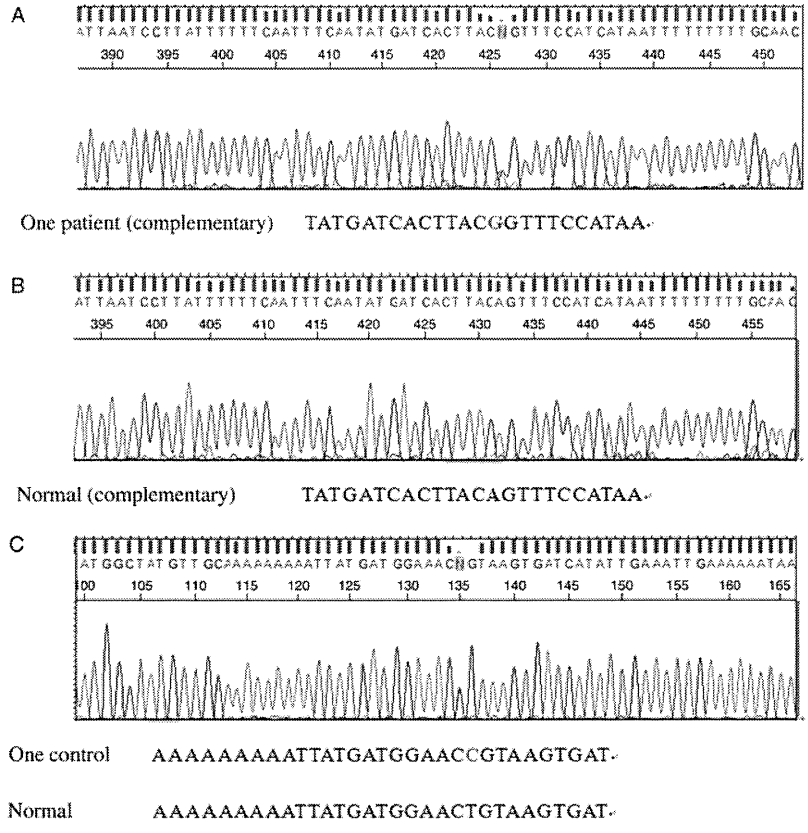

Figure 1 Nucleotide sequence results for the *SYCP3* gene in women with recurrent miscarriage and a control. (**A**) Heterozygous 657T>C mutation in exon 8 of the *SYCP3* gene of one patient with a history of six recurrent miscarriages. (**B**) Normal genotype in one patient with recurrent miscarriage. (**C**) Heterozygous 657T>C mutation in exon 8 of the *SYCP3* gene in one control with a history of one live birth and no miscarriages. From (A–C) sequences are all of the same region, and (A) and (B) sequences are complementary.

production of proteins that were mutated at the C-terminus. However, the effects of the *SYCP3* mutations on non-disjunction or the function of the synaptonemal complex have not been clear in mammals so far.

Our patient with 657T>C had repeated miscarriages with euploidy. It may be that the 657T>C mutation is a polymorphism without the specific function ascertained in the Bolor *et al.* (2009) study in humans. Further studies with larger numbers and a wide range of cases are needed to define whether the *SYCP3* mutations can be a cause of recurrent miscarriage.

Sycp3-deficient mice show complete meiotic arrest leading to male infertility (Yuan *et al.*, 2000). Miyamoto *et al.* (2003) identified in two azoospermia patients a 1 bp deletion of the *SYCP3* gene (643delA) that results in a premature stop codon and truncation of the C-terminal, coiled-coil-forming region of the SYCP3 protein. The mutant protein showed greatly reduced interaction with the wild-type protein *in vitro* (Miyamoto *et al.*, 2003). Reynolds *et al.* (2007) suggested that azoospermia associated with a decrease in the *DAZ* gene function in humans might, in part, be the consequence of failure at synapsis caused by reduced levels of the SYCP protein. However, no female patient with the 643delA mutation of SYCP3 has been reported. The infertile women might have the mutation because embryos with trisomy or monosomy except 45,X are frequently seen by PGD.

Our data showed that among the normal fetal karyotypes, XX and XY were found at a similar frequency, indicating that fetal rather than maternal karyotypes were obtained. In this study, about 90% of patients with abnormal and normal embryonic (fetal) karyotype tended to have repeat miscarriages with abnormal and normal karyotypes, respectively. The results suggest that unexplained recurrent miscarriage should be grouped as two types: one is miscarriage caused by abnormal embryonic karyotype and the other is 'real' unexplained recurrent miscarriage.

Moreover, the prognosis of a successful pregnancy for patients with an abnormal embryonic karyotype was better than for patients with a normal embryonic karyotype (Ogasawara *et al.*, 2000). No therapeutic approach to improve the rate of live birth could be found at this time (Kaandorp *et al.*, 2010). Thus, the gene associated with unexplained recurrent miscarriage with normal embryonic karyotype is more important (Suzumori and Sugiura-Ogasawara, 2010).

The results of our study suggest no clinical significance of routine screening for the presence of the *SYCP3* mutation in women with recurrent miscarriage because we detected only one benign mutation in 101 such patients. Future studies in mammalian animal models are likely to accelerate our understanding of the molecular mechanisms involved in recurrent miscarriage and will provide additional candidate genes to be screened in recurrent miscarriage patients and embryos with genetic factors.

Authors' roles

N.S., Y.O., M.N. and M.S.-O. were involved in conception and design; E.M., K.O. and C.Y-N. conducted data analysis; E.M., N.S. and M.S.-O. were involved in drafting the article. All authors agreed final approval of the version to be published.

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Uterine Anomaly and Recurrent Pregnancy Loss

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ABSTRACT

Women with recurrent pregnancy loss have a 3.2 to 6.9% likelihood of having a major uterine anomaly and a 1.0 to 16.9% chance of having an arcuate uterus. Bicornuate and septate uterine have a negative impact on reproductive outcomes and are associated with subsequent euploid miscarriage. The impact of an arcuate uterus on pregnancy outcome remains unclear. There are no definitive criteria to distinguish among the arcuate, septate, and bicornuate uteri. The American Fertility Society classification of Müllerian anomalies is the most common standardized classification of uterine anomalies. According to estimates, 65 to 85% of patients with bicornuate or septate uteri have a successful pregnancy outcome after metroplasty. However, 59.5% of the patients with such anomalies have a successful subsequent pregnancy without surgery, with a cumulative live birthrate of 78.0%. There is no case-control study to compare live birthrates in women who had surgery compared with those who did not. Strict criteria to distinguish between the bicornuate and septate uterus should be established. Further study is needed to confirm the benefits of metroplasty.

KEYWORDS: Bicornuate uterus, congenital uterine anomaly, recurrent pregnancy loss, septate uterus

Women with recurrent pregnancy loss have a 3.2 to 6.9% likelihood of having a major uterine anomaly and a 1.0 to 16.9% chance of having an arcuate uterus.[1–6] The impact of an arcuate uterus on the occurrence of pregnancy loss remains unclear. The American Fertility Society classification of Müllerian anomalies is the most common standardized classification of uterine anomalies.[7] Office hysteroscopy, hysterosalpingography (HSG), and/or two-dimensional (2D) ultrasound can be used as an initial screening tool. Combined hysteroscopy and laparoscopy, sonohysterography, and three-dimensional (3D) ultrasound can be used for a definitive diagnosis. However, there are no established criteria to distinguish among arcuate, septate and bicornuate uteri.

According to estimates, 65 to 85% of patients with bicornuate or septate uteri have a successful pregnancy outcome after metroplasty.[8–20] In the study by Sugiura-Ogasawara et al on the live birthrate in the absence of surgery, 59.5% of the patients with such anomalies had a successful first pregnancy after the examination as compared with 71.7% of the subjects with normal uteri ($p = 0.084$), and there was no difference in the cumulative live birthrate (78.0% versus 85.5%, respectively).[3] Congenital uterine anomalies have a negative impact on reproductive outcomes; they

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are being associated with further euploid (46, XX or 46, XY) miscarriage.[3]

There is no case-control study to compare live birthrates in women who had surgery compared with those who did not. Further study is needed to confirm the benefits of metroplasty.

DIAGNOSTIC CRITERIA FOR CONGENITAL UTERINE ANOMALIES

Uterine development involves three main stages[21,22]:

1. Organogenesis: development of both Müllerian ducts.
2. Fusion: the Müllerian ducts fuse at the lower end to form the upper vagina, cervix, and uterus (lateral fusion).
3. Septal absorption: after the Müllerian ducts fuse, the central septum starts to resorb at ~9 weeks, eventually leaving a single uterine cavity and cervix.

Congenital uterine anomalies may arise from malformations at any step of the Müllerian developmental process.[23] Buttram and Gibbons first proposed a classification of congenital uterine anomalies based on the degree of failure of the Müllerian ducts to develop normally, and they divided them into groups with similar clinical manifestations.[24]

This was revised by the American Fertility Society classification of Müllerian anomalies, which is currently considered the standard classification.[7] The classification has also been modified by a frequently used scheme by Strassmann.[25] The reason for providing the classification is its value to the practicing physician. The American Fertility Society classification is limited in that it does not specify the diagnostic methods or criteria that should be used to diagnose the anomalies and is based on the subjective impression of the clinician performing the evaluation. The committee had difficulty in deciding how to include arcuate uterus. The arcuate uterus could be classified as a form of a incomplete septate uterus because it is externally unified. However, the committee also proposed that the arcuate uterus could be classified separately because it appears to behave in a more benign fashion.

HSG is the most frequently used modality for the diagnosis of congenital anomalies; however, when used alone, it cannot distinguish between a septate and a bicornuate uterus.[7,25] Thus hysteroscopy/laparoscopy, which allows examination of both the uterine cavity and the external uterine contour, can precisely ascertain the uterine anomaly in accordance with the American Fertility Society classification of Müllerian anomalies.

It has been reported that an angle <75 degrees between the uterine horns is suggestive of a septate uterus and that an angle >105 degrees is indicative of a bicornuate uterus.[21,26] Tompkin's index has also been used to distinguish between arcuate uterus and an incomplete septate or bicornuate uterus.[27] A Tompkin's index >25% is considered to be consistent with the diagnosis of a septate or bicornuate uterus.

The advent of sonohysterography,[28] magnetic resonance imaging (MRI)[29] and 3D ultrasound now allows more accurate differential diagnosis,[30] although distinguishing an arcuate from a incomplete septate or bicornuate uterus still remains difficult. Troiano and McCarthy and Fedele et al considered a uterus to be septate rather than double (bicornuate or didelphys) in the presence of a fundal distal border indentation of ≤ 5 mm above the line joining the two ostia (interostial line).[26,31] Woelfer et al provided new 3D ultrasound criteria and indicated that a bicornuate uterus can be distinguished from a septate uterus when the fundal indentation dividing the two cornua was >10 mm.[30] According to a 3D ultrasound investigation, the incidence of the septate uterus is higher. Letterie and Wu et al also consider the uterus to be septate when the fundal indentation is <10 mm below the interostial line.[21,32] These criteria are useful for making a decision on transcervical resection (TCR) for a uterine septum.

Hysteroscopy allows direct visualization of the uterine cavity and ostia. It is therefore an accurate tool for identifying congenital uterine anomalies and is often used to establish a definitive diagnosis after an abnormal finding. Some authors consider the combination of hysteroscopy and laparoscopy to be the gold standard.[21,33–35] Based on a systematic review, Saravelos et al concluded the most accurate diagnostic procedures are combined hysteroscopy and laparoscopy, sonohysterography, and 3D ultrasound.[36] Preliminary studies suggest that MRI is a relatively sensitive tool. HSG and/or 2D ultrasound are used as initial screening tools.

Acién suggested the diagnosis of a bicornuate uterus is made when the external contour of the uterus at laparoscopy reveals any visible depression in the midline, associated with overall widening of the fundus.[37] The prevalence of bicornuate uterus may be higher if Acién's classical criteria are used; likewise, the prevalence of a uterine septum may be higher if the criteria of Fedele or Woelfer et al are used. It remains difficult to distinguish among arcuate, incomplete septum, and incomplete bicornuate uterus.

Distinction between bicornuate uterus and uterine septum is important for selecting appropriate treatment. However, the clinical significance of the distinction still remains unclear.

PREVALENCE OF MAJOR MALFORMATIONS

The frequency of congenital uterine anomalies has been reported to vary between 1.8% and 37.6% in women with

a history of recurrent miscarriage. The variation largely depends on the methods and the criteria selected for the diagnosis.[1–6]

Recurrent miscarriage traditionally was defined as three or more consecutive miscarriages occurring before 20 weeks postmenstruation.[38] However, such terminology is not uniformly accepted in studies, which may also influence the results. Because the terminology is so divergent, the following definitions are used in this article:

Recurrent early pregnancy loss: two or more miscarriages at <10 weeks of gestation.
Recurrent pregnancy loss: two or more pregnancy losses at any gestational age.
Recurrent early miscarriage: three or more consecutive miscarriages at <10 weeks of gestation.
Recurrent miscarriage: three or more consecutive miscarriages at <20 to 28 weeks of gestation (to include European publications)

Table 1 shows the incidence of uterine anomalies based on some studies that included ≥500 cases. Raga et al described that patients (6.3%; 54 of 868; $p < 0.05$) with a history of two or more consecutive pregnancy losses had a significantly elevated incidence of Müllerian anomalies in comparison with patients who were fertile (3.8%; 49 of 1289) or infertile (2.4%; 25 of 1024) cases.[1] The prevalence of arcuate uterus in this study was 1.0%, 1.6%, and 1.1%, respectively. Because arcuate uterus seems to be a normal variant, the incidence of major anomalies was 5.3% in this study. The diagnoses in the patients were confirmed by HSG and laparoscopy/laparotomy during the years 1980 to 1995.

Makino et al reported an incidence of uterine anomalies of 15.7% (188 of 1200) using HSG in 1992.[2] Of the 188, 133 (70.7%) had an arcuate uterus. The incidence of major anomalies was 4.6% (55 of 1200) in patients with two or more consecutive pregnancy losses.

In the study by Sugiura-Ogasawara et al, major malformations such as septate, bicornuate or unicornuate uterus, and didelphys were found in 3.2% of the patients.[3]

Several studies have reported that the prevalence of septate uterus is higher than that of bicornuate uterus. However, Lin et al concluded from a literature review that bicornuate, septate, arcuate, unicornuate, and didelphys uteri occurred at a prevalence of 37%, 22%, 15%, 4.4%, and 11%, respectively.[39] Our study, based on Acién's criteria, also indicated that bicornuate uterus occurs at the highest prevalence. Lin et al also concluded that arcuate uterus has little adverse impact on the reproductive outcome.

Based on a systematic review, Saravelos et al concluded the prevalence of congenital uterine anomalies was 6.7% in the general population, 7.3% in a

Table 1 Prevalence of Congenital Uterine Anomalies in Recurrent Pregnancy Loss

	n	Age Yrs (SD)	Bicornuate	Septate	Arcuate	Unicornuate	Didelphys	Total, Excluding Arcuate	Evaluation	RPL Definitions
Sugiura-Ogasawara et al, 2010[3]	1676	31.5 (3.5)	2.3%	0.6%	–	0.3%	0.1%	3.2%	HSG, laparoscopy, MRI	Two or more pregnancy loses
Salim et al, 2003[6]	509	34.9	1.2%	5.3%	16.9%	0.4%	0%	6.9%	TVS, 3D, US	Three or more unexplained first trimester
Raga et al, 1997[1]	868	28	1.9%	2.0%	1.0%	0.6%	0.7%	5.3%	HSG, laparoscopy	Two or more pregnancy losses
Clifford et al, 1994[4]	500	32.9	0.6%	1.2%	–	–	–	1.8%	US	Three or more miscarriages
Makino et al, 1992[2]	1200	31.4	–	4.1%	11.1%	0.4%	–	4.6%	HSG	Two or more pregnancy losses
Saravelos et al, 2008[36] (review)	1257	–	1.0%	5.0%	12.2%	0.4%	0.1%	3.9%	Hysteroscopy, laparoscopy, SHG, 3D US	Three or more miscarriages

RPL, recurrent pregnancy loss; HSG, hysterosalpingography; MRI, magnetic resonance imaging; TVS, transvaginal sonography; 3D, three dimensional; US, ultrasound; SHG, sonohysterography.

population of women with infertility, and 16.7% in a population with recurrent miscarriages.[36] The prevalence of an arcuate uterus in the three cohorts was 4.9%, 1.9% and 12.2%, respectively. Thus the prevalence of major anomalies in the three cohorts was 1.8%, 5.4%, and 4.5%, respectively. Saravelos et al concluded that arcuate uterus has a possible association with miscarriage because the prevalence in patients with recurrent miscarriages was higher than that in the general population.

Women with recurrent pregnancy loss have a 3.2 to 6.9% likelihood of having a major uterine anomaly and a 1.0 to 16.9% chance of having an arcuate uterus.[1–6] However, the impact of the arcuate uterus on miscarriage remains unclear.

MECHANISMS TO EXPLAIN THE ADVERSE EFFECTS OF UTERINE ANOMALIES ON RECURRENT PREGNANCY LOSS

The diminished size of the uterine cavity, as well as cervical incompetence, have been suggested as possible etiological factors.[40] The most widely accepted theory is that the septum consists of fibroelastic tissue with inadequate vascularization and altered relations between myometrial and endometrial vessels that exert a negative effect on fetal placentation.[40–43] Fedele et al suggests that the risk of miscarriage is related to the site of septal implantation.[43] Dabirashrafi et al found a significantly lower amount of connective tissue, higher amount of muscle tissue, and more vessels in the uterine septum.[44] Raga et al compared the mRNA expressions of vascular endothelial growth factor (VEGF) receptors in different endometrial locations of septate and normal uteri, and they suggest that a local defect of VEGF transmembranous receptor (KDR and Flt-1) expression in the endometrium covering the septal area may be responsible for recurrent pregnancy loss.[45]

Our previous clinical study results lend support to these suggested mechanisms.[3] The height of the defect/length of the remaining uterine cavity (defect/cavity [D/C]) ratio was calculated in cases of bicornuate and septate uteri and compared between patients having miscarriages and giving live births at the subsequent first pregnancy. We attempted to determine whether the D/C ratio might have a predictive value for further miscarriage in recurrent pregnancy loss cases. The mean values (standard deviation [SD]) of the D/C ratio in the miscarriage and live birth groups were 0.8332 (0.3974) and 0.4776 (0.2745), respectively ($p = 0.0057$; 95% confidence interval [CI], 0.1115 to 0.5998). When two patients with noneuploid miscarriages were excluded, the D/C ratio in the miscarriage group was found to be significantly higher than that in the live birth group ($p = 0.0051$).

From the receiving operating characteristic (ROC) curve, the cutoff value of the ratio was determined to be somewhere between 0.59 and 0.64, yielding the highest sensitivity and specificity at a value around 0.75 to 0.80. The area under the ROC curve, that is, the overall total diagnostic accuracy of the D/C ratio for live birth, was 0.808. From the logistic regression, a high D/C ratio was found to be an independent risk factor for failure of live birth after adjustment for age and number of previous miscarriages. The odds ratio for 0.1 increment of the D/C ratio was 1.42 (95% CI, 1.06 to 1.91).

In 2003, Salim et al found no significant difference in the relative frequency of various anomalies or depth of fundal distortion as determined by 3D ultrasound between women with and without a history of recurrent miscarriages, although abnormalities in uterine anatomy were more severe in women with a history of recurrent miscarriages.[6] In this context, the finding in our previous study that a high D/C ratio may be a predictor of further miscarriage in recurrent cases is clearly of interest.

Surgery

Affected patients are offered surgery in an attempt to restore the uterine anatomy. The first surgery for double uterus was the simple removal of the septum, performed by Ruge and Schroeder in 1882.[8] Strassmann reported vaginal metroplasty for bicornuate uterus.[9] His son, E.O. Strassmann, reviewed 128 cases, including 5 of his own, treated by plastic unification through the abdomen.[25] He described that the indications of unification were "habitual abortion" and "sterility" and that 85.6% of the postoperative pregnancies went through to full term, whereas only 3.7% of the preoperative pregnancies had lasted through to full term. However, he also described that 25 to 40% of women with a double uterus had no disturbances and did not need surgery. The Jones and Jones operation was reported in 1953.[10] They recommended surgery only when adequate investigation reveals no other causes for the recurrent miscarriage.

Table 2 summarizes the live birthrates after surgery in studies including a relative large number of subjects. Makino et al reported that 71 patients underwent modified metroplasties.[2] They found 84.8% (39 of 46) of postoperative pregnancies resulted in live births, whereas none of the 233 presurgical pregnancies were successful. The outcomes of the remaining 25 patients who underwent metroplasty remain unclear.

Candiani et al reported that among 102 cases with recurrent miscarriage and 42 with primary infertility, 68% (45 of 66) of the patients with a septate uterus and 76% (50 of 66) of the patients with a bicornuate uterus who underwent abdominal metroplasty had a successful pregnancy outcome.[11] Ayhan et al reported that among the 89 cases with recurrent miscarriage or preterm delivery, 65% (30 of 46) of the patients with a septate uterus and 83% (45 of 54) of the patients with a

Table 2 Live Birthrate after Metroplasty in Patients with Recurrent Pregnancy Loss Associated with Congenital Uterine Anomalies

	No. of Patients	Type of Anomaly	Method of Surgery	Indication	Live Birthrate Per Pregnancies
Candiani et al, 1990[11]	144	73 septate, 71 bicornuate	Tompkins, Jones, TeLinde, Strassmann	Recurrent miscarriage	Septate 45/66 (68%) Bicornuate 50/66 (76%)
Ayhan et al, 1992[12]	89	49 septate, 40 bicornuate	Tompkins, Jones, Strassmann	Recurrent miscarriage and preterm delivery	Septate 30/46 (65%) Bicornuate 45/54 (83%)
Makino et al, 1992[2]	71	Arcuate, septate	Abdominal	Recurrent miscarriage	39/46 (84.8%)
DeCherney et al, 1986[15]	72	Septate	Resectoscope	Recurrent miscarriage	58/72 (80%)
Daly et al, 1989[16]	55	Septate	Scissors	Recurrent miscarriage and preterm delivery	60/75 (80%)
Hickok, 2000[18] (review)	40	Septate	Resectoscope	Pregnancy loss or complication of pregnancy (28); infertility (10)	17/22 (77.3%)
Kormanyos et al, 2006[20]	94	Septate	Resectoscope	Two or more miscarriages	33/48 (68.8%)

bicornuate uterus had a successful pregnancy outcome.[12] However, the studies had no controls and the patients who did not become pregnant were not mentioned, hence infertility following surgery was not addressed.

Surgery via the transvaginal route for septate uterus was initially proposed by Ruge in 1882.[8] Edstrom performed the first hysteroscopic removal of the septum in 1974.[46] Chervenak and Neuwirth reported the live birthrate after hysteroscopic metroplasty.[13] Hysteroscopic surgery is accepted worldwide because of its advantages over other conventional abdominal procedures.[14–20] The primary advantage is the avoidance of laparotomy. The anesthesia time and recovery time are also shortened, the risk of infection is greatly reduced, the contraceptive duration for the subsequent pregnancy is shortened, and uterine incision is avoided, which means that the patients can be given a trial of vaginal delivery rather than be required to undergo a cesarean delivery.

Goldenberg et al described that the pregnancy wastage in women with recurrent miscarriage who underwent hysteroscopic resection of an intrauterine septum decreased from 87.5% to 44.4% postoperatively and that hysteroscopic resection of an intrauterine septum may benefit patients suffering from recurrent pregnancy wastage.[14] Hickok reported a preoperative pregnancy loss rate of 77.4%, a miscarriage rate of 18.2%, and an uncomplicated delivery rate of 77.3% after hysteroscopic septum resection.[18] Kormányos et al compared the pregnancy outcomes after removal of a septum between cases with and without a residual septum among patients with a history of two or more miscarriages, and they concluded that the live birthrate in cases with no remnant septum was significantly higher than that in the cases with a remnant septum.[20] However, the live birthrate in patients undergoing the first hysteroscopy was 35.1% (33 of 94) and the cumulative live birthrate after one or two removals was 54.3% (51 of 94).

EVIDENCE LEVELS OF STUDIES ON RECURRENT PREGNANCY LOSS ASSOCIATED WITH AN UTERINE ANOMALY

Surgical techniques to enlarge the uterine cavity have advanced. Almost all studies have compared the live birthrate between before and after surgery.[14–20] However, it is inappropriate to simply make comparisons before and after surgery because the prior miscarriage rate is usually 100%, but the subsequent success rate is never 0% in primary recurrent miscarriage. The subsequent live birthrate is expected to be 72% in patients with unexplained recurrent pregnancy loss in the absence of abnormal chromosomes in either partner, and it also decreases with the previous number of losses.[47,48] In the absence of a randomized trial, the subsequent live birthrate should be compared prospectively in patients with recurrent miscarriage associated with a uterine anomaly, treated and not treated with surgery. To date, there have been no prospective studies of this kind.

SUBSEQUENT PREGNANCY OUTCOMES IN PATIENTS WITH RECURRENT PREGNANCY LOSS CAUSED BY CONGENITAL UTERINE ANOMALIES IN THE ABSENCE OF SURGERY

Information concerning the prognosis of patients with congenital uterine anomalies not treated by surgery is limited. We conducted a case-control study of 1676 patients with a history of two or more (2 to 12)

consecutive miscarriages whose subsequent pregnancies were ascertained at least one time in our medical records between 1986 and 2007 at Nagoya City University Hospital.[3] HSG, chromosome analysis for both partners, determination of antiphospholipid antibodies (aPL), including lupus anticoagulant and $\beta 2$ glycoprotein I dependent anticardiolipin antibodies, and blood tests for hypothyroidism, diabetes mellitus, and hyperprolactinemia were performed in all patients before the subsequent pregnancy.

The pregnancy outcomes of all 1676 patients were examined. Of the total, 94 who had structural chromosomal abnormalities, including 73 translocations, in either partner, were excluded from the analysis; 75 patients exhibited persistent aPL and were treated by combined low-dose aspirin and heparin therapy.

Of the total, 54 (3.2%) had congenital uterine anomalies, including 38 with partial bicornis unicolli, 10 with uterine septum, 5 with unicornis, and 1 with didelphys. None had hypoplasia/agenesis or diethylstilbestrol (DES) drug-related anomalies. Two patients, one with a uterine septum and one with a bicornuate uterus, also had translocations in either partner.

We compared the pregnancy outcomes between the 42 patients with septate or bicornuate uteri not undergoing surgery and the 1528 patients without uterine anomalies or abnormal chromosomal karyotype in either partner. We found no differences in the baseline characteristics between the two groups.

Table 3 summarizes the subsequent pregnancy outcomes; 25 of the 42 patients with a septate or bicornuate uterus (59.5%) not treated with any kind of surgery had a successful outcome, compared with 1096 of the 1528 patients (71.7%) without a congenital uterine anomaly ($p = 0.084$). One patient underwent surgery after a further miscarriage. Thus, 32 of the 41 (78.0%) patients and 1307 of the 1528 (85.5%) patients with and without uterine anomalies could cumulatively have a live baby within the follow-up period, not significant. Live birth rates of patients with congenital uterine anomalies tended to be lower both at the first pregnancy after ascertainment, and cumulatively.

Furthermore, the abnormal chromosomal karyotype rates in the miscarriages in cases with and without uterine anomalies were 15.4% (2 of 13) and 57.5% (134 of 233), respectively, at the first pregnancy after ascertainment of uterine anomalies. The difference was highly significant ($p = 0.006$).

One of five patients with a unicornuate uterus succeeded in having an infant at the first pregnancy after evaluation, and four of five had an infant cumulatively. The patient with didelphys also succeeded at the first pregnancy after evaluation.

The benefits of surgical correction (open and hysteroscopic) on the pregnancy outcomes have yet to

Table 3 Successful Reproductive Outcomes after Diagnosis of Uterine Anomalies in Patients with Recurrent Pregnancy Loss

	Live Birthrates (% of Pregnancies)						Cumulative Live Birthrates (% of Couples)			
	With Anomalies ($n = 42$)	Bicornuate	Septum	Without Anomalies ($n = 1528$)	Difference in %	p Value	With Anomalies ($n = 41$)*	Without Anomalies ($n = 1528$)	Difference in %	p Value
Pregnancy after uterine anomaly was ascertained										
1st	25/42 (59.5%)[†]	21/37 (56.8%)	4/5 (80.0%)	1096/1526 (71.7%)	−12.2	0.084	25 (61.0%)	1096 (71.7%)	−10.7	0.133
2nd	5/9 (55.6%)	4/8 (50.0%)	2/2 (100%)	166/275 (60.4%)[‡]	−4.8	0.772	30 (73.2%)	1262 (82.6%)	−9.4	0.119
3rd	2/2 (100%)	2/2 (100%)	–	38/69 (55.0%)	+45.0	0.207	32 (78.0%)	1300 (85.1%)	−7.1	0.215
4th				4/18 (22.2%)				1304 (85.3%)		
5th				3/9 (33.3%)				1307 (85.5%)		
6th				0/6 (0%)				1307 (85.5%)		
Final follow up	–			–			32 (78.0%)	1307 (85.5%)	−7.5%	

Adapted from Sugiura-Ogasawara et al, 2010.[3]
*One patient underwent surgery between the first and second pregnancy after the confirmation of an anomaly; thus this case was excluded from the cumulative analysis.
[†]Comparison was performed between patients with uterine anomalies and normal uteri.
[‡]Patients who had a successful first pregnancy were excluded from the analysis of the second and subsequent pregnancies.

be assessed in a randomized trial. However, the D/C ratio might be useful for an appropriate selection of patients. Comparison of cases of anomalies treated and not treated by surgery is urgently needed in women with a history of recurrent pregnancy loss.

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Management of Recurrent Pregnancy Loss Associated with a Parental Carrier of a Reciprocal Translocation: A Systematic Review

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ABSTRACT

This study reviews systematically the effectiveness of management strategies for carriers of a reciprocal translocation involving two chromosomes, ascertained on the basis of recurrent pregnancy loss. Subsequent pregnancy outcomes were tabulated based on whether management was medical or involved in vitro fertilization/preimplantation genetic diagnosis (IVF/PGD). A total of 129 cases from 13 articles met the criteria, of which 89% were managed medically. Before management, the overall live birthrate was 4% (19 of 484 pregnancies). Management was medical in 109 cases and IVF/PGD in 20 cases. Cumulative live birthrate was 74% (81 of 109 cases) in the medical management group and 35% (7 of 20) in the IVF/PGD group. Based on this systematic review, successful pregnancy outcomes are high following either medical management or IVF/PGD for carriers of a reciprocal translocation, ascertained on the basis of recurrent pregnancy loss. But it is difficult to compare outcomes directly for these two strategies because of the different end points reported. Understanding the differences is essential for effective counseling. Until a well-designed study comparing the two strategies is performed, or at least prospective cohort studies with strict entry criteria and definitions, the cumulative experience and success of both medical management and IVF/PGD must be used to counsel patients who are carriers of a reciprocal translocation, ascertained on the basis of recurrent pregnancy loss.

KEYWORDS: Reciprocal translocation, recurrent pregnancy loss, recurrent miscarriage, in vitro fertilization, preimplantation genetic diagnosis

Recurrent pregnancy loss (RPL), defined as two or more miscarriages <20 weeks of gestation, affect ~5% of couples trying to establish a family.[1] It is a devastating reproductive problem with, unfortunately, few evidence-based treatment options.

Evaluation of recurrent pregnancy loss should be individualized, based on the pattern of presentation, the gestational ages at time of miscarriage, and cytogenetic results of miscarriages.[2] The prevalence of parental carriers of a structural chromosome rearrangement,

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most often a reciprocal or Robertsonian translocation, accounts for 2.5 to 7.8% of couples with RPL.[2–6] How often miscarriages in carriers of a structural chromosome rearrangement are due to errors in meiosis involving affected chromosomes, resulting in unbalanced rearrangements, is unfortunately not well documented because miscarriages are not routinely sent for chromosome testing. Stephenson and Sierra reported that 36% of miscarriages are unbalanced, based on a cohort of 51 carriers of a structural chromosome rearrangement, ascertained on the basis of recurrent pregnancy loss.[7]

Management of parental carriers of a reciprocal translocation, ascertained on the basis of RPL, remains controversial. Thus the objective of this systematic review was to compare subsequent pregnancy outcomes in carriers of a reciprocal translocation, ascertained on the basis of RPL, who were managed medically or with in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and preimplantation genetic diagnosis (PGD). The results of this systematic review may be useful for counseling such patients because it summarizes the cumulative experience and success of both medical management and IVF/PGD. With this information, carriers of a reciprocal translocation, ascertained on the basis of recurrent pregnancy loss, can make an informed decision on the management of subsequent pregnancies.

MATERIAL AND METHODS

A literature search was performed using PubMed, restricted to English-language articles published from January 1990 to December 2010, using the terms "*recurrent* or *repeated miscarriage* or *pregnancy loss* or *spontaneous abortion* or *embryonic demise* or *fetal demise*, or *habitual abortion*, combined with *reciprocal translocation, translocation,* or *structural chromosome rearrangement or abnormality*" An additional search was done combining all of these combinations with *preimplantation genetic diagnosis*. All original research articles were reviewed; abstracts were excluded. Further articles were obtained from references. Individual cases that met criteria were extracted.

Inclusion criteria were (1) history of recurrent pregnancy loss, defined as two or more miscarriages <20 weeks of gestation, (2) one of the partners was a carrier of a reciprocal translocation involving two chromosomes and either partner had no other structural chromosome rearrangement, and (3) obstetric history, subsequent management, and outcomes were described. In the medical management group, only cases with at least one subsequent outcome were included. In the IVF/PGD group, all cases with at least one cycle outcome were included.

The following articles were excluded because carriers of a reciprocal or a Robersonian translocation could not be differentiated: Goddijn et al, 2004; Carp et al, 2004; Franssen et al, 2006; and Fischer et al, 2010.[3,8–10] The articles by Verlinsky et al, 2005; Otani et al, 2006; and Ozawa et al, 2008, were excluded because they did not provide individual obstetric histories.[11–13] Escudero et al, 2008, and Lim et al, 2008, were excluded because the couples, in addition to carrier of a reciprocal translocation, had other structural chromosome rearrangements, including Robertsonian translocations and inversions.[14,15]

Cases were grouped according to the type of subsequent management, either "medical" or IVF/PGD. "Medical management" consisted of evaluation and management of concomitant factors, followed by "close monitoring," as defined by the individual study.

Pregnancy was defined according to the study and generally differed between the two management groups. With medical management, pregnancy was defined by a positive human chorionic gonadotropin (hCG). With IVF/PGD, pregnancy was usually defined by the presence of a gestational sac on ultrasound.

The primary outcome was defined as an ongoing pregnancy of at least 20 weeks gestation, which was assumed to be a live birth. The secondary outcome was defined as chromosome results of either miscarriages or ongoing pregnancies.

RESULTS

Approximately 358 articles were identified using the terms previously described. Of these, 13 articles had at least one case that met the criteria.[4,5,7,15–25] A total of 129 parental carriers of a reciprocal translocation, ascertained on the basis of recurrent pregnancy loss, were found. Table 1 reports the obstetric histories of 109 cases with subsequent medical management. Table 2 reports the obstetric histories of 20 cases with subsequent IVF/PGD management.

The sex of the reciprocal translocation carrier was reported in all cases; 61% ($n = 79$) were female, and 39% ($n = 50$) were male. Of the female carriers, 65 were from the medical management group and 14 from the IVF/PGD group. The specific chromosomes involved in the reciprocal translocations were reported in 76 of the 79 female carriers. In the female carriers, chromosome 2 was the most frequent chromosome involved in the reciprocal translocations ($n = 16$), followed by chromosome 6 ($n = 14$); chromosome 1 ($n = 12$); chromosome 7 ($n = 11$); chromosome 4 ($n = 10$); chromosome 10 ($n = 9$); chromosomes 1, 8, and 14 ($n = 8$, each); chromosome 18 ($n = 7$); chromosomes 5, 12, and 15 ($n = 6$, each); chromosomes 3, 9, 15, and 17 ($n = 5$, each); chromosome 22 ($n = 3$); chromosomes 13, 20, and 21 ($n = 2$, each); and chromosomes 16 and 19 ($n = 1$, each).

In the male carriers, 44 were from the medical management group and 6 from the IVF/PGD group. The specific chromosomes involved in the reciprocal

Table 1 Carriers of a Reciprocal Translocation with a History of Recurrent Pregnancy Loss, with Subsequent Medical Management ($n = 109$)

Carrier Status	Prior Pregnancies	Subsequent Pregnancies
Sugiura-Ogasawara et al, 2004[5]		
46, XX, t(2p;6p)	SA, SA, SA, SA	Term (balanced 46, XX, t(2p;6p)mat)
46, XX, t(6;10)(q23;p13)	SA, SA	SA (unbalanced 46, XX, der(10)t(6;10)(q23;p13)mat)
46, XX, t(3;5)(q23;q33.3)	SA, SA, SA	SA (unbalanced 47, XX, +der(3)t(3;5)(q23;q33.3)mat, der(5)t(3;5)(q23;q33.3)mat), SA, Term (46, XX)
46, XX, t(4;14)(q21.2;p11.2)	SA, SA, SA	Term (46, XY), **Success (46, XX)**
46, XX, t(5;9)(q31.1;q34.3)	SA, SA	SA (47, XX, +22), **IUFD at 38 wk (46, XY), SA,SA (unbalanced 46, XY, 8q+), SA (unbalanced 46, XY, +9(q32)), Term (balanced 46, XX, t(5;9)(q31.1;q34.3)mat)**
46, XX, t(6;8)(q25.1;q11.2)	SA, SA, SA	Term (46, XY), **Term (46, XX)**
46, XX, t(8;11)(q21;q13)	SA, SA	Term (balanced 46, XY, t(8;11)(q21;q13)mat), **Term (46, XX)**
46, XX, t(2;7)(p21;15)	SA, SA	SA
46, XX, t(4;6)(q31.1;q15)	SA, SA	SA (unbalanced 46, XX, der(6)t(4 ;6)(q31.1;q15)mat), SA, Term (balanced 46, XX, t(4;6)(q31.1;q15)mat)
46,XX, t(17;18)(p11.5;p11.2)	SA, SA, SA, SA, SA, SA	SA (unbalanced 46, XX, der(18)t(17;18)(p11.5;p11.2)mat), SA, SA, SA (unbalanced 46, XX, der(18)t(17 ;18)(p11.5 ;p11.2)mat), SA, SA, SA, **Preterm, SA**
46, XX, t(11;13)	SA, SA, SA	SA
46, XX, t(2;15)(p23;q15)	SA, SA, SA	SA (46, XX), SA (balanced 46, XX, t(2;15)(p23;q15)mat)
46, XX, t(3;7)(q27;p22)	SA, SA	SA, Term, **Success**
46, XX, t(2q-;8q+)	SA, SA, SA, SA	SA (48, XY, +16, +21), SA, SA, SA, Term (46, XX)
46, XX, t(8;20)(p21;p11.2)	SA, SA, SA, SA	SA, SA, SA (46, XX), SA, SA (46, XX), SA (46, XX), **Preterm** (balanced 46, XY, t(8;20)(p21;p11.2)mat), Term (balanced 46, XX, t(8;20)(p21;p11.2)mat), **Success**
46, XX, t(6;7)(q25.1;q21.2)	SA, SA, SA	SA
46, XX, t(1;6)(q44;q21)	SA, SA, SA, SA	SA (unbalanced 46, XX, der(1)t(1;6)(q44;q21)mat), Term (balanced 46, XY, t(1;6)(q44;q21)mat), **Term**
46, XX, t(4;11)(q35;q13.3)	SA, SA, SA	SA (unbalanced 46, XY, -4, +der(4)), SA, Term
46, XX, t(1;4)(q42.3;p12)	SA, SA, SA, SA	Term
46, XX, t(2;11)(q37;q13.1)	SA, SA	Term
46, XX, t(10;13)(q24.3;q21.2)	SA, SA	SA, SA (unbalanced 46, XX, der(10)t(10;13)(q24.3;q21.2)mat), SA (46, XX), Term (46, XX)
46, XX, t(11;22)(q23.3;q11.2)	SA, SA	SA (unbalanced 48, XX, +16, +der(22)t(11;22)(q23.3;q11.2)mat,), Term (balanced 46, XY, t(11;22)(q23.3;q11.2)mat)
46, XX, t(2;5)(q35;q35.3)	SA, SA	SA
46, XX, t(3;15)(q13.2;q21.2)	SA, SA	SA, **Term**
46, XX, t(12;17)(q24.1;p12)	SA, SA, SA	Term (46, XX)
46, XX, t(11;15)(p10;q10)	SA, SA, SA, SA, SA	SA, SA
46, XY, t(10p;13q)	SA, SA	SA (hydatidiform mole), Term (46, XX)
46, XY, t(lq;3q)	SA, SA	Term (balanced 46, XY, t(lq;3q)pat), Term (balanced 46, XY, t(lq;3q)pat), **Term (balanced 46, XY, t(lq;3q)pat)**
46, XY, t(11;15)(p11;p11)	SA, SA, **SA (balanced 46, XX, t(11;15)(p11;p11)mat)**	SA (unbalanced 46, XY, der(15)t(11;15)(p11;p11)pat)
46, XY, t(10;15)(q26.1;q22.1)	SA, SA, SA	SA (unbalanced 46, XX, der(10)t(10 ;15)(q26.1;q22.1)pat), SA (46,XX)
46, XY, t(7;8)(p11;p23)	SA, SA	Success (balanced 46, XY, t(7;8)(p11;p23)pat)
46, XY, t(4q;7q)	SA, SA	SA, SA, **GT (unbalanced 46, XY, der(4)t(4q;7q)pat),** SA, SA
46, XY, t(1;4)(q32.3;q31.3)	SA, SA, SA	SA (unbalanced 46, XY, der(1)t(1;4)(q32.3;q31.3)pat)
46, XY, t(2;7)(q31;q31.3)	SA, SA	SA (46,XY), Term, SA (47, XX, +22)
46, XY, t(8;13)(q22;q21)	SA, SA, SA, SA, SA	SA (47, XX, +trisomy)

Table 1 (*Continued*)

Carrier Status	Prior Pregnancies	Subsequent Pregnancies
46, XY, t(14;17)(q32.3;q21.1)	SA, SA	Term (balanced 46, XY, t(14;17)(q32.3;q21.1)pat)
46, XY, t(7;21)(q21.2;q11.2)	SA, SA, SA	Term (46, XY)
46, XY, t(8;15)(11.2;q25)	SA, SA, SA	SA (unbalanced 46, XY, der(8)t(8;15)(p11.2;q25)pat)
46, XY, t(3;4)(q12;q10)	SA, SA	Term
46, XY, t(3;10)(q23;q24)	SA, SA, SA	SA (unbalanced 46, XY, der(10)t(3;10)(q23;q24)pat), Term
46, XY, t(2;11)(q35;q14)	SA, SA, SA	SA (unbalanced 46, XY, der(11)t(2;11)(q35;q14)pat), SA (balanced 48, XY, t(2;11)(q35;q14)pat, +13, +16), SA (46, XX), **Term**
46, XY, t(6;7)(q16.2;q21.2)	SA, SA	Term
46, XY, t(12;13)(q21.3;q21.2)	SA, SA	Term (balanced 46, XX,inv(9)(p11q13)mat, t(12;13) (q21.3;q21.2)pat)
Jobanputra et al, 2005[17]		
46, XX, t(11;22)(q23;q11.2)	SA, SA, SA, SA, SA, SA, SA, SA, Term (balanced 46, XX, t(11;22)(q23;q11.2) Order not stated	SA (unbalanced 46, XY, +2,der(11)t(11;22)(q23;q11.2)mat, -22[4]/45, XY, der(11)t(11;22)(q23;q11.2)mat, -22[4]), Term (46, XX)
Stephenson and Sierra, 2006[7]		
46,XX, t(7;10)(p21;p13)	Term, ET (46, XY), SA, SA	Term (balanced 46, XY, t(7;10)(p21;p13)mat)
46,XX, t(4;6)(q35.2;q12)	SA, SA, SA	Term, SA (unbalanced 46, XY, der(4)t(4;6)(q35.2;q12) mat), Term
46,XX, t(2;6)(q33;q23)	Term, SA, SA, SA	Term
46,XX, t(2;4)(q36.3;q13.3)	SA, SA, Term, SA, SA	Preterm (balanced 46, XX, t(2;4)(q36.3;q13.3)mat)
46,XX, t(4;9)(q35;q31)	SA, SA (balanced 47, XX, t(4;9)(q35;q31)mat, +16), SA (balanced 46, XX, t(4;9)(q35;q31)mat)	Term (balanced 46, XX, t(4;9)(q35;q31)mat)
46, XX, t(1;6)(q42.1;q24.2)	SA, SA, SA	SA, Term (46, XX), SA (unbalanced 46, XY, der(1)t(1;6)(q42.1;q24.2)mat), Term
46, XX, t(8;12)(q22;q22)	SA, SA, SA, SA	SA, Term, SA (unbalanced 46, XY, -8, +der(12)t(8;12)(q22;q22)mat), SA (balanced 47, XX, t(8;12)(q22;q22)mat, +13)
46, XX, t(7;10)(q31.2;q23.2)	SA, SA, SA	Term (46, XY)
46, XX, t(2;12)(q13;q24.31)	SA, SA, SA, SA	Term
46, XX, t(3;19)(q25.1;q13.3)	ET, SA, SA	SA (unbalanced 47, XX, +der(19)t(13;19)(q22;q13)mat)
46, XY, t(5;12)(p15.1;p12.2)	SA, SA, SA	Term
46, XY, t(6;17)(q21;q24.2)	ET, SA, SA, SA (46, XX), SA	SA (47, XY, +13), SA, Term
46, XY, t(8;10)(p21.3;q24.3)	SA, SA (46, XX), SA	Term (46, XY)
46, XY, t(5;9)(q23.2;q22.3)	Term, SA, SA, SA	Term, Term
46, XY, t(8;18)(q11.2;q21.3)	SA, SA (69, XXY), SA, SA (unbalanced 46, XY, der(18)t(8;18)(q11.2;q21.3)pat)	Term
46, XY, t(7;13)(p13;q21.2)	SA, SA, SA, SA (unbalanced 46, XX, der(7)t(7;13)(p13;q21.2)pat)	SA (unbalanced 46, XX, der(13)t(7;13)(p13;q21.2)pat)
46, XY, t(6;13)(q10;q10)	SA, Term, SA, SA (unbalanced 47, XY, +6, der(6;13)(q10;q10)pat +16), SA (unbalanced 46, XY, +der(6;13)(q10;q10)pat, der(13;14)(q10;q10))	Term (balanced 46, XX, t(6;13)(q10;q10)pat)
46, XY, t(5;14)(q11.2;q32.1)	Term, SA, SA, SA	SA, SA, Term
46, XY, t(5;7)(p13;p15)	Term, Term, SA, SA, SA, SA (46,XY), SA	Term
46, XY, t(1;6)(p36.1;p22.1)	Term, SA, SA, SA (46, XY)	SA (46,XX), Term
Sugiura-Ogasawara et al, 2008[4]		

Table 1 (*Continued*)

Carrier Status	Prior Pregnancies	Subsequent Pregnancies
46, XX, t(1;10)(q21;p11.2)	SA, SA, SA, SA	SA
46, XX, t(1;10)(q42.1;q24.3)	SA, SA	SA
46, XX, t(1;11)(p11;q13)	SA, SA, SA	SA (47, XY, +4)
46,XX, t(1;15)(q32.1;q23)	SA, SA, SA	Term
46, XX, t(2;15)(p23;q15)	SA, SA, SA	Term
46, XX, t(2;15)(q31;q21.2)	SA, SA, SA, SA, SA, SA	Term
46, XX, t(2;18)(q33;p11.3)	SA, SA, SA	SA
46, XX, t(3;5)(p13;q33)	SA, SA, SA	Term
46, XX, t(3;7)(p25;p13)	SA, SA, SA	Term
46, XX, t(4;21)(p15.1;q22.2)	SA, SA	Term
46, XX, t(5;13)(p15.3;q21.2)	SA, SA, SA	Term
46, XX, t(6;7)(q25.1;p21)	SA, SA, SA	SA (46, XY, der(6)t(6;7)(q25.1;p21))
46, XX, t(6;8)[b]	SA, SA, SA, SA, SA, IUFD	SA (46, XX, del(6)(q23))
46, XX, t(6;8)(q23;p23)	SA, SA, SA, SA, SA, SA, IUFD	SA (46, XX, t(6;8)(q23;p23)
46, XX, t(7;11)(p13;q21)	SA, SA	Term
46, XX, t(7;18)(p15.3;p11.32)	SA, SA, SA	SA
46, XX, t(7;18)(q32;q13)	SA, SA, SA, SA	SA
46, XX, t(9;13)(q12;p12)	SA, SA, SA, SA	Term
46, XX, t(10;17)(q26;p12)	SA, SA, SA	SA (46, XX, der(17)t(10;17)(q26;p12)mat)
46, XX, t(10;21)p10;q10)	SA, SA, SA, SA	Term (46, XY, t(10;21)(p10;q10))
46, XX, t(11;22)(q23.3;q11.2)	SA, SA	Term
46, XX, t(11,22)(q23;q11.2)	SA, SA, SA	SA (46, XX [25]/46, XX, del(5)(p14) [5])
46, XX, t(17;20)(p13;q13.1)	SA, SA, SA, Term	SA
46, XX, t[b]	SA, SA	SA (47, XX or XY, +14)
46, XX, t[b]	SA, SA, SA	Term
46, XX, t[b]	SA, SA, SA	Term
46, XY, t(1;10)(p32;q26)	SA, SA, SA, SA	Term
46, XY, t(1;11)(p32.1;p15.1)	SA, SA	Term
46, XY, t(2;7)(p10;q10)	SA, SA, SA	Term
46, XY, t(3;7)(q25.3;q21.2)	SA, SA	Term
46, XY, t(3;7)(q25.3;q21.1)	SA, SA, SA, SA	Term
46, XY, t(3;15)(p22;q26.2)	SA, SA, SA	Term
46, XY, t(4;10)(q34;q21.2)	SA, SA	Term
46, XY, t(5;6)(q33.1;p11.2)	SA, SA, SA	Term
46, XY, t(5;9)[b]	SA, SA, IUFD, IUFD	Term
46, XY, t(5;10)(q22;q22)	SA, SA, SA	Biochemical
46, XY, t(7;8)(q21;q22)	SA, SA	SA (46, XX)
46, XY, t(7;8)(q32;q22)	SA, SA	Biochemical
46, XY, t(7;17)(q11.23;q23.3)	SA, SA, SA, SA, SA	Term
46, XY, t(8;12)(p21.3; q12)	SA, SA, SA, SA, Term	Term
46, XY, t(10;13)(q24;q34)	SA, SA, SA, Term	Term
46, XY, t(11;22)(q23.3;q11.2)	SA, SA, SA, Term	Term
46, XY, t[b]	SA, SA	SA (46, XX)
Pal et al, 2009[22]		
46, XX, t(9;14)(q34;31)	SA, SA, SA	SA, SA, SA, hydatidiform mole
46, XX, t(5;11)(q35;q13–25)	SA, SA, SA	Term

SA, spontaneous abortion or miscarriage; ET, ectopic; IUFD, intrauterine fetal demise; GT, genetic termination.
[b]Unknown specific translocation.
In the Sugiura-Ogasawara et al study,[4,5] only the number of prior miscarriages were included, not prior ongoing pregnancies. Additional subsequent outcomes or new information about pregnancies are in boldface type.

Table 2 Comparison of Prior and Subsequent Pregnancy Outcomes in Carriers of a Reciprocal Translocation Ascertained on the Basis of Recurrent Pregnancy Loss: Medically Managed

	No. of Carriers	Prior Pregnancies		Subsequent Pregnancies	
		Unsuccessful	Successful	Unsuccessful	Successful
Sugiura-Ogasawara et al, 2004[5]	43	124 miscarriages	Not stated	65 miscarriages, 1 fetal demise	29
Jobanputra et al, 2005[17]	1	8 miscarriages	1	1 miscarriage	1
Stephenson and Sierra, 2006[7]	20	67 miscarriages, 3 ectopics	9	13 miscarriages	21
Sugiura-Ogasawara et al, 2008[4]	43	169 miscarriages, 4 fetal demises	7	17 miscarriages	29
Pal et al, 2009[22]	2	6 miscarriages	0	3 miscarriages, 1 molar pregnancy	1
Totals	**109**	**94%** 374 miscarriages, 4 fetal demises, 3 ectopics	**6%** 17 successful pregnancies	**55%** 99 miscarriages, 1 fetal demise, 1 molar pregnancy	**45%** 81 successful pregnancies

translocations were reported in 48 of the 50 male carriers. Of the male carriers, chromosome 7 was the most frequent chromosome involved in the reciprocal translocations ($n = 14$), followed by chromosome 10 ($n = 10$); chromosomes 5 and 8 ($n = 8$); chromosomes 3, 6, and 13 ($n = 7$, each); chromosome 11 ($n = 5$); chromosomes 1, 2, 4, 12, and 15 ($n = 4$, each); chromosomes 9 and 14 ($n = 2$, each), and chromosomes 16, 18, 21, and 22 ($n = 1$, each).

Description of Medical Management Cases (Table 1)

Between 1986 and 2002, Sugiura-Ogasawara et al[5] evaluated 47 carriers of a balanced reciprocal translocation with a history of two or more consecutive first trimester miscarriages. Evaluation was performed for concomitant endocrine, uterine, autoimmune, infectious, and natural killer cell factors. Close monitoring included hospitalization for ~1 month, starting at 4 weeks of gestation, with ultrasonography twice weekly. The mean age at time of subsequent pregnancies was 30.7 years (standard deviation [SD]: 3.4). At least one subsequent pregnancy was reported in 43 of the 47 cases.

In 2005, Jobanputra et al[17] reported on a 34-year-old female carrier of a balanced reciprocal translocation with a history of recurrent pregnancy loss and a strong family history of breast cancer.

Between 1992 and 2005, Stephenson and Sierra[7] evaluated 28 carriers of a balanced reciprocal translocation and a history of recurrent pregnancy loss. The mean age at time of prior and subsequent miscarriages was 29.8 years (SD: 5.0) and 34.0 (SD: 4.3), respectively. Couples were screened for concomitant endocrine, uterine, autoimmune, and infectious factors. If one or more of the miscarriages was a fetal miscarriage (10 to 20 weeks of gestation), an inherited thrombophilia screen was also performed. Concomitant factors were identified in 12 cases; 8 women met criteria for the antiphospholipid syndrome and were treated with aspirin and heparin, two women had a luteal phase deficiency and were treated with progesterone suppositories or clomiphene citrate, and one woman had factor V Leiden and was treated with heparin. One woman had Crohn's disease and gestational diabetes and was treated with prednisone and insulin. Three women were treated empirically with aspirin and/or vaginal progesterone suppositories. Close monitoring consisted of serial βhCGs, starting within 1 week of a missed menses, endovaginal ultrasound at least at 6 and 10 weeks of gestation, and 24-hour physician coverage. At least one subsequent pregnancy was reported in 20 of the 28 cases.

Between 2003 and 2005, Sugiura-Ogasawara et al[4] evaluated 70 carriers of a balanced reciprocal translocation and a history of two or more consecutive miscarriages, of which 68 were treated medically. Evaluation was performed for concomitant autoimmune, endocrine, and uterine factors. With at least one positive antiphospholipid antibody, consisting of either the lupus anticoagulant, anticardiolipin, or β2-glycoprotein-I-dependent anticardiolipin antibodies, the patient was treated with low-dose aspirin and heparin. Supportive psychotherapy was provided. At least one subsequent pregnancy was reported in 43 of the 68 cases. The mean age at time of subsequent pregnancy was 31.4 years (SD: 4.4).

In 2005–2006, Pal et al[22] identified two carriers of a balanced reciprocal translocation with a history of three prior miscarriages, both of whom were referred to genetics for karyotyping. The mean age of the carrier at diagnosis was 27.0 years (SD: 2.8). Subsequent pregnancy outcomes were obtained by the medical record and phone interviews 12 to 24 months following

karyotyping. Evaluation and treatment of concomitant factors were not reported in the manuscript.

Summary of Medical Management (Table 2)

A total of 109 cases from five publications met the criteria for the medical management group, which consisted of evaluation and management of concomitant factors associated with recurrent pregnancy loss, followed by close monitoring of subsequent pregnancies. There were at least 397 prior pregnancies in the medical management group, of which 374 were miscarriages <10 weeks, which equates to a mean of 3.4 prior miscarriages (range: 2 to 8). In addition, there were 17 live births, 3 ectopics, and 4 fetal deaths.

Using the first subsequent pregnancy only, the subsequent live birthrate was 60% (65 of 109). If the carrier was female, the subsequent live birthrate was 52% (34 of 65), and if the carrier was male, 75% (33 of 44). Using all subsequent outcomes, the cumulative live birthrate was 74% (81 of 109 cases) in the medical management group.

Description of In Vitro Fertilization/ Preimplantation Genetic Diagnosis Management (Table 3)

In 1998, Munné et al[19] published three cases that met the criteria, with a mean maternal age of 33.7 ± 4.9 years. Methodology was limited to the description of the PGD. Polar body analysis following fluorescent in situ hybridization (FISH) with whole-chromosome painting DNA probes was performed. In addition, a telomeric probe was used in one of the cases. In the first case, three of eight polar bodies were balanced, of which two embryos were transferred; twins were delivered. In the second case, three of five polar bodies were normal, of which one embryo was transferred; pregnancy was ongoing at publication. In the third case, two of five polar bodies were either normal or balanced, but the transfer was cancelled because the embryos were developmentally abnormal.

Later in 1998, Munné et al[21] published one case that met the criteria, consisting of a woman 37 years of age. Six first polar bodies were analyzed following FISH with chromosome-painting probes. Three of the polar bodies were unbalanced, two were balanced, and one did not have a result because the polar body degenerated. Two embryos were transferred; pregnancy ended in miscarriage with a balanced translocation.

In 1999, Willadsen et al[25] published two cases that met the criteria, with a mean maternal age of 34 ± 4.2 years. Polar body analysis was performed on five oocytes following FISH and chromosome-painting probes. One embryo, with unclear FISH signals on first polar body analysis, was biopsied on day 3, fused with a frozen-thawed bovine M-II oocyte, which was followed by FISH using whole chromosome-painting probes. Repeat analysis of the metaphase-transformed blastomere nucleus was performed using spectral karyotyping (SKY), after transfer. The embryo was transferred on day 4; a preterm delivery resulted with normal female chromosomes. The newborn had a ventricular septal defect and underwent surgery without complication.

In the second case, first polar body analysis was informative for 7 of 11 oocytes; all were unbalanced or when balanced or normal, the oocytes did not fertilize. Three of the four oocytes with uninformative results fertilized and one or two blastomeres were biopsied and fused with bovine oocytes; analysis revealed the blastomeres were anuclear or unbalanced. Thus there were no embryos for transfer.

Munné et al[20] published three cases that met the criteria in 2000, with an average maternal age of 32.3 ± 2.5 years. Polar body analysis followed FISH with centromeric and telomeric probes for the chromosomes involved in the translocations. One to three embryos were transferred; pregnancy did not occur.

In 2000, Escudero et al[16] published two cases that met the criteria, with an average maternal age of 30 ± 4.2 years. Polar body biopsy, followed by FISH, using a combination of whole-chromosome painting and telomeric probes, was performed. Twelve polar bodies were obtained in the first case, of which nine were analyzed. One was balanced and the subsequent embryo was transferred; the pregnancy resulted in monozygotic (46, XY) twins. In the second case, eight polar bodies were obtained and analyzed. One was balanced and the subsequent embryo was transferred; pregnancy did not occur.

In 2000, Coonen et al[15] published two cases that met the criteria; maternal ages were not provided. In the first case, 18 embryos were biopsied, with one or two blastomeres aspirated on day 3. Following multitarget FISH, using three DNA probes, one embryo with a balanced reciprocal translocation was transferred on day 4. Pregnancy resulted in a successful term delivery with a balanced reciprocal translocation.

With the second case, the woman underwent three IVF cycles. The first cycle was cancelled due to poor ovarian stimulation. The second cycle yielded two embryos with normal and/or a balanced karyotype. Both karyotypically normal embryos were transferred, but pregnancy did not occur. In the third cycle, three embryos were biopsied; two were unbalanced and the results inconclusive in the third; no transfer was performed.

In 2003, Simopoulou et al[23] published four cases that met the criteria; mean maternal age was 33.3 ± 1.9 years. One or two blastomeres were aspirated on day 3, according to the developmental stage and

Table 3 Carriers of a Reciprocal Translocation with a History of Recurrent Pregnancy Loss, with Subsequent IVF/PGD Management ($n = 20$)

Carrier Status	Prior Pregnancies	Treatment	Subsequent Pregnancies
Munné et al, 1998[19]			
46, XX, t(7;20)(q22;q11.2)	SA, SA, SA, SA (balanced t(7;20)(q22,q11.2)mat)	IVF/±ICSI/PGD	Twins (balanced t(7;20)(q22;q11.2)mat)
46, XX, t(9;11)(p24 ;q12)	5 pregnancy losses and a healthy baby from a natural cycle	IVF/±ICSI/PGD	Ongoing pregnancy (normal)
46, XX, t(14;18)(q22;q11)	5 pregnancy losses	IVF/±ICSI/PGD	No transfer
Munne et al, 1998[21]			
46, XX, t(4:14)(p15.3;q24)	Repeated pregnancy loss; one was balanced t(4:14)(p15.3;q24)mat	IVF/±ICSI/PGD	SA (balanced t(4:14)(p15.3;q24)mat)
Willandsen et al, 1999[25]			
46, XX, t(9;11)(p24;q12)	History of habitual abortion	IVF/ICSI/PGD	Preterm (200 g) newborn (46, XX) with a ventricular septal defect, which was repaired at 5 mo
46, XX, t(11;16)(q21;q22)	History of recurrent miscarriage	IVF/ICSI/PGD	No transfer
Munné et al, 2000[20]			
46, XY, t(10;13)(q22.3;q14)	SA, SA, SA, SA, SA	IVF/PGD	Did not conceive
46, XX, t(10;14)(q26.1)(q22.1)	SA, SA	IVF/PGD	No transfer
46, XY, t(10;18)(q24.1;p11.2)	SA, SA, SA, SA, SA, SA, SA, SA, SA (unbalanced), SA (unbalanced), SA (unbalanced), SA (unbalanced), SA (unbalanced), 1 failed IVF cycle	IVF/PGD	Did not conceive
Escudero et al, 2000[16]			
46, XX, t(2;14)(q23;q24)	SA, SA, SA	IVF/±ICSI/PGD	Monozygotic twins (46,XY), with hydronephrosis
46, XX, t(2 ;14)(q31 ;q24)	Livebirth, SA, SA	IVF/±ICSI/PGD	Did not conceive
Coonen et al, 2000[15]			
46, XY, t(3;11)(q27.3;q24.3)	SA, SA, SA, SA, GT (unbalanced, 46, XX, -11, +der(11) t(3;11)(q27.3;24.3)pat), SA, SA, SA	IVF/PGD	Term (balanced 46, XX, t(3;11)(q27.3;q24.3)pat)
46, XX, t(3;11)(q27.3;q24.3)	SA, SA, fetal demise (24 wk, hydropic (46, XX, -11, +der(11) t(3 ;11)(q27.3 ;q24.3), SA, SA, SA, SA	IVF/PGD × 3 cycles	Did not conceive, No transfer done × 2 cycles
Simopoulou et al, 2003[23]			
46, XX, t(16;17)(p13,3;p11,1)	SA, SA, SA, SA	IVF/PGD	Biochemical SA
46, XX, t(8;12)(q11.2;q12)	SA, SA, SA, SA, SA	IVF/PGD	Term
46,XY, t(1;18)(p32;q23)	SA, SA	IVF/PGD	Did not conceive
46, XX, t(1;2)(q42.1;p23)	SA,SA,SA	IVF/PGD	Did not conceive
Sugiura-Ogasawara et al, 2008[4]			
46, XX, t(6;8)(q23;p23)	SA, SA	IVF/PGD	SA
46, XY, t(10;16)(p14;q12.2)	SA, SA	IVF/PGD	Did not transfer (single embryo unbalanced)
Wiland et al, 2008[24]			
46, XY, t(2;7)(p11.2;q22.1)	SA, SA	IVF/PGD	Triplet pregnancy (monochorionic diamniotic twins and a singleton) selective reduction of twins (46, XY, t(2;7)(p11.2;q22.1), term (46, XX)

SA, spontaneous abortion or miscarriage; GT, genetic termination.

embryo morphology. Following FISH, chromosomally balanced embryos were transferred on day 4. For the first case, seven embryos were biopsied, four were balanced, and three were transferred; a biochemical pregnancy loss resulted. For the second case, 13 embryos were biopsied, 2 were balanced, and 1 was transferred; a normal live birth resulted. For the third case, 11 were biopsied, 2 were balanced and both transferred; pregnancy did not occur. For the fourth case, 12 embryos were biopsied, 1 was balanced and frozen due to hyperstimulation during the IVF cycle. The embryo was subsequently transferred in a frozen cycle; pregnancy did not occur.

In 2008, Suguira-Ogasawara et al[4] published two cases that met criteria for the IVF/PGD group; mean maternal age was 35.5 ± 7.8 years. IVF/PGD details are not provided. The first case was noted to be a PGD failure. The second case did not result in an embryo transfer because the single embryo was unbalanced.

In 2008, Wiland et al[24] published one case that met criteria; maternal age was 29 years. Following a standard FISH protocol, a rehybridization occurred screening for the common aneuploidies of chromosomes 21, X, and Y. Nine embryos were biopsied and three were balanced, of which two were transferred. A triplet pregnancy resulted, with monozygotic twins and a singleton pregnancy. CVS was performed and then twins who were males were balanced chromosome carriers. Selective reduction to singleton was performed, and a live birth resulted.

Summary of In Vitro Fertilization/ Preimplantation Genetic Diagnosis Management (Table 4)

Twenty cases from nine publications met the criteria for the IVF/PGD group. There were an estimated 86 prior pregnancies, of which 82 were miscarriages <10 weeks, which equates to a mean of 4.1 miscarriages per carrier (range: 2–15). In addition there were two live births, one fetal demise, and one genetic termination.

Using the first subsequent pregnancy only, the subsequent live birth was 35% (7 of 20) per carrier and 32% (7 of 22) per IVF cycle starts. If the carrier was female, the subsequent live birthrate was 33% (5 of 15), and if the carrier was male, 33% (2 of 6). The cumulative live birthrate was the same as the first subsequent pregnancy rate. Of note, the cumulative live birthrate per transfer rate was 41% (7 of 17).

Cytogenetic Analyses of Prior and Subsequent Miscarriages

Only 21 miscarriages were karyotyped before medical or IVF/PGD management. In the medical management group, 33% (4 of 12) were unbalanced. In the IVF/PGD group, 78% (7 of 9) were unbalanced.

Fifty subsequent miscarriages were karyotyped. In the medical management group, 55% (27 of 49) were unbalanced, 29% (14 of 49) were 46,XX, 46,XY or balanced, and 16% (8 of 49) were trisomic, monosomic, or polyploid. There was only one subsequent miscarriage karyotyped in the IVF/PGD group; it was balanced.

DISCUSSION

RPL is a devastating problem affecting ~5% of couples trying to conceive. Pathogenesis of RPL is believed to be multifactorial including genetic, anatomical, autoimmune factors, alloimmune, infection, endocrine disturbances, and idiopathic.[6,26,27] Genetic factors include numeric chromosome errors in miscarriages, which are usually random events that increase in frequency with advancing maternal age.[28] Parental carriers of a structural chromosome rearrangement account for 2.5 to 7.8% of couples with RPL.[2–6,27,29] Reciprocal translocations is estimated to represent 60% of the structural chromosome rearrangement cases.[30] Yet whether an unbalanced translocation is the cause of a miscarriage is often not known because chromosome testing of miscarriages is not performed routinely.

Published data suggest that carriers of a reciprocal translocation may have poorer pregnancy outcomes than carriers of a Robertsonian translocation.[5,7] Therefore, it is of utmost importance to have evidence-based management strategies for such carriers.

This systematic review of carriers with a reciprocal translocation, ascertained on a history of RPL, suggests that the cumulative live birth is higher with medical management than IVF/PGD. It is difficult, however, to compare pregnancy outcomes directly.[31] With medical management, pregnancy is usually defined by a positive hCG. With IVF/PGD, pregnancy is usually defined by the presence of a gestational sac on ultrasound, which would result in an underestimation of miscarriage rate because biochemical pregnancy losses would not be included. In addition, with IVF/PGD, studies often report pregnancy outcome per embryo transfer, rather than per cycle started. With reporting per cycle started, the time and cost of repeated IVF/PGD cycles, in which embryo transfer did not occur, is not taken into consideration.

Despite the widespread use of IVF/PGD for carriers of a translocation,[32–34] we were only able to identify 20 cases that met inclusion criteria in this systematic review. Individual obstetric histories were inconsistently reported in the IVF/PGD articles. Surrogate end points, such as miscarriage rate, rather than live birthrate, were often reported in the IVF/PGD studies, which again is problematic.[35,36] Simply comparing miscarriages rates, before ascertainment of carrier status (which would be

Table 4 Comparison of Prior and Subsequent Pregnancy Outcomes in Carriers of a Reciprocal Translocation Ascertained on the Basis of Recurrent Pregnancy Loss: In Vitro Fertilization/Preimplantation Genetic Diagnosis

		Prior Pregnancies		IVF/PGD Outcomes			
	No. of Carriers	Unsuccessful	Successful	No. of Cycles	Did Not Conceive	Unsuccessful Pregnancies	Successful Pregnancies
Munné et al, 1998[19]	3	14 miscarriages	1	3	1	0	2 (twins; ongoing pregnancy)
Munné et al, 1998[21]	1	2 miscarriages*	0	1	0	1 miscarriage	0
Willadsen et al, 1999[25]	2	6 miscarriages†	0	2	1	0	1 (preterm)
Munné et al, 2000[20]	3	22 miscarriages	0	3	3	0	0
Escudero et al, 2000[16]	2	5 miscarriages	1	2	1	0	1 (monozygotic twins, hydronephrosis)
Coonen et al, 2000[15]	2	13 miscarriages, 1 fetal demise, 1 genetic termination	0	4	3	0	1 (term)
Simopoulou et al, 2003[23]	4	14 miscarriages	0	4	2	1 miscarriage (biochemical)	1 (term)
Sugiura-Ogasawara et al, 2008[4]	2	4 miscarriages	0	2	1	1 miscarriage	0
Wiland et al, 2008[24]	1	2 miscarriages	0	1	0	0	1 (triplet reduction, singleton term)
Totals	**20 carriers**	**98% total prior pregnancies** (82 miscarriages, 1 fetal demise, 1 genetic termination)	**4% total prior pregnancies** (2 successful pregnancies)	**22 cycles**	**12 did not conceive**	**3 miscarriages**	**7 successful pregnancies**

*Estimated, based on "repeated pregnancy loss."
†Estimated, based on "habitual abortion" and "recurrent miscarriage."
IVF/PGD, in vitro fertilization/preimplantation genetic diagnosis.