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Systematic Review

Live birth outcomes after cleavage-stage (day 3) versus blastocyst-stage (day 5) embryo transfer in IVF/ICSI cycles: a systematic review

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ABSTRACT

Background: The optimal timing of embryo transfer in IVF/ICSI is controversial. Although blastocyst transfer improves fresh-cycle success through embryo selection, its effect on cumulative live birth rate (CLBR) is uncertain. **In this study we aimed** to compare live birth outcomes after Day 3 cleavage-stage versus Day 5 blastocyst-stage embryo transfer in IVF/ICSI cycles. **Methods:** A PRISMA-guided systematic review was conducted using PubMed, Embase, and the Cochrane Central Register of Controlled Trials. Eligible studies included women undergoing fresh or frozen-thawed IVF/ICSI cycles comparing Day 5/6 blastocyst transfer with Day 2/3

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cleavage-stage transfer. **Results:** Seven studies were included. In women with a good prognosis blastocyst transfer was associated with higher live birth rates in fresh cycles. Recent large studies showed no significant difference in CLBR between blastocyst and cleavage-stage policies. In women with four or fewer zygotes, blastocyst transfer provided no advantage, while cleavage-stage quality is a predictive of success among transferred blastocysts. **Conclusion:** Blastocyst transfer benefit good-prognosis patients, but it does not improve cumulative live birth outcomes in IVF/ICSI populations. Embryo transfer timing should be individualized, with cleavage-stage transfer favored in patients with low embryo yield to reduce cycle cancellation risk.

Keywords: Blastocyst transfer; Cleavage-stage transfer; Day 3 versus Day 5 embryo transfer; In vitro fertilization; Intracytoplasmic sperm injection

Introduction

The advancement of in vitro culture systems has transformed assisted reproductive technology (ART), shifting the clinical focus toward optimizing embryo selection and timing of transfer. In the past, transferring embryos at the cleavage stage on Day 2 or 3 was common because of the limits of culture media. There has been a significant global trend toward transferring embryos at the blastocyst stage on Day 5 or 6 (Smeenk et al. 2023). Extended culture allows for "natural selection," helping to pick out embryos with greater potential for development with a better synchronization with the endometrial environment.

The effectiveness of transferring blastocysts during fresh cycles has been supported by several meta-analyses and randomized controlled trials (RCTs). Wang et al. (2014) show that blastocyst transfer improves live birth rates (LBR) when compared to cleavage-stage transfer during fresh IVF/ICSI. Papanikolaou et al. (2005) found that the live birth rate is much greater after transferring blastocysts if there are at least four good-quality embryos on the third day. Despite these advantages, the chance that the cycle could be stopped if none of the embryos develop into the blastocyst phase. This risk of attrition is an important issue for poor-prognosis patients or those with a low embryo yield. Neuhausser et al. (2020) found that for patients with less than 5 zygotes cleavage transfer is better to prevent losing embryos that may survive in the uterus. Xiao et al. (2019) found that when there is only one embryo available by Day 3, transferring it right away leads to better pregnancy and live birth rates than trying to develop the embryo to Day 5.

These results imply that the uterus is a better environment for fragile embryos compared to laboratory conditions. The way we measure success in assisted reproductive technology has changed from focusing on "successful fresh transfers" to looking at the total live birth rate (TLBR), which includes all fresh and frozen transfers from a single retrieval. Recent evidence, including a propensity score-matched study by Yin et al. (2017), indicates that the CLBR of Day 2/3 and Day 5/6 transfers are comparable. This parity is notable in patients who respond poorly; De Croo et al. (2022) found no advantage to transferring blastocysts in patients with four or fewer embryos. Even when embryos do reach the blastocyst stage, their earlier development still matters; Herbemont et al. (2017) showed that the morphology on Day 2 and Day 3 still has important predictive Value for implantation in high-quality blastocysts.

Although vitrification has led to successes in transferring frozen-thawed blastocysts (Takahashi et al. 2005), some research has pointed out worries about perinatal outcomes. Zhang et al. (2019) found

that extended in vitro culture is associated with higher birth weight Z-scores and an increased risk of "large-for-gestational-age" (LGA) infants. The purpose of this study is to assess the CLBR between Day 3 and Day 5 transfers within our particular group to offer more insight into individualizing embryo transfer methods.

Methods

This systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search was performed in online databases, including PubMed, Embase, and the Cochrane Central Register of Controlled Trials. The search used a combination of Medical Subject Headings (MeSH) and keywords: "blastocyst transfer," "cleavage-stage transfer," "day 3 versus day 5," "cumulative live birth rate," and "in vitro fertilization." The search was limited to human studies published in English. Reference lists of relevant studies, were screened to identify primary studies.

Inclusion and Exclusion Criteria

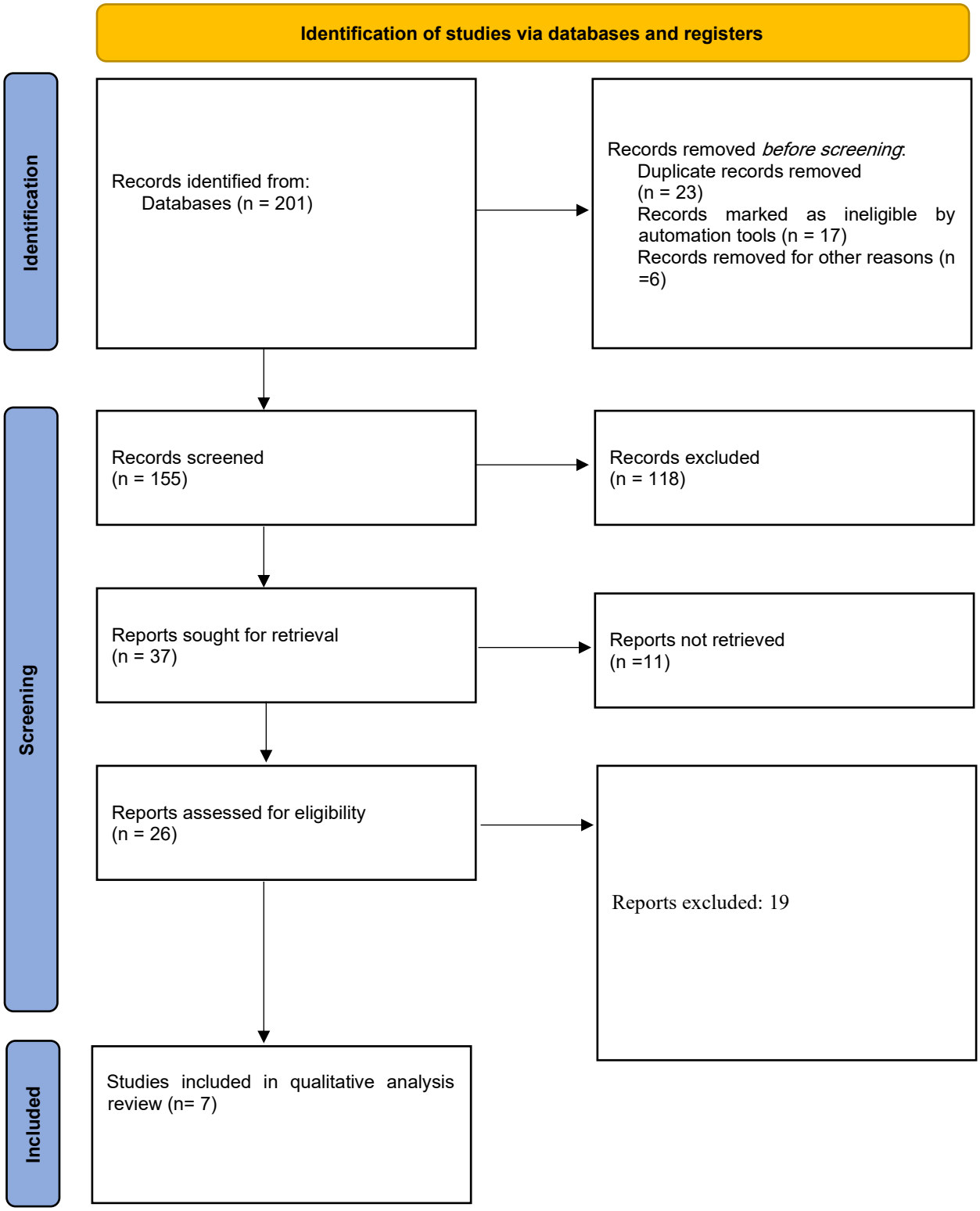
Studies were considered for inclusion if they satisfied the following PICO (Population, Intervention, Comparison, Outcome) requirements:(1) Population: Women undergoing fresh or frozen-thawed IVF/ICSI cycles; (2) Intervention: Embryo transfer at the blastocyst stage on Day 5 or 6; (3) Comparison: Embryo transfer at the cleavage stage on Day 2 or 3;(4) Outcomes: The primary outcome was the CLBR. Secondary outcomes included fresh LBR, CPR, cycle cancellation rates, and neonatal outcomes such as birth weight.

We included both randomized controlled trials (RCTs), and retrospective cohort studies that focused on patients, low responders or individuala with only one embryo available. Studies involving preimplantation genetic testing (PGT) were excluded to reduce factors that confuse the outcomes related to embryo selection. Two separate reviewers gathered information with a standardized form. The information collected included details about the study type, the ages of patients, how many zygotes or embryos were present on Day 3, and particular embryological protocols. When studies included newborn outcomes, data regarding gestational age and birth weight Z-scores were prioritized. Quality assessment was performed using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational and propensity score-matched studies.

Data Synthesis and Analysis

Data were synthesized to evaluate the effectiveness of treatments among various prognostic groups. A focus was placed on "indication bias," as pointed out by Cameron et al. (2020), to verify that the superiority of blastocyst transfer was not simply a reflection of higher embryo cohorts.

Fig 1: PRISMA flow chart



Results

The relative effectiveness of transferring blastocyst-stage (Day 5) embryos versus cleavage-stage (Day 3) embryos has been a primary concern in contemporary reproductive medicine. In the past, transferring fresh blastocysts resulted in higher rates of implantation and pregnancies per transfer due to the prolonged culture period that favored the selection of more viable embryos. Papanikolaou et al. (2005), showed a rise in live birth rates for blastocyst transfers (51% compared to 32%) in patients who had a minimum of four high-quality embryos on Day 3.as medical practices have evolved to focus on assessing the CLBR which takes into account results from all fresh and frozen-thawed transfers stemming from one egg retrieval, the benefits of blastocyst transfer have become less clear.

Recent large-scale studies indicate that although transferring fresh blastocysts might lead to a higher initial success rate, the cumulative live birth rate generally stays similar to that of cleavage-stage methods. The multicentre RCT by Cornelisse et al. (2024) revealed no notable difference in cumulative live birth rates between the two approaches (58.7% for blastocysts compared to 57. 8% for cleavage). Population-based research by Cameron et al. (2020) Showed that once controlling for indication bias, the possibility of a live birth after blastocyst transfer or cleavage-stage transfer was almost the same (adjusted odds ratio of 1.01).

In patients who do not respond well to ovarian stimulation, the advantages of prolonged culture are less significant. De Croo et al. (2022) found that in individuals with four or fewer zygotes, the cumulative live birth rate did not show a significant difference between Day 3 and Day 5 approaches (21. 0% compared to 20. 3%). This means that for those with poor responses, the likelihood of no embryos being ready for transfer on Day 5 due to culture problems may outweigh the benefits of embryo selection. Karacan et al. (2014) showed that transferring the same number of embryos at different stages led to similar chances of live births (35. 7% compared to 32. 1%). More than just the timing of the transfer, the quality of the embryo during the cleavage stage plays an important role in determining success. A study by Shen et al. (2020) showed that high -quality embryos that developed well during the cleavage-stage achieved significantly higher live birth rates. these results suggest that while transferring blastocysts might be beneficial in fresh cycles for patients with a good prognosis, it doesn't increase the success rate of an IVF cycle compared to cleavage transfer.

Table 1: characteristics of the included studies

Study	study design and setting	study population and inclusion criteria	Intervention	Sample Size	Methodological details
Cornelisse et al. (2024)	Multicentre randomized controlled trial (RCT) conducted in 21 hospitals and clinics in the Netherlands.	Women aged 18–43 years undergoing IVF/ICSI treatment with at least four embryos available on	Comparison of a blastocyst-stage embryo transfer policy (Day 5) versus a cleavage-stage policy (Day 3), including	1,202 women (601 in blastocyst group, 601 in cleavage group).	Primary focus was on CLBR within 12 months. The study utilized a non-inferiority design to evaluate if the blastocyst

Study	study design and setting	study population and inclusion criteria	Intervention	Sample Size	Methodological details
		day 2 after oocyte retrieval.	both fresh and subsequent frozen-thawed transfers.		policy was superior or equivalent.
De Croo et al. (2022)	Retrospective cohort study at the Department of Reproductive Medicine, Ghent University Hospital, Belgium.	Patients with a limited ovarian response, specifically defined as having four or fewer zygotes on Day 1 of culture.	Fresh cleavage-stage transfer (Day 2 or 3) followed by Day 5 vitrification versus fresh blastocyst transfer (Day 5) with vitrification of supernumerary blastocysts.	1,109 oocyte collection cycles (439 cleavage-stage policy, 670 blastocyst-stage policy).	Evaluated cumulative live birth rates per oocyte OCC to determine if extended culture is beneficial for low-responder patients.
Cameron et al. (2020)	Population-based retrospective cohort study using data from the Human Fertilization and Embryology Authority (HFEA), UK.	Women undergoing their first complete cycle of IVF or ICSI between 2012 and 2016.	Comparison of blastocyst-stage (Day 5) versus cleavage-stage (Day 2 or 3) embryo transfer in the first fresh cycle and subsequent frozen cycles.	51,246 women (33,454 cleavage-stage, 17,792 blastocyst-stage).	Performed adjustments for indication bias and utilized a multivariable logistic regression model to assess the odds of live birth across the entire cycle.
Shen et al. (2020)	Retrospective study at the Shanghai Ninth People's Hospital, China.	Patients undergoing single vitrified-warmed blastocyst transfer cycles, categorized by blastocyst quality (AA to CB).	Analysis of the impact of prior cleavage-stage embryo quality and development speed on the success of single blastocyst transfers.	3,386 single vitrified-warmed blastocyst transfer cycles.	Divided into four groups based on blastocyst grade (Group 1: AA/AB/BA; Group 2: BB; Group 3: BC; Group 4: CB) to isolate the influence of earlier developmental stages.
Rifasky et al. (2021)	Comparative cross-sectional study at Graha Amerta Hospital, Surabaya, Indonesia.	IVF participants meeting inclusion criteria based on medical records from January to December 2016.	Direct comparison of pregnancy rates following embryo transfer on Day 3 versus Day 5 of culture.	120 participants (40 cleavage-stage, 80 blastocyst-stage).	Used a comparative design to identify success rates within a specific hospital setting over a one-year period.
Karacan et al. (2014)	Retrospective analysis in a single IVF center in Turkey.	Couples with at least two previously unsuccessful IVF-ET attempts (repeated implantation failure).	Transfer of an equal number (exactly two) of cleavage-stage embryos versus blastocysts.	238 couples (143 cleavage-stage, 95 blastocyst-stage).	Aimed to evaluate if extended culture overcomes previous failures when the number of transferred embryos is held constant.
Papanikolaou et al. (2005)	Randomized prospective study at	Women younger than 37 years with at	Randomization to either Day 3 cleavage-stage	164 patients (82 in each group).	Assessed whether outcomes improved by

Study	study design and setting	study population and inclusion criteria	Intervention	Sample Size	Methodological details
	the University Hospital, Vrije Universiteit Brussel, Belgium.	least four good-quality embryos (≥6 cells) on the morning of Day 3.	transfer or Day 5 blastocyst-stage transfer.		extending culture specifically when a high number of good-quality embryos were available.

Table 2: main findings and outcomes of the included studies

Study	Primary outcome	cleavage-stage results	blastocyst-stage results	statistical significance and comparison	Key conclusion
Cornelisse et al. (2024)	Cumulative Live Birth Rate (CLBR) within 12 months.	57.8% (347/600)	58.7% (353/601)	RR: 1.02; 95% CI: 0.93–1.11.	No significant difference in CLBR between the two policies for women with ≥4 embryos on Day 2.
De Croo et al. (2022)	CLBR per oocyte OCC.	21.0%	20.3%	p = 0.79; OR: 0.96; 95% CI: 0.71–1.30.	For patients with ≤4 zygotes, there is no clinical benefit to a blastocyst-transfer policy over cleavage-stage transfer.
Cameron et al. (2020)	CLBR over one complete IVF cycle.	28.5% (fresh)	43.1% (fresh)	Adjusted OR for CLBR: 1.01; 95% CI: 0.96–1.07.	After adjusting for indication bias, the odds of a live birth do not differ between Day 3 and Day 5 policies.
Shen et al. (2020)	LBR per transfer.	High-quality cleavage: 45.4% (Group 2)	Poor-quality cleavage: 35.5% (Group 2)	Significant difference (p = 0.005) even when the final blastocyst grade was identical (BB).	Cleavage-stage quality and speed are valuable predictors of LBR, even for identical-grade blastocysts.
Rifasky et al. (2021)	Successful Pregnancy Rate.	35.0%	49.3%	p > 0.05	While the Day 5 percentage was higher, the study found no statistical impact of transfer day on pregnancy success.
Karacan et al. (2014)	LBR	32.1%	35.7%	P value > 0.05	Clinical pregnancy and live birth rates were similar in women with repeated IVF failure when transferring two embryos.
Papanikolaou et al. (2005)	Live Birth Rate per cycle.	32.0%	51.0%	p = 0.02	Blastocyst transfer significantly increases live birth rates when at least four good-quality embryos are available on Day 3.

Discussion

The optimal time for embryo transfer is a major topic of debate in assisted reproductive technology. Previous research and reviews indicated that transferring fresh blastocysts improves live birth rates compared to transferring at the cleavage stage.recent studies are shifting their focus more towards cumulative live birth rates and individualized patient outcomes.

The main benefit of prolonged culture is that it allows for the "self-selection" of embryos that are more likely to develop well. This is especially clear in patients who have a good chance of success; as established by Papanikolaou et al. (2005), the live birth rate is much higher after transferring blastocysts when there are at least four high-quality embryos available on the third day. This advantage does not apply to everyone. For patients with a limited embryo yield, the possibility of cycle cancellation due to developmental arrest in vitro continues to be a major issue.

Neuhausser et al. (2020) point out that for patients with a poor prognosis (5 or fewer zygotes), it is usually better to transfer at the cleavage stage to guarantee that a transfer takes place, a method that aligns with the PRECiSE trial's guidelines. Xiao and his team (2019), discovered that when there is just one embryo available on Day 3, transferring it right away to the uterus leads to higher rates of pregnancy and live births than trying to develop the embryo until Day 5, which questions that the lab incubator is more effective than the uterus. When assessing the success of an oocyte retrieval cycle, the differences between transfer days often become negligible. Yin et al. (2017) used a matching of propensity score to show that the outcomes from Day 2/3 and Day 5/6 are similar, suggesting that prolonged culture may alter the timing of success without increasing the total number of births.

This consistent with new research by De Croo et al. (2022), which found no difference in cumulative live birth rates for patients with four or fewer zygotes. Even after embryos develop to the blastocyst stage, their earlier developmental journey is still significant. Herbemont et al. (2017) found that the morphology on Day 2 and Day 3 still holds predictive value for implantation, even for blastocysts of equivalent top-grade quality additionally, it's important to think about the safety of newborns and outcomes related to childbirth. Although vitrification techniques have improved the safety and efficiency of transferring blastocysts (Takahashi et al. 2005), new concerns have a risen regarding "large-for-gestational-age" (LGA) infants. Research by Zhang et al. (2019) showed that incubating embryos until Day 5/6 resulted in higher birth weight Z-scores and increased number of LGA infants compared to transfers made on Day 3. These trends are reflected in broad registry data from ESHRE, which show a continued shift toward blastocyst transfer across Europe despite these nuances (Smeenk et al. 2023).

In conclusion, deciding between cleavage and blastocyst transfer should be done on a case-by-case basis rather than as a rigid rule. While culturing to the blastocyst stage is better for selecting patients who are likely to succeed, using a cleavage-stage approach can help prevent losses in patients with lower chances of success without affecting the overall rate of live births.

Conclusion

The shift to transferring embryos at the blastocyst stage has led to better implantation rates for fresh embryos due to better embryo selection; it doesn't automatically lead to a higher total live birth rate for each retrieval cycle. A universal method for extended embryo culture is not advisable; rather, a personalized approach is crucial. For patients who have few embryos or only one viable embryo, cleavage-stage transfer is the best option to reduce the loss during development in the lab. Even though vitrification has produced stable results, there is a need for long-term observation due to the possible impact on newborn weights.

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