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ORIGINAL RESEARCH Multicentre randomised controlled trial

Cumulative live birth rate of a blastocyst *v* cleavage stage embryo transfer policy during IVF in women with a good prognosis

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Study question Does embryo transfer at the blastocyst stage compared with cleavage stage improve cumulative live birth rates, including both fresh and frozen-thawed embryo transfers, in women undergoing in vitro fertilisation (IVF) with a good prognosis?

Methods This randomised controlled trial was conducted across 21 Dutch hospitals and clinics between 18 August 2018 and 17 December 2021. Overall, 1202 women with at least four embryos available on day 2 after oocyte retrieval were randomly assigned to either blastocyst stage embryo transfer (n=603) or cleavage stage embryo transfer (n=599). The primary outcome was the cumulative live birth rate. Secondary outcomes included cumulative pregnancy rates, pregnancy loss rates, live birth rate after fresh embryo transfer, number of embryo transfers needed, number of frozen embryos, and obstetric and perinatal outcomes.

Study answer and limitations The cumulative live birth rate did not differ between the blastocyst group and cleavage group (58.9% (355 of 603) *v* 58.4% (350 of 599; risk ratio 1.01, 95% confidence interval 0.84 to 1.22). The blastocyst group showed a higher live birth rate after fresh embryo transfer (1.26, 1.00 to 1.58), lower cumulative pregnancy loss rate (0.68, 0.51 to

Outcomes (primary and secondary) in intention-to-treat population. Values are number (percentage) unless stated otherwise

Cumulative rates	Blastocyst stage group* (n=603)	Cleavage stage group† (n=599)	Adjusted absolute difference‡ (95% CI)	Risk ratio‡ (95% CI)
Live birth§	355 (58.9)	350 (58.4)	0.4 (−5.1 to 5.9)	1.01 (0.84 to 1.22)
Ongoing pregnancy¶	362 (60.0)	357 (59.6)	0.4 (−5.1 to 5.8)	1.01 (0.84 to 1.22)
Clinical pregnancy**	378 (62.9)	388 (64.8)	−2.1 (−7.5 to 3.3)	0.97 (0.81 to 1.16)
Biochemical pregnancy††	430 (71.3)	448 (74.8)	−3.5 (−8.5 to 1.4)	0.95 (0.80 to 1.14)
Pregnancy loss‡‡	98 (16.3)	145 (24.2)	−7.9 (−12.4 to −3.4)	0.68 (0.51 to 0.89)

CI=confidence interval. Definitions for cumulative pregnancy and pregnancy loss rate were the same with the addition that at least one pregnancy or pregnancy loss occurred during the follow-up period of one year. Each woman could have multiple pregnancies as a result of a one year follow-up period. *23 women had at least two pregnancies with at least one pregnancy loss and one live birth. †47 women had at least two pregnancies with at least one pregnancy loss and one live birth. ‡Adjusted for age group. §Delivery resulting in live birth after 24 gestational weeks. ¶Viable intrauterine pregnancy with fetal heartbeat 10-12 weeks after oocyte retrieval. **Presence of at least one gestational sac 5-8 weeks after oocyte retrieval. ††Positive home pregnancy test result 14-17 days after oocyte retrieval. ‡‡Pregnancy loss after a positive pregnancy test result (<21 weeks).

0.89), and lower mean number of embryo transfers needed to result in a live birth (1.55 v 1.82; P<0.001). The incidence of moderate preterm birth (32 to <37 weeks) in singletons was higher in the blastocyst group (1.87, 1.05 to 3.34). The inclusion of only women with a minimum of four embryos limits the generalisability of the findings.

What this study adds Cumulative live birth rates were similar between blastocyst and cleavage stage embryo transfers in women with a good prognosis undergoing IVF treatment. Although the study was not powered for secondary outcomes, blastocyst stage transfers were associated with higher efficiency. Blastocyst stage transfers, however, raise concerns about the risk of preterm birth.

Funding, competing interests, and data sharing
Supported by a grant from the Leading the Change programme, which had no role in the development or execution of the trial. No competing interests declared. Data can be made available upon request.

FAST FACTS The importance of the day of embryo transfer during in vitro fertilisation

The timing of embryo transfer is an important element of in vitro fertilisation (IVF). This article describes the main phases of IVF treatment, embryo development and transfer policies, cumulative live birth rates, and key current findings.

In vitro fertilisation (IVF) is an established treatment for infertility and has been responsible for the birth of >10 million children since 1978.[1] An IVF cycle includes ovarian hyperstimulation with hormones, oocyte retrieval, and then fertilisation and embryo culture in the laboratory.[2 3] In most laboratories worldwide, embryos are cultured in vitro for 3-6 days, and the embryos with the highest chance of resulting in a live birth are selected for intrauterine transfer. Surplus embryos are cryopreserved for future use if an initial transfer is unsuccessful or more children are planned.

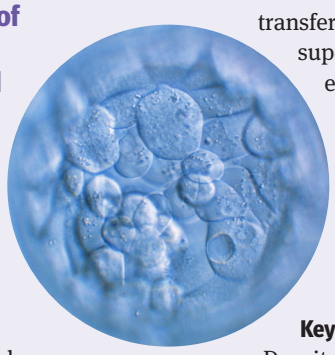
Embryo development and transfer policies

IVF, with or without intracytoplasmic sperm injection (ICSI), involves the handling of sperm cells, oocytes, and embryos outside the body. In IVF, thousands of sperm cells are used to inseminate oocytes, whereas in ICSI, one sperm cell is injected into each oocyte.[2 3] About 23 hours after fertilisation, cell division begins. On the second day after insemination/injection, the embryo should comprise four cells (blastomeres), and on the third day eight equally sized blastomeres ideally should be present—embryos can cleave at different rates.

The cleavage stage comprises the period from two cells to the morula stage, which occurs around day 4 of culture. During the morula stage a process called compaction begins, when the cells start to adhere tightly to each other. This process is crucial, as it increases cell-to-cell communication and prepares the embryo for differentiation. Cell division increases exponentially. In the subsequent blastocyst stage, around day 5 or 6, the embryo has >100 cells.[3]

Embryo transfer can occur at different stages of development. Traditionally, embryos were transferred on day 3, aligning with the cleavage stage of embryo development. After improvements to in vitro culture conditions and embryo cryopreservation, practice has shifted towards transferring embryos at the blastocyst stage, usually on day 5 or 6 after oocyte retrieval.[4-6]

With advances in cryopreservation methods, the success of embryo freezing and thawing has increased considerably



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Rationale behind transfer approaches

The rationale for embryo transfer at the blastocyst stage lies in the potential for enhanced embryo selection. In IVF, not all embryos develop into good quality blastocysts. Some embryos show arrested development and some exhibit lower implantation potential. Extended culture to the blastocyst stage helps to identify embryos with high implantation potential. Moreover, transferring embryos at the blastocyst stage is thought to align more closely with the natural timing of implantation, potentially increasing the chance of live birth for each transfer and reducing the number of embryo transfers needed.[4-6]

Committing to a blastocyst stage transfer carries the risk of poor embryo development, however, as debate is still ongoing about whether IVF culture conditions are truly optimised for human embryos. Embryos that might not survive extended in vitro culture might survive in vivo if transferred at the cleavage stage. Additionally, the number of supernumerary embryos available for cryopreservation at the cleavage stage is typically higher than those available at the blastocyst stage.[4]

Cumulative live birth rate

Success rates in IVF are increasingly measured by cumulative live birth rates, which include live births from all fresh and frozen-thawed embryo transfers resulting from a single oocyte retrieval. This metric better provides a more comprehensive reflection of the overall success rate of an IVF treatment cycle. Traditionally, IVF success rates were reported based on the live births for each fresh or first embryo transfer, excluding the outcomes of supernumerary frozen-thawed embryo transfers. With advances in cryopreservation methods, the success of embryo freezing and thawing has increased considerably, leading to higher cumulative live birth rates.[7]

Key findings and interpretation

Despite the widespread adoption of blastocyst stage embryo transfer, it remained unclear whether a blastocyst stage policy actually improved cumulative live birth rates.[4] In our study, we compared cumulative live birth rates between blastocyst and cleavage stage transfers.[10] The similar cumulative live birth rates observed in our study underscore the importance of considering other factors when choosing between cleavage and blastocyst stage transfers in women with a good prognosis. Although blastocyst stage transfers may enhance treatment efficiency, the increased risk of preterm birth necessitates careful evaluation.[10]

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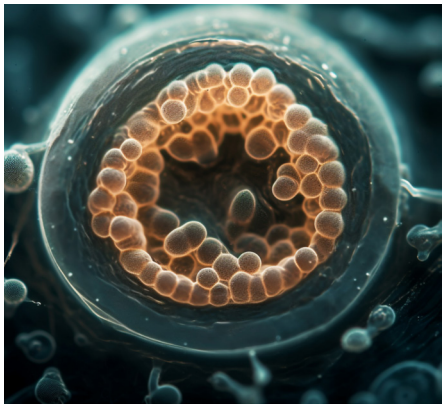
In assisted reproductive technology, the timing of embryo transfer after oocyte retrieval and in vitro fertilisation is crucial. Traditionally, embryos have been transferred at the cleavage stage (two or three days post-fertilisation). However, transferring embryos at the blastocyst stage (five or six days post-fertilisation) is increasingly common.

Most studies focus on outcomes from fresh embryo transfers, often overlooking the potential of surplus frozen embryos. Additionally, the effect of transfer stage on obstetric and neonatal outcomes has been underexplored. The study by Cornelisse and colleagues therefore represents an important advance in this area.[1] Their multicentre, randomised controlled trial (n=1202) compared outcomes over 12 months after embryo transfers on day 3 or day 5, analysing all embryo transfers within that timeframe. The study's thorough approach, which assessed cumulative live birth rates—including both fresh and frozen embryo transfers from a single oocyte retrieval—as well as obstetric complications, distinguishes it from previous research. The study found no difference in cumulative live birth rates (risk ratio 1.01, 95% confidence interval (CI) 0.84 to 1.22), whereas live birth rates after a fresh embryo transfer were higher after a blastocyst transfer (1.26, 1.00 to 1.58).

Although concerns remain about the risk of bias resulting from crossover and differences in freezing techniques in some women, these deviations are unlikely to have substantially influenced the results.[2]

Why wait?

The rationale for extending embryo culture to day 5 or 6 is based on the concept of self-selection. Many embryos stop developing between the cleavage and blastocyst stages, suggesting that those that reach the blastocyst stage have the highest potential for implantation. Additionally, embryos enter the uterine cavity at the blastocyst stage after natural conception, indicating that the endometrium is ready for implantation at this point. Transferring embryos at this stage therefore makes biological sense, potentially reducing the likelihood of unsuccessful transfers, as well as the emotional and financial burden on women.



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The results support the advantages of blastocyst stage transfers for important secondary outcomes

Previous evidence suggested that transfers at the blastocyst stage might be associated with higher clinical pregnancy and live birth rates for each fresh embryo transfer compared with transfers at the cleavage stage.[4] But other important outcomes, such as the results from transfer of surplus frozen embryos, were unclear. The few studies reporting cumulative clinical pregnancy rates were limited, using outdated slow freezing techniques.[5-8] Only one trial using a modern freezing technique (vitrification) suggested a potential benefit for blastocyst transfer, but with low certainty owing to the small sample size (120 participants).[9]

Study strengths and limitations

Cornelisse and colleagues' trial adds value because it analysed a larger sample size with a longer follow-up and found no significant differences in cumulative live birth rates, and it confirmed higher live birth rates for each fresh transfer in the blastocyst group. The study also showed a significantly lower cumulative rate for pregnancy loss and fewer transfers required to achieve a live birth in the blastocyst group, which could reduce costs, time, and emotional burden for women and their partners.[10]

The study highlighted a probable increase in moderate to late preterm births (between weeks 32 and 37) associated with blastocyst transfers (risk ratio 1.87, 95% CI 1.05 to 3.34), warranting careful consideration owing to its implications for perinatal outcomes.[11 12] In total, two randomised controlled trials, including the one by Cornelisse and colleagues, have been published since the last Cochrane review in 2022,[4-14] with similar results for fresh transfers but some differences in cumulative rates. These trials will add considerable value to the next systematic review update.

The authors acknowledged some important limitations of their trial. All participants had at least four embryos available on day 2, which could limit the generalisability of the findings to women with fewer fertilised oocytes. Some practitioners prefer cleavage stage transfers in women with a low response, to avoid any increased risk of cancelled transfers at the blastocyst stage. They argue that day 3 transfers might give the embryos a chance of implanting. Lack of evidence to guide decision making in this subgroup highlights the need for further research.

What should clinicians do?

Shared decision making around blastocyst stage transfers must balance the potential benefits of increased live birth rates for each fresh embryo transfer and the avoidance of unnecessary transfers that could result in negative outcomes, with the risks of increased perinatal complications, including premature delivery.[15] Decisions should be individualised for women, taking full account of their values and preferences. Decision aids could be instrumental in this process, offering structured guidance. Clear communication is essential to ensure women understand both the certainty and the limitations of the available evidence.

In conclusion, although Cornelisse and colleagues' study found no difference in cumulative live birth rates, the results support the advantages of blastocyst stage transfers for important secondary outcomes, particularly when four or more fertilised oocytes are available. The findings also underscore the importance of carefully weighing these advantages against potential obstetric risks. Questions remain for women with a limited number of embryos, so research must continue.[14] Shared decision making continues to be essential for women and clinicians navigating this complex evidence landscape.

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Comparative effects of drug interventions for the acute management of migraine episodes in adults

Karlsson WK, Ostinelli EG, Zhuang ZA, et al

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Study question What are the comparative efficacy, safety, and tolerability of licensed oral drugs for the acute treatment of migraine episodes in adults?

Methods This systematic review and network meta-analysis included double blind, randomised controlled trials comparing monotherapy using oral drugs with placebo or another eligible active treatment for the acute treatment of migraine episodes in adults (≥18 years). Trials were sourced from the Cochrane Central Register of Controlled Trials, Medline, Embase, ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Platform, and websites of regulatory agencies and pharmaceutical companies without language restrictions until 24 June 2023. Participants were outpatients with a diagnosis of migraine according to the International Classification of Headache Disorders. Only drugs and treatment dose ranges licensed for migraine or headache were considered eligible if they were recommended by at least one of seven international regulatory bodies. The primary outcomes were the proportion of participants who were pain-free at two hours post-dose and the proportion of participants with sustained pain freedom from two to 24 hours post-dose, both without the use of rescue drugs. Other efficacy measures and clinically important adverse events were also analysed. Quality of the evidence was graded using the confidence in network meta-analysis (CINeMA) online tool. Vitruvian plots were used to summarise findings.

Study answer and limitations 137 randomised controlled trials comprising 89 445 participants allocated to one of 17 active interventions or placebo were included. All active interventions showed superior efficacy compared with placebo for pain freedom at two hours (odds ratios from 1.73 (95% confidence interval (CI) 1.27 to 2.34) for naratriptan to 5.19 (4.25 to 6.33) for eletriptan, and most of them also for sustained pain freedom to 24 hours (odds ratios from 1.71 (1.07 to 2.74) for celecoxib to 7.58 (2.58 to 22.27) for ibuprofen). In head-to-head comparisons between active interventions, eletriptan 20-80 mg was the most effective drug for pain freedom at two hours (odds ratios from 1.46 (1.18 to 1.81) to 3.01 (2.13 to 4.25)), followed by rizatriptan 5-10 mg (1.59 (1.18 to 2.17) to 2.44 (1.75 to 3.45)), sumatriptan 25-100 mg (1.35 (1.03 to 1.75) to 2.04 (1.49 to 2.86)), and zolmitriptan 2.5-5 mg (1.47 (1.04 to 2.08) to 1.96 (1.39 to 2.86)). For sustained pain freedom from 2 to 24 hours, the most efficacious interventions were eletriptan 20-80 mg and ibuprofen 200-600 mg (odds ratios from 1.41 (1.02 to 1.93) to 4.82 (1.31 to 17.67)). Confidence in accordance with CINeMA ranged from high to very low.

What this study adds Overall, eletriptan, rizatriptan, sumatriptan, and zolmitriptan had the best profiles, and they were more efficacious than the recently marketed drugs lasmiditan, rimegepant, and ubrogepant.

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