

Subsequent pregnancy outcomes in recurrent miscarriage patients with a paternal or maternal carrier of a structural chromosome rearrangement

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Abstract Information concerning the prognosis of subsequent pregnancies in patients with reciprocal translocations is limited. This study was performed to determine the percentage success rate with first pregnancies after ascertainment of a carrier status. A total of 2,382 couples with a history of two or more consecutive miscarriages were studied in multicenters. The prevalence of an abnormal chromosome in either partner was examined, and subsequent success rates were compared between cases with and without an abnormal karyotype in either partner. A total of 129 couples (5.4%) had an abnormal karyotype in one partner excluding inversion 9 in 44 men and in 85 women. Thus, 2,253 couples had a normal karyotype in both partner. Eighty-five (3.6%) had translocations, 13 being Robertsonian translocations. Twenty-nine of the 46

cases (63.0%) who became pregnant with reciprocal translocations in either partner experienced a live birth with natural conception. In contrast, 950 of 1,207 cases (78.7%) with normal chromosomes had successful live births, the difference being significant ($P = 0.019$). No infant with an unbalanced translocation was found in 29 cases of successful pregnancy following recurrent miscarriage. Pregnancy prognosis was worsened with either maternal or paternal reciprocal translocations. Explanation of the success rate with natural conception should be provided before the subsequent pregnancy after ascertainment of carrier status.

Keywords Chromosome abnormality · Inversion · Recurrent miscarriage · Reciprocal translocation · Robertsonian translocation

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Introduction

An abnormal karyotype in either partner, especially when a translocation is involved, is considered to be the cause of recurrent miscarriage (RM) (De Braekeleer and Dao 1990). De Braekeleer et al. analyzed a computerized database covering 22,199 couples generated from the literature on cytogenetic studies and concluded a rate of 4.7% for chromosomal structural rearrangements in couples suffering two or more spontaneous abortions.

The number of centers performing preimplantation genetic diagnosis (PGD) worldwide has been steadily increasing since the procedure's introduction over a decade ago (Handyside et al. 1990). Munne et al. (2000) concluded that PGD could achieve a statistically significant reduction in the miscarriage rate from 95% to 13% in translocation carriers. However, as most RM patients visit hospital because they experience difficulty in having children, it is inappropriate to compare miscarriage rates before and after diagnosis in RM cases. To our knowledge, there have been no case–control studies comparing live-birth rates between PGD and natural pregnancies after parents are diagnosed as carriers of translocations. Thus, it is unclear whether PGD can improve the birth rate in patients with translocations, although it does prevent miscarriages.

It is difficult to conduct case–control studies because translocation carriers are relatively rare. Recently, several manuscripts concerning reproductive outcome after natural conception in RM patients with a parental carrier of a structural chromosome rearrangement have been published (Sugiura-Ogasawara et al. 2004; Carp et al. 2004; Goddijn et al. 2004; Stephenson and Sierra 2006; Franssen et al. 2006). Sugiura-Ogasawara's 2004 study indicated a success rate of about 31.9% (15 of 47) at the first pregnancy after the ascertainment of carrier status, which is much less than that with normal chromosomes (71.7%, 849 of 1,184), and a cumulative success rate of 68.1% (32 of the 47). They concluded that the prognosis of RM patients with reciprocal translocations is poor, given that the study was conducted over 17 years and included severe cases suffering ten and 13 miscarriages.

Recently, Franssen et al. (2006) reported cumulative success rates for RM patients with reciprocal translocations, Robertsonian translocations, and a normal karyotype to be 83.0%, 82.0%, and 84.1%, respectively, from their prospective case–control study. They thus concluded that the chance of having a healthy child is as high as in non-carrier couples, despite the higher risk of miscarriage.

However, available information on the prognosis of RM patients with a structural chromosome rearrangement is insufficient. This study therefore focused on success rate at the first pregnancy after ascertainment of carrier status.

Patients and methods

This multicenter study was performed in Nagoya City Johsai Hospital, Tokyo University Hospital, Osaka Medical Center and Research Institute for Maternal and Child Health, National Center for Child Health and Development, Toyama University Hospital, Tokai University Hospital, Nagoya City University Hospital, Nippon Medical School Hospital, Jikei University Hospital, and Keio University Hospital. Totally, 2,382 couples (4,764 individuals) with a history of two or more consecutive miscarriages who visited the hospitals between January 2003 and December 2005 were enrolled.

Hysterosalpingography, chromosome analysis for both partners, identification of antiphospholipid antibodies (aPL) such as lupus anticoagulant and β 2-glycoprotein-I-dependent anticardiolipin antibodies or anticardiolipin antibodies, and blood tests for hyperthyroidism, diabetes mellitus and hyperprolactinemia were performed for all cases before subsequent pregnancy. Their first pregnancies after ascertainment of carrier status were followed up till September 2007. Patients with at least one kind of aPL were treated with combined low-dose aspirin and heparin therapy. Interventions such as supportive psychotherapy were added to patients with both abnormal and normal karyotypes. Gestational age was calculated from basal body temperature charts. Dilution and curettage was performed when miscarriages were diagnosed, and the karyotypes of aborted conceptuses were ascertained with the use of a standard G-banding technique. Informed consent was obtained from all patients. Informed consent for the multicenter study was approved by the institutional review board in Nagoya City University.

In our study:

1. The frequencies of abnormal karyotypes in either partner in Japan were examined.
2. The subsequent success rates were compared between cases with reciprocal translocation and with a normal karyotype. Miscarriage rates for patients with a Robertsonian translocation or inversions were also assessed.

Statistical analysis

Differences in group values were analyzed using Stat view with an Apple Macintosh computer. A significance level of $P < 0.05$ was applied for all tests.

Results

1. A total of 129 of 2,382 couples (5.4%) had an abnormal karyotype in one partner excluding inversion 9: 44

were in men and 85 were in women. Seventy-two (3.0%) had reciprocal translocations: 28 in men and 44 in women. In addition, 13 had Robertsonian translocations (seven in men and six in women). Thus, the overall frequency of translocations was 3.6%. Other inversions existed in chromosomes 4, 7, and 8: in eight men; and 1, 2, 8, and 11: in 17 women. Twenty-six had low-frequency mosaicisms. Thus, 2,253 couples had a normal karyotype in both partner.

- Subsequent pregnancy outcomes for reciprocal translocation carriers and details are shown in Tables 1 and 2. Forty-six women were found to be pregnant by natural conception after 10.1 ± 7.7 months from the ascertainment of reciprocal translocation carrier status. Twenty-nine (63.0%) experienced a live birth. No infant with an unbalanced translocation was found in 29 cases of successful pregnancy following RM.

In contrast, of 1,207 women with a normal karyotype who became pregnant, 950 (78.7%) had a successful live birth. The live birth rate in cases with reciprocal translocations was significantly lower than that for cases with normal chromosomes in both partners ($P = 0.019$). The mean age of translocation carriers (31.0 ± 3.9) at the diagnosis of carrier status was lower than that in cases with normal chromosomes (32.9 ± 4.3 , $P = 0.0032$). There were no differences in mean numbers of previous miscarriages between reciprocal translocation carriers (3.1 ± 1.2) and patients with normal chromosomes (2.8 ± 1.1 , $P = 0.071$). Twenty-nine (2.4%) of the 1,207 control patients had uterine anomalies (14 bicornis, nine septum, three unicornis, three didelphys), and 26 (2.2%) had at least one kind of aPL. None of the 46 pregnant reciprocal translocation carriers had uterine anomalies and aPLs.

When cases with only two previous miscarriages were excluded, 23 of the 34 women (67.6%) experienced a live birth. When cases with a history of live birth were excluded, the figure was 62.5% (25/40). Three of the five cases (60.0%) who had a Robertsonian translocation were included in those who demonstrated a live birth subsequently (Table 3).

Details for all pregnancy outcomes after examination of the 18 couples who had other abnormal chromosomes such

as inversions are shown in Table 4. Five of the seven cases with inversions (71.4%) could give birth to live babies. We included 26 cases (1.09%) with low-frequency mosaicisms. Nine of the 17 women (52.9%) could have living babies.

Discussion

In this study, 129 couples (5.4%) had an abnormal karyotype in one partner excluding pericentric inversion of chromosome 9. The frequency is in line with previous studies (De Braekeleer et al. 1990), although it was 7.8% in Sugiura-Ogasawara's study because inversion 9, which is a normal variant, was included (Sugiura-Ogasawara et al. 2004). Reciprocal translocation is the most important problem in RM cases. Translocations are also found in infertile men, and thus, the frequency in women would be higher than that in men in RM cases after natural selection (Elghezal et al. 2006).

Five manuscripts concerning prospective reproductive outcome in RM patients with a parental carrier of a structural chromosome rearrangement have been published (Sugiura-Ogasawara et al. 2004; Carp et al. 2004; Goddijn et al. 2004; Stephenson and Sierra 2006; Franssen et al. 2006). Carp et al. examined the first pregnancy outcome after ascertainment of translocation carriers including Robertsonian translocations and described 19 of 44 (43.2%) carriers to feature live births. Franssen et al. conducted a case-control study and prospectively followed up patients for a mean of 5.8 years by telephone. They found cumulative success rates for RM patients with reciprocal translocations, Robertsonian translocations, and a normal karyotype to be 83.0%, 82.0%, and 84.1%, respectively. Generally, RM patients tend not to be followed up after examination in University Hospitals because of distances from their home towns. Indeed, in our study, a certain number of patients did not visit each hospital after examination, presumably when they did not conceive or the subsequent pregnancy was followed up in another hometown hospital. Thus, Franssen's conclusions have an important bearing not only for RM patients with translocations but also those with normal chromosomes. Whereas the success rate of patients with translocations at the first pregnancy after ascertainment of carrier status could not be obtained, that with all kinds of carriers was 62.0% (148/239).

Regarding success rates at the first pregnancy after ascertainment of reciprocal translocation carrier status, this study, Stephenson and Sierra's study (2006), and Sugiura-Ogasawara et al.'s earlier study (2004) generated figures of 63.0%, 65.0% (13/20), and 31.9%, respectively. The reason the prognosis of Sugiura-Ogasawara's patients was so poor is that the study included severe cases with large numbers

Table 1 Subsequent first pregnancy outcome in recurrent miscarriage couples

Parental karyotype	Live birth rates
Reciprocal translocation	29/46 (63.0%)
Robertsonian translocation	3/5 (60.0%)
Inversion	5/7 (71.4%)
Low-frequency mosaicism	9/17 (52.9%)
Normal	950/1207 (78.7%)

Table 2 Carriers of a reciprocal translocation with a history of recurrent miscarriage

Reciprocal translocation	Age	Previous miscarriage (Stillbirth)	Previous live birth	Pregnancy outcome	Chromosome
Female					
46,XX,t(1;4)(q42.1;p15.32)	39	3 (1)	0	Not available ^a	
46,XX,t(1;5)(q12;q22)	29	3	0	Not available	
46,XX,t(1;10)(q21;p11.2)	34	4	0	Failure	Not tested
46,XX,t(1;10)(q42.1;q24.3)	28	2	0	Failure	Not tested
46,XX,t(1;11)(p11q13)	Not available	2	0	Failure	47, XY,+4
46,XX,t(1;15)(q32.1;q23)	28	3	0	Success	
46,XX,t(2;12)(q36;p13.2)	34	2	0	Not conceive	
46,XX,t(2;15)(p23;q15)	23	3	0	Success	
46,XX,t(2;15)(q31;q21.2)	38	6	0	Success	
46,XX,t(2;18)(q33;p11.3)	42	3	0	Failure	Not tested
46,XX,t(3;5)(p13;q33)	27	3	0	Success	
46,XX,t(3;7)(p25;p13)	33	3	0	Success	
46,XX,t(3;9)(p13;q34)	27	2	0	Not available	
46,XX,t(3;16)(q13.2;q22)	35	2	0	Not available	
46,XX,inv(9)(p11p13), t(4;12)(q33;q23)	39	4	2	Success	
46,XX,t(4;21)(p15.1;q 22.2)	31	2	0	Success	
46,XX,t(4;5)(q23;q33.3)	33	2	0	Not conceive	
46,XX,t(5;13)(p15.3;q21.2)	33	3	0	Success	
46,XX,t(6;7)(q25.1;p21)	28	3	0	Failure	46,XY,der(6)t(6;7)(q25.1;p21)
46,XX,t(6;8) ^b	33	5 (1)	0	Failure	46,XXdel(6)(q23)
46,XX,t(6;8)(q23;p23)	35	6 (1)	0	Failure	46,XX,t(6;8)(q23;p23)
46,XX,t(6;20)(q22.3;p13)	30	2	0	PGD failure	Not tested
46,XX,t(7;8)(q11.2;q13)	35	3	0	Not available	
46,XX,t(7;11)(p13;q21)	26	2	0	Success	
46,XX,t(7;18)(p14;p11)	41	4	0	Not conceive	
46,XX,t(7;18)(p15.3;p11.32)	33	3	0	Failure	Not tested
46,XX,t(7;18)(q32;q13)	38	4	0	Failure	Not tested
46,XX,t(8;10)(q13;q11.2)	30	4	0	Not available	
46,XX,t(9;11)(q34.1;q23.1)	29	5	1	Not available	
46,XX,t(9;13)(q12;p12)	32	4	0	Success	
46,XX,t(10;16)(q26.3;p11.2)	25	2	0	Not conceive	
46,XX,t(10;17)(q26;p12)	28	3	0	Failure	46,XX,der(17)t(10;17)(q26;p12)mat
46,XX,t(10;21)(p10;q10)	27	4	0	Success	46,XY,t(10;21)(p10;q10)
46,XX,t(11;22)(q23.3;q11.2)	28	2	0	Success	
46,XX,t(11;22)(q23;q11.2)	29	3	0	Failure	46,XX[25]/46,XX,del(5)(p14)[5]
46,XX,t(11;22)(q23.3;q11.2)	27	3	0	Not conceive	
46,XX,t(12;21)(q13.3;q22.1)	23	3	0	Not conceive	
46,XX,t(13;19)(q14;p13.1)	31	2	0	Not available	
46,XX,t(16;20)(p11;p13)	37	3	0	Not available	
46,XX,t(17;20)(p13;q13.1)	31	3	1	Failure	Not tested
46,XX,t ^b	26	2	0	Failure	47,XX or XY,+14
46,XX,t ^b	33	3	0	Success	
46,XX,t ^b	35	3	0	Success	
46,XX,t ^b	42	4	0	Not conceive	

Table 2 continued

Reciprocal translocation	Age	Previous miscarriage (Stillbirth)	Previous live birth	Pregnancy outcome	Chromosome
Male					
46,XY,t(1;9)(q42.3;q22.3)	35	3	0	Not available	
46,XY,t(1;10)(p32;q26)	31	4	0	Success	
46,XY,t(1;11)(p32.1;p15.1)	33	2	0	Success	
46,XY,t(2;7)(p10;q10)	33	3	0	Success	
46,XY,t(3;5)(q26.2;p15.1)	35	5	0	Not available	
46,XY,t(3;7)(q25.3;q21.1)	31	4	0	Success	
46,XY,t(3;15)(p22;q26.2)	35	3	0	Success	
46,XY,t(4;10)(p14;q21.2)	42	2 (1)	0	Not available	
46,XY,t(4;10)(q34;q21.2)	29	2	0	Success	
46,XY,t(5;6)(q33.1;p11.2)	30	3	0	Success	
46,XY,t(5;9) ^b	32	2 (2)	1	Success	
46,XY,t(5;10)(q22;q22)	29	3	0	Failure	Chemical ^c
46,XY,t(6;14)(q13;q24),15p+	36	3	0	Not conceive	
46,XY,t(6;16)(q27;p13.1)	31	3	0	Success	
46,XY,t(7;8)(q21;q22)	33	2	0	Failure	46,XX
46,XY,t(7;8)(q32;q22)	25	2	0	Failure	Chemical
46,XY,t(7;16)(p22;q21)	35	3	0	Not available	
46,XY,t(7;17)(q11.23;q23.3)	25	5	0	Success	
46,XY,t(8;12)(p21.3;q12)	31	4	1	Success	
46,XY,t(9;13)(q32;q32), 46,XX,inv(9)	33	2	0	Success	
46,XY,t(10;13)(q24;q34)	28	3	1	Success	
46,XY,t(10;16)(p14;q12.2)	41	2	0	PGD not conceive	
46,XY,t(11;20)(q23.1;p13)	25	3	0	Not available	
46,XY,t(11;22)(q23.3;q11.2)	30	3	1	Success	
46,XY,t(11;22)(q24;q12), 46,XX,inv(9)	33	3	0	Success	
46,XY,t(13;17)(q14.1;q23)	32	3	1	Not available	
46,XY,t(17;21)(q21;q22)	34	3	0	Not conceive	
46,XY,t ^b	33	2	0	Failure	46,XX

PGD preimplantation genetic diagnosis

^a These patients were not followed up after ascertainment of carrier status

^b Details were unclear because these patients were examined in the previous hospital

^c Chemical abortion

of miscarriages. The success rate might depend on the women's age, number of previous miscarriages, and the positions of breakpoints. Another reason is that the study concerned clinical data collected over 17 years. It is well known that patients with translocations sometimes miscarry despite a normal or balanced embryonic karyotype. The success rates for patients both with and without translocations in our study were superior to that in Sugiura-Ogasawara's earlier study because intervention methods such as anticoagulant and supportive psychotherapy might have now improved.

Cytogenetic analysis of semen from carrier men with translocations suggests that 46.9% exhibit alternate

segregation in reciprocal translocation carriers and 88.7% with Robertsonian translocations (Gardner and Sutherland 2004). However, we cannot find who has difficulty in reaching successful delivery in RM patients with reciprocal translocations. For women with higher age or a high number of previous miscarriages, in vitro fertilization (IVF)–PGD might be able to save time and facilitate having a baby.

The live-birth rates with PGD per IVF in reciprocal translocation carriers (23.7%, 47.2%, and 6.2%) are comparable to or rather lower than those (63.0%) with the subsequent first natural conception, as presented by this study (Chun et al. 2004; Otani et al. 2006; Feyereisen et al.

Table 3 Carriers of a Robertsonian translocation with a history of recurrent miscarriage

Robertsonian translocation	Age	Previous miscarriage	Previous live birth	Pregnancy outcome	Chromosome
Female					
44,XX,der(13;22)(q10;q10), der(14;15)(q10;q10)	33	3	0	Success	
45,XX,der(13;14)(q10;q10)	25	3	0	Not available ^a	
45,XX,der(13;14)(q10;q10)	33	3	0	PGD on going	PGD
45,XX,der(13;14)(q10;q14)	32	3	0	Not conceive	
45,XX,der(14;14)(q10;q10)	32	3	0	Not available	
45,XX,der(14;21)(q10;q10)	33	3	0	Not available	
Male					
45,XY,der(13;14)(q10;q10)	32	2	1	Failure	Not tested
45,XY,der(13;14)(q10;q10)	27	2	0	PGD not available	
45,XY,der(13; 14)(q10;q10)	30	2 (1)	1	Failure	Not tested
45,XY,der(14;21)(q10;q10)	28	2	0	Not available	
45,XY,der(15;22)(q10;q10)	28	3	0	Not available	
45,XY,der(15;22)(q10;q10)	29	2	0	Success	
45,XY,dic(13;14)(p11.2;p11.2)	28	3	0	Success	

PGD preimplantation genetic diagnosis

^a These patients were not followed up after ascertainment of carrier status

Table 4 Carriers of inversions and other abnormalities with a history of recurrent miscarriage

Other abnormalities	Age	Previous miscarriage	Previous live birth	Pregnancy outcome	Chromosome
Female					
46,XX,ins(8)(q24.2q24.12q24.13)	33	2	0	Success	
46,XX,inv(1)(p11q21)	31	2	0	Success	
46,XX,inv(2)(p16q31)	28	2	1	Success	
46,XX,inv(8)(p11.2q22.1)	33	2 (1)	0	Not available ^a	
46,XX,inv(11)(p13q11)	35	3	0	Success	46,XX
46,XX,inv(17)(q21.3q23)	36	3	1	Success	
46,X,del(X)(q25)	24	3 (1)	0	Success	
46,XX,19cenh+ ^b	28	2	0	Ectopy	
47,XX,+mar	37	2	0	Failure	47,XX,+22
47,XXX	36	10	0	Not available	
47,XXX	30	3	0	Not conceive	
Male					
46,XY,inv(4)(q12q21.3)	43	2	1	Not available	
46,XY,inv(7) ^c	33	1	0	Success	
46,XY,inv(8) ^c	29	2	0	Failure	46,XX
46,XY,inv(8)(p11.2q24.1)	28	3	1	Failure	Not tested
46,XsmallY	26	3	0	Success	
47,XYY	35	2	0	Success	
46,XY,del(16) ^c	34	3	0	Not available	

^a These patients were not followed up after ascertainment of carrier status

^b Normal variants

^c Details were unclear because these patients were examined in the previous hospital

2007). It is difficult, however, to simply compare the superiority between IVF–PGD and natural conception in translocation carriers, because information on the live-birth rate in the subsequent first pregnancy and time-based, not cycle-based, cumulative pregnancies after IVF–PGD or natural conception is very limited. Importantly, RM couples, not physicians and scientists, make the final decision;

therefore, couples should be fully informed of advantages and disadvantages of both IVF–PGD and natural pregnancy. As the first step, we here report the outcome of subsequent first natural pregnancies in RM patients with translocation carriers based on data obtained from multiple centers, which should be useful information for such couples.

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References

- Carp H, Feldman B, Oelsner G, Schiff E (2004) Parental karyotype and subsequent live births in recurrent miscarriage. *Fertil Steril* 81:1296–1301
- De Braekeleer M, Dao TN (1990) Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod* 5:519–528
- Elghezal H, Hider S, Braham R, Denguezli W, Ajina M, Saad A (2006) Chromosome abnormalities in one thousand infertile males with nonobstructive sperm disorders. *Fertil Steril* 86:1792–1795
- Feyereisen E, Steffann J, Romana S, Lelorc'Äôh M, Ray P, Kerbrat V, Tachdjian G, Frydman R, Frydman N (2007) Five years' experience of preimplantation genetic diagnosis in the Parisian Center: outcome of the first 441 started cycles. *Fertil Steril* 87:60–73
- Franssen MTM, Korevaar JC, van der Veen F, Leschot NJ, Bossuyt PMM, Goddijn M (2006) Reproductive outcome after chromosome analysis in couples with two or more miscarriages: case-control study. *BMJ* 332:759–762
- Gardner RJM, Sutherland GR (2004) Chromosome abnormalities and genetic counseling, 3rd edn. Oxford University Press, Oxford
- Goddijn M, Joosten JH, Knecht AC, van der Veen F, Franssen MT, Bonsel GJ, Leschot NJ (2004) Clinical relevance of diagnosing structural chromosome abnormalities in couples with repeated miscarriage. *Hum Reprod* 19:1013–1017
- Handyside AH, Kontogianni EH, Hardy K, Winston RM (1990) Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. *Nature* 344:768–770
- Kyu Lim C, Hyun Jun J, Mi Min D, Lee HS, Young Kim J, Koong MK, Kang IS (2004) Efficacy and clinical outcome of preimplantation genetic diagnosis using FISH for couples of reciprocal and Robertsonian translocations: the Korean experience. *Prenat Diagn* 24:556–561
- Munne S, Sandalinas M, Escudero T, Fung J, Gianaroli L, Cohen J (2000) Outcome of preimplantation genetic diagnosis of translocations. *Fertil Steril* 73:1209–1218
- Otani T, Roche M, Mizuike M, Colls P, Escudero T, Munne S (2006) Preimplantation genetic diagnosis significantly improves the pregnancy outcome of translocation carriers with a history of recurrent miscarriage and unsuccessful pregnancies. *Reprod Biomed Online* 13:869–874
- Stephenson MD, Sierra S (2006) Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. *Hum Reprod* 21:1076–1082
- Sugiura-Ogasawara M, Ozaki Y, Sato T, Suzumori N, Suzumori K (2004) Poor prognosis of recurrent aborters with either maternal or paternal reciprocal translocations. *Fertil Steril* 81:367–373