Extended culture and the risk of preterm delivery in singletons: confounding by indication?

Sir,

We read with interest the recent article (Dar et al., 2013) suggesting that singletons born after extended culture may have a higher risk of preterm delivery than those born after Day 3 transfer. While the importance of optimizing embryo culture and improving obstetrical outcomes after in vitro fertilization should not be underestimated, we believe this study suffers from a serious methodological flaw, namely ‘confounding by indication’. Due to this bias, blastocyst-stage transfer—the most effective means of improving selection and reducing multiple gestation (Papanikolaou et al., 2006)—may be incorrectly blamed for this small difference in preterm delivery risk (17.2 versus 14.1%).

The authors hypothesize that ‘extended culture may cause differences in implantation and placentaion’ that presumably predispose to preterm delivery. However, the differences that they attribute to extended culture presuppose that the two populations (Day 3 transfer and Day 5/6 transfer recipients) have the same a priori risk of preterm delivery. In fact, this is unlikely to be the case.

It is well known that elective single embryo transfer (eSET) is underutilized. While eSET accounted for only 4.0% of cycles in Canada in 2006 (Gunby et al., 2011), 20.2% of the Day 5/6 deliveries in this study were after SET, compared with only 5.8% in the Day 3 group. Patients who have a contraindication to multiple gestation due to a prior preterm delivery, cervical incompetence, uterine anomaly or medical complication almost universally receive eSET and prior research has demonstrated that, likely due to these underlying factors, SET recipients may be at increased risk for preterm delivery (Grady et al., 2012). Even adjusting for the number of embryos transferred, as was performed by Dar et al., may not correct for this source of bias.

Furthermore, by not including any data on the number of embryos transferred or implantation rates, it is not possible to determine the probability of a term delivery per cycle initiated. Patients engage in infertility treatment with the goal of achieving a healthy term delivery. Since there are significantly more deliveries per blastocyst transfer than per Day 3 transfer, patients have a higher likelihood of a term delivery after blastocyst transfer. Though the authors of this study and a recent study looking at IVF singleton deliveries in the USA (Kalra et al., 2012) take the ‘glass half-empty’ interpretation, an optimist could look at blastocyst transfer as a way to increase term deliveries, especially when single blastocyst transfer is employed.

In order to properly assess the potential impact of extended culture on gestational age, future studies must control for the underlying risk of preterm delivery. Otherwise we fear that the concern raised by this study may have the unintended consequence of shifting more patients to cleavage-stage, multiple embryo transfers with resulting increased risk of preterm delivery due to multiple gestation.

References


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Reply: Extended culture and the risk of preterm delivery in singletons: confounding by indication?

Sir,

We read the above letter with interest and thank Drs Forman, Werner and Scott for their comments. We naturally agree that the goal of assisted reproduction techniques is a healthy baby, born at term, and that elective single embryo transfer (eSET) is the best way to avoid multiple pregnancy and its associated risk of preterm delivery and other complications.

In the majority of clinics worldwide, Day 3 embryo transfer is still the standard of care. A recent Cochrane meta-analysis showed the superiority, in terms of pregnancy and take home baby rates, of blastocyst transfer over Day 3 transfer when equal numbers of embryos were transferred.