The Clinical Effectiveness of Preimplantation Genetic Diagnosis for Chromosomal Translocation Carriers: A Meta-analysis

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Abstract

Published data on the relationship between pregnancy outcomes of preimplantation genetic diagnosis (PGD) in translocation carriers have implicated inconclusive results. To identify potentially eligible reports, an electronic search was conducted in several databases, including PubMed, Scopus, Web of Knowledge, and Cochrane. Pooled odd ratios (ORs) and 95% confidence intervals (Cis) were estimated based on a random-effect model to evaluate the strength of association between PGD and successful pregnancy outcome in translocation carriers. A total of six cohort studies were included in the current study. The meta-analysis of these studies revealed that the PGD method was associated with an increased successful pregnancy outcome of translocation carriers (OR = 8.58; 95% CI: 1.40–52.76). In subgroup analysis, there was no significant association according to the chromosomal translocation carrier origin and the type of translocated chromosomes, as well as country. In developed countries, the pregnancy outcome of PGD was significantly improved in translocation carriers (OR = 21.79; 95% CI: 1.93–245.52). The current meta-analysis demonstrated that the PGD method is associated with successful pregnancy outcome in both types of reciprocal and Robertsonian translocation carriers, especially in developed countries.

Keywords
► pregnancy outcome
► preimplantation genetic diagnosis
► meta-analysis
► translocation
► recurrent miscarriage

Introduction

Chromosome structural rearrangement, including reciprocal and Robertsonian translocation, is the most common type of chromosome abnormality.¹ It is the leading cause of implantation failure, infertility, recurrent miscarriage, and congenital abnormalities caused by an unbalanced karyotype in humans.² In these carriers, the segmental affinities between the translocated and normal chromosomal regions produces unbalanced rearrangements at high frequency, due to quadrivalent pairing rather than bivalent at meiosis.³ Reciprocal translocations—typically as an exchange of two terminal segments from different chromosomes—are found in approximately one in every 500 live births, whereas Robertsonian translocations, the centric fusion of two acrocentric
chromosomes, has a less prevalence in the population about 1 in 1,000.⁴

Although there is a high probability for a successfully natural outcome in many translocations, patients carrying translocations with a significant risk of viable abnormality are increasingly pursuing to improve their chances of a normal pregnancy with the help of preimplantation genetic diagnosis (PGD).⁵ PGD can select balanced embryos and avoid the transfer of embryos with unbalanced chromosomal rearrangements and thus reducing the risk of recurrent miscarriages or the birth of a child with chromosomal abnormalities.⁶–¹¹

In recent years, various studies indicated that PGD may play pivotal roles in increasing successful pregnancy outcome in translocation carriers.¹²–¹⁴ Several studies concluded that after PGD, the spontaneous abortion rate was significantly reduced in translocation carriers.¹⁵,¹⁶ Some studies, reported after PGD, stated that the chance of live birth is low for translocation carriers and natural conception will be a better option.¹²,¹⁷,¹⁸ However, the results from these studies are inconsistent.

The major reason for using PGD in translocation carriers is the reduction of miscarriages and more live births by eliminating the transfer of abnormal embryos. However, there is insufficient evidence regarding the pregnancy outcome for translocation carriers who underwent PGD and those of non-PGD patients. The statement that PGD increases successful pregnancy outcomes should be confirmed before the technique is applied for daily clinical practice. To improve informed decision making, we conducted a meta-analysis regarding clinical effectiveness and pregnancy outcomes after PGD, in couples carrying translocation chromosomal abnormality in comparison to none-PGD group. Until now, no meta-analysis has been performed to investigate this purpose. The aim of the present study was to assess the outcome of PGD in couples who at least one partner is a carrier of a reciprocal or Robertsonian translocations.

Methods

Search Strategy
The databases PubMed, Scopus, Web of Knowledge, and Cochrane were systematically searched for all available articles published till 2018, without considering limitation for any age range, time, or language. Publications with the following search words in the titles, abstract, or keywords of the original studies were included: “clinical effectiveness” OR “outcome” OR “pregnancy outcome” AND “preimplantation genetic diagnosis” OR “PGD” OR “PGP” OR “preimplantation genetic profiling” AND “translocation” OR “Chromosomal translocation.” We also improved this search by reviewing the reference lists of all of the retrieved publications and identifying supplementary relevant articles.

Inclusion and Exclusion Criteria
For our meta-analyses, articles with the following criteria were included: (1) any study published as an original study that focused on the pregnancy outcome of PGD in translocation carriers; (2) the numbers of case and control groups for each PGD and non-PGD group were reported or the relevant data were available; and (3) sufficient data were provided to estimate the odds ratio (OR) and 95% confidence interval (CI). In addition, we excluded reviews, editorials, comments, case reports, and overlapped articles or studies with overlapping data and inadequate information for pregnancy outcome of PGD.

Data Extraction
The articles were selected and extracted of the original data by two of the authors (M.M. and S.S.D.) independently using a standardized and consistent method. The following information was collected from each study: first author, year of publication, ethnicity of the patients, numbers of cases and controls, PGD method and variables adjusted for in the analysis, as well as multivariate adjusted ORs and 95% CIs.

Statistical Analysis
The pregnancy outcome of PGD in translocation carrier populations was estimated by calculating pooled ORs and associated 95% CI. The significant of the pooled OR was determined by Z-test. All statistical analyses were conducted using STATA software (version 12.0; Stata Corp LP, College Station, Texas, United States) and p < 0.05 and I² > 50%, random-effect model (the DerSimonian–Laird method) was employed.²⁰ We conducted a sensitivity analysis to explore heterogeneity when significant heterogeneity existed. Subgroup analysis was applied by country, female/male carrier, and the type of translocated chromosomes. Furthermore, both Begg’s and Egger’s tests were performed to evaluate publication bias, p < 0.05 for these tests indicate significant publication bias.

Results

Characteristics of the Included Studies
A detailed flow chart of the study selection process is shown in Fig. 1. According to search, a total of 428 potentially relevant articles were identified. After removing duplicates, 292 publications were included for further evaluation. Among these articles, 63 articles were selected for reviewing the full text. Overall 55 publications were excluded mainly because of no relevance, animal not human experiments, reviews, or meeting abstract. One study was excluded for the reason that it was not possible to calculate OR.²¹ At the final step, six full-text articles were included in the present meta-analysis. The main characteristics of included studies in the meta-analysis were summarized in Table 1. As shown in the table, two studies involved Asian and four involved developed countries.¹⁶,¹⁸,²²,²³ Three studies focused on the female carriers of chromosomal translocations,¹⁵,¹⁸,²³ and the remaining three studies were associated with one of the partner male/female carrier.¹⁶,¹⁷,²² All of the studies was evaluated the pregnancy outcome of PGD in both types of chromosomal translocations (Reciprocal and Robertsonian).
except one study in reciprocal translocation carriers. Translocated chromosomes 13 and 21 were analyzed by PGD in all of the studies. The other chromosomes, such as X and Y, were only studied in three papers. The main PGD method was fluorescent in situ hybridization (FISH) which was used in all of the included studies.

**Meta-analysis Results**

The forest plot of the meta-analysis for successful pregnancy outcome in translocation carriers is shown in Fig. 2. Overall, significant association was found between PGD and successful pregnancy outcome in the translocation carriers (OR = 8.58; 95% CI: 1.40–52.76; $I^2 = 96.8\%$). For the subgroup analysis,
### Table 1 Characteristics of studies in the meta-analysis

<table>
<thead>
<tr>
<th>ID</th>
<th>Study</th>
<th>Country</th>
<th>No. of cases</th>
<th>Year</th>
<th>Translocation type/chromosome</th>
<th>Translocation origin</th>
<th>Miscarriage rate</th>
<th>PGD method</th>
<th>Study design</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kyu Lim et al15</td>
<td>South Korea</td>
<td>18</td>
<td>2004</td>
<td>Both Rcp and Rob/ Rcp (1–22,Y) Rob 13–15, 21</td>
<td>Female</td>
<td>3</td>
<td>FISH</td>
<td>Cohort</td>
<td>$p = 0.02$</td>
</tr>
<tr>
<td>2</td>
<td>Munné et al16</td>
<td>USA</td>
<td>16</td>
<td>2000</td>
<td>Both Rcp and Rob/1–22</td>
<td>Male/female</td>
<td>2</td>
<td>FISH</td>
<td>Cohort</td>
<td>$p = 0.001$</td>
</tr>
<tr>
<td>3</td>
<td>Ikuma et al17</td>
<td>Japan</td>
<td>37</td>
<td>2015</td>
<td>Both Rcp and Rob/1–22</td>
<td>Male/female</td>
<td>3.37 ± 1.26</td>
<td>FISH</td>
<td>Cohort</td>
<td>$p = 0.101$</td>
</tr>
<tr>
<td>4</td>
<td>Keymolen et al18</td>
<td>Belgium</td>
<td>138</td>
<td>2012</td>
<td>Reciprocal translocation carriers (Rcp)/13, 18, 21, X and Y</td>
<td>Female</td>
<td>3–4</td>
<td>FISH</td>
<td>Cross-sectional</td>
<td>OR = 0.62 (CI: 0.16–2.31)</td>
</tr>
<tr>
<td>5</td>
<td>Verlinsky et al23</td>
<td>USA</td>
<td>43</td>
<td>2005</td>
<td>Both Rcp and Rob/13, 15, 16, 17, 18, 21, 22, X, Y</td>
<td>Female</td>
<td>0–4 or more</td>
<td>FISH</td>
<td>Cohort</td>
<td>$p = 0.001$</td>
</tr>
<tr>
<td>6</td>
<td>Fischer et al22</td>
<td>USA</td>
<td>69</td>
<td>2010</td>
<td>Both Rcp and Rob/X, Y, 8, 13–22</td>
<td>Male/female</td>
<td>3–7</td>
<td>FISH</td>
<td>Cohort</td>
<td>$p = 0.0001$</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FISH, fluorescent in situ hybridization; OR, odds ratio; PGD, preimplantation genetic diagnosis; Rcp, reciprocal translocation; Rob, Robertsonian translocation.

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**Discussion**

It is well known that chromosomal abnormalities, such as a structural chromosome abnormality, are one of the most common causes of recurrent miscarriage, and a live birth rate in couples with recurrent miscarriage carrying a structural chromosome abnormality, such as unbalanced translocations, is lower than that in normal couples. Prenatal diagnosis can improve the reproductive outcome in these couples, and PGD carried out in the early embryo with the consideration of the embryos’ karyotype is considered to be a superior method for those couples [23].

Our meta-analysis illustrated strong evidence for a significant association between the pregnancy outcome of PGD in couples carrying chromosomal translocations and the miscarriage rate. A comprehensive literature review showed that couples carrying chromosomal translocations are of important reasons for recurrent miscarriage [24], and the success rate of PGD in translocation carriers is significantly greater than in other chromosome groups [25–28].

Recent systematic reviews of PGD for carriers of a structural chromosome abnormality and a history of recurrent miscarriage, such as chromosomal abnormalities, have not shown benefit with this strategy. Moreover, a recent meta-analysis investigating the pregnancy outcome of PGD in translocation carriers [29] showed that the success rate of PGD in translocation carriers was not significantly different from the general population (OR = 1.07, 95% CI: 0.88–1.29) [30]. However, the success rates observed in the translocation carrier subgroup were quite different from the initial analysis (OR = 0.80, 95% CI: 0.68–0.94) [31].

**Publication Bias Analysis**

Funnel plots and Egger’s tests were executed to assess publication bias. Both funnel plots (Fig. 6) and Egger’s test (p = 0.15) suggested no evidence of publication bias in the meta-analysis.

**Heterogeneity Test and Sensitivity Analysis**

In the present meta-analysis, significant heterogeneity was observed. We performed a sensitivity analysis by removing the individual studies and meta-analysis. There was no significant difference from the initial analysis (OR = 0.79, 95% CI: 0.67–0.95) [32]. Finally, no significant differences in the success rate of PGD in translocation carriers were found between patients from different countries (OR = 1.11, 95% CI: 0.98–1.26) [33]. However, the translocation carrier subgroup was found in Asian countries (OR = 2.40, 95% CI: 1.35–4.52) [34].

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Fig. 2  The forest plot of the meta-analysis for successful pregnancy outcome in translocation carriers. CI, confidence interval; OR, odds ratio.

Fig. 3  The subgroup analysis, according to country. CI, confidence interval; OR, odds ratio.
### Fig. 4 Origin of the translocation carrier. CI, confidence interval; OR, odds ratio.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuy_Lim.ch (2004)</td>
<td>115.00 (21.12, 626.31)</td>
<td>13.40</td>
<td></td>
</tr>
<tr>
<td>Keymolen.K (2012)</td>
<td>1.39 (0.60, 2.43)</td>
<td>14.96</td>
<td></td>
</tr>
<tr>
<td>Verlinsky.y (2005)</td>
<td>33.25 (9.93, 111.28)</td>
<td>14.21</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>5.55 (0.77, 44.62)</td>
<td>57.51</td>
<td></td>
</tr>
<tr>
<td>both</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Munne.s (2000)</td>
<td>81.67 (12.29, 542.48)</td>
<td>13.02</td>
<td></td>
</tr>
<tr>
<td>Ikuma.Sh (2015)</td>
<td>0.52 (0.22, 1.23)</td>
<td>14.67</td>
<td></td>
</tr>
<tr>
<td>Fischer.j (2010)</td>
<td>72.95 (34.71, 153.31)</td>
<td>14.79</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>14.07 (0.36, 556.40)</td>
<td>42.49</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>8.58 (1.40, 52.76)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

### Fig. 5 The translocated chromosome subgroup analysis. CI, confidence interval; OR, odds ratio.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>chromosome(1-22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuy_Lim.ch (2004)</td>
<td>115.00 (21.12, 626.31)</td>
<td>13.40</td>
<td></td>
</tr>
<tr>
<td>Munne.s (2000)</td>
<td>81.67 (12.29, 542.48)</td>
<td>13.02</td>
<td></td>
</tr>
<tr>
<td>Ikuma.Sh (2015)</td>
<td>0.52 (0.22, 1.23)</td>
<td>14.67</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>5.62 (0.49, 63.80)</td>
<td>56.03</td>
<td></td>
</tr>
<tr>
<td>chromosome(X,Y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keymolen.K (2012)</td>
<td>1.39 (0.60, 2.43)</td>
<td>14.96</td>
<td></td>
</tr>
<tr>
<td>Verlinsky.y (2005)</td>
<td>33.25 (9.93, 111.28)</td>
<td>14.21</td>
<td></td>
</tr>
<tr>
<td>Fischer.j (2010)</td>
<td>72.95 (34.71, 153.31)</td>
<td>14.79</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>14.74 (0.88, 246.89)</td>
<td>43.97</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>8.58 (1.40, 52.76)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
reciprocal and Robertsonian translocation carriers. The findings from subgroup analysis indicated the significantly positive effect of PGD on pregnancy outcome in translocation carriers from developed countries not at Asian countries. However, Kyu Lim et al reported that spontaneous abortion rate could be significantly reduced by PGD in translocation carries from Korean population. Furthermore, in the current study, the pregnancy outcome of PGD in translocation carriers was not depended on the carrier origin and the type of translocated chromosomes.

In Asian studies, all of the participants had only translocation with two or more consecutive clinical miscarriages, while other studies in developed countries including all of infertility problems or RPL or still birth which may affect the overall outcome of their studies. Also the mean age of the patients who underwent PGD was significantly higher than control group in one of Asian studies, while there wasn’t significant difference between age of control and PGD group in other studies.

The clear evidence of heterogeneity in this meta-analysis should be discussed. Though a sensitivity analysis was performed, the origin of the heterogeneity among the studies was not found. The heterogeneity might have been due to other factors, such as diversity in the population characteristics (ethnicity, age, the type of translocation, etc.), PGD methods, and study design. Our meta-analysis was based on estimates without adjusting the data for these factors, which is the potential limitation of this study. Some another limitations of our meta-analysis was the insufficient number of studies, especially for subgroup analysis and languages of the publications.

**Conclusion**

In conclusion, this meta-analysis provide reliable evidence that the PGD method is associated with the development of pregnancy outcome in translocation carriers, especially in developed countries. However, it is required to conduct further larger scale, multicenter, and high-quality studies in the future.

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None.

**Conflict of Interest**

None declared.

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