Letters to the Editor

Multiple birth risks associated with IVF and extended embryo culture: USA, 2001

Sir,

We reviewed the manuscript by Kissin et al. (2005) with great interest. The authors suggest variations in live birth and multiple pregnancy rates across various patient groups who underwent embryo transfer with cleavage stage embryos on day 3 or blastocyst stage embryos on day 5 without significant differences. The authors analysed the data according to the day of embryo transfer and whether or not supernumerary embryos were frozen. There are several issues which make interpretation of the conclusions somewhat challenging. The authors have lumped all multiple pregnancies together in their analysis which makes an accurate evaluation of the outcomes difficult. There is no question that all multiple pregnancies are associated with a higher risk than that associated with singleton pregnancies, and that the goal of practitioners of assisted reproductive technologies should be to achieve a single healthy pregnancy. It would also be appropriate to state that the relative risks of twin versus high order multiple pregnancies are significantly different. The authors have concluded that a day 3 versus day 5 embryo transfer has no impact on multiple pregnancy despite the fact that fewer embryos were transferred with day 5 transfer. This conclusion may not be valid at all if either day 3 or day 5 transfer is associated with reduced likelihood of high-order multiples as compared to twins. In order to greatly enhance the value of this work, and given the ready accessibility of the data, we would strongly recommend that additional analyses differentiating twin and high order multiple pregnancy rates be incorporated into the tables. The current data set also does not provide specific information on implantation rates. The absence of this parameter makes interpretation of the effect of a differing stage of embryo transfer on multiple pregnancy rates difficult to interpret. This potentially could result in a significant alteration of the conclusions derived from this manuscript.

The data analysed from 2001 would have reflected practice guidelines published in 1999 which recommended that no more than two embryos be replaced in good prognosis patients in an effort to decrease the incidence of high order multiple pregnancies (Practice Committee of ASRM, 1999). These guidelines have had a major impact on reducing the incidence of high order multiple pregnancy, as has been demonstrated by Jain et al. (2004). It is important to note that within the USA, guidelines for the number of embryos to be transferred which recommended discussion of single embryo transfer in good prognosis patients were not published until September 2004 (Practice Committees of ASRM and SART, 2004) well after the data set included in this manuscript. It is important to note that, though the authors stress the importance of single embryo transfer, this manuscript does not provide information as to which patient groups, or either developmental stage or quality of embryos to be transferred, would achieve this goal with any degree of efficiency. It is interesting to note that in an analysis published as recently as October 2004, Pandian et al. (2004) in writing for the Cochrane data base felt that, based on the current literature, there was insufficient available evidence to recommend that single embryo transfer be the preferred approach for all patients undergoing IVF.

This manuscript clearly does not represent a definitive analysis of the relative benefits of day 3 versus day 5 embryo transfer in that the indications for these two procedures vary between clinics. There are those programmes that solely perform day 3 transfer, solely perform day 5 transfer, or perform blastocyst transfer based on clinic-specific criteria typically based on embryo quality and patient history. In spite of relatively large numbers of embryos transferred, it is virtually impossible to compare these two groups in the absence of data derived from equivalent patient groups.

We are concerned that the authors have relied upon the presence of supernumerary embryos available for cryopreservation as an indication of embryo quality. While there is some evidence for this relationship, in reality, there is no information regarding embryo quality for either of these groups which clearly can play a role in cycle outcome as well as the decision to consider day 3 versus 5 embryo transfer. Decisions about cryopreservation are also made for a variety of reasons that do not necessarily reflect embryo quality. Clearly differences in laboratory techniques as well as patient selection and internal laboratory protocol play a major role.

The labelling of patients undergoing day 3 transfer without cryopreservation as a ‘worst prognosis group’ is curious. The pregnancy rate for this group is markedly higher than that described by most investigators when describing patients with poor prognosis—a descriptor which is typically attributed to women with poor ovarian response, advanced maternal age, poor embryo quality, or multiple implantation failures. None of these characteristics is used in the current analysis. The statistic presented in this manuscript is clearly not representative of outcomes for poor responders as defined within the clinical community and should not serve as a basis for policy regarding transfer recommendations in this patient group.

References

Letters to the Editor


Eric Surrey1,5, Owen Davis2, William B.Gibbons3 and David Grainger4

1President, 2Immediate Past President, 3President-Elect, 4Vice-President and Research Committee Chairman, Society for Assisted Reproductive Technology

5To whom correspondence should be addressed. Eric S.Surrey, M.D., 799 E. Hampden Ave, #300, Englewood, CO 80113, USA.
E-mail: Esurrey@colocrm.com
doi:10.1093/humrep/dei360

Reply to: ‘Multiple-birth risk associated with IVF and extended embryo culture: USA, 2001’

Sir,

We appreciate the interest of Surrey et al. in our analyses of multiple-birth risk associated with extended embryo culture.

Dr. Surrey and colleagues are concerned that we chose multiple-birth risk and multiple pregnancy risk as outcome measures instead of presenting our results by multiple order (twins, triplets, etc.). We chose not to separate multiple pregnancies and births by the number of fetuses and infants because our focus is on the overall multiple birth problem, as it is one of the major public health issues pertaining to assisted reproductive technology (ART) and because, as Surrey et al. acknowledge, ‘all multiple pregnancies are associated with a higher risk than that associated with singleton pregnancies.’ Twin pregnancies and births, although to a lesser extent than higher order multiples, carry significant risks (Kiely, 1998; Senat et al., 1998; Martin and Park, 1999; ESHRE Capri Workshop Group, 2000; Martin et al., 2002; Pharoah, 2002; Novak et al., 2003). Furthermore, twin births account for the vast majority (∼90%) of the multiple-birth burden among ART patients. Thus, from a public health perspective, the total multiple-birth risk, which combines twin and higher order multiple births, is the appropriate outcome measure.

In our study of ART procedures performed in the USA in 2001, we found that extending culture to the blastocyst stage (day 5) was associated with the transfer of fewer embryos (average: 2.3) compared to transferring at the cleavage stage (day 3, average: 3.0 embryos). This extension of the culture period, however, did not result in a decrease of the total multiple-birth risk. Surrey et al. call attention to the point that blastocyst transfers are associated with a decrease of high-order multiple births. This is an important achievement: the proportion of live-born triplets and higher order multiples was lower when embryos were transferred on day 5 (2.7%) compared to day 3 (4.1%). During the same time period, however, the twin birth rate associated with day 5 transfers (36.4%) was higher than that associated with day 3 transfers (31.2%), as was the total risk of multiple births (39.2 versus 35.3%). Our analyses suggest that transferring more than one blastocyst may not have a clear impact on the multiple-birth problem, despite the reduced risk of high order multiple births. We agree with Surrey et al. that further research is needed to characterize the best candidates for single embryo transfer, a procedure that is still infrequent in the USA, accounting for <10% of all embryo transfers.

We recognize that the criteria used by clinics to determine whether patients undergo a 3 day or a 5 day embryo transfer may vary. However, those clinics that transferred exclusively on day 3 or on day 5 accounted for only 5% of all transfers in our sample, indicating that most clinics have adopted both procedures. Thus, the differences we observed are unlikely to be confounded by this clinic characteristic.

We acknowledged that our data were not from a randomized clinical trial comparing transfer of embryos on day 3 and on day 5. However, the large sample size allowed us to stratify our results by the most important predictors of live birth and multiple birth (i.e. the number of embryos transferred, the patient’s age, the day of embryo transfer, and the availability of supernumerary embryos). The latter variable is a surrogate measure of embryo quality, but it has been shown to be an important predictor of ART outcomes (Templeton and Morris, 1998; Schieve et al., 1999) and has been used as one of the criteria of embryo quality in ART practice guidelines (American Society for Reproductive Medicine, 1999; Practice Committee of SART and ASRM, 2004). To explore the possibility of residual confounding, we further restricted our analyses using such predictors of pregnancy and live-birth rates as the number of oocytes retrieved, the use of assisted hatching, ICSI, FSH level, a diagnosis of diminished ovarian reserve, and the number of previous ART procedures or births. These additional analyses confirmed the pattern of association, suggesting that our original stratification by the key predictive factors had captured most of the variability and is appropriate for use in analyses of ART success rates and multiple-birth risk.

While our analysis was not specifically designed to assess the impact of recent changes in ART practice guidelines, our data may nonetheless serve as the baseline for a future impact assessment. As ART use and the proportion of children born as the result of ART continue to grow in the USA and globally, surveillance of ART success rates and adverse effects will become an increasingly higher public health priority. We hope that our analyses of ART surveillance data in the USA will continue to contribute to the body of evidence used to inform ART practice guidelines and may serve as a tool for assessing their impact.

References