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Review

Clinical applications of digital twin technology in In Vitro Fertilisation

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ABSTRACT

Background: Digital twin technology, originating from aerospace and manufacturing industries, has emerged as a transformative tool in healthcare. In vitro fertilisation (IVF) faces persistent challenges including suboptimal embryo selection, unpredictable treatment outcomes, and limited personalisation of protocols. Despite advances in assisted reproductive technology, existing literature exhibits fragmentation: artificial intelligence applications in embryo selection, ovarian stimulation, and endometrial assessment have been developed independently without systematic integration into comprehensive treatment frameworks. Digital twin technology offers unprecedented opportunities to create virtual replicas of biological systems, enabling real-time monitoring, predictive modelling, and personalised treatment strategies.

Aim: This narrative review aims to critically examine the current applications of digital twin technology in IVF, evaluate its potential benefits and limitations, synthesize existing evidence into an integrative conceptual model, and identify future directions for implementation in reproductive medicine.

Method: A comprehensive narrative review was conducted using PubMed, Scopus, Web of Science, and IEEE Xplore databases. A narrative review approach was selected over systematic review to accommodate the heterogeneity of evidence types in this emerging field, including theoretical frameworks, simulation studies, and proof-of-concept implementations that would be excluded from systematic reviews. Search terms included "digital twin," "IVF," "in vitro fertilisation," "assisted reproductive technology," "embryo selection," and "predictive modelling." Studies published between 2015 and 2025 were included, focusing on original research articles, systematic reviews, and proof-of-concept studies describing digital twin applications in reproductive medicine.

Results: Digital twin technology in IVF demonstrates significant potential across multiple domains including embryo development simulation, ovarian response prediction, endometrial receptivity modelling, and personalised stimulation protocols. Current applications integrate artificial intelligence, machine learning algorithms, time-lapse imaging, and omics data to create comprehensive virtual models. Early evidence suggests improvements in embryo selection accuracy, ovarian response prediction, and treatment protocol optimization, though large-scale randomized controlled trials remain limited. Implementation challenges include data integration complexity, computational requirements, regulatory considerations, and validation requirements.

Conclusion: Digital twin technology represents a paradigm shift in IVF practice, offering personalised, predictive, and precision medicine approaches. This review synthesizes existing evidence to propose an integrative conceptual model for digital twin implementation across the IVF treatment spectrum, identifies critical knowledge gaps, and establishes research priorities to advance clinical translation. Despite current limitations, continued advancement promises improved success rates and patient outcomes.

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1. Introduction

In vitro fertilization (IVF) has revolutionized reproductive medicine since the birth of the first IVF baby in 1978, yet success rates remain modest, with average live birth rates per embryo transfer ranging between 25% to 30% globally for women around age 35, with outcomes declining in older age groups due to biological and clinical factors [1–3]. The global IVF market reflects substantial economic investment, with patients bearing significant financial burdens that vary across countries and healthcare systems. Beyond financial implications, IVF failure carries profound psychological consequences, with studies documenting clinically significant anxiety and depression in a substantial proportion of patients undergoing treatment, and quality of life impairments comparable to those experienced with serious medical diagnoses [4]. These multifaceted burdens underscore the urgent need for technological innovations that can improve success rates and reduce treatment cycles required to achieve pregnancy. Despite remarkable technological advances in embryology laboratories, genetic screening, and culture systems, the inherent complexity of human reproduction continues to challenge clinicians and embryologists. The traditional approach to IVF relies heavily on static assessments, standardised protocols, and retrospective data analysis, which fail to capture the dynamic, multifaceted nature of reproductive physiology and embryonic development [5]. This limitation has prompted the exploration of innovative technologies capable of providing comprehensive, real-time, and personalised insights into the IVF process.

Digital twin technology emerged in the early 2000s within aerospace engineering, where organizations utilized virtual replicas of equipment to simulate operations and predict failures. Since then, the technology has expanded across manufacturing, urban planning, and increasingly, healthcare sectors [6]. In manufacturing, digital twins optimize production lines and predict maintenance needs; in urban planning, they model traffic patterns and energy consumption. The healthcare sector has witnessed digital twin applications in cardiovascular disease modelling, surgical planning, and pharmaceutical development, demonstrating the technology's versatility in addressing complex biological systems [7]. This technological evolution provides a foundation for applying digital twin principles to reproductive medicine, where similar challenges of complexity, individual variability, and outcome prediction exist.

Digital twin technology, defined as a virtual representation of a physical system that mirrors its real-world counterpart through continuous data exchange and synchronisation, has demonstrated transformative potential across diverse industries, including aerospace, manufacturing, urban planning, and healthcare [6]. In medicine, digital twins enable clinicians to simulate physiological processes, predict disease progression, optimise treatment strategies, and personalise interventions based on individual patient characteristics [7]. The integration of artificial intelligence, machine learning, Internet of Things sensors, and big data analytics allows digital twins to evolve dynamically, incorporating new information and refining predictions over time. This capacity for continuous learning and adaptation makes digital twin technology particularly attractive for addressing the complex, patient-specific challenges inherent in assisted reproductive technology.

The theoretical foundation of digital twin applications in reproductive medicine rests on systems biology principles and complexity science frameworks [8]. Systems biology posits that biological phenomena emerge from dynamic interactions among multiple components rather than from isolated factors, requiring holistic, integrative analytical approaches. Applied to IVF, this theoretical lens recognizes that treatment success depends on the complex interplay of embryo developmental competence, endometrial receptivity, hormonal dynamics, immunological factors, and patient-specific variables. Digital twin technology operationalizes this systems perspective by creating comprehensive computational models that simulate these multifactorial interactions. The complexity science framework further informs digital twin development by acknowledging non-linear relationships, emergent properties, and adaptive behaviors characteristic of biological systems, guiding the selection of machine learning architectures and modeling approaches capable of capturing such complexity.

The application of digital twin technology in IVF represents a convergence of reproductive biology, computational modelling, artificial intelligence, and clinical practice. Unlike conventional predictive models that rely on limited datasets and static algorithms, digital twins create comprehensive, individualised virtual replicas of patients, embryos, and reproductive systems [9]. These virtual models integrate diverse data sources, including hormonal profiles, ultrasound imaging, time-lapse embryo monitoring, genetic information, metabolomic profiles, and clinical history, to generate dynamic simulations of reproductive processes [10]. By modelling ovarian response, embryo development, endometrial receptivity, and implantation potential, digital twins enable clinicians to anticipate outcomes, identify optimal intervention points, and customise treatment protocols with unprecedented precision. The conceptual architecture of digital twin systems in IVF comprises three interconnected layers: the physical patient and embryo, a data integration hub, and virtual computational models that continuously synchronize to enable personalized treatment optimization (Fig. 1). Unlike static predictive models, this bidirectional framework allows real-time data exchange and dynamic adaptation throughout the treatment cycle.

Current challenges in IVF include the inability to accurately predict which embryos will successfully implant, high rates of treatment failure despite morphologically normal embryos, significant interpatient variability in response to stimulation protocols, and limited understanding of the complex interactions between embryo quality and endometrial receptivity [11]. Traditional embryo selection relies primarily on morphological assessment and static timepoint observations, which capture only a fraction of the biological complexity underlying developmental competence [12]. Similarly, ovarian stimulation protocols follow standardised approaches that fail to account for individual patient characteristics, leading to suboptimal responses in many cases. These limitations result in extended treatment durations, increased financial burden, emotional distress for patients, and unnecessary exposure to potential complications. Digital twin technology offers a potential solution by enabling comprehensive, dynamic, and personalised approaches to every aspect of the IVF process.

Despite growing interest in artificial intelligence applications for reproductive medicine, existing literature exhibits four critical knowledge gaps that this review systematically addresses. First, previous reviews have examined isolated AI applications, such as embryo selection algorithms, ovarian response prediction models, or endometrial receptivity assessments, without exploring how these disparate technologies could be unified within an integrated digital twin framework that spans the entire treatment trajectory. The literature contains numerous standalone studies of specific AI tools, but lacks synthesis demonstrating how these components interconnect to form comprehensive patient and embryo digital twins. Second, no systematic analysis has evaluated the theoretical underpinnings, technical requirements, and implementation pathways for comprehensive digital twin systems spanning the entire IVF treatment trajectory from initial consultation through pregnancy establishment. While technical feasibility studies exist for individual components, the field lacks a roadmap articulating how to progress from current proof of concept implementations to validated, clinically deployed comprehensive systems. Third, critical questions regarding data integration standards, validation methodologies, regulatory pathways, and cost effectiveness remain inadequately addressed in the literature. These implementation considerations, essential for clinical translation, receive superficial treatment in most publications focused primarily on technical performance metrics. Fourth, the relationship between digital twin technology and existing reproductive biology theories has not been explicitly articulated, limiting theoretical

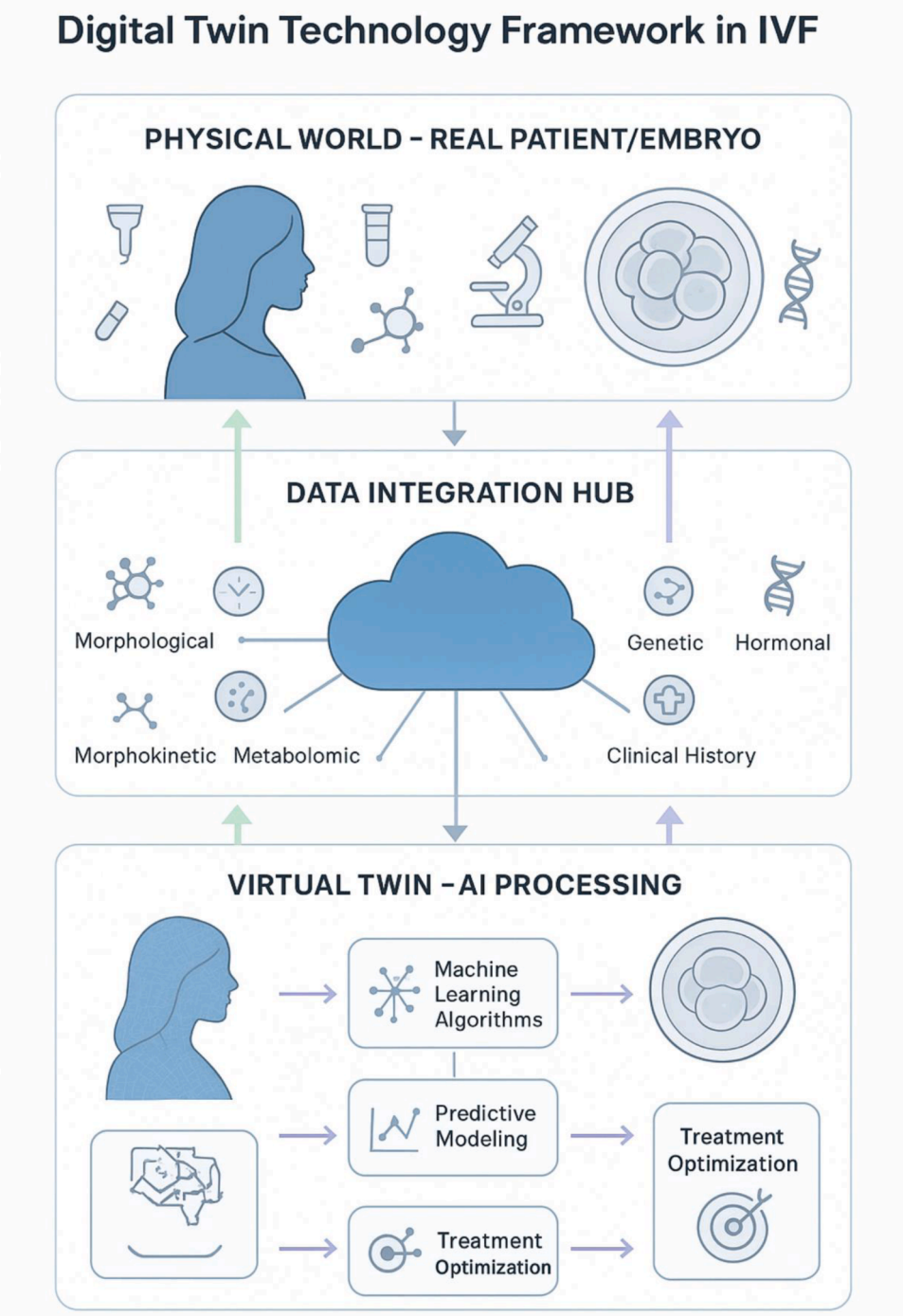

Fig. 1. Conceptual framework of digital twin technology in IVF showing bidirectional data exchange between physical and virtual systems. The digital twin integrates multimodal data sources including morphological, morphokinetic, metabolomic, genetic, hormonal, and clinical parameters into a unified computational platform. Real-time data from patients and embryos (top layer) flows through the data integration hub (middle layer) to create personalized virtual replicas (bottom layer). Machine learning algorithms and predictive models process integrated data to generate treatment recommendations and outcome predictions, which inform clinical decision-making. Bidirectional arrows represent continuous synchronization between physical reality and virtual simulation, enabling dynamic treatment optimization throughout the IVF cycle.

advancement in the field. Current implementations proceed largely atheoretically, without grounding in systems biology or complexity science frameworks that could guide more sophisticated modeling approaches and hypothesis generation.

The novelty of this review lies in its comprehensive synthesis of digital twin applications across the entire IVF treatment spectrum and its articulation of an integrative conceptual model that connects isolated technological components into a coherent framework. While existing literature has explored individual applications of artificial intelligence and predictive modelling in reproductive medicine, no previous narrative review has systematically analysed how digital twin technology can serve as a unifying paradigm for personalised IVF care, synthesizing embryo, patient, and treatment protocol modeling into an interconnected system. This review addresses the identified knowledge gaps by: (1) providing systematic mapping of how disparate AI applications can integrate within digital twin architectures; (2) articulating

theoretical foundations grounded in systems biology and complexity science; (3) comprehensively analyzing implementation barriers across technical, regulatory, ethical, and economic dimensions; and (4) proposing specific research priorities and translational pathways to advance the field from current fragmented approaches toward comprehensive digital twin systems.

The aim of this narrative review is to critically examine current applications of digital twin technology in IVF, evaluate the evidence supporting its clinical utility, identify implementation challenges and limitations, and propose future directions for research and clinical integration. Specifically, this review addresses the following research questions:

RQ1: What is the current state of evidence for digital twin applications across the IVF treatment spectrum (embryo selection, ovarian stimulation, endometrial preparation)?

RQ2: How do existing digital twin implementations integrate multimodal data sources and artificial intelligence architectures?

RQ3: What are the principal technical, regulatory, ethical, and economic barriers to clinical translation of digital twin technology in reproductive medicine?

RQ4: How can existing digital twin applications be synthesized into an integrative conceptual model, and what theoretical frameworks can guide future development and implementation of comprehensive digital twin systems for IVF?

The objectives include: (1) analysing the theoretical framework underlying digital twin applications in reproductive medicine; (2) evaluating current evidence for digital twin utilisation in embryo selection, ovarian stimulation, and endometrial preparation; (3) assessing the integration of artificial intelligence and machine learning within digital twin platforms; (4) identifying technical, regulatory, and ethical challenges; and (5) proposing recommendations for future research and clinical implementation.

This review makes three distinct contributions to the field:

Theoretical contribution: We synthesize systems biology and complexity science principles with reproductive physiology to articulate theoretical foundations for digital twin technology in IVF. By explicitly grounding digital twin applications in established biological theories, this review provides conceptual frameworks that can guide more sophisticated modeling approaches and hypothesis driven research, moving the field beyond purely empirical AI applications toward theoretically informed technology development.

Methodological contribution: We propose an integrative conceptual model that synthesizes isolated digital twin applications (embryo selection, ovarian response, endometrial receptivity) into a comprehensive framework spanning the entire IVF treatment spectrum. This model, visualized in Figs. 1 and 2, articulates how multimodal data streams, AI architectures, and clinical decision points interconnect to enable dynamic, personalized treatment optimization. Additionally, we introduce an analytical framework for evaluating digital twin systems across five dimensions, data integration capability, predictive accuracy, clinical utility, implementation feasibility, and economic sustainability, providing structured criteria for future research and development.

Practical contribution: We generate evidence-based recommendations for clinicians, embryologists, healthcare administrators, and policymakers regarding digital twin technology adoption, including specific guidance on validation requirements, regulatory pathways, workflow integration, and cost effectiveness considerations. The translational roadmap provides concrete milestones and timelines to guide the field

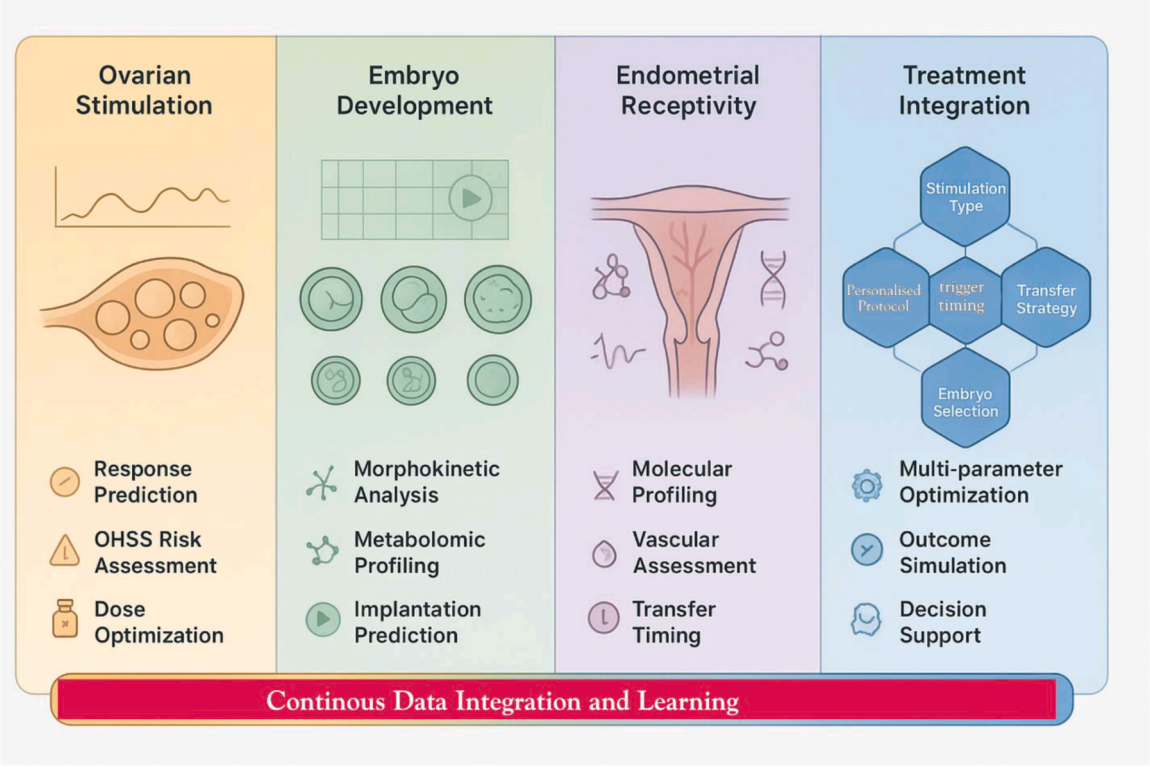

Fig. 2. Clinical applications of digital twin technology across the IVF treatment spectrum. Digital twins enable personalized interventions at four critical stages: (A) Ovarian stimulation phase with patient-specific response prediction, ovarian hyperstimulation syndrome (OHSS) risk stratification, and dynamic medication dose optimization; (B) Embryo development assessment through comprehensive morphokinetic analysis, non-invasive metabolomic profiling, and AI-driven implantation potential prediction; (C) Endometrial receptivity evaluation integrating molecular markers, vascular perfusion assessment, and personalized transfer timing determination; (D) Holistic treatment protocol optimization synthesizing multi-parameter data to simulate outcomes under different clinical scenarios and generate evidence-based recommendations. Continuous data integration across all phases enables dynamic treatment adaptation and improved clinical decision-making throughout the IVF cycle.

from current proof of concept implementations toward validated clinical systems.

2. Method

This narrative review was conducted following established methodological frameworks for synthesising literature on emerging technologies in healthcare. While narrative reviews do not adhere to systematic review protocols such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) or the Cochrane systematic review methodology, this approach was deliberately selected for several reasons. First, the heterogeneity of study designs, outcome measures, and technological implementations in digital twin research precludes standardised data extraction and meta-analysis required by systematic reviews. Second, the emerging nature of this field necessitates inclusion of diverse evidence types, including theoretical frameworks, simulation studies, proof-of-concept demonstrations, and early-stage clinical validations, that would be excluded under systematic review eligibility criteria. Third, narrative synthesis enables comprehensive examination of conceptual developments, technical innovations, and implementation considerations that are critical for understanding digital twin technology but are not captured by quantitative systematic review approaches. Fourth, the objectives of this review include synthesizing existing evidence into an integrative conceptual model and articulating theoretical foundations, analytical tasks appropriate to narrative synthesis but beyond the scope of systematic review methodologies focused on aggregating empirical evidence. This methodological choice prioritizes breadth and contextual understanding over the narrow focus and statistical precision of systematic reviews, which we deemed more appropriate for mapping this nascent field.

A comprehensive literature search was performed across multiple electronic databases including PubMed, Scopus, Web of Science, IEEE Xplore, and Google Scholar to capture both biomedical and engineering perspectives on digital twin technology. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free text keywords with the following Boolean operators and search strings:

PubMed: ("digital twin"[Title/Abstract] OR "virtual twin"[Title/Abstract] OR "in silico model"[Title/Abstract]) AND ("IVF"[Title/Abstract] OR "in vitro fertilisation"[Title/Abstract] OR "in vitro fertilization"[Title/Abstract] OR "assisted reproductive technology"[Title/Abstract] OR "ART"[Title/Abstract]) AND ("embryo selection"[Title/Abstract] OR "embryo development"[Title/Abstract] OR "ovarian stimulation"[Title/Abstract] OR "endometrial receptivity"[Title/Abstract] OR "predictive modelling"[Title/Abstract] OR "machine learning"[Title/Abstract] OR "artificial intelligence"[Title/Abstract])

Scopus: TITLE-ABS-KEY ("digital twin" OR "virtual twin" OR "in silico model") AND TITLE-ABS-KEY ("IVF" OR "in vitro fertilisation" OR "assisted reproductive technology" OR "embryo selection" OR "ovarian stimulation" OR "endometrial receptivity") AND TITLE-ABS-KEY ("predictive modelling" OR "machine learning" OR "artificial intelligence")

Web of Science and IEEE Xplore employed similar search string constructions adapted to each database's specific syntax requirements. The initial search was conducted in September 2025 and covered publications from January 2015 to August 2025, reflecting the recent emergence of digital twin applications in reproductive medicine.

Inclusion criteria comprised original research articles, systematic reviews, meta-analyses, conference proceedings, technical reports, and proof of concept studies describing digital twin technology or related computational modelling approaches in IVF or assisted reproductive technology contexts. Studies were included regardless of study design, sample size, or geographical location, provided they contained relevant information about digital twin applications, development, validation, or implementation in reproductive medicine. Exclusion criteria included non-English publications, abstracts without full text availability, opinion pieces without substantial technical or clinical content, and studies focusing solely on animal models without relevance to human IVF. Additionally, studies addressing only basic artificial intelligence applications without the integrative, dynamic characteristics of digital twin systems were excluded. Quality assessment criteria were not formally applied given the narrative review design and the exploratory nature of this emerging field. Formal quality assessment tools such as QUADAS-2 for diagnostic accuracy studies, PROBAST for prediction models, or the Cochrane Risk of Bias tool for intervention studies were not employed. This represents a significant methodological limitation, acknowledged in Section 10, that precludes systematic evaluation of methodological rigour across included studies and limits our ability to weight evidence according to study quality. However, we prioritized peer reviewed publications from established journals, conference proceedings from reputable organizations (e.g., IEEE, ACM), and studies with transparent methodological reporting. We acknowledged that this approach introduces potential quality variability in the included evidence base, which we address comprehensively in the limitations section.

Data extraction focused on identifying digital twin applications, technological components, validation methods, clinical outcomes, implementation challenges, and future directions. Given the narrative nature of this review, formal quality assessment and meta-analysis were not performed. Instead, the review synthesised findings thematically, organising content around key applications and implementation considerations. The narrative synthesis approach involved several steps: (1) thematic categorization of included studies according to primary application domain (embryo selection, ovarian response, endometrial receptivity, comprehensive protocols, AI/ML methods, implementation challenges); (2) extraction of key technological components, methodological approaches, and reported outcomes from each study; (3) identification of convergent and divergent findings across studies; (4) synthesis of implementation challenges and proposed solutions; (5) integration of isolated applications into a conceptual model articulating how digital twin components interconnect across the IVF treatment spectrum; and (6) generation of research gaps and future directions based on identified limitations and unanswered questions. This synthesis process was iterative, with themes refined as emerging patterns were identified across the literature. The narrative synthesis approach was selected as most appropriate given the heterogeneity of study designs, outcome measures, and technological approaches in this emerging field, allowing for comprehensive examination of diverse evidence types including theoretical frameworks, simulation studies, pilot implementations, and clinical validation studies.

3. Digital twin applications in embryo selection and development

Embryo selection represents one of the most critical and challenging aspects of IVF, directly determining treatment success. Traditional morphological assessment, while valuable, captures only superficial features at discrete timepoints, missing dynamic developmental processes and subtle indicators of embryo quality [13]. Digital twin technology offers a paradigm shift by creating comprehensive virtual models of embryo development that integrate morphological, morphokinetic, metabolomic, and genetic data to predict implantation potential and developmental competence. Time lapse imaging systems, which capture images of developing embryos at regular intervals, provide the raw data foundation for embryo digital twins, enabling detailed tracking of division timing, fragmentation patterns, and morphological changes throughout preimplantation development [14].

Several research groups have developed embryo digital twin platforms that analyse time lapse imaging data using deep learning algorithms [15]. These systems automatically identify key developmental events including pronuclear appearance and fading, first cleavage, subsequent divisions, blastulation, and expansion. Beyond simple event detection, digital twin models assess morphokinetic parameters such as the duration of specific developmental stages, synchrony of cell

divisions, and dynamic changes in embryo morphology. Machine learning algorithms trained on thousands of embryo images with known outcomes can identify subtle patterns imperceptible to human observers, correlating specific morphokinetic signatures with implantation success [16]. These embryo digital twins continuously update their predictions as development progresses, providing increasingly refined assessments of embryo viability.

The integration of metabolomic data into embryo digital twins adds another dimension of predictive power. Embryos secrete and consume various metabolites during development, and the metabolomic profile of spent culture media correlates with developmental potential [17]. Noninvasive analysis techniques including spectroscopy and chromatography can measure amino acid turnover, glucose consumption, pyruvate uptake, and other metabolic indicators without harming the embryo [18]. Digital twin platforms incorporating metabolomic data alongside morphokinetic assessment achieve higher predictive accuracy than either data type alone. Some advanced systems use biosensors integrated into culture systems to provide real time metabolomic monitoring, feeding continuous data streams into the embryo digital twin for dynamic prediction updating.

Genetic information, including preimplantation genetic testing results, adds crucial predictive value to embryo digital twins. Aneuploidies represent a major cause of implantation failure and pregnancy loss, and comprehensive chromosomal screening identifies embryos with abnormal chromosome numbers [19]. Digital twin platforms integrate genetic testing results with morphological and metabolomic data to generate comprehensive quality scores. For mosaic embryos containing both normal and abnormal cells, digital twins can model the likely impact on developmental potential based on the degree and distribution of mosaicism [20,21]. Some research explores non-invasive genetic assessment using cell free DNA in culture media, potentially enabling genetic profiling without embryo biopsy, and these approaches could provide continuous genetic monitoring throughout development for integration into digital twin models.

Table 1 presents a comprehensive overview of data sources and parameters integrated into embryo digital twin systems. However, this table currently provides only descriptive information without comparative analysis of the relative predictive value or cost-effectiveness of different data integration strategies across studies. Future research should conduct head-to-head comparisons of digital twin architectures incorporating different combinations of data modalities to identify optimal configurations balancing predictive accuracy, implementation complexity, and cost. Additionally, the table does not reflect the differential availability and feasibility of various data types across clinical settings, with metabolomic and genetic assessments requiring specialized equipment and expertise not universally accessible. Quantitative synthesis of existing studies could help determine the incremental predictive value gained by adding each data modality to baseline morphological assessment, informing evidence-based recommendations for digital twin system design. The artificial intelligence architectures underlying embryo digital twins vary in complexity and approach. Convolutional neural networks excel at analysing embryo images, automatically extracting relevant features and identifying patterns associated with successful implantation [14,22]. Recurrent neural networks and long short-term memory networks are particularly suited to time series analysis of morphokinetic data, capturing temporal dependencies and developmental trajectories. Ensemble methods combining multiple algorithms often achieve superior performance compared to single model approaches. Importantly, these systems require extensive training on large datasets with verified outcomes, and their performance depends critically on data quality and diversity. While digital twin models hold emerging potential for reproductive medicine, current validation studies have not yet demonstrated a statistically significant improvement in implantation outcomes compared to traditional morphology-based embryo selection [23–25]. Critical limitations include the lack of large-scale, prospective, randomized controlled trials; variability in algorithm performance across different clinics and patient populations; and the "black box" nature of deep learning models that obscures the biological mechanisms driving predictions. Furthermore, failed digital twin implementations, where algorithms underperformed conventional methods or produced clinically misleading predictions, are underreported in the literature due to publication bias, potentially inflating apparent effectiveness.

Table 1
Data sources and parameters in embryo digital twin systems.

Data Category	Specific Parameters	Acquisition Method	Predictive Value
Morphological [26,27]	Cell number, symmetry, fragmentation degree, zona pellucida thickness, inner cell mass quality, trophectoderm quality, blastocoel expansion	Time lapse imaging, static microscopy	Moderate; traditional assessment method with known limitations
Morphokinetic [16,28]	Time to pronuclear fading, time to 2 cell, 3 cell, 4 cell, 5 cell, 8 cell stages, duration of second cell cycle, synchrony of divisions, time to morulation, time to blastulation, blastocyst expansion rate	Time lapse imaging with automated annotation	High; captures dynamic development and subtle timing variations
Metabolomic [29]	Glucose consumption, pyruvate uptake, lactate production, amino acid turnover (asparagine, glycine, leucine), oxygen consumption, ATP production	Noninvasive spectroscopy, chromatography, biosensor systems	Moderate to high; reflects embryo viability and metabolic health
Genetic [26, 30]	Chromosome number and structure, ploidy status, mitochondrial DNA content, telomere length, DNA fragmentation index, specific gene expression patterns	Preimplantation genetic testing, non-invasive cell free DNA analysis, transcriptomic profiling	Very high; aneuploidy strongly predicts implantation failure
Environmental [26,31]	Culture medium composition, incubator temperature, pH levels, oxygen tension, humidity, volatile organic compounds	Incubator sensors, quality control monitoring	Moderate; affects embryo development but not inherent embryo quality
Maternal [32, 33]	Maternal age, body mass index, previous IVF outcomes, hormone levels at trigger, endometrial thickness, uterine morphology	Clinical records, laboratory tests, imaging	Moderate; contextualises embryo potential within patient specific factors

The clinical implementation of embryo digital twins faces several

practical challenges. Integration with existing laboratory workflows requires seamless data capture and transfer from time lapse incubators and other systems to the digital twin platform. User interfaces must present complex predictive information in clinically actionable formats that embryologists and clinicians can interpret quickly and confidently [34]. Regulatory approval for artificial intelligence based medical devices varies by jurisdiction, and digital twin systems must undergo rigorous validation and meet safety standards before clinical deployment. Additionally, the interpretability of deep learning algorithms remains a concern; clinicians need to understand not just the prediction but the reasoning behind it, necessitating explainable artificial intelligence approaches that provide insight into which features drive predictions. Despite these challenges, embryo digital twins represent one of the most mature applications of this technology in IVF, with several commercial systems already available and increasingly adopted in clinical practice.

4. Digital twin modelling of ovarian response

Ovarian stimulation protocols aim to recruit multiple follicles for egg retrieval, but patient responses vary dramatically [35]. Some patients respond poorly despite high medication doses, while others develop ovarian hyperstimulation syndrome due to excessive response. Predicting individual ovarian response and personalising stimulation protocols accordingly represents a major clinical need. Digital twin technology enables the creation of patient-specific virtual models of ovarian function that simulate responses to different stimulation protocols, allowing clinicians to optimise medication doses and treatment strategies before initiating actual stimulation [36]. These ovarian digital twins integrate patient characteristics, hormonal profiles, ovarian reserve markers, and historical data to predict follicular development trajectories.

The foundation of ovarian digital twins lies in mathematical models of folliculogenesis, the process by which primordial follicles develop into mature, ovulatory follicles. These models incorporate known biological mechanisms, including gonadotropin receptor dynamics, granulosa cell proliferation, follicular fluid accumulation, and hormone production. Differential equations describe how follicle populations change over time in response to follicle-stimulating hormone and luteinising hormone stimulation. Parameters in these mechanistic models are personalised based on individual patient data, including anti Müllerian hormone levels, antral follicle count, age, body mass index, and previous cycle outcomes [37]. This personalisation allows the model to reflect each patient's unique ovarian reserve and responsiveness.

Advanced ovarian digital twins incorporate machine learning to refine predictions beyond mechanistic models alone. By training on large datasets of previous IVF cycles, algorithms learn complex patterns linking patient characteristics to specific response patterns. Features including genetic polymorphisms in gonadotropin receptors, metabolic factors, lifestyle variables, and subtle ultrasound findings contribute to prediction accuracy. The digital twin updates dynamically during stimulation as new ultrasound and hormone measurements become available, refining its predictions about how many follicles will mature, when trigger timing should occur, and what egg retrieval yield to expect. This dynamic updating enables real-time protocol adjustments, such as modifying gonadotropin doses mid-cycle to optimise response.

Several clinical studies have demonstrated the utility of ovarian digital twin approaches. Research has shown that digital twin platforms and AI-driven multiphase prediction models can predict ovarian hyperstimulation syndrome (OHSS) risk with substantial accuracy, enabling preventive interventions such as trigger modification or cycle cancellation in high-risk patients [38,39]. Other investigations have suggested that digital twin-guided personalised protocols may reduce gonadotropin consumption while maintaining equivalent oocyte yields compared to standard protocols, potentially resulting in cost savings [40]. Studies have also explored whether digital twin predicted optimal trigger timing could improve mature oocyte retrieval rates compared to conventional approaches [41,42]. These findings suggest potential clinical benefits, though larger randomised controlled trials are needed to establish efficacy definitively. Critical analysis reveals that these studies often originate from single centres with specialized expertise and technological infrastructure, raising questions about generalizability to typical clinical settings. Moreover, the studies lack standardized outcome measures, making cross-study comparisons difficult. Publication bias may favour positive findings, with negative or null results less likely to be published and disseminated.

The integration of pharmacokinetic and pharmacodynamic models into ovarian digital twins adds further sophistication. Individual patients metabolise and clear gonadotropins at different rates depending on factors including renal function, body composition, and genetic polymorphisms in metabolic enzymes [43]. Pharmacokinetic models predict drug concentrations over time based on dosing regimens, while pharmacodynamic models link these concentrations to biological responses. Incorporating these models into digital twins enables true personalised dosing that accounts for individual absorption, distribution, metabolism, and excretion profiles. Some platforms utilise therapeutic drug monitoring, measuring actual gonadotropin levels in blood samples during stimulation and using these measurements to calibrate the digital twin model in real time.

5. Endometrial receptivity and digital twin integration

Successful embryo implantation requires not only a competent embryo but also a receptive endometrium prepared to accept and support the embryo [44]. Endometrial receptivity, the temporal window during which the endometrium is conducive to implantation, varies among individuals and cycles. Traditional assessment relies on endometrial thickness measurement and pattern evaluation via ultrasound, which provide limited information about molecular receptivity status [45]. Digital twin technology offers more comprehensive modelling of endometrial preparation and receptivity by integrating hormonal profiles, ultrasound characteristics, molecular markers, and blood flow parameters to predict the optimal transfer timing and implantation likelihood [25,46].

Molecular profiling of endometrial receptivity has advanced significantly with the development of endometrial receptivity arrays and similar tests that assess the expression of genes involved in implantation. These molecular signatures identify whether the endometrium is pre receptive, receptive, or post receptive, enabling personalised embryo transfer timing [47]. Digital twin platforms incorporating molecular receptivity data alongside clinical parameters create comprehensive models of individual endometrial physiology. Machine learning algorithms identify patterns linking specific transcriptomic profiles with successful implantation, accounting for interactions between endometrial status and embryo quality [48]. The digital twin can simulate how different embryo transfer protocols and timing strategies affect implantation probability for a specific patient.

Uterine blood flow represents another important factor in endometrial receptivity, as adequate perfusion is necessary for endometrial development and implantation support [49]. Doppler ultrasound measures blood flow in uterine arteries, and indices including the pulsatility index and resistance index correlate with pregnancy outcomes. Digital twins incorporating Doppler parameters alongside endometrial thickness and molecular markers provide more complete receptivity assessments [50]. Some advanced systems use three-dimensional power Doppler to create detailed vascular maps of the endometrium, and these imaging data are integrated into the digital twin model [26]. Machine learning algorithms trained on imaging data can identify subtle vascular patterns associated with receptivity that are not apparent in standard Doppler indices.

Hormonal dynamics during endometrial preparation critically influence receptivity, particularly progesterone levels which mediate the

transformation from proliferative to secretory endometrium [51]. In frozen embryo transfer cycles, exogenous progesterone supplementation prepares the endometrium, but absorption and metabolism vary among individuals [52]. Digital twin models of hormonal dynamics simulate how different progesterone dosing regimens affect endometrial transformation timing. Pharmacokinetic models predict progesterone serum levels based on formulation, route of administration, dose, and individual patient factors [53]. Pharmacodynamic models link these levels to molecular changes in the endometrium. Integrating these models enables optimisation of progesterone protocols for each patient, potentially explaining some cases of recurrent implantation failure due to inadequate luteal phase support.

Table 2 summarises the parameters integrated into endometrial receptivity digital twin models. Similar to Table 1, this table provides descriptive categorization of parameters without comparative analysis of their relative contributions to receptivity prediction or clinical outcome improvement. The integration of information presented in this table into narrative text could enhance readability and reduce redundancy, allowing for more critical discussion of how these parameters interact within digital twin models and which combinations yield optimal predictive performance. Future research should quantify the added value of each parameter category through ablation studies that systematically remove data types to assess their individual and combined contributions to prediction accuracy. The clinical application of endometrial digital twins faces unique challenges compared to embryo digital twins. Endometrial biopsies for molecular profiling are invasive and can only be performed in non-transfer cycles, limiting real time integration of molecular data. Noninvasive alternatives such as endometrial fluid analysis or circulating biomarkers are under investigation but not yet clinically validated. Additionally, the endometrium is a dynamic tissue that changes rapidly during the receptivity window, requiring precise timing of assessments and transfer. Digital twin models must account for this temporal evolution and uncertainty in receptivity window determination. Despite ongoing challenges, early clinical implementations of AI-guided personalized embryo transfer have shown promising results. Studies have reported that tailoring embryo transfer timing based on individualized endometrial receptivity assessments may improve implantation and clinical pregnancy outcomes in patients with previous implantation failures, compared to conventional timing approaches [54,55]. However, these studies remain limited in sample size, lack long-term outcome data (live birth rates), and have not been replicated across diverse clinical settings. The invasive nature of endometrial biopsy required for molecular assessment limits the scalability of these approaches, necessitating development of non-invasive biomarkers before widespread clinical adoption becomes feasible.

Table 2
Parameters integrated into endometrial receptivity digital twin models.

Parameter Category	Specific Measurements	Clinical Significance	Integration Method
Structural [56]	Endometrial thickness, endometrial volume, trilaminar pattern, endometrial polyps or fibroids, uterine anomalies	Provides anatomical foundation for receptivity; thickness correlates with pregnancy rates	Ultrasound imaging, three-dimensional reconstruction algorithms
Vascular [57, 58]	Uterine artery pulsatility index, resistance index, subendometrial blood flow, endometrial vascularisation index, spiral artery development	Adequate perfusion necessary for implantation support and pregnancy maintenance	Doppler ultrasound, power Doppler, contrast enhanced imaging
Molecular [59]	Gene expression profiles (BCL6, HOXN13, MFGE8, etc.), endometrial receptivity array score, cytokine levels, integrin expression, pinopode development	Directly reflects molecular receptivity status and implantation competence	Endometrial biopsy, transcriptomic analysis, immunohistochemistry
Hormonal [60]	Serum progesterone, oestradiol, luteinising hormone, thyroid hormones, prolactin, cortisol	Hormones orchestrate endometrial transformation; imbalances impair receptivity	Serum hormone assays, repeated measurements during cycle
Immunological [61]	Natural killer cell populations, regulatory T cells, cytokine profiles (IL 6, IL 10, TNF alpha), autoantibodies	Immune environment affects implantation success; dysregulation linked to failure	Endometrial biopsy, immunophenotyping, serum autoantibody testing
Microbiome [62,63]	Bacterial composition, Lactobacillus dominance, pathogenic bacteria presence, fungal elements	Endometrial microbiome influences receptivity; non-Lactobacillus dominance associated with poor outcomes	Endometrial fluid sampling, 16S ribosomal RNA sequencing, culture

6. Personalised treatment protocols through digital twins

Beyond specific applications in embryo selection, ovarian stimulation, and endometrial preparation, digital twin technology enables holistic personalisation of complete IVF treatment protocols [64]. Rather than following standardised protocols based on broad patient categories, digital twins create individualised treatment strategies optimised for each patient's unique physiology, preferences, and clinical circumstances. This comprehensive approach requires integration of all aspects of IVF care into a unified digital twin platform that models the entire treatment trajectory from initial consultation through pregnancy establishment. Such platforms synthesise data from ovarian reserve testing, previous treatment outcomes, genetic information, metabolic profiles, lifestyle factors, and psychosocial considerations to recommend optimised treatment pathways [65].

Personalised protocol selection begins with predicting treatment outcomes under different stimulation approaches. Patients may respond differently to antagonist versus agonist protocols, recombinant versus urinary gonadotropins, or different adjuvant treatments [66]. Digital twin simulations model expected outcomes with each protocol variant, accounting for individual patient characteristics and probability distributions rather than point estimates. These simulations generate not only expected oocyte yield but also stimulation duration, medication costs, hyperstimulation risk, embryo quality distributions, and cumulative live birth probability across multiple cycles [41]. Presenting this comprehensive information enables shared decision making, allowing patients to choose protocols aligned with their priorities regarding success probability, cost, treatment burden, and risk tolerance.

Machine learning algorithms within digital twin platforms continuously improve their recommendations by learning from outcomes across the patient population while maintaining personalisation for each individual [9]. Reinforcement learning approaches, which optimise decision making through trial and error, have been applied to IVF protocol selection [67]. These algorithms learn which protocol modifications

work best for patients with specific characteristics, gradually improving recommendations as more outcome data accumulates. Federated learning enables collaboration across multiple clinics without sharing raw patient data, allowing algorithms to learn from larger populations while preserving privacy [68]. As these systems mature, their recommendations should approach or exceed expert clinician judgment based on years of experience.

The integration of patient reported outcomes and preferences into digital twin platforms adds an important dimension often overlooked in purely biological models. Patient priorities vary; some prioritise maximising success rates regardless of cost or inconvenience, while others emphasise minimising treatment burden or financial expenditure. Quality of life considerations, including time off work, injection burden, and emotional stress, significantly impact patient satisfaction with IVF care [69]. Digital twin platforms can incorporate these preferences, generating recommendations that balance biological optimisation with patient values. Multi-objective optimisation algorithms identify solutions that achieve acceptable tradeoffs across competing objectives, presenting patients with Pareto optimal choices where improving one outcome necessarily compromises another. However, current digital twin systems lack robust frameworks for systematically eliciting, quantifying, and incorporating patient preferences, relying instead on clinician interpretation of patient values. This limitation reduces the person-centredness of ostensibly personalized recommendations and may perpetuate clinician biases about what patients value. Development of preference elicitation tools and incorporation of patient preference models represents a critical gap requiring attention in future digital twin development.

Economic modelling within digital twin platforms helps patients and clinicians understand cost effectiveness of different strategies [70]. IVF treatment involves substantial expenses including medications, procedures, genetic testing, and cycle repetition costs [71]. Digital twins can simulate expected cumulative costs to achieve live birth under different protocols, accounting for success probabilities at each stage and costs of additional cycles if initial attempts fail. This information enables more informed decision making about aggressive versus conservative approaches, single versus multiple embryo transfer, and utilisation of expensive add on technologies. Health economic analyses incorporating digital twin predictions help healthcare systems allocate resources efficiently and identify which personalisation strategies provide sufficient clinical benefit to justify additional costs [72]. However, cost-effectiveness analyses of digital twin systems themselves remain scarce. The substantial upfront investment required for digital twin platform development, implementation, and maintenance must be weighed against potential cost savings from reduced cycle failures and complications. Without rigorous economic evaluation, healthcare administrators cannot make evidence-based decisions about digital twin technology adoption, and reimbursement policies remain uncertain.

7. Artificial intelligence and machine learning in digital twin systems

Artificial intelligence and machine learning constitute the computational core of digital twin technology, enabling the extraction of insights from complex, high dimensional data and the generation of accurate predictions [73]. Multiple machine learning paradigms contribute to digital twin functionality in IVF, each offering unique capabilities [25]. Supervised learning algorithms, trained on labelled datasets where outcomes are known, form the basis of most predictive models. These algorithms learn relationships between input features (patient characteristics, embryo parameters, treatment protocols) and outcomes (implantation, pregnancy, live birth) by minimising prediction errors across training data. Common supervised learning approaches in IVF digital twins include logistic regression for binary outcome prediction, random forests for handling mixed data types and nonlinear relationships, and gradient boosting machines for achieving high predictive accuracy through ensemble methods [12].

Deep learning, a subset of machine learning using neural networks with multiple layers, excels at processing complex data types including images, time series, and genetic sequences. Convolutional neural networks have revolutionised image analysis in IVF, automatically learning relevant features from embryo images without manual feature engineering [74]. These networks achieve human level or superior performance in tasks such as blastocyst quality grading, aneuploid embryo identification, and implantation prediction from morphology. Recurrent neural networks and their variants, including long short-term memory and gated recurrent units, specialise in sequential data analysis, making them ideal for morphokinetic assessment and hormonal time series modelling [75]. Attention mechanisms, originally developed for natural language processing, enable these networks to focus on the most relevant timepoints or features when making predictions.

Unsupervised learning algorithms identify patterns and structures in data without predefined outcome labels, proving valuable for discovering patient subtypes and novel biomarkers. Clustering algorithms group patients or embryos with similar characteristics, potentially revealing distinct biological subtypes that respond differently to treatments [76]. Principal component analysis and other dimensionality reduction techniques identify the most informative features among thousands of potential variables, simplifying complex datasets while retaining critical information [77]. Autoencoders, a type of neural network, learn compressed representations of data that capture essential features, enabling anomaly detection and identification of embryos or patients with unusual characteristics warranting special attention [78].

Transfer learning leverages knowledge gained from large datasets to improve performance on smaller, related datasets [79]. Pre trained neural networks developed on massive image databases can be fine-tuned for embryo analysis with relatively small clinic specific datasets, achieving better performance than training from scratch [22]. This approach is particularly valuable in IVF where obtaining large labelled datasets from single centres is challenging. Similarly, models trained on general population data can be personalised to individual patients through online learning approaches that update model parameters as new patient specific data becomes available [80]. This continuous adaptation enables increasingly accurate predictions tailored to each patient's unique physiology.

Explainable artificial intelligence addresses the black box criticism of complex machine learning models by providing interpretable explanations of predictions [81]. Techniques including feature importance analysis identify which variables most strongly influence predictions, helping clinicians understand the reasoning behind recommendations. SHAP (SHapley Additive exPlanations) values quantify each feature's contribution to individual predictions, generating patient specific explanations [82]. Attention visualisation shows which regions of embryo images or which timepoints in development trajectories drive neural network decisions. These explainability tools build clinician trust and enable identification of model errors or biases, crucial for safe clinical deployment of artificial intelligence systems. Regulatory bodies increasingly require explainability for medical artificial intelligence applications, making these techniques essential for clinical translation of digital twin systems [83]. However, the tension between model complexity and interpretability remains unresolved. The most accurate deep learning models are often the least interpretable, while simpler, more transparent models sacrifice predictive performance. This tradeoff presents a fundamental challenge: should digital twin systems prioritize accuracy (potentially improving clinical outcomes but reducing clinician understanding) or interpretability (enhancing clinician comprehension but possibly limiting performance)? The optimal balance likely varies by application context, with high-stakes decisions requiring greater interpretability and routine tasks potentially tolerating less transparency. Establishing context-specific standards for the accuracy-interpretability tradeoff represents an important research and regulatory priority.

8. Data integration and interoperability challenges

The effectiveness of digital twin systems depends critically on comprehensive data integration from diverse sources, but achieving seamless interoperability presents substantial technical challenges [84]. IVF clinics utilise multiple systems including electronic medical records, laboratory information management systems, embryology databases, imaging equipment, hormone analysers, and genetic testing platforms, each storing data in proprietary formats with limited standardization [85]. Integrating these disparate data sources into unified digital twin platforms requires sophisticated data pipelines, standardised vocabularies, and interoperability frameworks [86]. The lack of universal data standards in reproductive medicine complicates integration efforts, as different vendors implement different data structures and terminology [85,87].

Data quality issues pose additional challenges for digital twin implementations. Missing data are common in retrospective IVF datasets, as not all measurements are routinely performed in clinical practice [88]. Machine learning algorithms can handle missing data through imputation techniques, but missing data may not be randomly distributed, potentially introducing biases [89]. Data entry errors, inconsistent measurement techniques, and variations in laboratory protocols across clinics affect data reliability. Digital twin systems must incorporate data quality assessment and cleaning procedures to identify and address these issues [7]. Automated anomaly detection algorithms flag implausible values or inconsistent records for review [90]. Standardised measurement protocols and quality control procedures improve data reliability, but implementing these across multiple clinics requires substantial coordination [87]. Concrete solutions to these data quality challenges have been proposed but not systematically implemented. For example, blockchain-based data verification systems could ensure data integrity and traceability; automated data validation rules embedded in data entry interfaces could prevent common errors at the point of capture; and standardized data dictionaries with controlled vocabularies could reduce semantic ambiguity. However, these solutions require substantial organizational change, financial investment, and cross-institutional coordination, explaining their limited adoption to date. The absence of regulatory mandates or financial incentives for data standardization perpetuates the current fragmented landscape.

Temporal alignment of different data types presents another challenge. Embryo images are captured at specific developmental timepoints, hormonal measurements occur at particular cycle days, and clinical assessments happen during scheduled visits [86]. Integrating these time stamped data requires careful alignment to construct coherent developmental and treatment timelines. Some measurements occur continuously (time lapse imaging), others at regular intervals (daily ultrasounds during stimulation), and others at irregular timepoints (genetic testing results). Digital twin systems must handle this temporal complexity, interpolating between measurements when necessary and accounting for uncertainty in precise timing [7]. Time series analysis techniques and dynamic modelling frameworks address these challenges, enabling cohesive integration of temporally diverse data [84].

Data volume and computational requirements scale rapidly as digital twin systems incorporate high resolution imaging, omics data, and continuous monitoring [84]. A single time lapse imaging session generates thousands of images, genetic sequencing produces gigabytes of data, and continuous sensor monitoring creates dense time series. Storing, managing, and processing these large datasets requires substantial computational infrastructure including high performance computing resources, large-scale storage systems, and efficient data processing pipelines [7]. Cloud computing platforms offer scalable infrastructure, but data privacy regulations and institutional policies may restrict cloud utilisation for protected health information. Edge computing approaches, processing data locally near its source, can reduce bandwidth requirements and latency while addressing privacy concerns [91].

Interoperability standards are gradually emerging to address these challenges. Health Level Seven (HL7) Fast Healthcare Interoperability Resources (FHIR) provides a modern standard for healthcare data exchange, enabling different systems to share information using common formats and application programming interfaces [92]. Adoption of FHIR in reproductive medicine is increasing, with efforts to develop FHIR profiles specific to IVF data including treatment cycles, embryology observations, and pregnancy outcomes [93]. Digital Imaging and Communications in Medicine (DICOM) standards, traditionally used for medical imaging, are being extended to embryology imaging, enabling standardized storage and exchange of embryo images. International classification systems including SNOMED CT provide standardised terminology for clinical concepts, facilitating consistent data representation across systems [94]. Despite these advances, widespread adoption remains limited, and significant technical and organisational barriers to true interoperability persist [87].

9. Validation, regulation, and clinical implementation

Rigorous validation represents an essential prerequisite for clinical implementation of digital twin systems in IVF [95]. Unlike purely research tools, clinical decision support systems must demonstrate safety, accuracy, and reliability across diverse patient populations and clinical settings. Validation studies should follow established frameworks for predictive model assessment, including evaluation on independent datasets not used in model development, assessment of calibration (agreement between predicted probabilities and observed outcomes), and analysis of performance across clinically relevant subgroups [96,97]. External validation studies, testing models on data from different clinics, geographical regions, and time periods, provide particularly strong evidence of generalizability [98]. Prospective clinical trials, where digital twin recommendations guide actual treatment decisions and outcomes are compared to standard care, represent the gold standard for clinical validation [84]. However, the current evidence base falls far short of these standards. Most published studies report internal validation on datasets from the same institution where models were developed, which systematically overestimates performance. External validation studies are scarce, and those that exist often show substantial performance degradation when models are applied to new populations or clinical settings. Prospective randomized controlled trials comparing digital twin-guided care to standard practice are exceedingly rare, with most evidence deriving from retrospective analyses or non-randomized prospective cohorts susceptible to selection bias and confounding. This weak evidentiary foundation raises concerns about premature clinical adoption before adequate validation has been established.

Regulatory pathways for digital twin systems vary by jurisdiction and intended use. In the United States, the Food and Drug Administration regulates medical device software, including clinical decision support systems, under frameworks that consider the risk level and autonomy of the software [99]. Systems that autonomously diagnose or treat fall under stricter regulation than those providing information to support clinician decision making. The European Union's Medical Device Regulation and In Vitro Diagnostic Regulation establish requirements for software medical devices, including clinical evaluation, risk management, and quality management systems. Achieving regulatory clearance or approval requires substantial documentation including clinical validation studies, risk analyses, software verification and validation testing, and post market surveillance plans. The regulatory landscape for artificial intelligence medical devices is evolving rapidly, with agencies developing specific guidance for machine learning based systems that continue learning after deployment [100].

Post market surveillance and continuous quality monitoring are essential for maintaining digital twin system performance in clinical practice [101]. Unlike static medical devices, machine learning systems

can degrade over time as patient populations shift or clinical practices evolve, a phenomenon termed concept drift. Continuous monitoring of prediction accuracy, calibration, and fairness identifies performance deterioration requiring model retraining or recalibration [102]. Feedback loops where clinicians report errors or unexpected recommendations enable rapid identification and correction of problems. Version control systems track model updates and changes, ensuring traceability and reproducibility [100]. Some regulatory frameworks require software manufacturers to notify agencies of significant algorithm changes, treating them as device modifications requiring evaluation [99]. However, systematic post-market surveillance infrastructure for AI medical devices remains underdeveloped. Many commercial digital twin systems lack transparent performance monitoring dashboards, real-world effectiveness data are rarely published, and mechanisms for clinician feedback and error reporting are informal or non-existent. This surveillance gap creates potential safety risks, as performance degradation or emerging failure modes may go undetected until adverse outcomes accumulate. Establishing mandatory post-market surveillance requirements, standardized performance metrics, and public registries of AI medical device real-world performance represents a critical regulatory priority.

Clinical implementation beyond technical development requires attention to human factors, workflow integration, and clinician training [103]. User interface design significantly impacts system usability and safety; poorly designed interfaces can lead to misinterpretation of predictions or recommendations. Involving end users (embryologists and clinicians) throughout system design through user centred design methodologies ensures interfaces meet clinical needs. Workflow analysis identifies optimal integration points where digital twin recommendations can be incorporated without disrupting efficient clinic operations. Training programmes familiarise users with system capabilities, limitations, and appropriate use. Change management strategies address resistance to adopting new technologies, emphasising benefits while acknowledging uncertainties [103]. However, implementation science research on digital twin adoption in IVF settings is virtually absent. We lack systematic understanding of implementation barriers and facilitators, optimal training approaches, workflow redesign strategies, and change management tactics specific to this technology. This knowledge gap increases the risk of implementation failures, where technically sound systems fail to achieve clinical impact due to poor organizational fit, inadequate user training, or resistance to workflow changes. Investment in implementation research parallel to technical development would enhance the likelihood of successful clinical translation.

10. Limitations of the review

This narrative review, while comprehensive, has several limitations that warrant acknowledgement. First, the rapidly evolving nature of digital twin technology means that some developments may have occurred after the literature search completion in August 2025, and recent innovations may not be captured. The narrative review methodology, while appropriate for synthesising diverse evidence types in an emerging field, lacks the systematic rigour of systematic reviews or meta-analyses, potentially introducing selection bias in included studies. Specifically, our literature selection process relied on author judgment about relevance and quality rather than predefined, reproducible inclusion criteria and dual independent screening. This approach may have inadvertently favoured studies aligned with our conceptual framework while potentially overlooking contradictory evidence or alternative perspectives. Additionally, we did not employ formal quality assessment tools such as QUADAS-2 for diagnostic accuracy studies, PROBAST for prediction models, or the Cochrane Risk of Bias tool for intervention studies. This omission precludes systematic evaluation of methodological rigour across included studies and limits our ability to weight evidence according to study quality. These methodological limitations are intrinsic to narrative reviews and represent a necessary tradeoff for achieving breadth and contextual understanding in emerging fields where evidence is too heterogeneous for systematic synthesis. The absence of formal quality assessment means that our synthesis gives equal consideration to studies of varying methodological rigor, potentially overweighting findings from lower quality studies. Future systematic reviews employing rigorous quality assessment and meta-analytic techniques should validate and refine the patterns identified through our narrative synthesis. The heterogeneity of digital twin definitions, implementations, and outcome measures across studies precluded quantitative synthesis and meta-analysis, limiting the ability to generate precise estimates of effect sizes.

Second, the integrative conceptual model proposed in this review represents a synthesis of existing evidence and theoretical principles rather than an empirically validated framework. While we articulate how isolated digital twin applications could integrate into comprehensive systems, we acknowledge that this proposed integration has not been implemented or validated in clinical practice. The conceptual model serves as a roadmap for future development rather than a description of currently operational comprehensive digital twin platforms. Claims regarding this model as a "unified framework" should be understood in this context, it unifies disparate conceptual elements from the literature into a coherent theoretical structure, but does not represent a de novo theoretical innovation or an empirically tested system. Future research must empirically validate whether the proposed integrations are technically feasible, clinically beneficial, and economically viable. The gap between our conceptual synthesis and actual implementation represents a significant limitation that underscores the need for translational research to operationalize the proposed framework.

Third, much of the evidence base for digital twin applications in IVF consists of proof of concept studies, simulation research, and retrospective analyses rather than prospective randomised controlled trials. While these study designs provide valuable insights into technical feasibility and potential benefits, they offer limited evidence regarding real world clinical effectiveness and cost effectiveness. Publication bias may favour positive findings, with unsuccessful or negative studies less likely to be published, potentially inflating apparent effectiveness. Additionally, many studies originate from well resourced research centres with technical expertise, raising questions about generalisability to typical clinical settings with more limited resources and capabilities. The concentration of digital twin research in a small number of elite academic institutions and well funded commercial entities may create an innovation gap, where technologies are optimized for settings with abundant resources, specialized personnel, and sophisticated infrastructure but perform poorly in resource constrained environments. This bias toward well-resourced settings undermines equitable access and may exacerbate existing disparities in IVF outcomes across different socioeconomic and geographic contexts. Future research should explicitly evaluate digital twin performance across diverse implementation settings, including community clinics, resource limited healthcare systems, and international contexts with varying regulatory and economic landscapes.

Fourth, the review focused primarily on English language publications, potentially excluding relevant work published in other languages, particularly given substantial reproductive medicine research conducted in non-English speaking countries. Countries including China, Japan, Israel, and several European nations have active reproductive medicine research programmes, and language restrictions may have excluded important contributions from these regions. The geographic concentration of included studies predominantly in North America, Western Europe, and Australia limits the generalisability of findings to other populations with different genetic backgrounds, environmental exposures, dietary patterns, and healthcare structures. Biological and clinical factors affecting IVF outcomes may vary across populations, and digital twin models trained primarily on data from limited geographic regions may not perform well when applied to diverse global populations. This

geographic bias represents a significant limitation requiring attention in future research through international collaborations and multi-regional validation studies. The exclusion of grey literature, including conference abstracts without full text, technical reports from industry, and unpublished data, may have omitted relevant information. Access to proprietary commercial systems and their validation data was limited, as companies may not publish detailed technical information or clinical performance data for competitive reasons. This commercial data gap is particularly problematic because several digital twin systems already deployed in clinical practice are proprietary products whose algorithmic details, training datasets, and performance characteristics remain undisclosed. This lack of transparency prevents independent verification of manufacturer claims, limits scientific scrutiny, and creates information asymmetry that disadvantages clinicians and patients attempting to make informed decisions about technology adoption. Regulatory requirements for public disclosure of AI medical device performance data could partially address this limitation.

Fifth, the review did not systematically assess study quality or risk of bias using formal tools, as explicitly acknowledged in the Methods section. This represents a critical limitation affecting the reliability of our synthesis. Studies included in the review vary in methodological rigour, sample size, follow up duration, and outcome assessment, affecting the reliability and generalisability of their findings. Specific quality concerns include: inadequate sample sizes leading to overfitting of complex machine learning models; lack of temporal validation where models tested on contemporary data may not generalize to future time periods; inadequate reporting of model development processes, hyperparameter tuning, and validation procedures, preventing reproducibility; and selective outcome reporting, where multiple models may be tested but only the best performing results published. These quality issues are endemic in the machine learning literature and particularly problematic in medical AI research where clinical deployment decisions should be based on robust, reproducible evidence. The lack of reporting standards specific to digital twin systems in reproductive medicine compounds these problems. Developing and enforcing reporting guidelines analogous to TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) specifically tailored to digital twin applications would improve evidence quality. The lack of long term outcome data represents another significant limitation; most studies report immediate outcomes such as embryo selection accuracy or implantation rates rather than ultimate outcomes including live birth rates and child health. Critically, virtually no studies examine long term child health outcomes following digital twin guided IVF treatment. Concerns about potential epigenetic effects of assisted reproductive technologies, developmental programming effects of prenatal exposures, and long term health trajectories of children conceived through ART necessitate extended follow up beyond birth. The absence of such data leaves important questions unanswered about whether optimizing short term outcomes through digital twin technology might have unintended long term consequences for child health and development. Establishing registries linking digital twin guided treatments to long term child health outcomes represents a critical research priority. The scarce data on cost effectiveness limits understanding of whether digital twin technologies provide sufficient clinical benefit to justify their additional costs. Cost effectiveness analyses require long term follow up, comprehensive cost accounting, and utility assessments from patient perspectives, all of which are absent from current digital twin literature. Without robust economic evidence, healthcare systems cannot make informed decisions about technology adoption, payers lack justification for reimbursement, and patients cannot weigh costs against benefits. The high upfront investment required for digital twin implementation may be justified by cumulative cost savings from reduced treatment failures, complications, and psychological distress, but this remains hypothetical without empirical economic evaluation.

Sixth, ethical, regulatory, and implementation considerations received relatively brief treatment compared to technical and clinical aspects, despite their critical importance for successful translation. Specific ethical issues requiring deeper examination include: algorithmic bias and fairness, where digital twin models trained predominantly on data from certain demographic groups may perform poorly for underrepresented populations, potentially exacerbating existing healthcare disparities; informed consent challenges, as patients may not fully understand how AI systems generate recommendations or the limitations and uncertainties inherent in algorithmic predictions; data privacy and security risks associated with aggregating comprehensive patient data into centralized digital twin platforms, particularly concerning genetic information, reproductive history, and other sensitive data; questions of liability and accountability when digital twin recommendations lead to adverse outcomes, should responsibility lie with clinicians who accepted the recommendations, technology developers, healthcare institutions, or be distributed across multiple parties?; and the risk of automation bias, where clinicians may over rely on algorithmic recommendations, potentially neglecting contradictory clinical information or their own expertise. The review did not comprehensively examine patient perspectives, preferences, or experiences regarding digital twin technology, representing an important gap given the importance of patient centred care. Qualitative research exploring how patients understand and value digital twin technology, their preferences regarding AI involvement in reproductive decision making, their trust in algorithmic recommendations, and their concerns about privacy, autonomy, and human connection in increasingly technologized fertility care is notably absent. This patient perspective gap risks developing technologies that optimize technical metrics without addressing what patients actually value and desire from their IVF care. Incorporating patient voices throughout technology development, validation, and implementation is essential for ensuring digital twin systems serve patient interests rather than solely advancing technical capabilities or commercial objectives. Similarly, clinician attitudes, acceptance, and concerns regarding artificial intelligence and digital twin systems warrant deeper exploration than provided in this review. Systematic investigation of clinician perspectives could identify barriers to adoption, concerns about deskilling or professional autonomy erosion, perceived threats to the therapeutic relationship, and preferences regarding human AI collaboration models. Understanding these professional perspectives is critical for designing systems that augment rather than replace clinical expertise and for developing implementation strategies that address legitimate professional concerns. The complex sociotechnical challenges of implementing sophisticated digital twin systems in real world clinical settings, including organisational readiness, change management, and sustainability, deserve more extensive analysis. Digital twin implementation represents not merely a technological change but a fundamental transformation of clinical workflows, decision making processes, professional roles, and organizational culture. Successful implementation requires alignment across technical infrastructure, clinical processes, organizational structures, professional capabilities, patient expectations, and regulatory frameworks. The sociotechnical systems perspective, which views technology implementation as a process of mutual adaptation between technical systems and social contexts, has been underutilized in digital twin research. Applying implementation science frameworks such as the Consolidated Framework for Implementation Research (CFIR) or the Non adoption, Abandonment, Scale up, Spread, and Sustainability (NASSS) framework could provide systematic approaches for understanding and addressing implementation challenges.

The clinical translation of digital twin technology in IVF will require a phased developmental approach, progressing from current proof of concept implementations through near term multi omics integration and clinical validation, ultimately achieving comprehensive personalized treatment platforms with demonstrated clinical efficacy and regulatory approval (Fig. 3). This roadmap highlights critical milestones including federated learning for multi-center collaboration, prospective randomized controlled trials, and cost effectiveness demonstration necessary for

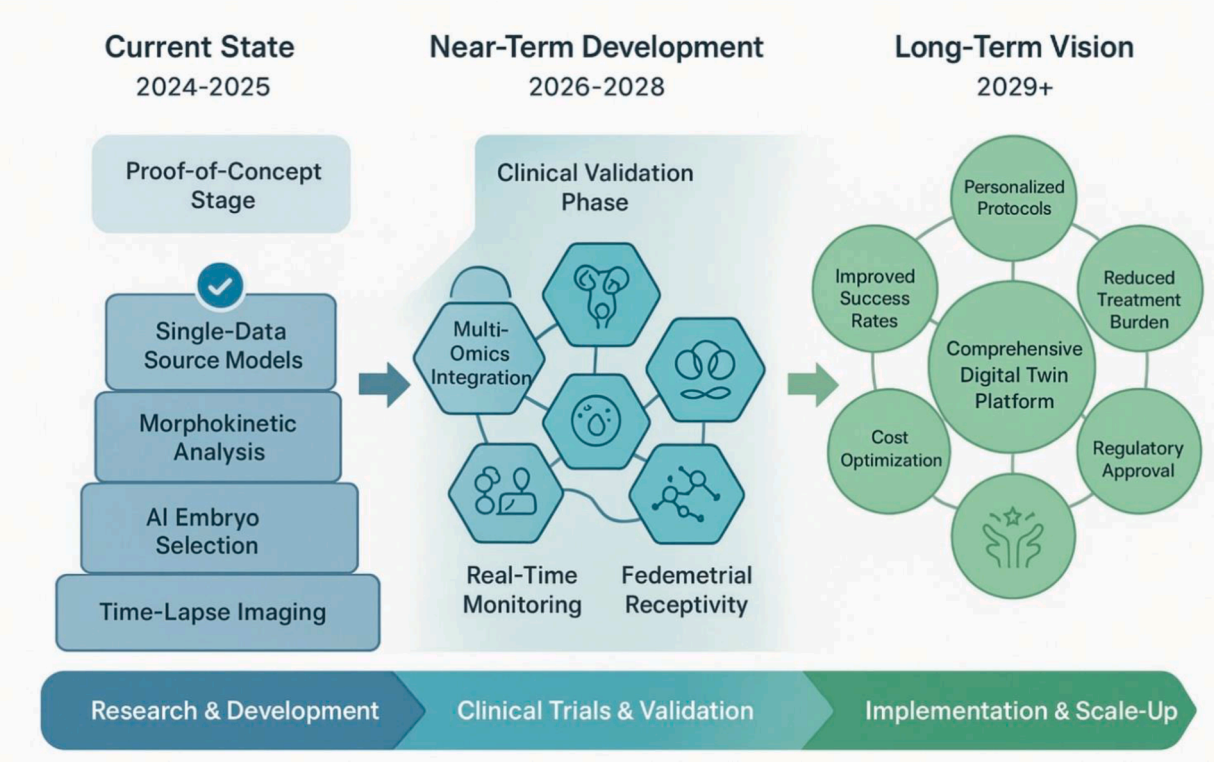

Fig. 3. Roadmap for clinical translation of digital twin technology in IVF. The trajectory from current proof-of-concept models to validated clinical systems involves three overlapping phases. The Research & Development phase (current to 3–5 years) focuses on multi-omics data integration, real-time monitoring capabilities, and federated learning infrastructure enabling multi-center collaboration while preserving data privacy. The Clinical Trials & Validation phase (3–7 years) emphasizes prospective randomized controlled trials demonstrating clinical efficacy, external validation across diverse populations and settings, and cost-effectiveness analyses. The Implementation phase (5–10 years) involves regulatory approval and standardization, widespread clinical adoption of comprehensive digital twin platforms enabling fully personalized IVF protocols, and continuous quality improvement through post-market surveillance. Timeline estimates are approximate and depend on research funding, regulatory evolution, and successful resolution of identified technical and organizational challenges. Achievement of comprehensive, validated, widely-adopted digital twin systems will require sustained investment and coordinated efforts across research, clinical, regulatory, and commercial stakeholders.

widespread clinical adoption and healthcare reimbursement. However, the timeline for achieving each milestone remains uncertain and depends on substantial additional research investment, regulatory framework development, and resolution of the technical, ethical, and implementation challenges identified throughout this review.

11. Conclusion

Digital twin technology represents a transformative paradigm in IVF care, offering unprecedented opportunities for personalisation, prediction, and precision medicine. By creating comprehensive virtual models of embryos, patients, and reproductive systems that integrate diverse data sources and continuously update as new information becomes available, digital twins enable dynamic, individualised treatment optimisation throughout the IVF journey. Current applications demonstrate significant potential across multiple domains including embryo selection, ovarian stimulation, endometrial receptivity assessment, and personalised protocol development, with early evidence suggesting improvements in success rates, efficiency, and patient satisfaction.

The technical foundation of digital twin systems rests on advances in artificial intelligence, machine learning, mathematical modelling, and data integration. Sophisticated algorithms extract meaningful patterns from complex, high dimensional data including time lapse embryo imaging, hormonal profiles, genetic information, and metabolomic measurements. Deep learning architectures achieve human level performance in challenging tasks such as embryo quality assessment and implantation prediction. Mechanistic models grounded in reproductive biology provide interpretable frameworks for simulation and prediction. The synthesis of data driven and mechanistic approaches creates robust digital twin systems capable of accurate, explainable predictions that support clinical decision making.

Despite promising early results, substantial challenges must be addressed before digital twin technology achieves widespread clinical adoption in IVF. Technical challenges include data integration from disparate sources, computational scalability, model validation across diverse populations, and performance monitoring over time. Regulatory pathways for artificial intelligence medical devices continue evolving, requiring manufacturers to navigate complex requirements for clinical evidence, risk management, and quality assurance. Implementation challenges encompass workflow integration, clinician training, user interface design, and change management. Ethical considerations including algorithmic fairness, data privacy, informed consent, and preservation of clinical autonomy demand careful attention. Economic sustainability requires demonstrating sufficient clinical benefit to justify additional costs.

The evidence base supporting digital twin applications in IVF, while growing, remains limited compared to established clinical approaches. Much current evidence derives from retrospective studies, proof of concept investigations, and single centre implementations rather than large scale, prospective, randomised controlled trials with long term outcome assessment. Publication bias may inflate apparent effectiveness, and generalisability across diverse clinical settings remains uncertain. Specific evidence gaps include: absence of adequately powered randomized controlled trials comparing digital twin guided care to standard practice for patient centered outcomes including live birth rates, treatment burden, psychological wellbeing, and cost effectiveness; limited external validation across different populations, geographic regions, and clinical settings; inadequate reporting of algorithmic details,

training datasets, and validation procedures, preventing independent verification and reproducibility; scarcity of data on long term child health outcomes following digital twin guided conception; lack of systematic investigation of implementation barriers, facilitators, and optimal strategies; and insufficient exploration of patient and clinician perspectives, preferences, and concerns. Addressing these evidence gaps through rigorous, transparent, multi center research is essential for establishing digital twin technology as evidence-based practice rather than experimental innovation. The field would benefit from standardised validation frameworks, multi-institutional collaborations, and rigorous comparative effectiveness research. Cost effectiveness analyses are particularly needed to inform healthcare policy and reimbursement decisions. Without demonstrating value for money, digital twin technology risks remaining accessible only to affluent patients in well-resourced settings, exacerbating healthcare disparities.

This review has synthesized existing evidence to propose an integrative conceptual model that articulates how isolated digital twin applications can interconnect across the IVF treatment spectrum. This conceptual integration, grounded in systems biology and complexity science frameworks, provides a theoretical foundation and roadmap for future development. However, we acknowledge that this represents conceptual synthesis rather than empirical validation, the proposed comprehensive digital twin system has not been implemented or validated clinically. The gap between conceptual integration and operational reality underscores critical research priorities.

Looking forward, digital twin technology in IVF is poised for continued evolution and maturation. Specific research priorities to advance the field include:

1. **Multi omics integration:** Developing computational frameworks that seamlessly integrate genomic, transcriptomic, proteomic, metabolomic, and microbiome data into unified digital twin models. Current systems typically incorporate one or two data modalities; comprehensive multi omics integration could capture biological complexity more completely but requires addressing substantial data integration, computational, and interpretability challenges.
2. **Longitudinal patient modelling:** Extending digital twin capabilities beyond single IVF cycles to model patients' reproductive trajectories across multiple treatment attempts, spontaneous conceptions, and long term reproductive health. Longitudinal models could identify optimal timing for treatment initiation, predict cumulative success probabilities, and personalize strategies for patients with recurrent failures.
3. **Federated learning infrastructure:** Establishing technical and governance frameworks enabling collaborative model training across multiple institutions while preserving data privacy. Federated learning could dramatically expand training dataset sizes and diversity, improving model generalisability, but requires resolving data standardization, quality assurance, and equitable benefit sharing challenges.
4. **Novel sensor technologies:** Developing and validating non invasive sensors for continuous monitoring of embryo metabolism, endometrial receptivity biomarkers, and hormonal dynamics. Current digital twins rely primarily on intermittent measurements; continuous monitoring could enable real time optimization and earlier intervention for emerging problems.
5. **Causal inference methods:** Moving beyond correlative prediction to causal understanding of treatment effects and biological mechanisms. Current machine learning models identify associations but cannot distinguish causation from correlation. Incorporating causal inference methods could enable more robust treatment recommendations and facilitate knowledge discovery about reproductive biology.
6. **Standardization initiatives:** Developing consensus data standards, reporting guidelines, validation frameworks, and performance benchmarks for digital twin systems. Standardization would enable meaningful comparisons across systems, facilitate regulatory evaluation, and accelerate clinical translation.
7. **Implementation science research:** Systematically investigating organizational, professional, and patient level factors influencing digital twin adoption and sustained use. Understanding implementation determinants and mechanisms could inform strategies for successful scale up beyond early adopter settings.
8. **Equity focused research:** Explicitly examining digital twin performance across diverse patient populations, implementation feasibility in resource limited settings, and strategies for equitable access. Ensuring benefits extend to underserved populations rather than exclusively privileged patients is essential for socially responsible innovation.
9. **Patient centered outcomes research:** Evaluating digital twin impact on outcomes patients value including emotional wellbeing, treatment burden, decisional satisfaction, and long term family health. Technical metrics like prediction accuracy may not align with what patients ultimately care about; patient centered research ensures technology development serves patient interests.
10. **Health economics research:** Conducting comprehensive cost effectiveness and budget impact analyses from societal, healthcare system, and patient perspectives. Robust economic evidence is essential for reimbursement decisions, resource allocation, and ensuring digital twin technology represents value for money.
11. **Empirical validation of the integrative conceptual model:** Testing whether the proposed integration of isolated digital twin applications into comprehensive systems is technically feasible, clinically beneficial, and economically viable. This research priority directly addresses the gap between our conceptual synthesis and operational reality.

As these developments unfold, digital twins may fundamentally reshape IVF practice, moving from reactive, standardised care toward proactive, personalised treatment strategies optimised for each patient's unique biology and circumstances. However, realizing this vision requires more than continued technical advancement. It demands sustained research investment, thoughtful regulatory framework development, commitment to equitable access, attention to patient values and preferences, and careful navigation of ethical complexities. The promise of digital twin technology is substantial, but transforming promise into practice will require coordinated efforts across research, clinical, regulatory, commercial, and patient advocacy communities.

In conclusion, digital twin technology offers a compelling vision for the future of reproductive medicine, combining cutting edge computational methods with deep biological understanding to improve outcomes for couples struggling with infertility. While significant work remains to realise this vision fully, the foundation has been established, early evidence is promising, and momentum is building. Continued investment in research, development, validation, and implementation of digital twin systems holds the potential to increase IVF success rates, reduce treatment burden, and make personalised reproductive care a reality for all patients. The journey from current proof of concept systems to mature, validated, widely adopted clinical tools will be challenging, requiring rigorous science, thoughtful regulation, substantial investment, and commitment to serving patient interests. If these challenges are successfully navigated, digital twin technology could represent a paradigm shift in reproductive medicine, fulfilling the promise of precision medicine for one of life's most important endeavors: building families.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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