CASE REPORT

Pericentric inversion of chromosome 9 causing infertility and subsequent successful *in vitro* fertilization

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ABSTRACT

One of the most common and benign variants of normal human karyotype is pericentric inversion of chromosome 9 (inv[9][p11q13]). Despite being categorized as a normal variant, there are several reports of its association with various disease conditions. Here, we report a 27 year old female, who presented to us with primary infertility. The woman was diagnosed with inv (9)(p11q13) which was acknowledged as the reason for her otherwise unexplained infertility. The couple thereupon underwent *in vitro* fertilization using donor oocyte resulting in live birth. The clinical significance of this minor chromosomal rearrangement, need for genetic counseling, and subsequent reproductive guidance is highlighted in this report.

Key words: *In vitro* fertilization, infertility, pericentric inversion of chromosome 9

INTRODUCTION

Chromosomal aberrations are found among 2–7% of the couples presenting with unexplained infertility.[1] Pericentric inversion of chromosome 9 (inv[9][p11q13]) is a frequently seen chromosomal alteration in humans due to its structural organization, making it more prone to breakage. The incidence estimated is 1–3% of the general population with the lowest among Asians around 0.25%.[2] With several conflicting views on its clinical impact, some studies claim it to be a normal variant while some others have associated it with several diseases such as infertility and bad obstetric history. Among the various types, inv(9)(p11q12) and inv(9)(p11q13) are the most common. Variable clinical manifestations have been observed from normal to multiple malformations among babies born to carriers of such structurally balanced chromosomal aberration.[3]

CASE REPORT

The patient was a 27-year-old woman with a 5-year history of unprotected intercourse and regular cycles presented with primary infertility. The couple was phenotypically normal and nonconsanguineous. There was no relevant medical history. A pedigree evaluation found neither birth defect nor genetic disorder in the family. The couple was subjected to various investigations to find out the cause of infertility. Semen analysis was normal. Baseline transvaginal ultrasound showed a normal-sized uterus and good antral follicle count (10 in each ovary). Hormone markers were normal. Diagnostic hysterolaparoscopy showed bilateral free spill in both the tubes and normal cavity. She underwent three cycles of ovulation induction with timed relationship with clomiphene citrate. All the cycles were ovulatory. Five cycles of intrauterine inseminations with gonadotropins (human menopausal gonadotropin) were performed; in spite of good postwash sperm count and motility, she failed to conceive.

In view of unexplained infertility, karyotyping was carried out on the cultures of peripheral blood lymphocytes, which was analyzed by the GTG-banding technique. It revealed that her karyotype was 46 × X, inv (9)(p11q13) while her

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husband's karyotype was normal (46 × Y). The couple was then advised *in vitro* fertilization (IVF) with preimplantation genetic diagnosis (PGD) after embryo biopsy. However, the couple was not willing for PGD and instead opted for donor oocyte IVF program. A suitable donor was screened for infectious and hereditary diseases and stimulated with gonadotropins for 11 days. The oocytes were retrieved after 34 h of GnRH agonist (injection triptorelin 0.2 mg) trigger. Using husband's sperm, IVF was done and embryos were cryopreserved. Using a GnRh agonist suppressed hormone replacement cycle, endometrial preparation was done with estradiol valerate (Progynova, Bayer), and two cleavage stage embryos were transferred after adequate endometrium was obtained. Pregnancy was confirmed by serum beta human chorionic gonadotropin after 2 weeks of embryo transfer. Ultrasound done at 6 weeks gestational age showed a dichorionic diamniotic twin pregnancy. Routine pregnancy care was given. She delivered healthy twin male babies at 38 weeks gestation.

DISCUSSION

Inv(9)(p11q13) is the most commonly observed structurally balanced rearrangement of chromosome involving the heterochromatic region. Although it is widely debatable, most cytogeneticists believe that this variant is a chromosomal polymorphism of the normal human karyotype without any clinical significance.[4] Contradictorily, many clinical investigators have suggested several associations of inv(9) with clinical diagnoses, particularly with idiopathic reproductive failure. Various reports on its association with infertility, recurrent miscarriages, hydatidiform moles, azoospermia, congenital anomalies, growth retardation, and rarely abnormal phenotype have been published.[5] Sasiadek *et al*. have reported inv(9) in 2.3% of all couples presenting with infertility and recurrent abortions.[6] Šípek *et al*. have published the largest study on inv(9) and have found a higher frequency among females than in males, especially among those who suffer from infertility.[7] We agree with this observation as it is evident in our case as well.

Various types of pericentric inversions have been reported which includes inv(9)(p11q12), inv(9)(p11q13), inv(9)(p11q21), inv(9)(p12q13), inv(9)(p13q13), and inv (9)(p13q21). Researchers believe that the various disturbances manifested by this variant depend on the position of the breakpoints in the chromosome which is preferentially located at 9p12 or 9q13–21.1 regions. In this case, the patient had inv(9)(p11 q13) which is one of the most common variants. The carriers of inv(9)(p11 q13) commonly express secondary infertility although our patient suffered from primary infertility.[8]

The possible phenomena for this variant to cause infertility are all hypothetical and still remain unclear. It requires more research at the molecular level to understand the significance of various chromosomal breakpoints with the help of modern cytogenetic approaches.

Studies have reported that the carriers of such balanced structural aberrations have an increased chance of having an offspring with an unbalanced karyotype. The probability of them producing abnormal gametes as a result of meiotic crossing-over ranges from 1% to 10%. Higher incidence of Downs syndrome and other abnormalities in the progeny of these carriers has been documented.[9] Interestingly, the sperm DNA integrity of a male patient with infertility and inv(9) karyotype was studied by García-Peiró *et al*. and was found to have high sperm DNA fragmentation, significant meiotic alterations, anomalous aneuploidy, and altered seminogram parameters; all of these can result in chromosomal imbalance in the progeny.[10]

For couples with idiopathic infertility, cytogenetic analysis is a crucial investigation to provide appropriate genetic counseling and reproductive guidance. The advent of IVF as a solution for infertility has created the chance to study the chromosomal constitution of the human embryos. Before which, a genetic counselor or the reproductive physician should ensure that the patients are explained about the consequence of this variant on their child along with the benefits and limitations of PGD analyses by polymerase chain reaction. PGD of the biopsied blastomeres from an embryo can reduce the risk of conceiving a child with genetic disease as a result of chromosomal imbalance.

Therefore, it is desirable that these patients undergo PGD, especially for those who suffer from infertility requiring IVF. It also enhances pregnancy success with the transfer of euploid embryos for patients with infertility. As for this case, the patient chose donor oocyte which can also be opted as an option to prevent the inheritance of chromosomal rearrangements. Donor oocyte or sperm is an alternative option for these patients who were in a well-screened donor's gametes are used to produce healthy embryos.

CONCLUSION

This case was instrumental in strengthening our belief that inv (9)(p11q13) cannot be categorized as normal and that it has a harmful effect on fertility as evidenced from the existing literature. This report stresses the importance of studying the chromosome as a routine for couples with unexplained infertility. The outcome of this balanced chromosomal rearrangement and appropriate options available for reproduction is highlighted. We conclude that for these patients, IVF with PGD is momentous. In circumstances where PGD cannot be performed, well-screened donor gametes can be opted by the couple.

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Conflicts of interest

There are no conflicts of interest.

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