Reproductive outcomes in men with karyotype abnormalities: Case report and review of the literature

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Cite as: *Can Urol Assoc J* 2015;9(9-10):E667-70. http://dx.doi.org/10.5489/cuaj.2902
Published online September 9, 2015.

Abstract

Reciprocal translocations of autosomal chromosomes are present in about 1/625 men, yet often there are no symptoms except primary infertility. Abnormal segregation during meiosis often produces sperm and subsequent embryos with unbalanced translocations that often ultimately result in spontaneous abortions. We report on a 37-year-old man and his 39-year-old wife who complained of primary infertility. Previous in vitro fertilization (IVF) had resulted in pregnancy, but two spontaneous abortions. Upon chromosomal testing, the man was diagnosed with a reciprocal translocation and his wife was diagnosed with mosaic Turner's syndrome. Through testicular sperm extraction (TESE) and IVF with preimplantation genetic screening (PGS), they succeeded in having two healthy children. Since men with different karyotype abnormalities can have male infertility, we reviewed the literature and summarized the reproductive outcomes for men with both autosome and sex chromosomal karyotype abnormalities.

Case report

A 37-year-old man and his 39-year-old wife presented due to a complaint of primary infertility. They had been trying to conceive for 12 years. Two years previously, the patient had undergone bilateral testicular biopsies with successful sperm retrieval and conception. Unfortunately, the couple experienced recurrent pregnancy loss (both during first trimester) following two cycles of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) without genetic testing. On examination, the man had bilaterally descended testis with a right testicular size of 18 cc and a left testicle size of 16 cc. No varicocele was palpable; the vas deferens and epididymis were palpable bilaterally. Testosterone levels were 241 ng/dL, follicle stimulating hormone levels 7 mIU/mL, and luteinizing hormone levels were 5 mIU/mL. Semen analysis revealed no sperm. Based on the evaluation and previous operation at the outside institution, the patient was diagnosed with azoospermia likely secondary to epididymal obstruction.

The couple was sent for genetic evaluation due to recurrent pregnancy loss. Genetic evaluation showed that the husband had a reciprocal translocation involving chromosomes 4 and 8 [46,XY;t(4;8)(q31.1;q22.3)]. In addition, his wife had 45,X/46,XX mosaicism. The patient underwent a successful right testicular sperm extraction (TESE) with IVF/ICSI combined with pre-implantation genetic screening (PGS). The result was a successful live birth. Two years later, a repeat TESE was performed for another IVF/ICSI/PGS cycle, and the couple had a second healthy child.

Discussion

The prevalence of reciprocal translocations in the general population is about 1/625.[1] This prevalence is greater in infertile couples (1/166), in couples who have failed to achieve a pregnancy after >10 total embryos transferred for IVF (1/31), and in couples who have experienced ≥3 consecutive first-trimester spontaneous abortions (1/11).[2] Studies have shown that for couples in whom the male has a reciprocal translocation, 75% of natural pregnancies will result in a spontaneous abortion, with a live birth rate of only 4.9%.[3,4] Increased frequency of male infertility in men with reciprocal translocations is due to abnormal meiosis during spermatogenesis.[5] Abnormal segregation during meiosis can result in sperm with unbalanced translocations (i.e., chromosomal duplications and deletions).[6] Embryos with unbalanced translocations are at a high risk of spontaneous abortion, stillbirth, or neonatal anomalies, and only 11.5% experience births of healthy infants. This explains why couples with a reciprocal translocation have significant problems conceiving and carrying to term.[7]

In recent years, preimplantation genetic screening (PGS) has significantly improved the frequency of healthy births in couples with genetic abnormalities. Screening the embryo

Table 1. Summary of literature pertaining to sperm retrieval in patients with autosomal and sex chromosome abnormalities

Study	Age	Year	Karyotype abnormality	No. cases	Semen analysis	Sperm retrieval	Assisted Fertility	Pregnancy
Autosomal chromosome abnormality								
Current case	42	2015	46,XY,t(4;8)(q31.1;q22.3)	1	Azoospermia	Yes	Yes	Yes
Ananthapur et al.[8]	34	2013	46, XY, t (2;11) (p14;q21)	1	Oligospermia	No	No	Yes (3)
Almeida et al.[9]	31	2012	46,XY,t(2;2)(p25.1;q23)	1	Oligoasthenozoospermia	No	No	Yes
Motoyama et al.[10]	28	2011	46,XY, t(10; 21)(q11.2; p11.2)	1	Oligoasthenozoospermia	Yes	Yes	Yes
Joly-Helas et al.[11]	35	2007	46,XY,t(4;11)(q34;q13.5)	1	Oligospermia	No	Yes	Yes
Drouineaud et al.[12]	34	2003	45,XY, der(13;14),(q10;q10)	1	Azoospermia	Yes	Yes	Yes
Cai et al.[13]	35	2000	46,XY,t(7;9)(q22;p24),ins(8;7)(q21.2;q22q32).ish der(9)(wcp7+);ins(8;7)(wcp8+,wcp7+)	1	Oligospermia	No	No	Yes
Belin et al.[14]	NA	1999	46,XY,t(20;22)(q12.0;q11.21)	1	Oligospermia	NA	Yes	Yes
Meschede et al.[15]	NA	1997	46,XY,t(1;9)(q44;p11.2)	1	Oligospermia	NA	Yes	Yes
Veld et al.[16]	41, NA	1997	45,XY,der(13;13)(q10;q10)/46,XY,t(13;13)(p10;p10),der(13p;13p) AND 45,XY,der(13;14)(q10;q10)	2	Oligospermia	No	Yes	Yes
Sex chromosome abnormality								
Flannigan RK et al.[17]	27	2014	45,X/46,XY	1	Azoospermia	Yes	Yes	No
Abdel-Razic et al.[18]	23-40	2011	47,XYY	9	Oligospermia (7) Azoospermia (2)	No	Yes (2)	Yes (1)
Kilic et al.[19]	25-32	2010	45,X/46,XY	3	Azoospermia (2) Oligospermia (1)	Yes (2)	Yes (1)	No
Spinner et al.[20]	NA	2008	46,Xr(Y)	1	Oligospermia	Yes	Yes	Yes
Sugawara et al.[21]	27	2005	46, XX/46, XY	1	Azoospermia	Yes	Yes	Yes

prior to implantation assures that only those embryos with appropriate numbers of chromosomes are implanted. For couples in whom one or more partners have a reciprocal translocation, preimplantation genetic diagnosis (PGD) reduced the frequency of spontaneous abortions to 12.5% and increased the live birth rate to more than 80%.[3,4]

Due to the complexity of translocations and the high incidence of chromosomal aneuploidy with similar phenotypes, a review of the existing literature was critical (Table 1). Most patients with chromosomal abnormalities, with the notable exception of patients with 45,X/46,XY including those with complex chromosomal rearrangements, can still achieve pregnancies. This literature review reveals that sperm retrieval appears necessary in the presence of many sex chromosomal abnormalities, whereas patients with autosomal chromosomal abnormalities are often oligospermic and thus do not require testicular sperm extraction. Further, it appears that for patients with sex chromosomal abnormalities, including those with Kleinfelter syndrome, sperm retrieval combined with assisted fertility treatment offers a good prognosis for pregnancy.

While in this case report the IVF/ICSI attempts resulted with two healthy, live births, there is an ethical concern that an abnormal karyotype might be passed onto the prodigy. In countries where the law does not preclude assisted reproductive techniques for couples with a balanced chromosomal translocations, the couple ought to be referred to genetic counselling and be advised that an abnormal karyotype might be passed onto the prodigy before starting assisted reproductive techniques.

Conclusion

We report a successful pregnancy using TESE and IVF/ICSI in a couple in whom both individuals had abnormal karyotypes. The use of sperm extraction techniques and assisted fertility treatments, including pre-implantation genetic screening, dramatically helped these patients with chromosomal abnormalities achieve viable pregnancies. We expect genetic defects in men with infertility will be diagnosed with greater precision (beyond translocation) since molecular diagnostics, such as next-generation sequencing and microarray-based comparative genomic hybridization (array-CGH) analysis, have now been incorporated into clinical labs.

Table 1. Summary of literature pertaining to sperm retrieval in patients with autosomal and sex chromosome abnormalities

Study	Age	Year	Karyotype abnormality	No. cases	Semen analysis	Sperm retrieval	Assisted Fertility	Pregnancy
Kleinfelter syndrome								
Sabbaghian et al.[22]	32 (mean)	2014	47, XXY	134	Azoospermia	Yes (38)	Yes (18)	Yes (4)
Greco et al.[23]	35 (mean)	2013	47,XXY	38	Azoospermia	Yes (15)	Yes (11)	Yes (11)
Vicdan et al.[24]	35	2011	47, XXY	1	Azoospermia	Yes	Yes	Yes
Ramasamy et al.[25]	33 (mean)	2009	47,XXY	68	Azoospermia	Yes (45)	Yes (45)	Yes (33)
Yarali et al.[26]	32 (mean)	2009	47,XXY	33	Azoospermia	Yes (22)	Yes (22)	Yes (7)
Kyono et al.[27]	30 (mean 2) 38 (mean 1)	2007	47,XXY	17	Azoospermia	Yes (6)	Yes (6)	Yes (5)
Koga et al.[28]	36 (mean)	2007	47,XXY	26	Azoospermia	Yes (13)	Yes (13)	Yes (3)
Schiff et al.[29]	24-52	2005	47,XXY (39) AND 46, XX/47,XXY(3)	42	Azoospermia	Yes (29)	Yes (29)	Yes (18)
Okada et al.[30]	25-43	2005	47,XXY	51	Azoospermia	Yes (26)	Yes (26)	Yes (12)
Seo et al.[31]	26-42	2004	47,XXY (25) AND 46, XY/47,XXY(11)	36	Azoospermia	Yes (10)	Yes (10)	Yes (4)
Vernaeve et al.[32]	29.5 (mean)	2004	47,XXY	50	Azoospermia	Yes (24)	NA	NA
Westlander et al.[33]	33 (mean)	2003	47,XXY	18	Azoospermia	Yes (5)	Yes (5)	Yes (2)
Yamamoto et al.[34]	NA	2002	47,XXY	24	Azoospermia	Yes (12)	Yes (12)	Yes (4)
Friedler et al.[35]	28.7 (mean)	2001	47,XXY	12	Azoospermia	Yes (5)	Yes (5)	Yes (5)
Cruger et al.[36]	28	2001	47,XXY	1	Oligospermia	No	Yes	Yes
Poulakis et al.[37]	33,35	2001	47,XXY	2	Azoospermia	Yes	Yes	Yes
Levron et al.[38]	NA	2000	47,XXY	20	Azoospermia	Yes (8)	Yes (8)	Yes (4)
Ron-El et al.[39]	31	2000	47,XXY	1	Azoospermia	Yes	Yes	Yes
Nodar et al.[40]	39	1999	47,XXY	1	Azoospermia	Yes	Yes	Yes
Tourmaye et al.[41]	NA	1997	47,XXY	15	Azoospermia	Yes (8)	Yes (7)	Yes (2)

Competing interests: The authors all declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. Van Dyke DL, Weiss L, Roberson JR, et al. The frequency and mutation rate of balanced autosomal rearrangements in man estimated from prenatal genetic studies for advanced maternal age. *Am J Hum Genet* 1983;35:301-8.
2. Stern C, Pertile M, Norris H, et al. Chromosome translocations in couples with in-vitro fertilization implantation failure. *Hum Reprod* 1999;14:2097-101. http://dx.doi.org/10.1093/humrep/14.8.2097
3. Keymolen K, Staessen C, Verpoest W, et al. Preimplantation genetic diagnosis in female and male carriers of reciprocal translocations: clinical outcome until delivery of 312 cycles. *Eur J Hum Genet* 2012;20:376-80. http://dx.doi.org/10.1038/ejhg.2011.208
4. Munne S, Sandalinas M, Escudero T, et al. Outcome of preimplantation genetic diagnosis of translocations. *Fertil Steril* 2000;73:1209-18. http://dx.doi.org/10.1016/S0015-0282(00)00495-7
5. Lipshultz LI, Howards SS and Niederberger CS. *Infertility in the male.* 4th ed. New York,NY: Cambridge University Press; 2009. http://dx.doi.org/10.1017/CBO9780511635656
6. Brandriff B, Gordon L, Ashworth LK, et al. Cytogenetics of human sperm: Meiotic segregation in two translocation carriers. *Am J Hum Genet* 1986;38:197-208.
7. Verlinsky Y, Tur-Kaspa I, Cieslak J, et al. Preimplantation testing for chromosomal disorders improves reproductive outcome of poor-prognosis patients. *Reprod Biomed Online* 2005;11:219-25. http://dx.doi.org/10.1016/S1472-6483(10)60961-3
8. Ananthapur V, Avvari S, Veena K, et al. Non-Robertsonian translocation t (2;11) is associated with infertility in an oligospermic man. *Andrologia,* 2014;46:453-5. http://dx.doi.org/10.1111/and.12120
9. Almeida C, Dória S, Moreira M, et al. Normal sperm in a 2;2 homologous male translocation carrier. *J Assist Reprod Genet* 2012;29:665-8. http://dx.doi.org/10.1007/s10815-012-9770-6
10. Motoyama M, Takahashi K, Ogawa S, et al. Chromosome analysis by spectral karyotyping of spermatozoa from an oligoasthenozoospermic carrier of a 10; 21 reciprocal translocation. *Hum Cell* 2011;24:146-9. http://dx.doi.org/10.1007/s13577-011-0035-y
11. Joly-Helas G, de La Rochebrochard C, Mousset-Siméon N, et al. Complex chromosomal rearrangement and intracytoplasmic sperm injection: A case report. *Hum Reprod* 2007;22:1292-7. http://dx.doi.org/10.1093/humrep/del507
12. Drouineaud V, Sagot P, Faivre L, et al. Birth after intracytoplasmic injection of epididymal sperm from a man with congenital bilateral absence of the vas deferens who had a robertsonian translocation. *Fertil Steril* 2003;79(Suppl 3);1649-51. http://dx.doi.org/10.1016/S0015-0282(03)00341-8

13. Cai T, Yu P, Tagle DA, et al. A de novo complex chromosomal rearrangement with a translocation 7;9 and 8q insertion in a male carrier with no infertility: Case report. *Hum Reprod* 2001;16:59-62. http://dx.doi.org/10.1093/humrep/16.1.59
14. Belin V, Farhat M, Monset-Couchard M. Intracytoplasmic sperm injection pregnancy with trisomy 20p and monosomy 22q in a newborn resulting from a balanced paternal translocation. *Neonatology* 1999;75:398-401. http://dx.doi.org/10.1159/000014121
15. Meschede D, Louwen F, Eiben B, et al. Intracytoplasmic sperm injection pregnancy with fetal trisomy 9p resulting from a balanced paternal translocation. *Hum Reprod* 1997;12:1913-4. http://dx.doi.org/10.1093/humrep/12.9.1913
16. Veld PA, Weber RF, Los FJ, et al. Two cases of Robertsonian translocations in oligozoospermic males and their consequences for pregnancies induced by intracytoplasmic sperm injection. *Hum Reprod* 1997;12:1642-4. http://dx.doi.org/10.1093/humrep/12.8.1642
17. Flannigan RK, Chow V, Ma S, et al. 45,X/46,XY mixed gonadal dysgenesis: A case of successful sperm extraction. *Can Urol Assoc J* 2014;8:E108-E10. http://dx.doi.org/10.5489/cuaj.1574
18. Abdel-Razic MM, Abdel-Hamid IA, ElSobky ES. Nonmosaic 47,XYY syndrome presenting with male infertility: Case series. *Andrologia* 2012;44:200-04. http://dx.doi.org/10.1111/j.1439-0272.2010.01129.x
19. Kilic S, Yukse B, Tasdemir N, et al. Assisted reproductive treatment applications in men with normal phenotype but 45,x/46,xy mosaic karyotype: Clinical and genetic perspectives. *Taiwan J Obstet Gyne* 2010;49:199-202. http://dx.doi.org/10.1016/S1028-4559(10)60042-3
20. Spinner NB, Saitta SC, Delaney DP, et al. Intracytoplasmic sperm injection (ICSI) with transmission of a ring(Y) chromosome and ovotesticular disorder of sex development in offspring. *Am J Med Genet A* 2008;146A:1828-31. http://dx.doi.org/10.1002/ajmg.a.32358
21. Sugawara N, Tokunaga Y, Maeda M, et al. A successful pregnancy outcome using frozen testicular sperm from a chimeric infertile male with a 46, XX/46, XY karyotype: Case report. *Hum Reprod* 2005;20:147-8. http://dx.doi.org/10.1093/humrep/deh587
22. Sabbaghian M, Modarresi T, Hosseinifar H, et al. Comparison of sperm retrieval and intracytoplasmic sperm injection outcome in patients with and without klinefelter syndrome. *Urology* 2014;83:107-10. http://dx.doi.org/10.1016/j.urology.2013.09.021
23. Greco E, Scarselli F, Minasi MG, et al. Birth of 16 healthy children after ICSI in cases of nonmosaic Klinefelter syndrome. *Hum Reprod* 2013;28:1155-60. http://dx.doi.org/10.1093/humrep/det046
24. Vicdan K, Akarsu C, Vicdan A, et al. Birth of a healthy boy using fresh testicular sperm in a patient with Klinefelter syndrome combined with Kartagener syndrome. *Fertil Steril* 2011;96:577-9. http://dx.doi.org/10.1016/j.fertnstert.2011.06.011
25. Ramasamy R, Ricci JA, Palermo GD, et al. Successful fertility treatment for Klinefelter's syndrome. *J Urology* 2009;182:1108-13. http://dx.doi.org/10.1016/j.juro.2009.05.019
26. Yarali H, Polat M, Bozdag G, et al. TESE-ICSI in patients with non-mosaic Klinefelter syndrome: A comparative study. *Reprod Biomed Online* 2009;18:756-60. http://dx.doi.org/10.1016/S1472-6483(10)60023-5
27. Kyono K, Uto H, Nakajo Y, et al. Seven pregnancies and deliveries from non-mosaic Klinefelter syndrome patients using fresh and frozen testicular sperm. *J Assist Reprod Genet* 2007;24:47-51. http://dx.doi.org/10.1007/s10815-006-9079-4
28. Koga M, Tsujimura A, Takeyama M, et al. Clinical comparison of successful and failed microdissection testicular sperm extraction in patients with nonmosaic Klinefelter syndrome. *Urology* 2007;70:341-5. http://dx.doi.org/10.1016/j.urology.2007.03.056
29. Schiff JD, Palermo GD, Veeck LL, et al. Success of testicular sperm injection and intracytoplasmic sperm injection in men with Klinefelter syndrome. *J Clin Endocr Metab* 2005;90:6263-7. http://dx.doi.org/10.1210/jc.2004-2322
30. Okada H, Goda K, Yamamoto Y, et al. Age as a limiting factor for successful sperm retrieval in patients with nonmosaic Klinefelter's syndrome. *Fertil Steril* 2005;84:1662-4. http://dx.doi.org/10.1016/j.fertnstert.2005.05.053
31. Seo JT, Park YS, Lee JS. Successful testicular sperm extraction in Korean Klinefelter syndrome. *Urology* 2004;64:1208-11. http://dx.doi.org/10.1016/j.urology.2004.07.013
32. Vernaeve V, Staessen C, Verheyen G, et al. Can biological or clinical parameters predict testicular sperm recovery in 47,XXY Klinefelter's syndrome patients? *Hum Reprod* 2004;19:1135-9. http://dx.doi.org/10.1093/humrep/deh253
33. Westlander G, Ekerhovd E, Bergh C. Low levels of serum inhibin B do not exclude successful sperm recovery in men with nonmosaic Klinefelter syndrome. *Fertil Steril* 2003;79(Suppl 3);1680-2. http://dx.doi.org/10.1016/S0015-0282(03)00403-5
34. Yamamoto Y, Sofikitis N, Mio Y, et al. Morphometric and cytogenetic characteristics of testicular germ cells and sertoli cell secretory function in men with non-mosaic Klinefelter's syndrome. *Hum Reprod* 2002;17:886-96. http://dx.doi.org/10.1093/humrep/17.4.886
35. Friedler S, Raziel A, Strassburger D, et al. Outcome of ICSI using fresh and cryopreserved-thawed testicular spermatozoa in patients with non-mosaic Klinefelter's syndrome. *Hum Reprod* 2001;16:2616-20. http://dx.doi.org/10.1093/humrep/16.12.2616
36. Crüger D, Toft B, Agerholm I, et al. Birth of a healthy girl after ICSI with ejaculated spermatozoa from a man with non-mosaic Klinefelter's syndrome: Case report. *Hum Reprod* 2001;16:1909-11. http://dx.doi.org/10.1093/humrep/16.9.1909
37. Poulakis V, Witzsch U, Diehl W, et al. Birth of two infants with normal karyotype after intracytoplasmic injection of sperm obtained by testicular extraction from two men with nonmosaic Klinefelter's syndrome. *Fertil Steril* 2001;76:1060-2.
38. Levron J, Aviram-Goldring A, Madgar I, et al. Sperm chromosome analysis and outcome of IVF in patients with non-mosaic Klinefelter's syndrome. *Fertil Steril* 2000;74:925-9. http://dx.doi.org/10.1016/S0015-0282(00)01556-9
39. Ron-El R, Strassburger D, Gelman-Kohan S, et al. A 47,XXY fetus conceived after ICSI of spermatozoa from a patient with non-mosaic Klinefelter's syndrome: Case report. *Hum Reprod* 2000;15:1804-06. http://dx.doi.org/10.1093/humrep/15.8.1804
40. Nodar F, De Vincentiis S, Olmedo SB, et al. Birth of twin males with normal karyotype after intracytoplasmic sperm injection with use of testicular spermatozoa from a nonmosaic patient with Klinefelter's syndrome. *Fertil Steril* 1999;71:1149-52. http://dx.doi.org/10.1016/S0015-0282(99)00151-X
41. Tournaye H, Camus M, Vandervorst M, et al. Surgical sperm retrieval for intracytoplasmic sperm injection. *Int J Androl* 1997;20(Suppl 3):69-73.

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