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[Intervention Review]

# Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology

Demián Glujovsky<sup>1</sup>, Debbie Blake<sup>2</sup>, Cindy Farquhar<sup>3</sup>, Ariel Bardach<sup>4</sup>

<sup>1</sup>Reproductive Medicine, CEGYR (Centro de Estudios en Ginecología y Reproducción), Buenos Aires, Argentina. <sup>2</sup>Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. <sup>3</sup>Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. <sup>4</sup>Cochrane Iberoamerican Center, Argentina, Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina

Contact address: Demián Glujovsky, Reproductive Medicine, CEGYR (Centro de Estudios en Ginecología y Reproducción), Viamonte 1432, Buenos Aires, Argentina. [demian.glujovsky@gmail.com](mailto:demian.glujovsky@gmail.com).

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## ABSTRACT

### Background

Advances in cell culture media have led to a shift in in vitro fertilization (IVF) practice from early cleavage embryo transfer to blastocyst stage transfer. The rationale for blastocyst culture is to improve both uterine and embryonic synchronicity and enable self selection of viable embryos thus resulting in higher implantation rates.

### Objectives

To determine if blastocyst stage (Day 5 to 6) embryo transfers (ETs) improve live birth rate and other associated outcomes compared with cleavage stage (Day 2 to 3) ETs.

### Search methods

Cochrane Menstrual Disorders and Subfertility Group Specialised Register of controlled trials, Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, EMBASE and Bio extracts. The last search date was 21 February 2012.

### Selection criteria

Trials were included if they were randomised and compared the effectiveness of early cleavage versus blastocyst stage transfers.

### Data collection and analysis

Of the 50 trials that were identified, 23 randomised controlled trials (RCTs) met the inclusion criteria and were reviewed (five new studies were added in this update). The primary outcome was rate of live birth. Secondary outcomes were rates per couple of clinical pregnancy, cumulative clinical pregnancy, multiple pregnancy, high order pregnancy, miscarriage, failure to transfer embryos and cryopreservation. Quality assessment, data extraction and meta-analysis were performed following Cochrane guidelines.

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## Main results

Twelve RCTs reported live birth rates and there was evidence of a significant difference in live birth rate per couple favouring blastocyst culture (1510 women, Peto OR 1.40, 95% CI 1.13 to 1.74) (Day 2 to 3: 31%; Day 5 to 6: 38.8%,  $I^2 = 40\%$ ). This means that for a typical rate of 31% in clinics that use early cleavage stage cycles, the rate of live births would increase to 32% to 42% if clinics used blastocyst transfer.

There was no difference in clinical pregnancy rate between early cleavage and blastocyst transfer in the 23 RCTs (Peto OR 1.14, 95% CI 0.99 to 1.32) (Day 2 to 3: 38.6%; Day 5 to 6: 41.6%) and no difference in miscarriage rate (13 RCTs, Peto OR 1.18, 95% CI 0.86 to 1.60). The four RCTs that reported cumulative pregnancy rates (266 women, Peto OR 1.58, 95% CI 1.11 to 2.25) (Day 2 to 3: 56.8%; Day 5 to 6: 46.3%) significantly favoured early cleavage. Embryo freezing rates (11 RCTs, 1729 women, Peto OR 2.88, 95% CI 2.35 to 3.51) and failure to transfer embryos (16 RCTs, 2459 women, OR 0.35, 95% CI 0.24 to 0.51) (Day 2 to 3: 3.4%; Day 5 to 6: 8.9%) favoured cleavage stage transfer.

## Authors' conclusions

This review provides evidence that there is a small significant difference in live birth rates in favour of blastocyst transfer (Day 5 to 6) compared to cleavage stage transfer (Day 2 to 3). However, cumulative clinical pregnancy rates from cleavage stage (derived from fresh and thaw cycles) resulted in higher clinical pregnancy rates than from blastocyst cycles. The most likely explanation for this is the higher rates of frozen embryos and lower failure to transfer rates per couple obtained from cleavage stage protocols. Future RCTs should report miscarriage, live birth and cumulative live birth rates to enable ART consumers and service providers to make well informed decisions on the best treatment option available.

## PLAIN LANGUAGE SUMMARY

### Cleavage stage versus blastocyst stage embryo transfer in assisted conception

Embryos from assisted reproductive technologies (in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), thawed embryo cycles) are commonly transferred into the woman's uterus at either the early cleavage stage (Day 2 to 3 after egg collection) or blastocyst stage (Day 5 to 6 after egg collection). The current thinking is that transferring embryos at the blastocyst stage is the most biologically correct stage for embryos to be in the uterus as earlier stages are naturally in the fallopian tube, and longer culture in the laboratory may give the scientist greater ability to select the best quality embryo(s) for transfer.

This review of 25 studies did not find a difference in the chance of becoming pregnant between early cleavage and blastocyst stage embryo transfer. Disappointingly, only half of the included studies reported miscarriage or live birth rates. These 12 studies showed a small improvement in live birth rate per couple for blastocyst transfers. This would mean that for a typical rate of 31% in clinics that use early cleavage stage cycles, the rate would increase to 32% to 42% live births if clinics used blastocyst transfer. In the 13 studies that reported miscarriage rate, there was no difference between early cleavage and blastocyst stage transfers. Interestingly, in the four studies that reported cumulative pregnancy rates (after both fresh and frozen thaw embryo transfers) there was an increase in those women who had cleavage stage compared with blastocyst stage transfer.

Apart from a lowered cumulative pregnancy rate in women who had blastocyst transfer, other disadvantages included a lower rate of excess embryos available for freezing per couple and a higher chance that there were no embryos that survived up to the stage of transfer. For couples who obtain a high number of good quality embryos (high prognosis), however, the chance that there are no embryos for transfer in blastocyst cycles is no different from cleavage stage transfers. These two factors may explain why there is a greater chance of cumulative pregnancy in early cleavage stage than blastocyst stage cycles, where couples have received embryos for transfer in the initial ovarian stimulated cycle, had excess embryos frozen, and then received thawed embryos in subsequent natural or controlled cycles.