Cureus
Part of SPRINGER NATURE

Open Access Case Report

Extremely Low Blastocyst Formation Followed by Live Birth in a Female Carrier of a Balanced Reciprocal Translocation t(4;12)(q33;q15): A Case Report

Review began 11/03/2026
Review ended 11/12/2026
Published 11/18/2026

© **Copyright** 2026
Inukai et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.119868

Kana Inukai [1], Hiromasa Kuroda [1], Risa Usui [2], Naoko Murakami [1], Atsushi Haruki [1]

1. Obstetrics and Gynecology, Haruki Ladies Clinic, Osaka, JPN 2. Genetic Counseling, Haruki Ladies Clinic, Osaka, JPN

Corresponding author: Hiromasa Kuroda, monjirota@gmail.com

Abstract

Balanced reciprocal translocations (BRTs) may contribute to miscarriage and impaired embryonic development through the formation of unbalanced gametes during meiosis; however, their association with blastocyst formation failure remains insufficiently understood. The patient had undergone multiple oocyte retrievals at another clinic but had experienced difficulty obtaining blastocysts. Despite repeated cleavage-stage embryo transfers, she did not achieve a live birth and was referred to our clinic at 32 years of age. During the second oocyte retrieval cycle after referral, one blastocyst was cryopreserved. A frozen-thawed single-blastocyst transfer was performed in a hormone replacement cycle, resulting in pregnancy; however, a missed miscarriage occurred at eight weeks of gestation. Because this was her second miscarriage, including the miscarriage at the previous clinic, an etiologic evaluation for recurrent pregnancy loss was undertaken. Cytogenetic analysis of the products of conception suggested a parental reciprocal translocation, and chromosomal analysis of the couple revealed that the woman was a carrier of a BRT (46,XX,t(4;12)(q33;q15)). Following genetic counseling, the patient declined preimplantation genetic testing for structural rearrangements (PGT-SR) and elected to continue oocyte retrieval without PGT-SR. Blastocyst acquisition remained difficult. Across six oocyte retrieval cycles at our clinic, we retrieved 130 oocytes, of which 86 were mature (66.2%), and 57 were normally fertilized (66.3%); however, only three blastocysts were cryopreserved, corresponding to an extremely low cryopreservation-quality blastocyst rate of 5.3%. One blastocyst obtained during the sixth retrieval cycle was transferred as a frozen-thawed single blastocyst in a hormone replacement cycle, resulting in pregnancy and a live birth at 38 weeks of gestation. This rate was markedly lower than the blastocyst formation rates reported in cohorts of reciprocal translocation carriers undergoing PGT-SR (approximately 40-55%). In addition to early developmental arrest of chromosomally abnormal embryos caused by meiotic segregation errors, the exceptionally low blastocyst formation rate raises the possibility that genes near the 12q15 breakpoint involved in early embryonic development, including CNOT2, MDM2, and YEATS4, may have contributed to the phenotype. Although the precise breakpoint could not be determined by G-banding, and thus direct gene disruption could not be confirmed, this possibility cannot be excluded. Nevertheless, a live birth was ultimately achieved after the third blastocyst transfer. This case indicates that in BRT carriers with extremely poor blastocyst formation, obtaining blastocysts for testing may itself become the principal constraint on PGT-SR.

Categories: Obstetrics/Gynecology, Genetics
Keywords: balanced reciprocal translocation, blastocyst, blastocyst formation failure, genetic counseling, recurrent pregnancy loss

Introduction

Miscarriage occurs in 15-25% of clinically recognized pregnancies [1]. Two consecutive miscarriages are experienced by fewer than 5% of women, whereas approximately 1% experience three or more miscarriages [2]. Recurrent pregnancy loss (RPL) is defined as two or more miscarriages [3]. The principal recognized causes include fetal chromosomal abnormalities, antiphospholipid syndrome, congenital uterine anomalies, structural chromosomal abnormalities in either partner, and endocrine or metabolic disorders such as thyroid disease and diabetes mellitus [1]. Chromosomal abnormalities in either partner, particularly balanced reciprocal and Robertsonian translocations, have been reported in approximately 2-5% of couples with RPL [4]. However, frequencies exceeding 5% have also been reported, depending on the study population, indications for testing, and definition of the number of miscarriages [5].

Carriers of a balanced reciprocal translocation (BRT) are usually phenotypically normal because no genetic material is lost or gained; however, their gametes may be unbalanced. In BRT carriers, the derivative chromosomes and their normal homologs form a quadrivalent during meiosis and may undergo several modes of segregation, including alternate, adjacent, and 3:1 segregation. Alternate segregation produces normal or balanced gametes, whereas adjacent and 3:1 segregation produce unbalanced gametes, thereby increasing the number of chromosomally unbalanced embryos after fertilization [6-8]. Clinically, a parental BRT therefore manifests mainly as miscarriage of chromosomally unbalanced conceptions. This is distinct

from poor blastocyst formation, which reflects arrest of embryonic development before implantation; unbalanced embryos can develop to the blastocyst stage, and a BRT per se is not generally expected to impair blastocyst formation. Whether and how a BRT may nonetheless be associated with failure of blastocyst formation is less well understood.

Reports of the BRT 46,XX,t(4;12)(q33;q15) with identical breakpoints are extremely limited in the field of reproductive medicine. Neither chromosome 4 nor chromosome 12 is acrocentric, and the quadrivalent configuration predicted from the breakpoints is not one in which an increased frequency of 3:1 segregation would be of particular concern. Nevertheless, adjacent segregation may produce a partial trisomy and a partial monosomy involving 4q33-qter and 12q15-qter, potentially resulting in embryonic developmental arrest, implantation failure, or miscarriage [7]. Here, we report a case involving a female carrier of the BRT 46,XX,t(4;12)(q33;q15), who exhibited extremely poor blastocyst formation across multiple oocyte retrieval cycles but ultimately achieved a live birth following repeated assisted reproductive technology (ART) treatment.

Case Presentation

The patient was a 32-year-old woman, gravida 1, para 0. Her menstrual cycles were regular, occurring every 25-30 days. Beginning at 26 years of age, she underwent six cycles of timed intercourse and six cycles of intrauterine insemination at a previous clinic without achieving pregnancy, after which treatment was advanced to assisted reproductive technology (ART). Although four oocyte retrievals were performed, no blastocysts were obtained. She subsequently underwent six frozen-thawed cleavage-stage embryo transfers and conceived once, but miscarried at nine weeks of gestation. Her medical history included subclinical hypothyroidism, for which she was taking levothyroxine sodium. She had no history of smoking and no notable family history. Her husband was 43 years old at the time of her first visit; his semen analysis showed a volume of 2.0 mL, a sperm concentration of 88×10^6/mL, and a motility of 43.2%, all within the World Health Organization reference limits.

At her first visit to our clinic, her serum anti-Müllerian hormone level was 9.81 ng/mL, the antral follicle count was 12 (six in each ovary), and thyroid function was within the reference range on levothyroxine (Table *1*). The first oocyte retrieval cycle was conducted using an antagonist protocol. Beginning on menstrual cycle day four, follitropin delta was administered at 6.0 μg/day, together with letrozole at 5 mg/day for five days. Ganirelix acetate was added for two days beginning on cycle day 11. Buserelin acetate was administered intranasally on cycle day 13, and oocyte retrieval was performed 36 h later. A total of 22 oocytes were retrieved, of which 17 were mature. Six normally fertilized oocytes were obtained by conventional in vitro fertilization and six by intracytoplasmic sperm injection; however, embryonic development was poor, only one embryo reached the blastocyst stage, and it did not meet the criteria for cryopreservation.

Parameters	Result	Reference range
Serum AMH (first visit), ng/mL	9.81	Age-dependent*
TSH (first visit, on levothyroxine), μIU/mL	0.953	0.61-4.23
Free T4 (first visit, on levothyroxine), ng/dL	1.57	0.82-1.63
Antinuclear antibody, titer	1:80	<1:40
Anticardiolipin IgG antibody, U/mL	<4.0	≤12.3
Anticardiolipin IgM antibody, U/mL	<2.5	≤20.8
Anticardiolipin-β2-glycoprotein I complex antibody, EU/mL	1.2	<3.5
Lupus anticoagulant, ratio	1.0	≤1.2

TABLE 1: Laboratory findings at the first visit and in the evaluation for recurrent pregnancy loss.

*No fixed reference range is established for AMH because serum levels vary with age; the value was interpreted relative to the patient's age. Values reported as "<" indicate results below the detection limit of the assay. Reference ranges are those of the clinical laboratory used by our clinic.

AMH: anti-Müllerian hormone; TSH: thyroid-stimulating hormone; T4: thyroxine

During the second oocyte retrieval cycle, progestin-primed ovarian stimulation was performed using follitropin delta at 6.0 μg/day. A total of 14 oocytes were retrieved, yielding 13 mature oocytes and nine normally fertilized embryos. Two embryos reached the blastocyst stage; one of them, derived from

conventional in vitro fertilization (grade 4AC), met the criteria for cryopreservation and was cryopreserved, whereas the other (grade 3CC) did not. A frozen-thawed single-blastocyst transfer was performed in a hormone replacement cycle, resulting in pregnancy; however, a missed miscarriage occurred at eight weeks of gestation, and uterine evacuation was performed. G-banded chromosomal analysis of cultured chorionic villi from the products of conception (20 metaphases analyzed at the 400-band level) revealed 46,XX,der(4)t(4;12?)(q31;q13?), in which the question marks denote provisional band assignments at the resolution of the analysis. The presence of a derivative chromosome 4 without the reciprocal derivative chromosome 12 indicated an unbalanced karyotype and suggested a parental reciprocal translocation.

On the basis of this finding, chromosomal analysis of the couple was performed and identified a BRT in the woman, with breakpoints at chromosome 4q33 and chromosome 12q15 (46,XX,t(4;12)(q33;q15)) (Figure *1*). No karyotypic abnormality was detected in her husband. In light of the maternal karyotype, the derivative chromosome in the products of conception was reinterpreted as der(4)t(4;12)(q33;q15)mat, corresponding to monosomy for 4q33→qter and trisomy for 12q15→qter, the imbalance expected from adjacent-1 segregation (Figure *1*). Because the maternal karyotype is balanced and contains both derivative chromosomes, this unbalanced karyotype could not have arisen from maternal cell contamination and was considered to be of fetal origin. Subsequent screening for recurrent pregnancy loss showed a positive antinuclear antibody titer of 1:80 (upper reference limit: <1:40), a low titer that was not considered clinically significant and did not prompt treatment, whereas no clear abnormalities were found in the other assessments, including antiphospholipid antibodies (Table *1*). Hysterosalpingography suggested mild fimbrial adhesions but showed no hydrosalpinx. Hysteroscopy revealed no abnormal findings in the uterine cavity, and endometrial microbiota testing demonstrated a *Lactobacillus crispatus*-dominated microbiota.

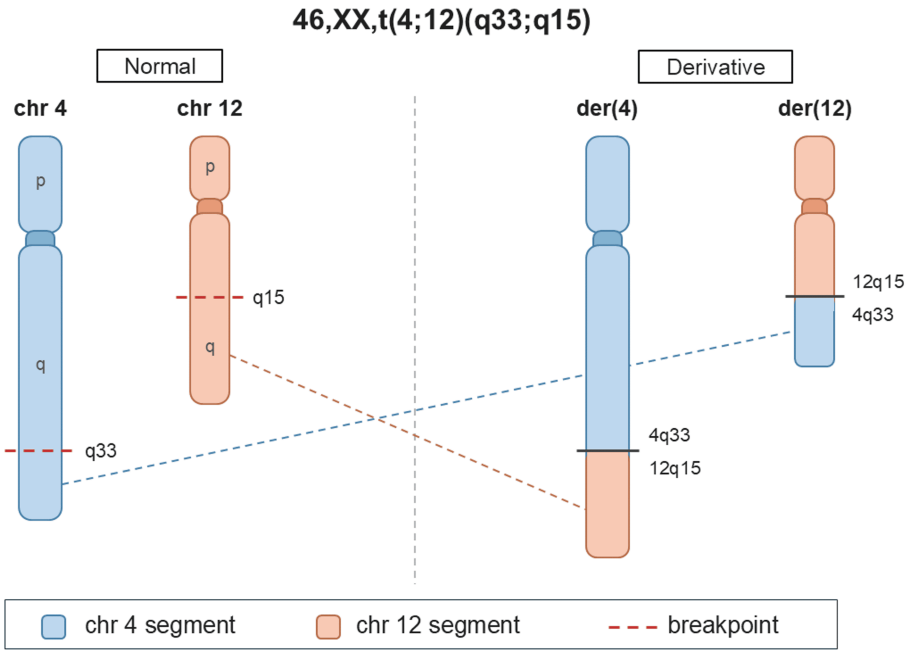


FIGURE 1: Schematic representation of the maternal balanced reciprocal translocation 46,XX,t(4;12)(q33;q15).

Normal chromosomes 4 and 12 are shown on the left, and the derivative chromosomes der(4) and der(12) are shown on the right. Chromosome 4 material is shown in blue and chromosome 12 material in orange. Dashed lines indicate the breakpoints at 4q33 and 12q15 and the direction of the reciprocal exchange. In ISCN notation, the derivative chromosomes are described as der(4)(4pter→4q33::12q15→12qter) and der(12)(12pter→12q15::4q33→4qter). Adjacent-1 segregation transmitting der(4) together with a normal chromosome 12 results in partial trisomy for 12q15→qter and partial monosomy for 4q33→qter; this corresponds to the unbalanced karyotype identified in the products of conception in this case, der(4)t(4;12)(q33;q15)mat.

ISCN: International System for Human Cytogenomic Nomenclature

This image was created by the authors of this study using Microsoft PowerPoint (Redmond, WA: Microsoft Corp.).

During genetic counseling, the couple was informed that preimplantation genetic testing for structural rearrangements (PGT-SR) could avoid the transfer of unbalanced embryos, that PGT-SR could not completely prevent miscarriage, that blastocyst acquisition was a prerequisite for testing, that PGT-SR entailed additional costs, that continuing treatment without PGT-SR was also an option, and that prenatal diagnosis by chorionic villus sampling or amniocentesis would be available in any subsequent pregnancy.

Because of the previous difficulty in obtaining blastocysts and the financial burden of treatment, the patient chose to continue oocyte retrieval without PGT-SR.

In subsequent retrieval cycles, a high proportion of immature oocytes, delayed cleavage after fertilization, and poor blastocyst formation were repeatedly observed. Accordingly, the ovarian stimulation protocol (antagonist or progestin-primed), the allocation of oocytes to conventional in vitro fertilization or intracytoplasmic sperm injection, and the use of calcium ionophore for artificial oocyte activation were adjusted from cycle to cycle, whereas time-lapse culture and hyaluronan-based sperm selection (physiological intracytoplasmic sperm injection {PICSI}) were used in all cycles (Table 2). During the fourth retrieval cycle, one blastocyst (grade 3BC) produced by intracytoplasmic sperm injection was cryopreserved. A frozen-thawed single-blastocyst transfer was performed in a hormone replacement cycle but did not result in pregnancy. Oocyte retrieval was continued, and one blastocyst (grade 5BC) derived from intracytoplasmic sperm injection was cryopreserved during the sixth retrieval cycle. Following frozen-thawed single-blastocyst transfer in a hormone replacement cycle, pregnancy was confirmed at four weeks and four days of gestation, when the serum hCG level was 1,152 mIU/mL. At five weeks and four days, the hCG level had increased to 13,656 mIU/mL, and transvaginal ultrasonography confirmed a single intrauterine gestational sac. Fetal cardiac activity was confirmed at six weeks and four days. The pregnancy subsequently progressed without complication, and the patient was referred to a delivery facility at eight weeks of gestation. The remainder of the pregnancy was uneventful, and an elective cesarean delivery was performed at 38 weeks and four days for breech presentation. The neonate weighed 2,960 g and had no congenital anomalies, and the pregnancy was free of obstetric complications. Neither prenatal nor postnatal chromosomal analysis of the child was performed.

Variables	First cycle	Second cycle	Third cycle	Fourth cycle	Fifth cycle	Sixth cycle
Ovarian stimulation protocol	Antagonist	PPOS	PPOS	Antagonist	Antagonist	PPOS
Calcium ionophore activation	No	Yes	Yes	Yes	Yes	Yes
Retrieved oocytes, n	22	14	20	17	25	32
Mature oocytes, n	17	13	8	9	18	21
Normally fertilized embryos (IVF), n	6	3	1	4	8	7
Normally fertilized embryos (ICSI), n	6	6	4	2	4	6
Blastocysts (all grades), n	1	2	0	1	0	1
Cryopreservation-quality blastocysts, n	0	1	0	1	0	1
Outcome of blastocyst transfer	-	Miscarriage	-	No pregnancy	-	Live birth

TABLE 2: Treatment characteristics and embryological outcomes across six oocyte retrieval cycles.

Data are shown for each oocyte retrieval cycle performed at our clinic. Time-lapse culture and hyaluronan-based sperm selection (PICSI) for ICSI were used in all cycles. Normally fertilized embryos were defined as those showing two pronuclei on the day after insemination; all normally fertilized embryos were cultured to the blastocyst stage, and no embryos were cryopreserved at the cleavage stage. Blastocysts (all grades) include every embryo that reached the blastocyst stage irrespective of morphology. Cryopreservation-quality blastocysts were defined as those with an expansion grade of ≥3 and an inner cell mass or trophectoderm grade of B or better according to the Gardner criteria; blastocysts graded CC were not cryopreserved. Each cryopreserved blastocyst was transferred singly in a subsequent hormone replacement cycle.

IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; PICSI: physiological intracytoplasmic sperm injection; PPOS: progestin-primed ovarian stimulation; -: no blastocyst available for transfer

Across six oocyte retrieval cycles at our clinic, 130 oocytes were retrieved, of which 86 were mature (66.2%) and 57 were normally fertilized (66.3%). All normally fertilized embryos were cultured to the blastocyst stage. Five embryos developed into blastocysts, corresponding to an overall blastocyst formation rate of 8.8% per normally fertilized embryo, and only three of these met our cryopreservation criteria, corresponding to a cryopreservation-quality blastocyst rate of 5.3% (Table 2).

Discussion

This case involved a woman carrying the BRT 46,XX,t(4;12)(q33;q15), who exhibited extreme blastocyst formation failure over multiple oocyte retrieval cycles but ultimately achieved a live birth after blastocyst transfer. Whereas a blastocyst formation rate of approximately 50% per normally fertilized embryo has been reported in female reciprocal translocation carriers undergoing PGT-SR, the overall blastocyst formation

rate in this case was 8.8%, and only 5.3% of normally fertilized embryos reached cryopreservation quality [9]. A distinctive feature of this case was that, in addition to the identification of a reciprocal translocation as a cause of recurrent miscarriage, blastocyst formation remained markedly impaired despite the retrieval of a substantial number of oocytes and the availability of a consistent number of normally fertilized embryos. In light of this case, we discuss the possibility that a maternal BRT may contribute to blastocyst formation failure.

Carriers of BRTs may exhibit several meiotic segregation patterns, resulting in chromosomally unbalanced embryos after fertilization and potentially causing embryonic developmental arrest, implantation failure, or miscarriage [7]. In this case, cytogenetic analysis of the products of conception identified an unbalanced karyotype, der(4)t(4;12)(q33;q15)mat, consistent with adjacent-1 segregation of the maternal translocation; this finding provides a genetic explanation for that miscarriage. By contrast, the cause of the poor blastocyst development observed across retrieval cycles remains unproven. Chromosomally abnormal embryos frequently develop to the blastocyst stage, albeit with a tendency toward delayed development and poorer morphology when large chromosomes are involved, and the embryos in this case were not genetically tested. Chromosomal imbalance resulting from meiotic segregation errors may therefore have contributed to, but cannot be assumed to explain fully, the poor embryonic development observed [10].

The utility of PGT-SR in BRT carriers is well established, and its principal advantage is a reduction in the miscarriage rate by avoiding the transfer of unbalanced embryos [7,8]. Indeed, PGT-SR may reduce the risk of miscarriage after establishment of pregnancy in BRT carriers and may therefore lessen the physical and psychological burden of recurrent miscarriage. However, PGT-SR can be performed only when embryos obtained by oocyte retrieval reach the blastocyst stage, and it constitutes a viable treatment only when embryos deemed suitable for transfer are ultimately obtained [9]. Therefore, in patients with few embryos reaching the blastocyst stage, PGT-SR may yield no embryos available for testing or no transferable embryos after testing, while still incurring its cost. In this case, the benefits, limitations, and costs of PGT-SR were explained during genetic counseling; nevertheless, the patient declined PGT-SR because of the difficulty in obtaining blastocysts and for financial reasons. We speculate that when translocation-associated blastocyst formation failure is suspected, embryos that do reach the blastocyst stage might be less likely to carry an unbalanced translocation; however, this remains unproven because unbalanced embryos can also develop to the blastocyst stage, and the transferred blastocysts in this case were not tested [10]. The outcome in this patient therefore should not be taken as evidence for or against PGT-SR. Rather, blastocyst-forming capacity should be regarded not as a stand-alone criterion for recommending or withholding PGT-SR but as an important practical consideration in individualized reproductive genetic counseling, which should also address prenatal diagnostic options when PGT-SR is declined.

The mechanisms underlying the extreme blastocyst formation failure in this case remain uncertain. Several possible factors warrant consideration. Importantly, the translocation involved chromosome 4. When embryos with abnormalities involving the largest chromosomes (chromosomes 1-5) were compared with embryos carrying aneuploidies of the smallest chromosomes (chromosomes 21 and 22), embryos with imbalances of larger chromosomes showed a strong tendency toward delayed development and poorer inner cell mass and trophectoderm quality [10]. In a retrospective cohort of PGT-SR cycles, Wu et al. reported that the rate of usable blastocysts (graded ⩾3BC) per embryo cultured was lower when a translocation involved one of the large chromosomes 1-5 than when it involved a medium-sized chromosome (41.49% vs. 46.01%; adjusted p=0.027), whereas the location of the breakpoints had no effect on fertilization or blastocyst development [11]. In another PGT-SR cohort, the blastocyst formation rate per normally fertilized embryo was lower in female than in male reciprocal translocation carriers (50.0% vs. 55.3%, p=0.001), although the aneuploidy rate did not differ [9]. The direction of these findings is consistent with the present case of a female carrier of a translocation involving chromosome 4; however, these comparators are PGT-SR cohorts in which all oocytes were fertilized by intracytoplasmic sperm injection, their definitions of blastocyst formation differ from each other and from ours, and the results of a single patient cannot be compared formally with cohort data. In female carriers, chromosomal segregation errors during oogenesis may affect the earliest stages of embryonic development and clinically manifest as a reduced blastocyst formation rate. Nevertheless, the magnitude of the difference between the present case (8.8% overall; 5.3% cryopreservation-quality) and these cohorts led us to consider, as a hypothesis, that the breakpoint may disrupt, or lie in close proximity to, a gene critical for early embryonic development. Several genes near 12q15, one of the breakpoints in this case, may be involved in development to the blastocyst stage. YEATS4, CNOT2, and MDM2 are involved in cell proliferation, chromatin regulation, post-transcriptional regulation, and the p53 pathway, and mouse models have shown that loss of related gene functions is associated with developmental arrest at the blastocyst stage. YEATS4 is an essential subunit of the Tip60/p400 and SRCAP complexes, and deficiencies in components of these complexes have been reported to affect the maintenance of mouse embryonic stem cell identity and development to the blastocyst stage [12-14]. CNOT2 encodes a core subunit of the CCR4-NOT complex; together with CNOT1 and CNOT3, it is expressed in the inner cell mass and contributes to the maintenance of pluripotency. Impaired function of the CCR4-NOT complex may induce aberrant differentiation toward the trophectoderm lineage [15], and Cnot3-null embryos exhibit a severe inner cell mass outgrowth defect [16]. Because CNOT2 is also a core component of this complex, it may similarly play an important role in early embryonic development. MDM2 is essential for p53 regulation, and homozygous Mdm2-deficient mice die around the blastocyst stage; this phenotype is known to be rescued by p53 deficiency [17,18]. We emphasize that this mechanism is hypothetical;

conventional G-banding does not define breakpoints at the nucleotide level, no molecular breakpoint analysis was performed, and disruption or altered expression of these genes was not demonstrated. The possibility that the breakpoint near 12q15 affected these genes or their regulatory regions therefore cannot be excluded but remains untested, and this hypothesis is offered to prompt molecular investigation in similar cases.

In this case, the ovarian stimulation protocol, the allocation of oocytes to conventional in vitro fertilization or intracytoplasmic sperm injection, and the use of artificial oocyte activation were adjusted in each cycle, ultimately enabling blastocyst acquisition and live birth. This clinical course also suggests the importance of individualizing treatment strategies according to the response in each cycle, even in translocation carriers with blastocyst formation failure. Particularly in patients from whom a consistent number of oocytes and normally fertilized embryos can be obtained, continued modification of treatment with consideration of the possibility of blastocyst acquisition may be a viable option.

This case has several limitations. As a single case report, it cannot establish or generalize a causal relationship between maternal 46,XX,t(4;12)(q33;q15) and blastocyst formation failure, and the comparison with published PGT-SR cohorts is limited by differences in study populations, fertilization methods, and definitions of blastocyst formation. In addition, chromosomal analysis was not performed on the blastocysts obtained, and neither prenatal nor postnatal chromosomal analysis of the child was performed; therefore, it remains unknown whether the transferred embryos were chromosomally normal or carried the balanced translocation, and the live birth does not by itself establish that the transferred embryo was balanced. Furthermore, G-banding in this case could not identify the breakpoints at the nucleotide level, and it was not directly confirmed whether YEATS4, CNOT2, or MDM2 was disrupted, damaged, or altered in expression; moreover, available cohort data do not support an effect of breakpoint location on blastocyst development, which argues against a generalizable breakpoint-specific mechanism [11]. In similar cases, breakpoint analysis using next-generation sequencing, when feasible, may enable more detailed investigation of the association between reciprocal translocations and blastocyst formation failure.

Conclusions

This case highlights extreme blastocyst formation failure, with an overall blastocyst formation rate of 8.8% and a cryopreservation-quality blastocyst rate of 5.3%, in a female carrier of a balanced reciprocal translocation. The underlying mechanisms remain uncertain, and a contribution of genes near the 12q15 breakpoint is a hypothesis that remains to be tested at the molecular level. PGT-SR is an important option that may reduce the miscarriage rate; however, in patients with marked blastocyst formation failure, the acquisition of embryos suitable for testing may itself become a therapeutic constraint. Therefore, blastocyst-forming capacity should be considered, together with the benefits, limitations, and costs of PGT-SR and the availability of prenatal diagnosis, in the individualized counseling of BRT carriers.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Hiromasa Kuroda, Kana Inukai

Acquisition, analysis, or interpretation of data: Hiromasa Kuroda, Kana Inukai, Risa Usui, Atsushi Haruki, Naoko Murakami

Critical review of the manuscript for important intellectual content: Hiromasa Kuroda, Risa Usui, Atsushi Haruki, Naoko Murakami

Supervision: Hiromasa Kuroda, Atsushi Haruki

Drafting of the manuscript: Kana Inukai

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Review Board of Haruki Ladies Clinic issued approval #2026-5. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Evaluation and treatment of recurrent pregnancy loss: a committee opinion . Fertil Steril. 2012, 98:1103-11. 10.1016/j.fertnstert.2012.06.048
2. Stirrat GM: Recurrent miscarriage I: definition and epidemiology. Lancet. 1990, 336:673-5. 10.1016/0140-6736(90)92159-f
3. van den Boogaard E, Kaandorp SP, Franssen MT, et al.: Consecutive or non-consecutive recurrent miscarriage: is there any difference in carrier status?. Hum Reprod. 2010, 25:1411-4. 10.1093/humrep/deq089
4. Franssen MT, Korevaar JC, Leschot NJ, et al.: Selective chromosome analysis in couples with two or more miscarriages: case-control study. BMJ. 2005, 331:137-41. 10.1136/bmj.38498.669595.8F
5. Stephenson MD, Sierra S: Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Hum Reprod. 2006, 21:1076-82. 10.1093/humrep/dei417
6. Desjardins MK, Stephenson MD: "Information-rich" reproductive outcomes in carriers of a structural chromosome rearrangement ascertained on the basis of recurrent pregnancy loss. Fertil Steril. 2012, 97:894-903. 10.1016/j.fertnstert.2012.01.110
7. Li S, Zheng PS, Ma HM, et al.: Systematic review of subsequent pregnancy outcomes in couples with parental abnormal chromosomal karyotypes and recurrent pregnancy loss. Fertil Steril. 2022, 118:906-14. 10.1016/j.fertnstert.2022.08.008
8. Lim CK, Cho JW, Kim JY, Kang IS, Shim SH, Jun JH: A healthy live birth after successful preimplantation genetic diagnosis for carriers of complex chromosome rearrangements. Fertil Steril. 2008, 90:1680-4. 10.1016/j.fertnstert.2007.08.016
9. Song H, Shi H, Yang ET, Bu ZQ, Jin ZQ, Huo MZ, Zhang YL: Effects of gender of reciprocal chromosomal translocation on blastocyst formation and pregnancy outcome in preimplantation genetic testing. Front Endocrinol (Lausanne). 2021, 12:10.3389/fendo.2021.704299
10. Alfarawati S, Fragouli E, Colls P, et al.: The relationship between blastocyst morphology, chromosomal abnormality, and embryo gender. Fertil Steril. 2011, 95:520-4. 10.1016/j.fertnstert.2010.04.003
11. Wu S, Zhang J, Guan Y, et al.: Effects of chromosomal translocation characteristics on fertilization and blastocyst development - a retrospective cohort study. BMC Med Genomics. 2023, 16:10.1186/s12920-023-01715-4
12. Hu Y, Fisher JB, Koprowski S, McAllister D, Kim MS, Lough J: Homozygous disruption of the Tip60 gene causes early embryonic lethality. Dev Dyn. 2009, 238:2912-21. 10.1002/dvdy.22110
13. Fazzio TG, Huff JT, Panning B: An RNAi screen of chromatin proteins identifies Tip60-p400 as a regulator of embryonic stem cell identity. Cell. 2008, 134:162-74. 10.1016/j.cell.2008.05.031
14. Hsu CC, Zhao D, Shi J, et al.: Gas41 links histone acetylation to H2A.Z deposition and maintenance of embryonic stem cell identity. Cell Discov. 2018, 4: 10.1038/s41421-018-0027-0
15. Zheng X, Dumitru R, Lackford BL, et al.: Cnot1, Cnot2, and Cnot3 maintain mouse and human ESC identity and inhibit extraembryonic differentiation. Stem Cells. 2012, 30:910-22. 10.1002/stem.1070
16. Neely GG, Kuba K, Cammarato A, et al.: A global in vivo Drosophila RNAi screen identifies NOT3 as a conserved regulator of heart function. Cell. 2010, 141:142-53. 10.1016/j.cell.2010.02.023
17. Jones SN, Roe AE, Donehower LA, Bradley A: Rescue of embryonic lethality in Mdm2-deficient mice by absence of p53. Nature. 1995, 378:206-8. 10.1038/378206a0
18. Luna RM, Wagner DS, Lozano G: Rescue of early embryonic lethality in mdm2-deficient mice by deletion of p53. Nature. 1995, 378:203-6. 10.1038/378203a0