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Editorial

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Bridging *In Silico* Models to IVF Through Digital Twin Technology

Nearly five decades have passed since the development of assisted reproductive technologies (ARTs) and the birth of Louise Brown as the first child resulting from IVF. Since then, the diagnosis and treatment of infertility have evolved considerably, positioning ART among the great medical achievements of the last century. This culminated in Professor Edwards being awarded the Nobel Prize in 2010 for this breakthrough (1).

ART has made substantial progress in offering suitable treatment options for every infertile couple. However, many unknowns about the physiology of reproduction, incomplete knowledge of the underlying causes of infertility, the low success rate of ART, and finally the costs and complexity of treatment methods continue to generate great concern and stress, along with social problems for infertile couples. Although the development of treatment methods has almost solved the problems related to the risk of multiple pregnancies and ovarian hyperstimulation syndrome, management of severe male factor infertility using ICSI, IMSI, TESE, PESA, mTESE, as well as application of PGT for detection of genetic abnormalities in embryos before transfer. Further advances in infertility treatment techniques and refinements are expected with future advances in medical knowledge. Yet, it is not possible to definitively answer the question of infertile couples about the success rate of their subsequent cycle due to many intervening factors (2).

It is thought that a digital twin could be a good solution to this problem. A digital twin is a virtual model of a physical item. It spans the object's lifecycle and uses real-time data from the object to simulate its behavior and monitor its operations. Digital twins can simulate many real-world items, from individual parts of an instrument to whole facilities, such as a massive hydroelectric dam, traffic networks, and even the entire operations and activities in a crowded city. Digital twin technology allows us to monitor the performance of a complex assembly with multiple components, identify potential faults, and make real decisions about its maintenance and lifecycle. In the context of infertility treatment, the digital twin refers to a mathematical model of human reproductive biology, including hormonal responses, follicular development, endometrial changes along the cycle, sperm characteristics, oocyte fertilization, embryo development, implantation, clinical pregnancy, continuation of a singleton pregnancy, and the birth of a healthy baby using data collected from previous cycles, laboratory results, and wearable devices to provide real-time fertility-related data. This model enables physicians to run simulations for outcome prediction and treatment optimization before initiating a new treatment cycle, thereby providing clear and individualized prediction of treatment outcomes for each couple. This represents personalized medicine, supported by advanced algorithms and biological modeling. The adoption of digital twins in IVF is still in its early stages, but through their application, the potential to increase clinical pregnancy rates while reducing patient stress is enormous (3).

The AI-driven IVF ecosystem in the near future will incorporate digital twin principles to simulate different ovarian stimulation protocols, predict ovarian responses, analyze embryo development under various *in vitro* conditions, predict implantation rate for different transfer scenarios, and optimize embryo transfer timing using hormonal and uterine data. This shift will enable physicians to customize each step of the IVF cycle, reducing trial and error and improving IVF outcomes. A recent study that used digital modeling to optimize ovarian stimulation showed a 12% improvement in oocyte quality and maturation rates among patients who had previously experienced failed cycles. Similarly, AI-enhanced cycle simulations have facilitated better synchronization of the endometrium with *in vitro* developing embryos, leading to fewer failed transfers due to embryo-endometrium asynchronization. With digital twin technology, IVF is no longer limited to static decision-making. Instead, IVF clinics can now make couple-centered, predictive, personalized, and evidence-based decisions that lead to fewer cycle cancellations, improved success rates, and reduced patient anxiety and cost burden. The digital twin evolves by continuously learning from data, becoming more accurate with each case it encounters (3, 4).

The expansion and deployment of digital twin technology in IVF industry requires a paradigm shift from reactive and standardized procedures to precision and preventive medicine. Current IVF live-birth rates per embryo transfer are less than 30% in women aged 35 years and decrease with advancing age, imposing significant financial and psychological burdens. Current care relies on static embryo assessment and standardized protocols based on retrospective data, which do not reflect the individualized and dynamic reproductive biology. Moving from current proof-of-concept models to completely mutual and future-ready

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clinical platforms requires a comprehensive understanding of the history, practices, considerations, and conditions outlined in the reproductive medicine literature. Although several AI-based tools support selected stages of IVF such as prediction of ovarian stimulation, embryo grading, or evaluation of endometrial receptivity as independent static predictive dashboards, they remain fragmented rather than integrated across IVF journey. Digital twins could address this gap by applying systems biology and complexity science to model interactions among embryonic, endometrial, hormonal, and maternal factors in real time. True digital twin technology enables continuous bidirectional synchronization and counterfactual simulation to optimize treatment procedures (4, 5).

Although digital twin models offer significant potential for predicting side effects and optimizing drug dosing, most of them are largely exploratory and theoretical, largely preliminary, and use static data rather than the real-world data required for a true digital twin. Therefore, what are now being called digital twins in the fields of fertility and infertility require rigorous clinical validation, improved data integration, and ethical frameworks to make these simulations reliable tools for use in routine reproductive care. Critical feedback also emphasizes the need to distinguish true digital twins from broader applications of AI to ensure scientific and clinical clarity. Widespread clinical adoption of digital twin technology in IVF depends on overcoming technical, regulatory, and data integration hurdles while validating these platforms through prospective trials to confirm improvements in take-home baby success rates.

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