Determination of the Effective Factors in Predicting ART Outcome in Women With RIF (Recurrent Infertility Failure)

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Abstract- Recurrent implantation failure (RIF) remains a significant challenge in assisted reproductive technology (ART), affecting a substantial proportion of patients undergoing treatment. While advancements in ART have improved outcomes, the multifactorial nature of RIF complicates its management. This study aims to evaluate the factors influencing RIF and identify potential predictors of ART success in affected patients. A retrospective analysis was conducted on 123 women with at least two failed implantation attempts. Demographic, clinical, and laboratory data were collected, including age, body mass index (BMI), uterine abnormalities, sperm quality, and embryo formation. Statistical analyses were performed to evaluate the relationships between these variables and ART outcomes. Most participants (62.6%) were under 35 years of age, and BMI was significantly associated with the number of embryos formed (P=0.037). Among the participants, 69.91% had bilaterally patent fallopian tubes, while uterine abnormalities were linked to reduced implantation success. Sperm motility showed a significant correlation with embryo formation (P<0.05), whereas sperm count, and morphology were not statistically significant predictors. Despite comprehensive evaluations, only 1.6% of patients achieved live births, underscoring the complexity of RIF. This study highlights the critical roles of maternal age, BMI, uterine health, and sperm motility in influencing ART outcomes. Addressing modifiable factors such as BMI and uterine abnormalities and optimizing sperm quality may enhance the likelihood of successful implantation. Further research is needed to explore additional predictors and develop personalized treatment strategies for patients with RIF.

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Introduction

Assisted reproductive technology (ART) represents a cornerstone in the management of infertility, encompassing procedures that manipulate eggs or embryos outside the human body to achieve successful pregnancies and healthy offspring. The primary modalities of ART include in vitro fertilization (IVF), often accompanied by intracytoplasmic sperm injection (ICSI) (1). Since its inception in 1978, ART has led to the birth of over eight million children globally, offering hope to couples struggling with infertility (2). Despite significant advancements in ART, its application is not without complications. The procedure is associated with both short- and long-term perinatal risks, including neurodevelopmental disorders, preterm birth, and other adverse outcomes, raising questions about whether these challenges stem from the procedure itself, infertility-

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related factors, or broader environmental influences (1).

Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, affects an estimated 70 million couples worldwide, according to the World Health Organization (3). As infertility rates rise, driven by delayed childbearing, lifestyle factors, and environmental influences, ART has emerged as a critical tool in addressing this global challenge (1,2). Continuous advancements in ART have significantly improved outcomes, with implantation rates reaching approximately 60% in optimal conditions (3). However, even with tailored treatment approaches, success rates—as measured by live births—remain suboptimal, particularly for patients with recurrent implantation failure (RIF) (4-6).

Recurrent implantation failure (RIF) is a complex clinical phenomenon defined as the failure to achieve a clinical pregnancy following the transfer of at least four good-quality embryos across a minimum of three fresh or frozen IVF cycles in women under 40 years of age (7). Affecting approximately 10% of couples undergoing IVF, RIF can result from a variety of factors, including embryonic aneuploidy, endometrial receptivity issues, immunological factors, and uterine abnormalities (6). Thorough evaluations are critical to identifying underlying causes, including assessments of ovarian reserve, sperm DNA fragmentation, and uterine pathology through advanced imaging techniques and hysteroscopy (7). However, the lack of a universally accepted definition or standardized diagnostic protocol for RIF continues to impede progress in understanding and managing this condition effectively (6).

The European Society of Human Reproduction and Embryology (ESHRE) proposes defining RIF as a secondary phenomenon unique to ART, characterized by repeated failures to achieve implantation with viable embryos. This definition underscores the need for individualized approaches to treatment, tailored to the unique biological and clinical characteristics of each patient. Factors such as maternal age, embryo quality, endometrial receptivity, and even sociocultural determinants significantly influence ART outcomes, highlighting the importance of personalized treatment protocols to optimize success (8).

Multiple predictive models have been developed to estimate ART outcomes, incorporating variables such as maternal age, tubal factor infertility, and embryo quality. While promising, many of these models lack external validation and practical implementation in clinical settings. A limited number of validated models, such as those by Templeton and Nelson, have shown predictive accuracy, but further refinement and accessibility are needed to improve their clinical utility (9). Additionally, factors such as treatment history, sperm quality, male body mass index (BMI), and socioeconomic variables, including access to ART services and financial constraints, can significantly impact treatment outcomes, underscoring the multifaceted nature of infertility and its management (5,10).

Despite the challenges, evidence suggests that many couples with RIF can achieve successful pregnancies through clinical interventions and tailored treatment approaches (4,6).

Addressing the unmet need for precise prediction and prevention strategies in ART, particularly for patients with RIF, holds the potential to transform reproductive healthcare (6,8). By identifying and targeting the most influential factors, clinicians can not only enhance ART success rates but also alleviate the emotional and financial burdens faced by couples undergoing repeated treatment cycles (4,10).

This study aims to identify the key factors influencing ART outcomes in women with RIF and to contribute to the growing body of evidence supporting individualized treatment strategies. Understanding these determinants is crucial for advancing ART practices and improving the prospects for couples struggling with infertility.

Materials and Methods

Study population, sample size, and sampling method

The study population consisted of women who underwent two consecutive unsuccessful embryo transfer cycles over a three-year period (2019-2022) at Nahal-Gorgan Infertility Treatment Center, affiliated with Golestan University of Medical Sciences. Eligible participants met specific inclusion criteria, as outlined below.

Inclusion criteria

1. Women aged 20 to 42 years, grouped into different age categories for analysis.
2. Evidence of a normal uterine cavity confirmed by recent hysteroscopy.
3. At least two embryo transfers of good-quality embryos (grade A, B, or blastocysts) within the three-year period.

Exclusion criteria

1. Diagnosed genetic disorders (e.g., Rokitansky syndrome).
2. Known disorders of platelet or thromboxane

synthesis.

Data collection methods and tools

Participants were selected using a simple headcount method. This historical cohort study utilized existing patient records from Nahal Infertility Center. Data was extracted using a standardized checklist that included:

Demographic data: Female BMI, parity, cause and duration of infertility, and results of previous pregnancies.

Spouse information: Age, BMI, semen quality, and sperm analysis.

Clinical and laboratory parameters

• Antral follicle count (AFC) categorized as poor ovarian reserve (≤10 follicles) or normal ovarian reserve (>10 follicles).

• AMH and FSH levels on day 3 of the menstrual cycle.

• Ovarian stimulation protocol details, including type, changes in protocol, gonadotropin dosages, and dose adjustments.

• Egg and embryo quality from previous cycles, number of eggs and embryos obtained, and their grades.

• Estrogen and progesterone levels on the day of HCG injection.

• Endometrial thickness and progress.

To minimize the confounding effect of age on oocyte yield, only ovarian stimulation cases conducted within one year of each other were included in the study.

Outcome measures

The primary outcomes were pregnancy-related variables, including:

• Number, grades, and maturity of embryos obtained.
• Estrogen and progesterone levels on the day of HCG injection.

• Endometrial thickness and clinical progress.

• Fertilization rate, implantation rate, clinical pregnancy rate, and ongoing pregnancy outcomes.

Data analysis

Data were analyzed using SPSS version 16. Descriptive statistics were used to summarize demographic and clinical characteristics. Comparisons of qualitative variables were made using the chi-square test, while the Student's t-test or one-way ANOVA was employed for quantitative variables. A P of <0.05 was considered statistically significant.

Results

This study included 123 participants who met the inclusion criteria, each having experienced at least two failed embryo transfer attempts. Key findings are presented below:

1. Participant demographics

• Maternal Age: The majority of women (62.6%) were under 35 years old, while only 13.8% were aged 40–42 years.

• Paternal Age: Most male partners (63.4%) were under 40 years old.

• BMI: Obesity and overweight were prominent, with 63.41% of participants weighing 70–85 kg and 21.13% having a BMI above 30. Notably, one participant had a BMI of 45.93.

2. Fertility characteristics

• Infertility Duration: The majority (69.1%) had infertility lasting less than 5 years, but some cases extended up to 29 years.

• Fallopian Tube Conditions: Most participants (69.91%) had bilateral open fallopian tubes, while others exhibited abnormalities such as unilateral stenosis, occlusion, or salpingectomy. A significant association between fallopian tube condition and the number of embryos formed was observed (Chi-square test, p=0.003; Table 1).

3. Pregnancy history and outcomes

• Only two participants (1.6%) successfully delivered during the study period.

• Previous reproductive histories included ectopic pregnancy (5.7%), curettage (8.1%), and cesarean delivery (13%).

• Abdominal surgeries were reported in 33.3% of participants, with 17.8% related to gynecology.

4. Semen parameters

• Sperm Morphology: Nearly half of participants (47.15%) had normal mature sperm (4-10%), while 30.08% exceeded 10%.

• Sperm Motility: Normal motility (4-48%) was observed in 58.53% of cases.

• Sperm Count: A majority (73.98%) had counts above 15 million/mL.

5. Embryo formation

• Most participants (50.40%) formed 5-10 embryos,

while 33.33% formed fewer than 5 embryos.

• The blastocyst formation rate was low at 26.5%, reflecting challenges in embryo quality.

• No significant relationship was found between maternal age and the number of embryos formed (ANOVA test, $P>0.05$).

6. Significant factors influencing outcomes

• BMI: A higher BMI was significantly associated with fewer embryos formed (ANOVA test, $P=0.037$; Table 1).

• Sperm Motility: A positive correlation was found between sperm motility and the number of embryos formed (ANOVA test, $P=0.009$, Table 1). However, sperm morphology and sperm count did not show significant associations.

• Prolactin Levels: No significant relationship was observed between prolactin levels and the number of embryos formed (ANOVA test, $P=0.073$, Table 1).

• Infertility Years: The duration of infertility did not significantly impact the number of embryos formed (ANOVA test, $P=0.334$, Table 1).

• Fallopian Tube Condition: A significant association was observed between fallopian tube condition and the number of embryos formed (Chi-square test, $P=0.003$; Table 2).

Table 1. Statical comparison of variables and embryo formation

Variable	Sum of squares	df	Mean squares	F	*P*
BMI	123.003	70	1.709	2.402	0.037
Sperm Motility	45.781	15	3.052	3.891	0.009
Prolactin	7.033	2	3.517	2.671	0.073
Infertility years	29.619	19	1.559	1.133	0.334

Table 2. Fallopian tube condition

Condition	Frequency	Percent (%)
Bilateral open	86	69.91
Bilateral closed	7	5.69
Unilateral stenosis	10	8.13
Other abnormalities	20	16.27

7. Hormonal and clinical factors

• TSH Levels: Showed a significant relationship with the formation of type A embryos (ANOVA test, $P=0.003$), while FSH and LH levels had no significant impact.

• Prolactin: No significant correlation was found between prolactin levels and embryo formation (ANOVA test, $P>0.05$).

Discussion

Recurrent implantation failure (RIF) remains one of the most significant challenges in assisted reproductive technology (ART), substantially affecting the outcomes of infertility treatment (11,12). This study analyzed 123 patients with at least two failed implantation attempts to identify and evaluate factors associated with RIF.

Maternal factors

In our study, the majority of participants (62.6%) were under 35 years old, while only 13.8% were over 40 years. These findings align with previous research indicating that advanced maternal age significantly reduces oocyte quality and increases the likelihood of aneuploid embryos, contributing to RIF (3,13). Younger patients generally exhibited better ART outcomes, underscoring the importance of early interventions for women with infertility (13).

The body mass index (BMI) was another important factor observed in our study. Although a significant proportion of participants were overweight, those with a BMI>30 demonstrated reduced implantation success. While the association between obesity and endometrial dysfunction has been established in previous studies (14). Our study observed that 50.40% of participants formed between 5 and 10 embryos, with no significant correlation between maternal age and the number of embryos formed. BMI demonstrated a significant relationship with the number of embryos formed in our cohort, as indicated by statistical analysis ($P=0.037$). This finding underscores the potential impact of metabolic health on ovarian response and embryo formation, emphasizing the need for tailored interventions to optimize ART outcomes.

Endometrial and uterine

Health Our findings revealed that 69.91% of

participants had bilaterally patent fallopian tubes, while the remaining patients experienced varying degrees of tubal stenosis or abnormalities. Participants with uterine abnormalities, including bilateral or unilateral stenosis, exhibited poorer ART outcomes (3). These results are consistent with previous studies highlighting the detrimental effects of uterine anomalies such as fibroids, adhesions, and hydrosalpinx on implantation success (3,12).

Although endometrial receptivity was not directly evaluated in this study, its critical role in implantation is well-documented (15,16). Personalized strategies such as identifying the implantation window using endometrial receptivity array (ERA) have shown promise in optimizing implantation success, particularly for RIF patients. Future studies should consider including detailed evaluations of endometrial health to better understand its role in RIF (17,18).

Sperm analysis revealed that 73.98% of participants had sperm concentrations exceeding 15 million/mL, and 47.15% demonstrated normal morphology within the 4-10% range. While sperm motility showed a statistically significant relationship with embryo formation (P=0.009), normal morphology and sperm count did not exhibit a significant impact. These findings suggest that sperm motility may play a more critical role in fertilization and early embryonic development, consistent with previous research (19).

Live birth outcomes

Only 1.6% of participants in our study achieved live births. Both successful cases involved younger mothers (30-35 years) with no uterine abnormalities or hormonal dysfunctions. These results emphasize the multifactorial nature of implantation success and highlight the challenges associated with achieving live births in RIF patients. Factors such as maternal BMI, absence of uterine pathologies, and optimal embryo quality contributed to the observed successes (12,14).

Clinical implications

The findings of this study underscore the complexity of RIF and the importance of comprehensive evaluations and individualized treatment approaches.

Platelet-Rich Plasma (PRP) therapy has been explored as a complementary treatment for women with severely diminished ovarian reserve and premature ovarian insufficiency. Intracellular injection of PRP appears to have rejuvenating effects on the ovaries (20).

Key clinical implications include:

1. Pre-treatment Optimization: Addressing modifiable factors such as obesity and thyroid dysfunction should be a priority before ART cycles.

2. Personalized Embryo Transfer Strategies: Tailoring embryo transfer protocols based on individual patient characteristics, including BMI and uterine health, may improve outcomes.

3. Uterine and Endometrial Assessments: Detailed evaluations of uterine anatomy and endometrial receptivity should be integrated into pre-ART workups.

Limitations

Several limitations should be acknowledged. First, the retrospective design of the study may introduce selection bias. Second, certain critical factors, including immune profiles, genetic testing, and detailed endometrial receptivity assessments, were not included. Finally, the relatively small sample size limits the generalizability of our findings. Future prospective studies with larger cohorts and standardized protocols are warranted to validate these results.

Recurrent implantation failure represents a complex and multifactorial challenge in ART. This study highlights several key factors associated with RIF, including maternal age, BMI, uterine abnormalities, and sperm motility. While the majority of participants experienced suboptimal outcomes, the few live births observed reinforce the importance of comprehensive evaluations and tailored interventions.

Moving forward, integrating personalized embryo transfer strategies, advanced sperm analysis, and uterine optimization techniques holds promise for improving ART outcomes. Addressing modifiable factors such as obesity and thyroid dysfunction, combined with early intervention, may significantly enhance success rates. Future research should focus on exploring endometrial receptivity and immune modulation as potential strategies to overcome RIF, offering hope to couples facing this challenging condition.

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