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Human Genetics

FIRST SUCCESSFUL TWIN DELIVERY IN INDIA AFTER PREIMPLANTATION GENETIC DIAGNOSIS FOR BRCA1 MUTATION.

Firuza R. Parikh	Director, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India.
Dattatray J. Naik	Embryologist, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India.
Nandkishor J. Naik	Embryologist, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India.
Rupesh R. Sanap	Genetic Technologist, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India.
Prochi F. Madon	Consultant Geneticist, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India.
Mangesh V. Sanap	Embryologist, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India.
Suresh B. Dhumal	Embryologist, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India.
Anahita D. Pandole	Obstetrician, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India.
Arundhati S. Athalye*	Consultant Geneticist, Department of Assisted Reproduction and Genetics. Jaslok Hospital and Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai 400026, India. *Corresponding Author

ABSTRACT A mutation in Breast Cancer 1 or 2 genes (BRCA1 or BRCA2) can predispose women to breast and ovarian cancers and men to prostate, colon and breast cancers. A couple with 3 miscarriages, with the female partner being heterozygous for BRCA1 (autosomal dominant) mutation approached us for their desire to have a child free of BRCA1 mutation. Preimplantation genetic diagnosis (PGD) for BRCA1 mutation was offered. Pre-PGD genetic work up was carried out. The couple underwent ICSI with antagonist protocol and stimulation with HMG+FSH. For PGD, trophectoderm cells were biopsied from six blastocyst embryos and subjected to chromosomal aneuploidy screening. Of these, 2 euploid embryos were tested for BRCA1 mutation. Both embryos were free of the mutation and hence a frozen embryo transfer was performed in the subsequent cycle. The woman conceived and successfully delivered twin babies free of BRCA1 mutation.

KEYWORDS : PGD for BRCA1, PGD, BRCA1, trophectoderm biopsy

Introduction:

Breast cancer is one of the leading causes of death. Some forms of breast cancer and ovarian cancer are hereditary. This condition is called Hereditary Breast and Ovarian Cancer Syndrome. There are 2 tumour suppressor genes, Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2)[1,2]. A mutation in these genes can predispose a woman to breast cancer and ovarian cancer and men to Prostate cancer, Colon cancer and Breast cancer. Having this mutation can even cause an early menopause. Estimates of prevalence of BRCA1 mutation between different populations varies between 0.5 to 3.5% [3]. In the Indian population, in a study reported by Singh et al., (2018), out of 304 cases of breast and/or ovarian cancer where different mutations were detected, 84.9% of those mutations were detected in the BRCA1/2 genes as compared to non-BRCA genes[4]. Hence it is important to identify breast cancer mutations in women where there is a known history of Breast Cancer in the family.

Introduction of Preimplantation Genetic Diagnosis (PGD) has brought a major breakthrough in the detection of known gene disorders in embryos obtained through ICSI prior to implantation. In this, the embryos are allowed to develop till the blastocyst stage where trophectoderm cells start herniating out from the breach in Zona Pellucida which is created by LASER hatching on day 3 of the embryo. Five to eight trophectoderm cells are biopsied and are further tested for the specific genetic mutation along with preimplantation genetic screening (PGS) in order to select euploid embryos. The unaffected euploid and mutation free embryos are used for implantation. This technology helps to avoid the use of affected or aneuploid embryos thus preventing the birth of an affected child as well as reducing the trauma of medical termination of an affected pregnancy.

There are a few hundred births reported worldwide after PGD for BRCA1[5]. We report a successful twin delivery through PGD for BRCA1 at Jaslok Hospital and Research Centre.

A couple came to our clinic with history of previous 3 recurrent miscarriages through IUI and IVF treatment. The maternal side of the female partner had a strong history of ovarian as well as breast cancer. Her grandmother and 2 of her maternal aunts had breast cancer, her mother had ovarian cancer and her maternal uncle had prostate cancer. She herself was found to be heterozygous for BRCA1 mutation c.68_69delAG. As this was an autosomal dominant condition, there was a high risk of having cancer in future progeny. Hence we counseled the couple and offered PGD for BRCA1 mutation through the ICSI procedure. After transfer of mutation-free embryos, the woman carried a twin pregnancy and gave birth to two normal male children at full term.

This is the first report from India of live twin births after PGD for BRCA1.

Material and methods:

Based on the history, 3ml blood of the wife was collected in EDTA and subjected to pre-PGD work up for BRCA1 mutation c.68_69delAG.

Simultaneously, the couple was tested by karyotyping analysis to check for any chromosomal aberrations.

Informed consent was obtained from the couple as per ICMR and PCPNDT guidelines and rules before the actual procedure.

The stimulation cycle was carried out using Antagonist Protocol with HMG+FSH. After oocyte collection, MII grade oocytes were fertilized with the husband's sperm using the ICSI technique. A total of 6 blastocysts were available for biopsy. Using a DIODE LASER beam, 5-6 trophectoderm cells were biopsied from each of the 6 embryos and tubed. The tubes were numbered with the patient's initials and embryo numbers. The biopsied embryos were subjected to the vitrification process.

The tubed cells were first subjected to whole genome amplification (WGA) followed by chromosomal aneuploidy screening by next generation sequencing (NGS) technology. The 2 euploid embryos were further subjected to BRCA1 mutation c.68_69delAG detection by Sanger sequencing.

Two BRCA1 mutation unaffected euploid embryos were implanted in the subsequent frozen transfer cycle. After 14 days beta HCG levels were checked to confirm the pregnancy.

Results:

The parental karyotype showed a normal 46, XY and 46,XX status for the husband and wife respectively. The pre-PGD work up for BRCA1 c.68_69delAG mutation confirmed the possibility of offering PGD on the embryos.

After ICSI, fertilization resulted in the formation of 6 blastocyst embryos. These were subjected to trophectoderm biopsies.

After PGS testing 2 euploid embryos were further subjected to PGD for BRCA1 c.68_69delAG mutation. The testing showed absence of mutation in both the embryos.

In the subsequent frozen transfer cycle both unaffected euploid embryos were used for implantation. The first beta-HCG report after 14 days confirmed the presence of a pregnancy.

Discussion:

BRCA1 mutation is an autosomal dominant condition. This means that one copy of the mutated gene is sufficient to cause a high risk of developing cancer. A heterozygous parent can pass either a normal copy or an abnormal copy of the mutated gene to the offspring. Each offspring has a 50% chance of inheriting the mutation. In women with BRCA1 mutation, there is a 50-80% risk of developing breast cancer in life[6]. In this situation, when we counseled the couple, we had discussed all the possibilities of inheritance. After knowing the heterozygous BRCA1 status of the female partner, the couple wanted to make sure that their child would not be predisposed to this hereditary condition. The couple already had infertility issues and had lost previous 3 pregnancies due to spontaneous miscarriages for unknown reasons. Hence the couple wanted a way out to avoid an affected pregnancy after IVF treatment.

Jasper et al., in 2008 reported the first live birth with PGD for BRCA1[7]. After this, different groups reported altogether a few hundred live births after PGD for BRCA1 mutation[5,8,9,10]. Thus we offered the couple PGD for the BRCA1 mutation c.68_69delAG. To avoid another miscarriage due to aneuploidy or the birth of a baby who will be at a high risk of developing cancer in future, the couple opted for PGS as well as PGD testing for BRCA1 mutation.

After obtaining 2 mutation free euploid embryos, frozen embryo transfer was carried out. Beta HCG values followed by subsequent sonography confirmed the twin pregnancy. It was a dichorionic twin pregnancy which progressed well. Finally the mother delivered 2 normal male children at full term.

This is the first report from India after PGD for BRCA1 with twin delivery. We are offering PGS for many chromosomal aberrations including translocations, inversions and PGD for many gene disorders such as beta thalassemia, hemophilia, Duchene Muscular Dystrophy, sickle cell anemia, Leigh Syndrome and Neurofibromatosis.

Conclusion:

PGD is a better option for couples where either one or both the partners are carriers of a known genetic disorder.

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