes to its concealment, thereby increasing its negative connotation. Ultimately, all of this negatively affects self-esteem and may increase social isolation, which are important aspects for the elaboration process of infertility and identity construction (Greil, 1991). At the same time, the procedures involved in the medicalization of infertility as well as their repeated failure cause both partners, and especially women, to repeatedly experience loss of control, feelings of helplessness, and perception of body fragmentation (Greil, 2002).

In this perspective, the repeated experience of embryo implantation failure can exacerbate anxious emotional states, therefore representing a potentially traumatic event. Temporally, the transfer occurs after a series of medically invasive and psychologically overwhelming steps, as well as frequent waiting periods. Indeed, ART procedures such as IVF and ICSI involve

numerous medical, genetic, functional, and structural investigations; almost daily trans-vaginal ultrasound scans; hormonal stimulations for the woman that are frequently carried out through daily injections (potentially correlated with humoral variation); a waiting period until oocyte retrieval; sperm retrieval; finally, further wait before knowing whether the oocyte has been fertilized in culture and embryos for the transfer have been obtained. The moment of the transfer represents the "final" decisive step in accessing pregnancy and therefore is highly emotionally invested with expectations. After the transfer, the couple must wait further to know whether embryo implantation was successful. If the procedure fails, the woman can proceed for another transfer attempt depending on the number of blastocysts obtained from culture fertilization. Once there are no available embryos (or those qualitatively suitable for transfer) the cycle must begin again from ovarian stimulation. In Recurrent Implantation Failure (RIF) this procedure fails 3 or more times, or, alternatively, culminates in a biochemical pregnancy.

Therefore, from a psychological point of view, the complex medical process of ART journeys carries a high traumatic likelihood, which is increased by consecutive treatment repetitions to achieve parenthood. The imagined child may come to be highly desired, likely to embody the function of identity confirmation of the partners' parental identity (Argentieri, 2014). In this direction, it is not surprising that infertile women who undergo ART treatments show what Langher et al. (2019) have defined as a "radical" desire for motherhood (p. 303). This qualitative study found indeed a remarkable disposition to endure the suffering and hardship (physical and emotional) involved in the ART medical protocol to realize the desire for parenthood. This propensity is sustained by the belief that the wished-for outcome of pregnancy will materialize as a result of their efforts.

Given these observations, the potentially traumatic features inherent in repeated implantation failures can include the uncertainty of the outcome and the possibility of acquiring parenting-related functions; the recurrent intrusion of the body and medicalization of couples' sexuality; the perceived lack of control over events and one's own body; subsequent feelings of impotence and inadequacy following each failure (Benyamini et al., 2009; Cousineau & Domar, 2007). Greil (2002) described how the treatment experience for infertile patients could be represented by three paradoxes: firstly, the sense of loss of control over one's own fertility (and, precisely, over the possibility to fulfil the desire for biological parenthood) leads to treatments, during which patients may perceive an even greater loss of control; secondly, the loss of body integrity as a result of the diagnosis of infertility leads to highly invasive treatments, during which the body becomes an object of the medical procedures (Thompson, 2005); thirdly, medical treatments

may lead partners to the experience of not being treated as whole people, contributing to their identity loss issues related to the infertility condition (Greil, 2002; Thompson, 2005). Besides, the condition of RIF can lead to a sense of estrangement toward one's own body and its processes, which, together with the experience of intrusion and the impersonality of medicalized treatments, seem to further suggest the potentially traumatic feature of RIF. Ambivalence toward the body – experienced partly as a betrayer regarding the promise of biological parenthood and partly as betrayed when subjected to the invasiveness of treatments (Fusco et al., 2023) – could exacerbate self-recognition and represent an additional identity loss (Cipolletta & Faccio, 2013; Clarke et al., 2006; Riccio, 2017). Thus, it becomes clear how repeated cycles of ART could significantly exacerbate the paradoxical perception of this experience. Moreover, the three dimensions highlighted by Greil seem to be related to the sense of control, impotence, body integrity, and identity that, in turn, appear to be closely implicated in traumatic experiences.

In summary, the experiences related to repeated failure of ART attempts, such as embryo RIF and biochemical pregnancy, recall the characteristics of traumatic events from many perspectives. In addition, ART couples may represent a vulnerable population to the development of trauma-related clinical conditions.

To date, several studies have analyzed the phenomena of RIF and biochemical pregnancy from a medical point of view. However, their main focus has been to investigate the organic factors underlying the failure to establish pregnancy in the woman's body. In turn, research has yet to explore the traumatic potential of these conditions from a psychological perspective. Further examination is needed in this direction, eventually allowing the development of specific clinical psychological interventions for ART couples.

5. Future research perspectives and implications for clinical work

Building on the extant literature, we argue that psychological interventions for couples experiencing RIF in ART pathways should take into consideration both the psychosocial and bodily aspects that can potentially affect these experiences.

On the one hand, infertile couples who face RIF must in fact process different experiences of psychological, interpersonal, and social loss, as well as the affective implications of infertility. On the other hand, it also seems crucial to consider the prominence of body dimension and medicalization associated with ART treatments. The integration of the physical and psychic components is particularly relevant in clinical interventions for infertile couples: first, the body is significantly involved in reproductive processes, especially in ART procedures where treatments target mainly women's bodies; second, the body symbolically takes on different

meanings that are related to identity dimensions and require, besides psychological elaboration, recognition of the individual as a psychosomatic unit (Cipolletta & Faccio, 2013; Clarke et al., 2006; Riccio, 2017). Moreover, given the evidence provided by the theoretical and clinical literature on trauma and assuming that RIF is a potentially traumatic condition, it is important to consider the body from an integrated psychosomatic perspective. Indeed, the body "gives voice" to traumatic memories inaccessible to verbalization (Van Der Kolk, 2015). Clinical research on trauma has shown that recounting the traumatic event does not automatically allow for the integration of traumatic memories and their processing. Because of the characteristics of traumatic memories and the ways they are stored in memory, it has been observed that physiological states experienced at the time of trauma are reactivated in front of stimuli that recall the traumatic event. In the context of RIF, psychological processing and integration of events into one's history thus involves elaborating the somatic component of traumatic memories. In this direction, several studies have demonstrated the efficacy and positive effects of integrated mind-body interventions of psychological support, especially for women (Gaitzsch et al., 2020; Kim et al., 2014). These studies support the importance of including the bodily dimension in psychological treatment programs.

Given these observations, it appears clear that an integrated multifocal approach (Righetti et al., 2007) involving multi-disciplinary and multi-professional interventions (by physicians, biologists, nurses, and psychologists) can enable global care of the infertile couple. In this framework, the collaboration between the psychologist and the medical team would also allow the training of health professionals within assisted reproduction services. The team training would aim at structuring tailored ART pathways that take into consideration the psychological, affective, family, and social resources available to the couple, allowing thus to prevent the development of clinical conditions that could generate suffering and relevant psychological distress for the partners (Righetti & Luisi, 2007).

Besides, we argue that Burnham's (2012) concepts of visible/invisible and voiced/unvoiced for the therapists' understanding of patients' embodied social inequalities could be relevant concerning the invisible nature of infertility. Indeed, it would be necessary for couples facing this condition to experience occasions in which they may voice and be helped in voicing their infertility-related experiences. Clinical settings may provide opportunities for naming, expressing, and, thus, making infertility visible for the couples' and clinicians' joint psychological work. In this direction, it could be relevant to work on the empowerment of those struggling with infertility through the reinforcement of mechanisms (e.g., behavioral activation) that have

been found to enhance well-being and a sense of control over one's life, which appears to be particularly compromised by the infertility experience (Myles & Merlo, 2022).

In conclusion, it is possible to advance research directions to study RIF as potentially traumatic experiences in the context of unsuccessful ART treatments. Future investigation should include: empirical research to assess the time of onset and evolution of possible traumatic experiences related to RIF and biochemical pregnancies; the identification of the couple's psychological dynamics involved in these pathways from both the individual and dyadic perspective; the identification of the factors that contribute to the reiteration or, rather, discontinuation of ART treatments following RIF; possible gender differences in heterosexual couples regarding vulnerability to perceive RIF as traumatic events, to the extent that available data show that women experience greater psychological consequences of infertility and reproductive failures; finally, the exploration of the psychological correlates associated with the choice to interrupt ART pathways following RIF, as well as the grieving process associated with the failure to achieve biological parenthood in these contingencies.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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