

Are more babies born if embryos are cultured for three or five days in the lab? Trial suggests that age matters

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Women are just as likely to give birth to live babies after fertility treatment if embryos are transferred to their wombs three days after fertilization in the laboratory rather than five. However, the women's age can affect the outcomes, according to new research presented to the 39th



annual meeting of the European Society of Human Reproduction and Embryology (ESHRE).

Dr. Simone Cornelisse, a researcher and resident in obstetrics and gynecology at Radboud University Medical Center, Nijmegen (The Netherlands), told the conference that among 1202 women from 21 Dutch fertility centers who were randomly assigned to have embryos transferred to their wombs after three or five days, there was no difference in the cumulative live birth rate—the birth rate derived from transferring fresh and frozen embryos following a single round of egg retrieval.

Until now, there has been no evidence about whether the cumulative live birth rate differed depending on how long embryos were cultured in the laboratory before being transferred to the womb. There has been a trend among fertility centers towards transferring embryos when they have reached the blastocyst stage (after five days) rather than the cleavage stage (after three days). It was thought that it was easier to select the most viable embryos if they had reached the blastocyst stage. It was also thought that the womb was more receptive after five days. However, culturing embryos for longer outside the womb carries risks, and the effects on the offspring in later life are still unclear.

The study, <u>presented</u> at the European Society of Human Reproduction and Embryology's 39th Annual Meeting, is the first large randomized controlled trial to provide 'gold standard' evidence focusing on the outcome that parents care most about: will it result in the birth of a live baby?

Dr. Cornelisse said, "Most studies have focused on the outcome of transferring fresh embryos, but they do not have data on the cumulative live birth rate of all transfers from one egg collection, including embryos that have been frozen and stored for later use. Therefore, it is still not



clear whether patients benefit from the recent change of policy to blastocyst-stage transfers. The cumulative live birth rate is undoubtedly the most relevant outcome for parents, and for researchers who are evaluating the success of IVF programs."

Among 603 women who had blastocyst-stage embryos transferred, the cumulative live birth rate was 58.9% (355 live births). If cleavage-stage embryos were transferred, the live birth rate was 58.4% (350 live births out of a total of 599 women). There was no difference in the time it took women to achieve a pregnancy that resulted in a live birth.

The women all had good prognoses, which was defined as having at least four embryos available to be transferred after two days of culturing in the laboratory.

The researchers also looked at the cumulative live birth rates by age, dividing the women into those aged younger than 36 and those who were 36 or older. "We found a potential benefit from transferring cleavage-stage embryos in women who were aged up to 36 years, but the difference was not statistically significant: a 67% cumulative live birth rate for cleavage-stage embryos compared to a 63% rate for blastocyst-stage embryos," said Dr. Cornelisse. "This was in contrast to women aged 36 years or older, in whom we found a potential, but not statistically significant benefit from transferring blastocyst-stage embryos: a 52% cumulative live birth rate for these versus a 43% rate for cleavage-stage embryos."

The researchers suggest that although some of these results are not statistically significant, they are still clinically significant. "If we look at this in a larger group of women, the results would probably reach statistical significance," said Dr. Cornelisse.

When the researchers looked at the live birth rate following the transfer



of fresh embryos only, they found a significant difference in favor of blastocyst-stage transfer: 37% (223 live births among 603 women) compared to 29.5% (177 births among 599 women) for cleavage-stage embryos. Previous studies have also had similar results.

This difference was even more marked when they looked at the live birth rates by age. In women aged 36 years or older, the live birth rate was 35% for blastocyst-stage fresh embryos compared to 18.5% for cleavage-stage embryos (76 births among 215 women compared to 40 births among 216 women). For women aged younger than 36 years, the difference was not statistically significant: 38% for blastocyst-stage embryos versus 36% for cleavage-stage embryos (147 births among 388 women versus 137 births among 383 women).

"Our study shows that the cumulative live birth rate is similar between women who have embryos transferred at the blastocyst stage or the cleavage stage. However, clinicians and their patients should consider the effects of age," said Dr. Cornelisse.

"In women aged 36 years or older, with a good prognosis, we saw a clinically relevant higher cumulative live birth rate and live <u>birth</u> rate after transferring fresh embryos, when the embryos were transferred at the blastocyst stage. It is noteworthy that in younger women with a good prognosis, cleavage-stage transfer is a good strategy and just as successful as blastocyst-stage transfer."

She concluded: "In assisted reproduction, many new developments and techniques are often introduced into <u>clinical practice</u>, as with blastocyst-stage transfers, with little or no evidence. Furthermore, the final benefit for the patients, data on cumulative live births, is often not reported. It is important that new fertility developments and treatments are first properly evaluated in <u>clinical trials</u> before being introduced into clinical practice, in order to allow clinics and patients to make a balanced choice



based on solid data."

Dr. Cornelisse and her colleagues are now conducting a cost-benefit analysis of the study to see if one option is more cost effective than another and for which age groups. They will also analyze potential risks and the burden of treatment on patients.

The researchers emphasize that their findings are applicable only for women with good prognoses (at least four embryos available) and may not hold true for all <u>women</u> undergoing fertility treatment.

The chair of ESHRE, Professor Carlos Calhaz-Jorge from the Northern Lisbon Hospital Center and the Hospital de Santa Maria in Lisbon (Portugal), was not involved in this research. He commented, "The results from this randomized controlled trial are very important and may have significant implications for patients. This study provides relevant data to support evidence-based decisions in an area where the current options lack some structured, long-term evidence. The current trend towards extending the time that embryos are cultured in the laboratory has occurred without sufficient evidence to support it. The study by Dr. Cornelisse and her colleagues shows that it may not always be the best strategy for all patients."

"It will be interesting to see the results from larger groups of patients, and also the <u>cost-benefit analysis</u>, when it may be possible to see the different effects of three-day and five-day transfers on patients, both financially and in terms of their mental and physical health."

More information: Presentation no: O-005, "The ToF-study—comparing the cumulative live birth rate of blastocyst-stage versus cleavage-stage embryo transfers in good prognosis IVF patients: a multicenter randomized controlled trial", presented by Dr Simone Cornelisse et al, Session 02: New insights into embryo development, Hall



A, 10.30 hrs CEST, Monday 26 June 2023.

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