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 placentation’ 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.
and randomization occurred on Day 3. However, this was only true for ‘good prognosis patients’; there was no advantage to blastocyst culture for unselected or ‘poor prognosis patients’ (Glujovsky et al., 2012). In addition, transfer of more than one blastocyst resulted in a higher multiple pregnancy rate.

Among some differences that have been reported between Days 3 and 5 embryos are increased monozygotic twinning and a higher male–female ratio in pregnancies after blastocyst transfer. In a recent meta-analysis, the odds ratio for monozygotic twins was 3.04 [95% confidence interval (CI): 1.54–6.01] and for male–female ratio was 1.29 (95% CI 1.10–1.51) (Chang et al., 2009). Babies born after Day 5 embryos are also larger for gestational age when compared with Day 3 embryos (Mäkinen et al., 2013). These findings, in our opinion, cannot be explained by differences in the a priori risk of the two populations, but rather stem from embryonic factors related to Day 3 versus Day 5 culture.

In order to further address the valid concerns of Forman et al., we re-analyzed our data for primiparas alone (i.e. excluding women who had a prior preterm delivery or cervical incompetence). They represented 82% of our population. In this subpopulation, preterm birth remained significantly increased in the Day 5 group (14.4% for Day 3 versus 17.8% for Day 5, P < 0.001). Unfortunately, we do not have data for other contraindications for multiple gestations, such as uterine anomalies or serious underlying medical conditions, but we would hazard to guess that these indications would represent a small minority of this population. Therefore, controlling for these remaining factors is unlikely to alter the findings, but this needs to be evaluated in future studies.

The three studies published recently (Källén et al., 2010; Kalra et al., 2011; Dar et al., 2013) represent the aggregated data from over 68 000 cleavage stage transfers and 27 000 blastocyst transfers, and each showed a significant difference in preterm births. As we pointed out in Dar et al. (2013), animal studies also support a biological plausibility that culture media components and culture systems involved in prolonged culture could affect embryo development and subsequent fetal–placental development. Therefore, we still contend that future studies should address safety and improvements in culture media and/or culture systems in order to reduce potential adverse effects of extended culture on human embryos, and also to investigate methods to improve Day 3 embryo selection, potentially reducing the need for prolonged in vitro culture.

References


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