Pregnancy outcomes of reciprocal translocation carriers who have a history of repeated pregnancy loss

Cytogenetic investigation of 2,324 Japanese couples with repeated pregnancy loss revealed that 4.91% of couples (n = 114) had chromosome abnormalities including reciprocal translocation (n = 74), Robertsonian translocation (n = 23), and inversion (n = 10). Parental reciprocal translocation was a significant predictor of subsequent miscarriage (adjusted odds ratio: 3.6, 95% confidence interval: 1.8–7.1), and most of the miscarriages of the carrier couples were inevitable because of abnormal karyotypes, despite appropriate treatments. (Fertil Steril® 2008;90:1301–4. ©2008 by American Society for Reproductive Medicine.)

Repeated pregnancy loss (RPL) occurs in 2% to 5% of all couples trying to conceive (1). Several causes have been reported to be responsible for RPL, although most of them are speculative at present (1). Structural abnormalities of a parental chromosome is one of the most reliable etiologies, and the increased prevalence of balanced rearrangements has been observed in the couples with RPL (1, 2). Although they are phenotypically normal, balanced carriers may present reduced fertility, repeated miscarriage, or an offspring with an abnormal phenotype, because unbalanced gametes are produced through unequal meiotic segregation or recombination during gametogenesis (3). The reproductive risk of reciprocal translocation depends on the extent of genetic imbalance as well as on the numbers and breakpoints of the chromosomes involved (3, 4).

Recent technical progress both in the genetic and reproductive fields allows the transfer of embryos without inherited abnormalities by means of preimplantation genetic diagnosis (PGD), which would be expected to improve the reproductive performance of the couples with RPL and chromosome abnormalities (3). The effectiveness of IVF with PGD, however, remains elusive, because the spontaneous likelihood of having a miscarriage or an affected offspring as a result of unbalanced chromosome abnormality is not fully understood. It is therefore important to evaluate the reproductive consequence in natural pregnancies of couples with RPL and chromosome abnormalities as part of the introduction of IVF with PGD. We reviewed the cytogenetic findings of 2,324 Japanese couples with RPL who visited the infertility clinic at Keio University Hospital in Japan during the period of 1983 to 2002 and investigated their natural pregnancy outcomes during the period of 1983 to 2004. Informed consent was obtained from the couples before cytogenetic analysis of their blood samples and miscarriage specimens.

All couples had a history of two or more consecutive pregnancy losses, such as a miscarriage or stillbirth, regardless of the rest of their reproductive history. Cytogenetic analysis was performed by the G-banding technique using cultured peripheral lymphocytes at metaphase, and high-resolution banding was applied if necessary. Chromosome abnormalities were found in 4.91% of couples (n = 114) and were categorized as follows: reciprocal translocation (n = 74, 3.18%), Robertsonian translocation (n = 23, 0.99%), inversion (n = 10, 0.43%), and others (n = 9, 0.39%). Statistically, more carriers of Robertsonian translocations were found to be female (n = 17, 0.73%) than male (n = 6, 0.26%; P = .021). Apart from chromosome abnormalities, we found 81 couples with pericentric inversion (9) [inv(9)] (3.49%) and found 14 with normal variants (0.6%).

The couples with RPL and chromosome rearrangements were offered genetic counseling, and treated for other possible causes of RPL in the same manner as were those who did not have chromosome rearrangements. After becoming pregnant, all the RPL patients underwent transvaginal ultrasonographic examination at least once each week or 2 weeks, and if they had symptoms of threatened abortion, they were advised to be hospitalized for bedrest. When the pregnancy resulted in miscarriage, a dilation and curettage was performed, and the karyotypes of the product of miscarriage were analyzed by standard G-banding techniques using cultured chorionic villi. Amniocentesis was performed at 16–18 weeks’ gestation according to the couples’ choice. We performed the following treatments for the couples with RPL who had a reciprocal translocation (n = 36), who had the other chromosome rearrangements (n = 71), and who did not have chromosome rearrangements (n = 820); surgical treatments including metroplasty and/ or cervical cerclage (respectively, n = 3, 8.3% vs. n = 0, 0% vs. n = 100, 12.2%; with a reciprocal translocation vs. with the other chromosome rearrangements vs. without chromosome rearrangements); hormonal treatments for...
<table>
<thead>
<tr>
<th>Parental chromosome</th>
<th>Normal</th>
<th>Reciprocal translocation</th>
<th>Robertsonian translocation</th>
<th>Inversion</th>
<th>Inversion (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First pregnancy outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of couples&lt;sup&gt;a&lt;/sup&gt;</td>
<td>820</td>
<td>36</td>
<td>15</td>
<td>8</td>
<td>48</td>
</tr>
<tr>
<td>No. of past RPLs&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.8 ± 0.9</td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 0.9</td>
<td>3.0 ± 1.7</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>Maternal age&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32.1 ± 4.0</td>
<td>31.3 ± 3.3</td>
<td>32.1 ± 5.0</td>
<td>33.5 ± 3.3</td>
<td>32.6 ± 4.1</td>
</tr>
<tr>
<td>Delivery (%)</td>
<td>615 (75.0)</td>
<td>17 (47.2)</td>
<td>10 (66.7)</td>
<td>5 (62.5)</td>
<td>29 (60.4)</td>
</tr>
<tr>
<td>Miscarriage (%)</td>
<td>205 (25.0)</td>
<td>19 (52.8)</td>
<td>5 (33.3)</td>
<td>3 (37.5)</td>
<td>19 (39.6)</td>
</tr>
<tr>
<td>Adjusted OR&lt;sup&gt;c&lt;/sup&gt; (95% CI)</td>
<td>Reference</td>
<td>3.6 (1.8–7.1)</td>
<td>1.5 (0.5–4.5)</td>
<td>1.6 (0.4–7.0)</td>
<td>2.0 (1.1–3.6)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>0.479</td>
<td>0.520</td>
<td>0.026</td>
<td></td>
</tr>
</tbody>
</table>

Cytogenetic analysis of miscarriage

| No. of couples<sup>b</sup> | 91 | 10 | 3 | 0 | 10 |
| Maternal age<sup>b</sup> | 32.9 ± 4.5 | 32.8 ± 2.3 | 34.0 ± 0.6 | — | 32.8 ± 4.2 |
| Normal karyotype (%) | 36 (39.6) | 1 (10.0) | 1 (33.3) | — | 3 (30.0) |
| Balanced | 1<sup>d</sup> | 1<sup>e</sup> | 1<sup>e</sup> | 1<sup>e</sup> | 1<sup>e</sup> |
| Abnormal karyotype (%)<sup>f</sup> | 55 (60.4) | 9 (90.0) | 2 (66.7) | — | 7 (70.0) |
| Aneuploid or polyploid | 55 | 2<sup>g</sup> | 1<sup>h</sup> | 1<sup>k</sup> | 7 |
| Unbalanced<sup>d</sup> | 0 | 7<sup>i</sup> | 1<sup>k</sup> | 0 | 0 |

Note: OR = odds ratio; CI = confidence interval.

<sup>a</sup>Pregnancy test positive (ectopic and molar pregnancies were excluded).

<sup>b</sup>Mean ± SD. The medians are not significant among groups (Kruskal-Wallis test).

<sup>c</sup>Odds ratios of subsequent miscarriage were adjusted for the number of past RPLs and maternal age (logistic regression analysis).

<sup>d</sup>De novo occurrence of reciprocal translocation.

<sup>e</sup>The same chromosome rearrangement as the parental carrier.

<sup>f</sup>The proportions are not significant among groups (logistic regression analysis).

<sup>g</sup>46,XY/92,XXYY, 47,XY,–i;8.

<sup>h</sup>46,XX,der(1)t(1;11)(q42.1;q23.3), 46,XY,der(11)t(11;17)(q21.2;q11.2),–17, 46,XY,der(8)t(1q;8q).46,XX,der(13)t(7q;13q), 46,XX,der(13)(8p;13q).

<sup>k</sup>46,XY,der(14;21)(q10;q10),–21.
luteal insufficiency, thyroid dysfunction, hyperprolactinemia, diabetes, and endometriosis (n = 5, 13.9% vs. n = 39, 54.9% vs. n = 220, 26.8%); anti-coagulant treatments with low-dose aspirin and/or heparin (n = 2, 5.6% vs. n = 9, 12.7% vs. n = 41, 5.0%); other treatments including Chinese herbal treatments, immunization with paternal lymphocytes, and intravenous immunoglobulin administration (n = 6, 16.7% vs. n = 21, 29.6% vs. n = 437, 53.3%); and close monitoring only (n = 25, 69.4% vs. n = 21, 29.6% vs. n = 169, 20.6%).

As shown in Table 1, the rate of subsequent miscarriage was significantly high in carrier couples with reciprocal translocation, as compared with the normal subjects (52.8% vs. 25.0%). After controlling for the number of past RPLs and maternal age at pregnancy, the adjusted odds ratio of subsequent miscarriage turned out to be 3.6 (95% confidence interval: 1.8–7.1, P < .001). In contrast, the adjusted odds ratio in the couples with Robertsonian translocation or inversion in either partner did not demonstrate statistical significance, although the number of the subjects was small. Recently, several studies have reported that the success rates of the subsequent natural pregnancies in the couples with RPL and translocations after appropriate treatments ranged from 30% to 70% (5–7). These wide variations may be attributable to differences in the enrollment criteria for the RPL patients, evaluation and treatment used, and/or a great variety of reciprocal translocation patterns. Indeed, in the cytogenetic analyses of semen from male reciprocal translocation carriers, the frequencies of balanced gametes produced through alternate segregation vary considerably, from 23% to 81% (8). Thus, the cytogenetic evaluation of each translocation case is necessary for predicting the risk of further miscarriage.

Although the statistical proof had low power because of the small sample size, cytogenetic analyses showed the high prevalence of chromosome abnormalities in the miscarriages from the couples with RPL who had translocations (Table 1), in agreement with the results of a study elsewhere (7). Especially in reciprocal translocation cases, 9 (90.0%) of 10 miscarriages had chromosome abnormalities, and most of them were associated with parental chromosome abnormalities. However, the frequencies of unbalanced karyotypes in amniocentesis were 7.1% (1/14) in reciprocal-translocation carrier couples and 0 (0/5) in Robertsonian-translocation carrier couples. These findings suggest that the conceptus with unbalanced karyotypes that is generated in the couples with RPL and translocations is susceptible to natural selection during the early development of the fetus. A study elsewhere also indicated that the type of reciprocal translocation was different between modes of ascertainment of carrier status and that carriers ascertained to have affected offspring have a greater risk of having another child with an unbalanced karyotype (4).

Interestingly, the adjusted odds ratio of subsequent miscarriage in the couples with inv(9) in either partner was significantly higher (Table 1), although inv(9) generally is thought to have no adverse effect on reproduction as a normal variant. There is much controversy in the literature concerning the role of inv(9), and its clinical consequences remain unclear (2). The cytogenetic results of miscarriages in the couples with inv(9) could not fully account for the increased rate of miscarriage in the present study. Further detailed studies with a large number of carriers will be necessary to investigate the effect of inv(9) on meiotic process and reproduction.

Essentially, the indication of PGD should be determined in case the miscarriage rate is expected to be high in a natural pregnancy. However, it has been reported recently that IVF and preimplantation genetic screening procedures per se result in a lower ongoing pregnancy rate for women of advanced maternal age (9). Thus, PGD cannot be generalized as a standard treatment for couples with RPL and translocations. However, considering the present result that miscarriages resulting from cytogenetic abnormalities of the conceptus were frequent and inevitable, PGD may be considered as an alternative treatment for a certain subset of the couples with RPL and reciprocal translocation. Although it is difficult to differentiate cases that require PGD, reports elsewhere suggested that cytogenetic findings such as the karyotypes of the past miscarriage specimens (3) and the distribution of balanced and unbalanced karyotypes in the ejaculated sperm of male carriers (10) may help to determine whether PGD will be beneficial. It is also important to evaluate which type of translocation has a high probability for repeated miscarriage. For that purpose, further studies will be needed that include a long follow-up of the carrier couples, taking into account the type of translocation as classified by the cytogenetic characteristics, such as the number and breakpoint of the chromosome involved and the potential imbalance that will be produced through malsegregation.

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REFERENCES


