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The "Groundhog Day": The Logic of Repeated Embryo Transfers Revisited

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Abstract

Recent data demonstrate impressive cumulative live birth rates following multiple embryo transfers, reinforcing the prevailing view that reproductive success is primarily determined by embryonic competence. However, persistent implantation failures despite the transfer of morphologically and chromosomally normal embryos challenge this paradigm. Implantation represents a dynamic, multifactorial process requiring optimal interaction between embryo and maternal environment, and overemphasis on cumulative statistics risks overlooking other factors that contribute to implantation failure. This perspective argues for a diagnostic model that integrates endometrial and immune assessment into assisted reproduction protocols, moving beyond repetitive embryo transfer toward individualized care. Understanding and addressing maternal factors in implantation could redefine standards of clinical practice and may improve success rates, shorten time to pregnancy, and reduce emotional and financial burden.

Keywords

Embryo Transfers, Pregnancy, Immunological Factors

1. Introduction

Current clinical practice in assisted reproductive technologies (ART) prioritizes the optimization of embryo quality as the principal determinant of implantation success. Advances in preimplantation genetic testing for aneuploidy and in culture and vitrification techniques have enabled clinicians to identify and transfer

embryos with the highest developmental potential. Failure to achieve pregnancy following multiple morphologically and chromosomally normal embryo transfers is considered a stochastic occurrence, and each successive transfer increases the likelihood of eventual success.

Dhaenens *et al.* [1] reported a cumulative live birth rate (LBR) of up to 78% after the tenth blastocyst transfer. These findings complement previous studies showing remarkably cumulative live birth rates of 95.2% after three [2] and 98.1% after five euploid blastocyst transfers, reinforcing the hypothesis that the chances of pregnancy are primarily embryonic in origin [3].

However, we believe these data deserve a more refined and critical interpretation, as they raise substantive clinical and methodological questions that may significantly influence how the findings are understood and applied in clinical practice. High cumulative success rates may reflect the average outcome of heterogeneous populations, influenced by differences in embryo selection (tested versus untested embryos), patient attrition over successive treatment cycles, and clinical heterogeneity, rather than indicating that implantation failure is purely stochastic for all patients.

Although the data illustrate cumulative success, they also prompt a fundamental question: why do 2% - 5% of euploid embryos fail to implant even after multiple transfers under optimal conditions? This persistent outcome points to the presence of other factors—particularly endometrial and myometrial, and immunological—that deserve deeper investigation.

2. Standard Approach

Recurrent implantation failure (RIF) is described as "the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and/or interventions" [4]. The recommended threshold for the cumulative predicted chance of implantation to identify RIF for the purposes of initiating further investigation is arbitrarily established at 60% [4]. This definition presents different challenges in clinical practice. Firstly, ART patients represent a heterogeneous cohort regarding the indication for treatment. The individual chances of achieving pregnancy will differ significantly, and a prediction model that takes into consideration all factors known to be disruptive to implantation is currently not available. Secondly, the lack of validated diagnostic tests and interventions addressing issues beyond embryonic features creates difficulties when trying to provide clinical guidelines in this area. Consequently, clinicians often refrain from offering personalized therapies, defaulting instead to empiric management through repeated transfers until pregnancy occurs.

3. Patient's Perspective

While cumulative success is statistically noteworthy, the emotional, physical, time-consuming, and economic costs associated with undergoing five to ten embryo

transfer cycles are substantial. With each failed cycle, patients often experience significant psychological distress, anxiety, and frustration, which can undermine adherence and the couple's relationship and cause high dropout rates. It is important to note that many women, particularly those of advanced maternal age or with poor ovarian response, may never generate three euploid embryos. For these patients, each embryo is a scarce and precious resource, and each failed transfer represents not only a clinical setback but also a deeply personal loss. The physical burden includes repeated hormonal stimulation, invasive procedures, and associated risks. Moreover, time to pregnancy is considerably prolonged, and the financial burden, often running into thousands of euros or dollars per cycle, can be prohibitive. These costs seem magnified in the absence of an individualized diagnostic and therapeutic plan.

4. New Perspective

The role of embryo quality, especially euploidy, is undeniably important; assuming it to be the primary or exclusive determinant of implantation oversimplifies a highly complex, multifactorial biological process. Maternal age, ovarian response, and blastocyst formation rates are well-known contributors to embryo quality. However, this statistical framework may delay or overlook treatable causes in patients who would benefit from an investigation of endometrial, immunological, or systemic maternal factors that can have other health complications [5].

Observational studies and selected clinical cohorts [6] suggest that carefully selected patients with evidence of immune dysregulation may benefit from individualized immunomodulatory strategies, including corticosteroids, intralipid therapy, intravenous immunoglobulin, or other targeted interventions. However, the quality of evidence remains heterogeneous, patient selection criteria are not standardized, and routine use in unselected ART populations cannot currently be recommended. Further prospective randomized studies are required to determine which patients derive clinically meaningful improvements in ongoing pregnancy and live birth rates.

Several independent lines of evidence further support the need for a broader diagnostic perspective:

- Gestational surrogacy provides one of the most compelling arguments for expanding our diagnostic perspective. In women with RIF or recurrent pregnancy loss (RPL), pregnancy success often improves dramatically when their embryos are transferred to a surrogate [7].
- The low but actual implantation of aneuploid embryos suggests the existence of compensatory mechanisms within the maternal environment—mechanisms yet to be fully characterized.
- Immune dysregulation, particularly in women with autoimmune diseases, has been associated with reduced implantation success even when genetically and morphologically optimal embryos are used, highlighting the importance of maternal immune regulation as a determinant of implantation and early plac-

entation [8].

- Low- to medium-level mosaic embryos have developmental potential equivalent to euploid embryos, with similar live birth and neonatal outcomes and no increased risk of abnormal phenotype in most cases [9].

Scientific inquiry should not only aim to describe what usually works but also seek to understand the reasons behind failure. Rather than reinforcing a default strategy of repetitive transfers, we advocate for a broader diagnostic insight in a patient-specific approach, within the framework of personalized reproductive medicine, to individualize risk stratification and to adjust therapeutic interventions.

Although no universally accepted algorithm exists, the threshold for initiating additional investigations should be defined by explicit clinical trigger points rather than by repeated empirical embryo transfer alone. Such trigger points could include failure after two consecutive transfers of high-quality blastocysts in women with a favorable prognosis, failure after transfer of one or more confirmed euploid embryos, recurrent implantation failure reaching the ESHRE-recommended predicted implantation threshold, recurrent biochemical pregnancies, or implantation failure occurring in the presence of clinical features suggestive of maternal pathology (e.g., adenomyosis, autoimmune disease, or recurrent pregnancy loss). Beyond these thresholds, a structured evaluation of maternal factors should complement reassessment of embryonic variables, with targeted treatment offered when evidence-based interventions are available.

A pragmatic clinical workup should include assessment of the uterine cavity and targeted investigation for immune dysregulation or thrombophilia. Such an approach acknowledges that implantation is dependent upon both embryonic competence and a receptive maternal environment. Endometrial immune profiling in patients with RIF, RPL, or unexplained infertility, for instance, can identify subpopulations with immune dysregulation who may benefit from specific therapies [10] [11].

Immunoskeptics may argue that the rationale for successive transfers lies in the high cumulative success rates with euploid embryos and the lack of validated interventions for immunological or endometrial dysfunction in unselected populations. However, we assert that the lack of validation in unselected populations does not preclude benefit in selected subgroups. Indeed, this highlights the need for improved stratification and the continued development of precision diagnostics.

A strategy based on a primarily statistical perspective, rather than individualized evaluation, increases patient burden, extends time to pregnancy, and may reflect a missed opportunity to improve outcomes through personalized care. In addition, this practice may inadvertently promote a form of genetic selection that is not justified by the actual clinical risk, given the high rate of normal outcomes and the technical limitations and potential overestimation of mosaicism in trophectoderm biopsy.

Nevertheless, expanding immune or endometrial investigation should not be interpreted as advocating indiscriminate testing or treatment. Many proposed biomarkers lack robust analytical validation, false-positive findings may lead to unnecessary immunosuppressive therapy, and additional investigations increase treatment costs and patient burden. Future adoption of broader diagnostic strategies, therefore, requires prospective randomized trials using standardized diagnostic criteria, validated biomarkers, and live birth as the primary outcome to identify patient populations that derive genuine clinical benefit.

5. Conclusion

In conclusion, while the available data might seem to support the eventual success achievable through repeated embryo transfer, we propose the proactive need for a rigorous investigation into the causes of implantation failure. Such an investigation should follow a structured, evidence-informed pathway that prioritizes established diagnostic assessments while reserving emerging immune and molecular testing for carefully selected patients or research settings until stronger evidence becomes available. A truly patient-centered, scientific approach must consider the full range of embryonic, endometrial, myometrial, immunological, and systemic maternal factors. By identifying and addressing potentially avoidable causes, we improve pregnancy outcomes and simultaneously reduce the emotional, physical, and financial burden on patients. This approach would not only enhance clinical effectiveness but also move us toward a more ethical, less invasive model of reproductive care.

Author Contributions

SSR and MRR made the primary contributions to the conception, drafting, and writing of the manuscript. ECA contributed to the writing of specific sections of the manuscript. All authors critically reviewed the manuscript, provided intellectual input, approved the final version, and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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