Cleavage-stage or blastocyst transfer: what are the benefits and harms?

Demian Glujovsky, M.D., M.Sc.[a] and Cynthia Farquhar, M.D., M.P.H.[b]

[a] Department of Reproductive Medicine, Center of Studies of Genetics and Reproduction (CEGYR), Buenos Aires, Argentina; and [b] Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand

ET is a critical step in an assisted reproduction cycle. Over the past decade there has been an increasing trend to extending culture from cleavage-stage to blastocyst transfer. There has also been a trend to single ET and reporting the success of an assisted reproductive cycle as a cumulative live-birth rate after using both fresh and frozen embryos. There is low evidence that fresh blastocyst transfer is associated with improved live-birth rates compared with fresh cleavage-stage embryos. However, in the few studies that report cumulative pregnancy rates after fresh and frozen transfers, no significant difference was found. Cleavage-stage transfer is associated with greater numbers of embryos available for freezing, and blastocyst transfer is associated with increased number of cycles with no embryos to transfer. Further well-designed studies are warranted to evaluate the outcomes for blastocyst transfer including cumulative live-birth rate after fresh and frozen transfers, time to live birth, costs of the different transfer strategies, and perinatal mortality and severe perinatal morbidity. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: XXX

Discuss: You can discuss this article with its authors and with other ASRM members at

As many as one in six couples will experience difficulty conceiving and may seek assisted reproduction to achieve a pregnancy. One of the most important steps during an assisted reproduction cycle is the transfer of the embryo from the laboratory to the uterus. Traditionally, cleavage-stage embryos were transferred on day 3, but over the past decade there has been a move to transferring blastocysts on day 5 or 6. Transfer at this stage is considered to be a more physiologically appropriate time as it more closely mimics the time of natural implantation and may improve synchrony between the endometrium and embryo development. The proportion of assisted reproduction cycles that transfer blastocysts has been steadily increasing over the past decade. In Australia they have risen from less than 30% of cycles in the 2004–7 to over 60% of assisted reproductive technology (ART) cycles in 2013 (1, 2). Similar increases have been reported in the United States and the United Kingdom, with approximately more than one third of ART cycles in 2012 being blastocyst transfers (3, 4).

At the same time that blastocyst transfer was increasingly used, there were a number of other developments occurring in the fertility laboratory. The introduction of sequential culture media (although this is now being questioned with the introduction of time lapse systems), vitrification programs as an alternative to slow freezing techniques, single ET (SET), freeze-all policies to improve outcomes for both the woman and the embryo, and the move to preimplantation genetic screening of embryos (which requires blastocyst development) are some of these new developments. Ideally each of these should be evaluated, but the focus of this paper is to consider whether blastocyst transfer is more effective than cleavage-stage transfer.

Direct comparisons between the two stages of embryo development appear to support the use of blastocyst transfers in clinical practice. Women who undergo fresh blastocyst transfers achieve higher live-birth rates compared with those who receive fresh cleavage-stage transfers (5). However, the results are not quite so conclusive when the transfers of frozen embryos are considered. These concerns are reflected in guidance provided for day of transfer. The American Society for Reproductive Medicine and the 2013 fertility guidelines published by NICE have both voiced concern over the use of the blastocyst transfer method for assisted reproduction (6, 7). These statements conclude that because the number of surviving embryos

Received April 30, 2016; revised June 14, 2016; accepted June 15, 2016.
D.G. has nothing to disclose. C.F. has nothing to disclose.
Reprint requests: Cynthia Farquhar, M.D., M.Sc., Department of Obstetrics and Gynaecology, FMHS, Private Bag 92019, Auckland 1142, New Zealand (E-mail: c.farquhar@auckland.ac.nz).

Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.06.029

diminishes with the length of time in vitro, extending culture to the blastocyst stage may reduce the number of viable embryos available for cryopreservation and subsequent thaw transfer. The NICE guidelines from the United Kingdom also suggest that extending the culture period into the blastocyst stage increased the risk of a woman having undergone treatment for no benefit (7). This review aims to provide an evidence-based assessment of the benefits and harms of blastocyst transfer in comparison with traditional cleavage-stage transfers.

METHODS

We based our search strategy on the Cochrane systematic review that compared blastocyst and cleavage-stage ETs (5). We searched for systematic reviews, of both randomized controlled trials (RCTs) and observational studies, published since the search date listed in the most recent Cochrane review update (5). We used the keywords "blastocyst," "embryo transfer," and "systematic reviews" to search the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CGFG, PsycINFO, and CINAHL databases. We also searched for systematic reviews that included some secondary outcomes (for example, the prevalence of monochorionic twins) that were not well reported in the Cochrane systematic review. The date of the search was April 2016.

COCHRANE REVIEW OF CLEAVAGE-STAGE VERSUS BLASTOCYST TRANSFER

The increasing trend towards blastocyst transfers over the last decade has occurred against a background of conflicting clinical trials. A Cochrane systematic review of 27 RCTs, published as an update in 2016, with four new studies, compared cleavage-stage and blastocyst transfer (5, 8–11).

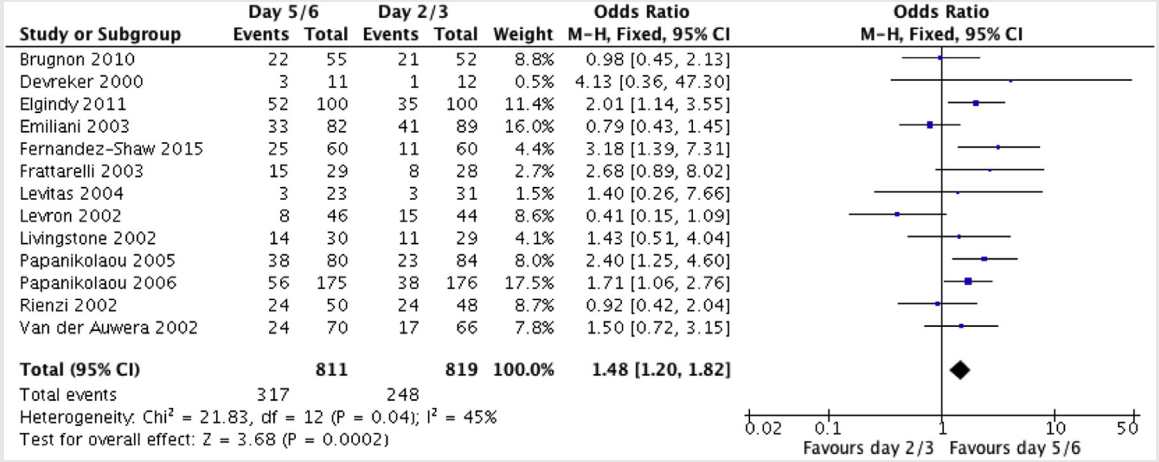
PREGNANCY OUTCOMES

Of the 27 RCTS, only 13 reported live-birth rate per couple, in which live-birth rates were significantly higher when using fresh embryos transferred at the blastocyst stage compared with the earlier cleavage stage (1,630 women; odds ratio [OR], 1.48; 95% confidence interval [CI], 1.20–1.82; day 2 to 3: 30.3%; day 5 to 6: 39.1%; $I^2 = 40\%$) (5). This means that if a clinic has a live-birth rate of 29% using fresh early cleavage-stage transfers, then this would increase to between 32%–42% if clinics were to use fresh blastocyst transfer method instead (Fig. 1).

Twenty-seven RCTs reported significantly higher clinical pregnancy rates after fresh blastocyst transfer (4,031 women; OR = 1.30; 95% CI, 1.14–1.47; day 2 to 3: 37.2%; day 5 to 6: 43.2%; $I^2 = 56\%$). There was no evidence of a difference in miscarriage rates (2,917 women; 18 RCTs; OR = 1.15; 95% CI, 0.88–1.50).

However, these data only considered fresh transfers. Cumulative pregnancy rates reflect the true success rate for couples undergoing assisted reproduction by taking into account all implantation attempts from both fresh and frozen embryos. Only five of the RCTs in the Cochrane review reported cumulative pregnancy rates after transferring both fresh and frozen embryos. There is no difference in the cumulative pregnancy rates between cleavage-stage and blastocyst transfer (647 women; OR = 0.82; 95% CI, 0.60–1.12; day 2 to 3: 51.7%; day 5 to 6: 47.0%) when compared with blastocyst transfer (Fig. 2). We should consider that cumulative rates could be affected not only by the success rates of fresh transfers (which have improved for blastocyst transfers in the last few years) but also by the technique of embryo freezing (given that vitrification is different from slow freezing). The four studies that used slow freezing reported that cleavage stage was associated with an improved cumulative pregnancy rate, while the only study that used vitrification is the newest one (12), which showed higher cumulative rates in blastocyst

FIGURE 1



Live-birth rate in fresh cleavage-stage transfers and fresh blastocyst transfers.

Glujovsky. ■■■. Fertil Steril 2016.

Q1

REV 5.4.0 DTD ■ FNS30287_proof ■ 12 July 2016 ■ 5:23 pm ■ ce S

print & web 4C/FPO