


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


D.M.Kissin1,2, L.A.Schiefve1, M.A.Reynolds1 and M.Macaluso1
1Women’s Health and Fertility Branch, Division of Reproductive Health, NCCDPHP, Centers for Disease Control and Prevention, Atlanta, USA
2To whom correspondence should be addressed: Women’s Health and Fertility Branch, Division of Reproductive Health, Centers for Disease Control and Prevention, 4770 Buford Highway NE, MS K-34, Atlanta, GA 30341-3724, USA.
E-mail: Dtk3@cdc.gov

doi:10.1093/humrep/dei361

Preimplantation genetic diagnosis for translocations

Sir,
The Opinion article of Sugiura-Ogasawara and Suzumori (2005) compares the frequency of live birth in the first natural conception after reciprocal translocation was ascertained, with the outcome of preimplantation genetic diagnosis (PGD) for translocations. Their conclusions, based on a small sample of 47 couples who tried to conceive naturally and 43 undergoing PGD which was cited from literature reported by a Korean group, is that the success rate (live birth) is similar, though for those using natural conception it takes close to 2 years to give birth and pregnancy losses keep occurring. After PGD for reciprocal translocations, they cited 32% pregnancy rate per cycle, based on 43 patients and 59 cycles, or 23% per cycle, compared to 32% in natural conception but within 2 years (or 24 menstrual cycles). They also compared the live success rate for Robertsonian translocation and after PGD; the pregnancy rate that they reported per cycle was 16%, compared to 63% in natural conception, but they observed only 11 cases who tried to conceive naturally, which is too small a number to make any meaningful estimate. Moreover, they only included those patients who could be followed up, thus excluding patients who experienced further miscarriage but did not go all the way to their institution to report it.

Surprisingly, based on these numbers the authors concluded that PGD is not warranted. Even from a coldly numerical point of view which disregards the well-being of the patient, their data lack number of cases needed to make any conclusive statement.

As for the human factor, carriers of translocations usually suffer recurrent miscarriages which are devastating for a woman. For instance, the authors quote a 68% pregnancy loss without PGD for carriers of reciprocal translocation, and a 36% loss rate for carriers of Robertsonian translocations. Unfortunately for these patients, the health insurance system and genetics establishments of many countries, particularly Japan, are deaf to their suffering. The Japanese Society of Obstetrics and Gynecology society generally does not permit the use of PGD except in extremely unusual cases, of which there have been only three so far. Not surprisingly, IVF patients are organizing legal action against their position.

The point that these researchers are missing is that the major reason for patients wanting to undergo PGD is to minimize recurrent miscarriages and the associated suffering. If, in addition, they are infertile because most of their gametes are abnormal, PGD is an obvious choice as they already need IVF. Moreover, missed abortion, which is the usual manner of miscarriage in patients with translocation, can lead to sterility in 8% of cases according to Polishuk et al. (1974).

Our unpublished data on 471 PGD cycles of translocations is shown in the Table I below. The pregnancy rate for Robertsonian translocations, per cycle, was 36% and the loss rate a mere 2%. That, compared to 64% natural conception within unspecified time (they did not report time needed for conception, but their observation was for 17 years and certainly not per cycle!), and a risk of 36% loss rate, makes PGD quite attractive.

For reciprocal translocations the outlook is less favourable in general since they produce more chromosome abnormalities, but again a 21% pregnancy rate per cycle and a mere 2% loss rate after PGD compared to 32% live birth rate within 2 years (not per cycle!) and 68% risk of miscarriage makes PGD highly desirable.

<table>
<thead>
<tr>
<th>Type</th>
<th>Average age (years)</th>
<th>Cycles</th>
<th>No transfer</th>
<th>Not pregnant</th>
<th>Pregnant</th>
<th>Lost pregnancy</th>
<th>Delivered or &gt;3rd trimester</th>
<th>% lost pregnancy</th>
<th>% delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROB</td>
<td>34.0</td>
<td>133</td>
<td>16</td>
<td>67</td>
<td>50</td>
<td>2</td>
<td>48</td>
<td>2</td>
<td>36.1</td>
</tr>
<tr>
<td>REC</td>
<td>36.1</td>
<td>338</td>
<td>106</td>
<td>153</td>
<td>79</td>
<td>7</td>
<td>72</td>
<td>2</td>
<td>21.3</td>
</tr>
</tbody>
</table>

ROB = Robertsonian translocation; REC = reciprocal translocation.

Letters to the Editor

839