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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, 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.
Our manuscript entitled 'Poor prognosis of recurrent aborters with either maternal or paternal reciprocal translocations' (Sugiura-Ogasawara et al., 2004). There has been no prospective controlled study comparing preimplantation genetic diagnosis (PGD) and natural course regarding subsequent pregnancy outcome in recurrent aborters with reciprocal translocation to our knowledge. Only positive findings in such a study would allow the conclusion that PGD is warranted. We found few studies including the number of patients and focusing on the reciprocal translocation with a history of recurrent abortions (not including infertility).

We clinicians should explain both the merit and drawbacks of any proposed treatment before patients undergo therapy. The merit of PGD is in prevention of further miscarriages. Drawbacks are side-effects, the expense of IVF-PGD and the failure rate with IVF. We should also explain the possibility of a natural pregnancy course accurately. Now, Japanese patients wanting PGD misunderstand that it is a ‘miracle treatment’. Some patients cannot become pregnant and some patients undergo further miscarriage in spite of PGD. Do such patients who do not succeed in giving birth feel a strong negative emotional impact? Patients should be informed and understand this possible drawback.

Indeed, clinical researchers in the recurrent miscarriage field well know the emotional impact patients feel after a miscarriage. We have also reported findings concerning this issue (Aoki et al., 1998) and never underestimate this aspect after miscarriage. However, we should not stress miscarriage and disregard the long-term influence of biopsy from 8-cell embryos, because the long-term follow-up has not been reported after live birth.

We have one patient who gave natural birth at her 14th pregnancy after 13 miscarriages. She suffered several further miscarriages after the live birth and we offered PGD because her success rate may be estimated to be only one of 14. However, she refused this option and only a few patients wish for PGD after information on PGD and natural pregnancy outcomes are fully explained in our hospital. A patient with a history of six miscarriages who requested PGD gave successful birth recently while waiting for preparation of PGD.

Japan has no law concerning PGD and the Japanese Society of Obstetrics and Gynecology (JSOG) ruled that a member should make an application for each case wishing for PGD so that the JSOG committee members can discuss the ramifications, because Japanese handicapped people are strongly against PGD for selection of normal embryos which is associated with exclusion of handicapped people. One doctor performed PGD for sex selection without application and was expelled from the membership of the JSOG. He started PGD for recurrent miscarriages after expulsion and appealed to withdraw the expulsion. I believe that discussion is needed before a treatment can be offered whose safety has not been confirmed.

PGD for reciprocal translocation will be permitted soon because it is not associated with exclusion of handicapped people. The information in the previous paper (Sugiura-Ogasawara and Suzumori, 2005) will help patients to choose PGD or the natural course.

\[\text{References}\]

