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Reviews

Can Elective Single Embryo Transfer (eSET) with AI Integration Become the Future of IVF?

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This manuscript examines whether elective single embryo transfer (eSET) should be mandated in all IVF cycles, assessing its clinical benefits, challenges, and global implementation. Evidence shows that eSET significantly reduces multiple pregnancies and associated complications while maintaining cumulative live birth rates. However, ethical, regulatory, and practical considerations complicate universal enforcement. While a standardized eSET policy offers advantages, potential drawbacks include restricted patient autonomy and the need for additional IVF cycles in some instances. To navigate these complexities, the manuscript advocates for a balanced approach: promoting eSET as the preferred standard while allowing individualized decisions based on patient-specific factors. Alternative policy models—such as partial mandates or incentive-based strategies—are explored to enhance outcomes without imposing rigid requirements. This nuanced perspective balances patient safety, treatment efficacy, and shared decision-making in fertility care.

INTRODUCTION AND BACKGROUND

In modern IVF practice, the transfer of a single high-quality embryo through elective single embryo transfer (eSET) has become increasingly common as the primary approach to prevent multiple pregnancies. Advances in embryo selection and cryopreservation have since enabled eSET to emerge as a safer, viable alternative.[1] This shift in practice addresses one of the most critical complications associated with IVF—multiple pregnancies—which has been well-documented as adding significant complexity and risk to pregnancies.[2]

The historical context for this change is important to understand. Initially, multiple embryo transfers were common in IVF due to low implantation rates, as practitioners attempted to increase the likelihood of successful pregnancy. However, this approach led to increased risks of multiple pregnancies, which can cause serious maternal complications including preeclampsia and hypertension, as well as fetal risks such as preterm birth, low birth weight, and cerebral palsy.[3,4]

Research has demonstrated that when high-quality embryos are available, eSET can maintain success rates while eliminating the risk of multiple pregnancies.[2] However, the implementation of eSET requires careful patient selection, as individual variability in fertility factors remains a significant consideration in determining the most appropriate treatment approach.[3]

CLINICAL OUTCOME SUCCESS RATES

Research has shown that while eSET may result in lower immediate pregnancy rates compared to double embryo transfer in fresh IVF cycles, this difference can be effectively overcome through subsequent frozen embryo transfers.[5,6] The ‘one plus one’ strategy—eSET followed by a frozen embryo transfer— optimizes outcomes has proven to be more effective than transferring multiple embryos simultaneously, as it leads to increased implantation chances while avoiding multiple gestations.

Real-world implementation data supports the effectiveness of eSET programs. In Switzerland, a universal eSET approach achieved cumulative pregnancy rates of 48.9% and live birth rates of 33.4% per oocyte collection, while completely eliminating multiple pregnancies.[7] Similarly, Belgium saw a dramatic reduction in multiple pregnancy rates from 25% to 11.9% following the implementation of mandatory SET for patients under 36 years.[8]

The success of eSET has been demonstrated across different age groups. Studies have shown that eSET can be ef-

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fectively applied to women aged 36-39 years, maintaining comparable cumulative pregnancy and live birth rates while significantly reducing multiple birth risks.[9,10] When combined with frozen embryo transfers, Devroey et al.[11] reported no significant difference in cumulative live birth rates (42.9% vs. 38.8%, $p > 0.05$).[11]

However, it's important to note that while eSET significantly reduces multiple pregnancy risks, it may decrease the chance of live birth in a fresh IVF cycle.[8,12] This initial difference is typically overcome through subsequent frozen embryo transfers, leading to comparable cumulative success rates while maintaining the safety benefits of single embryo transfer.[9]

BENEFITS AND EVIDENCE SUPPORTING ESET

The primary benefit of eSET lies in its proven ability to significantly reduce multiple pregnancy rates without compromising overall success rates. Studies have demonstrated that implementing eSET can reduce multiple pregnancy rates from 25% to as low as 5%.[13] This reduction is particularly significant given that twin gestations are associated with a 5-10 fold increase in fetal and maternal complications.[14]

Modern embryo selection techniques have enhanced the effectiveness of eSET. The use of comprehensive chromosome analysis for embryo selection has optimized eSET outcomes by identifying embryos with the highest developmental potential.[14] This advancement has made it possible to achieve acceptable pregnancy rates while minimizing the risk of multiple pregnancies.[15]

Cost-effectiveness analyses have shown that eSET can be economically advantageous. Despite potentially requiring more cycles to achieve pregnancy, the overall costs associated with eSET are comparable to or lower than multiple embryo transfer approaches due to reduced complications and neonatal care expenses. Gerris et al.[16] found eSET reduced neonatal costs by €5,000 per case. Studies have demonstrated that while maternal costs remain similar, the neonatal care costs are significantly lower with eSET compared to double embryo transfer.[17]

The benefits of eSET extend across different patient populations. While initially recommended primarily for younger patients with good prognosis, research now supports extending eSET to women of advanced maternal age, as it can maintain treatment efficacy while improving safety outcomes.[18] This approach has become particularly meaningful for older women undergoing assisted reproductive technology, given their increased risk of obstetrical complications.[19]

Leading professional organizations now recognize that successful IVF treatment should be measured by singleton birth rates rather than just pregnancy rates, acknowledging that a single healthy baby represents the optimal outcome.[20] This shift in perspective has helped establish eSET as the most efficient approach to achieve better perinatal and neonatal outcomes.[21]

CHALLENGES AND CONSIDERATIONS

The successful implementation of eSET programs faces several significant challenges that must be carefully considered. A primary challenge is the need for advanced embryo selection capabilities, as the success of eSET heavily depends on the ability to identify embryos with the highest implantation potential.[22] This becomes particularly crucial for older patients, where aneuploidy presents a major hurdle to success.[23]

The quality of available embryos significantly impacts treatment decisions. Sadeghi[24] suggests poor-quality embryos may release factors inhibiting high-quality embryo implantation. This understanding has led to recommendations focusing on transferring only top-quality embryos, even if this means transferring fewer embryos overall.

Access to treatment represents another significant challenge, particularly in regions where IVF services are not covered by public healthcare systems or private insurance.[25] The financial burden of multiple IVF cycles can influence both provider and patient decision-making regarding embryo transfer strategies.

A crucial consideration in eSET implementation is the balance between medical recommendations and patient autonomy. While eSET may be clinically preferable, factors such as advanced maternal age, prolonged infertility, and patient preferences must be carefully weighed in the decision-making process.[26] Patients may prioritize immediate success over safety, necessitating tailored counseling. The success of eSET programs ultimately depends on effective patient education about both benefits and limitations, combined with a comprehensive approach that includes successful cryopreservation programs and access to subsequent frozen embryo transfers.[22]

IMPLEMENTATION AND REGULATION WORLDWIDE

Implementation of eSET varies considerably worldwide, with adoption being most successful in countries that combine regulatory oversight with financial support for fertility treatments.[27] The combination of insurance coverage and restrictions on embryo numbers has proven particularly effective in encouraging eSET adoption.[27,28]

Regional differences in eSET adoption are striking. While Europe achieved 38% eSET rates in 2016 across 1,200 clinics,[28] the United States reaches 71%, Southeast Asia reports only about 10.2% of cycles using single embryo transfer.[29] Countries with state-funded fertility treatment and strong regulatory frameworks, such as Australia, have achieved particularly high eSET rates of over 75%, resulting in multiple pregnancy rates below 6%.

Japan provides a notable example of successful regulatory implementation. Following the introduction of specific guidelines by medical societies in 2007-2008, Japan saw significant improvements in outcomes, including a dramatic reduction in twin pregnancies from 33.9% to 13% and decreased rates of preterm delivery and low birth weight.[30]

The primary barriers to widespread eSET implementation include treatment costs, lack of legislative policies in some regions, and inconsistent availability of ART services.[29] Patient education has emerged as an important tool in implementation strategies, with studies showing that focused education about maternal and perinatal risks can effectively reduce patient preference for multiple embryo transfers.[27]

THE INTEGRATION OF AI IN EMBRYO SELECTION

The integration of AI in embryo selection offers significant advantages, addressing longstanding challenges in IVF practice. Traditional embryo assessment methods have been subjective, time-consuming, and prone to variability.[31] AI systems provide standardized, objective evaluations, outperforming trained embryologists by up to 24.7% in identifying implantation-capable embryos.[32]

KEY BENEFITS OF AI IN EMBRYO SELECTION

Reduced Observer Variability: AI-based systems eliminate inter- and intra-observer variability in embryo assessment.[33] This consistency is essential as the demand for ART treatments continues to grow, increasing manual workload.[34]

Efficiency in Data Processing: AI tools efficiently process large datasets while maintaining consistent quality standards. They expedite calculations and improve precision, reducing the manual workload for embryologists.[35]

Improved Patient Experience: By optimizing treatment plans, AI systems help reduce the financial, physical, and emotional burden on patients, minimizing the need for repeated IVF cycles.[36]

Enhanced Clinical Insights: Deep learning techniques support more objective and accurate results, offering a non-invasive, efficient approach to embryo selection.[37,38]

LIMITATIONS AND CHALLENGES

Despite the advancements in AI-driven embryo selection, the ultimate decision-making authority remains with clinicians. The effectiveness of these systems depends significantly on how closely clinicians adhere to AI-generated recommendations.[37]

AI TOOLS AND TECHNOLOGIES IN EMBRYO SELECTION. MACHINE LEARNING-BASED IMAGE ANALYSIS (TABLE 1)

Time-Lapse Integration Systems

- AI systems combine continuous observation with analysis to track developmental timing and morphokinetic parameters.[40]
- Compatible with existing IVF laboratory protocols.[45]

CLINICAL IMPLICATIONS

Clinical studies indicate that combining AI with time-lapse imaging improves embryo selection outcomes. AI-based selection systems have achieved up to 75% accuracy in predicting pregnancy success, compared to 65% accuracy by embryologists.[46] AI tools like iDAScore have reduced evaluation time while maintaining consistent performance.[43] See Appendix 1 for standardized eSET protocols.

FUTURE DIRECTIONS AND CHALLENGES

The future of AI in embryo selection lies in the development of multi-modal models integrating morphological, genetic, and metabolic data. Machine learning algorithms may soon assist with optimizing endometrial receptivity and predicting IVF success based on lifestyle factors.[47] Challenges include integrating diverse datasets while addressing ethical concerns like AI bias and patient data security

CONCLUSION

While eSET should not be universally mandated due to patient variability, it should be the default for good-prognosis cases. The adoption of eSET has demonstrated significant benefits in improving IVF safety, reducing complications from multiple pregnancies while maintaining comparable success rates. The integration of advanced embryo selection techniques, supported by AI technologies, continues to enhance outcomes. Regulatory frameworks and patient education are essential to successful implementation worldwide, with future innovations likely to further optimize embryo selection and improve fertility treatment success rates.

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COMPETING INTEREST

None

SUBMISSION DECLARATION & DECLARATION OF INTEREST

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Table 1. AI tools and technologies in embryo selection

Technology/System	Functionality	Key Features/Performance	Reference
Machine learning-based image analysis Algorithms learn from morphological features like cell cleavage, fragmentation, and clinical factors	Evaluates embryo development	- Analyzes cell cleavage, fragmentation, clinical factors - Processes single and time-lapse images	Afnan et al.[39]; del Arco de la Paz et al.[40]
Convolutional neural networks (CNNs)	Assesses implantation capability	- 90% accuracy in image analysis - Outperforms embryologists by 24.7% in binary classification	Mishra[41]; Bormann et al.[31]; VerMilyea et al.[32]
STEM/STEM+	Predicts blastocyst formation	High accuracy in blastocyst prediction	Cimadomo et al.[42]
CHLOE	Evaluates embryo quality	Consistent performance vs. expert embryologists	Cimadomo et al.[43]
IVY	Scores embryos for implantation potential	Deep learning-based scoring	Tran et al.[44]
DeepEmbryo	Predicts pregnancy success	75% accuracy in pregnancy prediction	Borna et al.[45]

Notes: AI = artificial intelligence; CNNs = convolutional neural networks.
Sources: Adapted from cited studies in the reference list.

Literature Comparison Table

Paper	Technology Used	Evaluation Method	Clinical Validation
del Arco de la Paz et al.[40]	Non-invasive AI analysis	Accuracy, AUC, sensitivity, specificity	Clinically validated with retrospective data
Bormann et al.[31]	Deep learning, CNN, genetic algorithms	Accuracy, AUC, sensitivity	97 patient cohorts, 97 euploid embryos
VerMilyea et al.[32]	Deep learning ensemble modeling	Sensitivity 70.1%, specificity 60.5%	Retrospective data from 8886 embryos
Cimadomo et al.[42]	3D CNN (iDAScore v1.0)	AUC 0.60 for euploidy prediction	Validated on 3604 blastocysts
Tran et al.[44]	Time-lapse video AI	5-fold cross-validation, AUC	Retrospective with potential clinical application
Borna et al.[45]	CNN (AlexNet, ResNet, Inception)	Precision, Recall, F-Score	Retrospective analysis

More information can be found in Appendix 2.

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APPENDICES

APPENDIX: 1

Protocol for Selective Embryo Transfer (SET)

Section	Details
Objective	Maximize pregnancy success while minimizing multiple gestations by transferring the best-quality embryo(s).
Pre-Transfer Preparation	
Patient Selection	- Age ≤ 35 with good prognosis (first cycle, good ovarian reserve, high-quality embryos). - Previous successful IVF cycles. - Medical contraindications for multiple gestations.
Embryo Selection	- Morphology: Blastocyst stage (Day 5/6) with excellent grading (e.g., AA). - PGT-A tested for euploid status. - Regular cell division with minimal fragmentation.
Endometrial Preparation	- Natural cycle: Monitor LH surge and confirm ovulation. - HRT cycle: Estrogen priming and progesterone initiation. - Endometrial thickness ≥7 mm with trilaminar appearance.
Embryo Transfer Procedure	
Day of Transfer	- Confirm embryo quality and endometrial readiness. - Obtain informed consent from the patient.
Procedure Steps	1. Position patient in lithotomy position. 2. Clean cervix with sterile saline. 3. Insert soft catheter through cervix under ultrasound guidance. 4. Transfer embryo(s) 1-2 cm from uterine fundus. 5. Withdraw catheter and verify embryo placement on ultrasound.
Post-Transfer Care	- Rest for 10-15 minutes post-transfer. - Luteal phase support with progesterone (oral, vaginal, IM).
Post-Transfer Monitoring	
Follow-Up Tests	- Serum β-hCG test 10-14 days post-transfer. - Transvaginal ultrasound at 4-6 weeks to confirm pregnancy.
Outcome Assessment	- Track implantation, pregnancy, and live birth rates. - Evaluate embryo selection effectiveness.
Best Practices	- Prioritize blastocysts with confirmed euploid status. - Optimize lab culture conditions. - Educate patients on SET benefits, especially younger women with favorable prognosis.
Reference Guidelines	- American Society for Reproductive Medicine (ASRM). - European Society of Human Reproduction and Embryology (ESHRE).

EMBRYO TRANSFER PROTOCOLS: ASRM AND ESHRE

ASRM Embryo Transfer Protocol

Age Group	Recommended Embryo Transfer
< 35 years	Single embryo transfer (SET) recommended, regardless of embryo stage.
35–37 years	Strong consideration for single embryo transfer.
38–40 years	Up to 3 cleavage-stage embryos or 2 blastocysts; if euploid embryo available, transfer a single blastocyst.
41–42 years	Up to 4 cleavage-stage embryos or 3 blastocysts; if euploid embryo available, transfer a single blastocyst.
≥ 43 years	Insufficient data for specific recommendations.

Source: American Society for Reproductive Medicine (ASRM)

ESHRE Embryo Transfer Protocol

Factor	Recommendations
Clinical Factors	Patient age, ovarian response, embryo quality, and previous IVF outcomes should guide the decision on the number of embryos transferred.
eSET	Recommended for patients with a good prognosis to minimize multiple pregnancy risks.
Non-Clinical Factors	Patient preferences, psychosocial aspects, and financial considerations should be included in counseling.
Individualized Treatment	Embryo transfer plans should be personalized to balance pregnancy success with the risk of multiple gestations.
Patient Education	Encourage shared decision-making to help patients understand the benefits and risks of embryo transfer options.

Source: European Society of Human Reproduction and Embryology (ESHRE)

APPENDIX: 2

USING AI TECHNOLOGY FOR SELECTING THE EMBRYO TO TRANSFER

Artificial intelligence (AI) is increasingly being integrated into in vitro fertilization (IVF) protocols to enhance embryo selection and improve pregnancy outcomes. While specific standardized AI-based protocols are still under development, several AI-driven systems have demonstrated promising results:

AI ALGORITHMS FOR EMBRYO VIABILITY ASSESSMENT

- **Deep Learning Models:**
  Studies have introduced AI algorithms capable of analyzing static images of embryos at various post-insemination intervals. These models predict pregnancy outcomes with higher accuracy than traditional morphological assessments, achieving accuracy rates of up to 75%.
  Reference:
  An artificial intelligence algorithm to select the most viable embryos considering current processes in IVF labs. Front. Artif. Intell., 30 May 2024. * Medicine and Public Health, Volume 7 - 2024, DOI: https://doi.org/10.3389/frai.2024.1375474
- **Automated Blastocyst Evaluation:**
  AI systems have been developed to assess blastocyst quality by assigning scores that correlate with the likelihood of clinical pregnancy. This aids in selecting embryos with the highest implantation potential.
  Reference:
  Yael Fruchter-Goldmeier, Ben Kantor, Assaf Ben-Meir, Tamar Wainstock, Itay Erlich, Eliahu Levitas, Yoel Shufaro, Onit Sapir, Iris Har-Vardi. An artificial intelligence algorithm for automated blastocyst morphometric parameters demonstrates a positive association with implantation potential. *Scientific Reports*, 5 September 2023; 13(1):14617 DOI: 10.1038/s41598-023-40923-x

AI-DRIVEN EMBRYO SELECTION PLATFORMS

AIVF's EMA Platform:
This AI-powered system evaluates embryo viability by analyzing biological data from fertilization through blastocyst stages. It assigns scores based on the probability of successful implantation, aiming to standardize embryo evaluations and reduce subjectivity.

AiVF: Non-invasive AI can ID genetic characteristics in embryos. Israel Hayom. 2024 Aug 6. Available from: https://www.israelhayom.com.

ERICA (Embryo Ranking Intelligent Classification Algorithm):
ERICA uses deep learning and artificial vision to non-invasively rank embryos according to their genetic status and implantation potential. This enhances objectivity and accuracy in embryo selection.

Reference:
Chavez-Badiola A, et al. Deep learning for automatic determination of blastocyst embryo development stage. Fertil Steril. 2019;112(3 Suppl):e276.doi:10.1016/j.fertnstert.2019.07.809

3. CONSIDERATIONS FOR CLINICAL PRACTICE

While these AI technologies are promising, it is crucial to note that standardized AI-based embryo selection protocols are still evolving. Clinics adopting AI tools should:

- Ensure rigorous validation of AI algorithms before implementation.
- Provide training for embryologists and clinical staff on AI tool utilization.
- Continuously monitor and assess AI performance to maintain accuracy and reliability.

By integrating AI into IVF protocols, clinics can potentially improve embryo selection accuracy, enhance pregnancy outcomes, and offer patients a more efficient and personalized fertility journey.