Reproductive outcome of male carriers of chromosomal abnormalities: multidisciplinary approach for genetic counseling and its implications

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ABSTRACT. Chromosomal abnormality is the most common genetic cause of infertility. Infertility, as a psychological problem, has received an increasing amount of attention. Psychological interventions have been shown to have beneficial effects on infertile patients with chromosomal abnormalities. The present study explored reproductive outcome of male carriers of chromosomal abnormalities, who accepted genetic counseling and psychological support. Cytogenetic analysis

was performed using cultured peripheral blood lymphocytes and G-banding. The detection rate of chromosomal abnormalities was 10.3% in pre-pregnancy counseled males, with polymorphisms being most common, followed by 47,XXY and balanced translocation. Follow-up of 170 carriers with normozoospermia, after 3 years, showed that 94.7% of the cases resulted in live births. In the carriers of polymorphisms, balanced translocation, inv(9), Robertsonian translocation, inversion, and 47,XYY, live birth rates were 96.8, 85.7, 100, 83.3, 75, and 100%, respectively. Follow-up of 54 carriers with oligozoospermia or azoospermia, after 3 years, showed that 14.8% of the cases resulted in live births. In the carriers of 47,XXY with severe oligozoospermia or azoospermia, 80 or 5.9% of the cases resulted in live births, respectively. Therefore, timely psychological support would be beneficial and multidisciplinary approach should be preferentially considered for the management of individuals with chromosomal abnormalities.

Key words: Chromosomal abnormality; Reproductive outcome; Genetic counseling; Multidisciplinary approach; Infertility

INTRODUCTION

Chromosomal abnormality is the most common genetic cause of infertility (Zhang et al., 2015b). Male carriers of chromosomal abnormalities have often been found to be azoospermic or oligozoospermic (Naasse et al., 2015; Zhang et al., 2015b). Although balanced chromosomal forms exert no phenotypic effect on the carriers, they show variable influence on sperm counts, which can range from normal counts to oligozoospermia or even result in a total absence of sperm in the ejaculate (Zhang et al., 2015c). Hence, reproductive outcomes of the carriers often show normal fertility or infertility. For male carriers, the success rates of natural pregnancies range from 30 to 70% (Ozawa et al., 2008). Nearly two-thirds of the carriers are likely to have a normal outcome in subsequent pregnancy (Kochhar and Ghosh, 2013), and cumulative live birth rate is 64.3% for couples in which the male has a chromosomal anomaly (Flynn et al., 2014).

For the carriers of chromosomal abnormalities, preventive care should be provided from the time of diagnosis, preferentially using a multidisciplinary approach, including clinical psychologist or psychiatrist, urologist, geneticist, sexologist, and a fertility team (Gies et al., 2014). Infertility, as a psychological problem, has received an increasing amount of attention (Zhang et al., 2015b). Psychological distress in carriers of chromosomal abnormalities should be taken seriously (Spitczok von Brisinski, 2013; Wang et al., 2016). Severe depressive symptoms are significantly associated with increased infertility-related distress at individual and partner levels (Peterson et al., 2014). Psychological interventions have beneficial effects on infertile patients with chromosomal abnormalities (Cousineau and Domar, 2007).

For counseling individuals with chromosomal abnormalities, accurate information and assessment of associated medical conditions should be offered at diagnosis and should be followed by psychological counseling (Gies et al., 2014; Zhang et al., 2015a; Wang et al., 2016). In this study, reproductive outcome of male carriers of chromosomal abnormalities, who

accepted genetic counseling and psychological support, has been reported and its implications in genetic counseling have been discussed.

MATERIAL AND METHODS

Patients

Patients who sought pre-pregnancy counseling at the andrology outpatient's clinic of First Hospital of Jilin University, from January 2012 to December 2012, were consecutively recruited for this study. Total 2282 men were recruited, including 234 men with chromosomal abnormalities. Patients were considered to have oligozoospermia, if their last three semen samples had sperm counts less than 20 x 10^6 sperm/mL, severe oligozoospermia, if the sperm count was less than 5 x 10^6 sperm/mL, or azoospermia, if no sperm were found in the ejaculate after centrifugation.

For all carriers of chromosomal abnormalities, we provided genetic counseling and psychological support. For each carrier, we introduced an appropriate way to conceive, applied assisted reproductive technology, assessed the success rate and the impact on the child's birth, etc. The carriers chose their own mode of reproduction. After 3 years, we performed a follow-up to determine the reproductive outcomes. The process is shown in Figure 1. The study protocol was approved by the Ethics Committee of First Hospital of Jilin University, Changchun, China, and all participants provided their written informed consent.

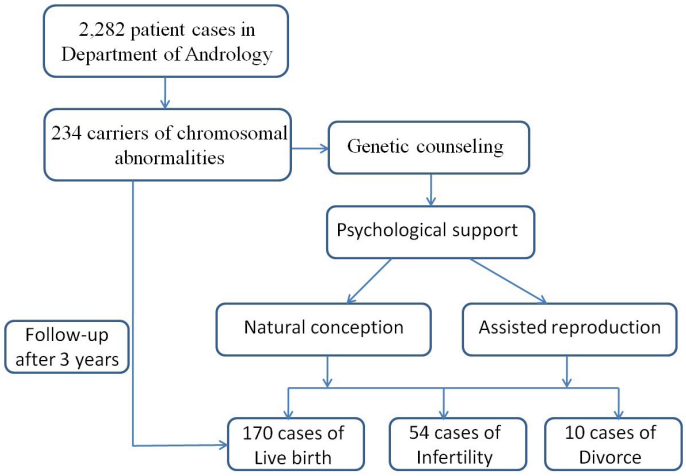

Figure 1. Flow chart of genetic counseling, psychological support, and follow-up of patients.

Cytogenetic analysis

Peripheral blood from all subjects was collected in sterile tubes containing 30 U/mL heparin. G banding was performed using cultured peripheral blood lymphocytes. Lymphocytes were cultured in lymphocyte culture fluid (Yishengjun; Baidi Biological Pharmaceutical Co., Ltd., Guangzhou, China). The karyotypes of metaphase were analyzed for each subject (Wang et al., 2016).

Pregnancy outcome

An elaborate questionnaire was completed, during follow-up visits, by the physician who attended the delivery. Follow-up questionnaire was provided to each carrier to collect their information, including pregnancy outcome, number of pregnancies, the way to conceive, number of abortions, assisted reproductions, number of live births, marital history, smoking history and frequency, alcohol consumption, occupational status, etc.

RESULTS

Among the 2282 male patients given pre-pregnancy counseling, 234 carriers (10.3%) of chromosomal abnormalities were included. Karyotype and number of patients are presented in Table 1. Most cases, around 136 (58.1%), were carriers of polymorphism.

Table 1. Karyotype and percentage of male carriers with various chromosomal abnormalities.

Karyotype	Number of cases (N = 234)	Percentage (%)
Polymorphism	136	58.1
47,XXY	47	20.1
Balanced translocation	22	9.4
Inv(9)	13	5.6
Robertsonian translocation	7	3.0
Inversion	5	2.1
47,XYY	2	0.8
Chimera	2	0.8

Among the 234 carriers of chromosomal abnormalities, clinical features showed normozoospermia, oligozoospermia, or azoospermia. Clinical features and reproductive outcomes of carriers exhibiting normozoospermia are presented in Table 2.

Table 2. Clinical features and reproductive outcomes of carriers of chromosomal abnormalities carrier exhibiting normozoospermia.

Karyotype	No. of cases	Cases of live birth (%)
Polymorphism	124	120 (96.8)
Balanced translocation	21	18 (85.7)
Inv(9)	13	13 (100)
Robertsonian translocation	6	5 (83.3)
Inversion	4	3 (75)
47,XYY	2	2 (100)
Total	170	161 (94.7)

Follow-up study showed that 10 carriers got divorced (Figure 1), including 2 carriers with polymorphism and 8 carriers with 47,XXY. Clinical features and reproductive outcomes of carriers exhibiting oligozoospermia or azoospermia are presented in Table 3.

Table 3. Clinical features and reproductive outcomes of carriers of chromosomal abnormalities exhibiting oligozoospermia or azoospermia.

Karyotype	Clinical features	No. of cases	Cases of live birth (%)
Polymorphism	Azoospermia	10	1 (10.0)
47,XXY	Severe oligozoospermia	5	4 (80.0)
	Azoospermia	34	2 (5.9)
Balanced translocation	Azoospermia	1	0 (0)
Robertsonian translocation	Oligozoospermia	1	1 (100)
Inversion	Azoospermia	1	0 (0)
Chimera	Azoospermia	2	0 (0)
Total		54	8 (14.8)

DISCUSSION

Karyotype analysis is the most powerful and widely used application in reproductive medicine (Pasquier et al., 2016). Chromosomal abnormality is associated with infertility, and its incidence ranges from 2.1 to 15.5% in infertile men (Ananthapur et al., 2014). In this study, the detection rate of chromosomal abnormalities was 10.3% (234/2,282). Of these 234 carriers with chromosomal abnormalities, polymorphism was the most common abnormality (136 cases), followed by 47,XXY (47 cases) and balanced translocation (22 cases). Patients with Klinefelter syndrome (KS) are often diagnosed late (Grace, 2004). Most patients with KS were diagnosed because of concerns regarding their reproductive capacities (Zhang et al., 2015a). Carriers with balanced translocations may be phenotypically normal, but are associated with an increased risk of pregnancy loss (Godo et al., 2013). They are often diagnosed because they face reproductive problems.

The inability to conceive children is a stressful situation experienced by both individuals and couples all over the world (Cousineau and Domar, 2007). Therefore, infertile individuals with chromosomal abnormalities often receive double psychological distress. We explored reproductive outcomes of male carriers of chromosomal abnormalities, who accepted genetic counseling and psychological support. In this study, follow-up of the 170 carriers with normozoospermia showed that 161cases (94.7%) resulted in live births. For the carriers of polymorphisms, balanced translocations, inv(9), Robertsonian translocation, inversions, and 47,XYY, the cases of live birth were 120 (96.8%), 18 (85.7%), 13 (100%), 5 (83.3%), 3 (75%), and 2 (100%), respectively. Chromosomal polymorphisms usually occur in the pericentric heterochromatin on the long arms of chromosome 1, 9, and 16 and in the heterochromatin on the short arms, satellites, or stalks of chromosome 13, 14, 15, 21, and 22 (Guo et al., 2012). Guo et al. (2012) reported that chromosomal polymorphisms seem to have deleterious effects on spermatogenesis, contributing to male infertility. Dong et al. (2014) reported that chromosomal polymorphisms do not have significantly lower live birth rates than non-carrier couples. For male translocation carriers, the success rates of natural pregnancies and live birth rates range from 30 to 70% (Ozawa et al., 2008; Kochhar and Ghosh, 2013; Flynn et al., 2014). The limitation of this study was that it was a single center investigation with only 3 years of follow-up. A longer follow-up might have reported a higher live birth rate.

With the application of assisted reproductive technology, sperm can be obtained by testicular biopsy, testicular fine needle aspiration, and microdissection testicular sperm extraction. Hence, viable sperm were obtained from individual testicular tubules by biopsy, allowing for the patients with oligozoospermia or azoospermia to become fathers (Nieschlag,

2013). In this study, follow-up of the 54 carriers with oligozoospermia or azoospermia showed that 8 cases resulted in live births. Among the 5 carriers of 47,XXY and severe oligozoospermia, 4 cases resulted in live births. Among the 34 carriers of 47,XXY and azoospermia, 2 cases resulted in live births. In very few cases, KS men ejaculate spermatozoa and result in the birth of healthy children, following intracytoplasmic sperm injection (Zhang et al., 2015a). The technological development in testicular sperm extraction-intracytoplasmic sperm injection has assisted over 50% KS patients, providing them with the opportunity of having biological children (Bar et al., 2014).

The present study explored reproductive outcome of male carriers of chromosomal abnormalities, who accepted genetic counseling and psychological support. Live birth rate among the carriers of polymorphisms and balanced translocations was higher than that reported in the literature (Ozawa et al., 2008; Pal et al., 2009; Flynn et al., 2014). These may be associated with psychological support. Hence, a multidisciplinary approach should be preferentially considered for carriers of chromosomal abnormalities.

In summary, 10.3% of the males enrolled in pre-pregnancy counseling were carriers of chromosomal abnormalities. Prospective study provided genetic counseling and psychological support to male carriers of chromosomal abnormalities. Follow-up of carriers with normozoospermia showed that 94.7% cases resulted in live births, whereas follow-up of carriers with oligozoospermia or azoospermia showed that 14.8% cases resulted in live births. Timely psychological support might be beneficial; therefore, multidisciplinary approach should be preferentially considered for the management of individuals with chromosomal abnormalities.

Conflicts of interest

The authors declare no conflict of interest.

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