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Blastocyst or cleavage-stage embryo transfer?

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Key issue

- Does blastocyst embryo transfer offer benefit over cleavage-stage embryo transfer in assisted conception treatment?

What do we know?

- Following natural conception, the embryo is traversing the fallopian tube at cleavage stage; it is in the uterus at blastocyst stage.
- Embryo development to cleavage stage occurs under maternal genomic control.
- To reach blastocyst stage, embryos need to develop under their own genomic control.
- Selection of embryos, in order to replace the embryo or embryos with maximal viability, has presented a challenge.

What do we think we know?

- Implantation rates of blastocysts tend to be higher than those for cleavage-stage embryos. Should not the chance of success with a blastocyst culture and transfer policy be higher than that with cleavage-stage embryo transfer?
- It might be possible to select couples who would benefit from blastocyst culture on the basis of milestones at certain stages of an in-vitro fertilization (IVF) cycle.

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- It might it be possible for clinics to reduce the multiple pregnancy rate and maintain the pregnancy rate by employing blastocyst culture.

What do we not know?

- Whether a policy of blastocyst culture offers genuine advantages by either increasing the chance of success of IVF/intracytoplasmic sperm injection or reducing the chance of multiple pregnancy.
- Which couples, if any, benefit from blastocyst culture.

Key words: blastocyst; cleavage stage; embryo transfer; ICSI; IVF.

Improving the outcome of assisted reproductive technology (ART) treatments through in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) is a continual challenge for fertility services.

The fledgling era of ART ended in the mid 1990s when success rates, that had remained relatively static until that time, began to rise substantially. Numerous factors probably contributed to the improving success rates, including new techniques, high-quality consumables and equipment, sophisticated ovarian stimulation regimens, and a wealth of clinical experience that had been accumulated by this time. Fertility specialists are continually inspired to trial newly reported innovations in the pursuit of improved livebirth outcomes for their patients. However, unravelling the hype of new techniques from the reality of their effectiveness is essential for global advances. As the rate of human implantation is intrinsically low, it is difficult to establish small but significant improvements. Systematic meta-analysis of all randomized controlled trials (RCTs) is therefore the only way to establish definitively if an innovation, such as extended embryo culture to the blastocyst stage, offers a true advance.[1]

Traditionally, embryos have been transferred at the cleavage stage, 2–3 days after egg collection, although allowing human embryos to develop to the blastocyst stage in IVF programmes is not novel. What is new, however, is the accessibility and range of reportedly successful media products, resulting in a widespread rise in the acceptability and use of this approach.[2] Initial reports of blastocyst culture involved a single culture medium consisting of a mixture of a complex and simple media formulation[3] or co-culture.[4] More recently, the development of stage-specific sequential media has been claimed to allow 36–66% of embryos to develop to blastocysts with a high viability of up to 50% implantation rate.[5,6]

There are two central reasons why an alternative to cleavage-stage embryo transfer was proposed. Firstly, it has long been recognized that it is physiologically premature to expose early-stage embryos to the uterine environment. In vivo, embryos travel through the fallopian tubes and do not reach the uterus before the morula stage[7], which equates to at least day 4 of in-vitro culture. The uterus provides a different nutritional milieu from the fallopian tube; it has been postulated that this may cause homeostatic stress on the embryo, resulting in a reduced implantation potential.[8] Secondly, there are widely acknowledged shortcomings of the morphological criteria used for selection of cleavage-stage embryos for transfer on day 2 or 3. There is substantial debate over the correlation of embryo morphological features with pregnancy rates.[9,10] Prior to day 3 of culture, when genomic activation and compaction begins, embryonic development is primarily controlled by transcripts and stored RNA messages of maternal origin.[11] Only after this transitional stage does development proceed under the control of an activated embryonic genome, resulting in the expression of numerous growth factors and receptors. Furthermore, it is suspected that a large

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