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Case Report

A Case Report of Normal Genotype Male Offspring Successfully Delivered by ICSI in A Patient Carried Full Mutation of the *FMR1* Gene

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Abstract

Objective: To report one case of normal baby delivered by a patient carried full mutation of the *FMR1* gene after assisted reproduction, to share the experience of Intro-Cytoplasmic Sperm Injection-Embryo Transfer (ICSI-ET) and the importance of strengthening prenatal diagnosis in the second trimester.

Methods: The first successful case of a patient carried full mutation of the *FMR1* gene who delivered a baby with normal genotype by ICSI in the reproductive center of the Second Affiliated Hospital of Zhengzhou University was described and analyzed combined the literature.

Results: The patient was diagnosed by pre-pregnancy genetic testing before ICSI, and a normal male offspring with normal genotype was delivered after prenatal diagnosis in the second trimester. Conclusion Pre-pregnancy genetic screening, genetic counseling and prenatal diagnosis are effective methods to prevent the birth of *FMR1*-affected children in patients with unknown mental retardation or autism-like symptom.

Keywords: Full mutation of the *FMR1* gene; *In vitro* fertilization-embryo transfer; Pre-pregnancy genetic testing; Prenatal diagnosis

Introduction

Fragile X syndrome (FXS) is a hereditary mental retardation disease with an incidence second only to Down syndrome, and is also the most important single-gene genetic disease that causes autism spectrum disorder. The incidence rate in mental retardation diseases is 1%-2% [1-3]. At present, it is difficult to make a clear diagnosis only by clinical symptoms. *Fragile X Mental Retardation* gene 1 (*FMR1*) detection is the only way to diagnose FXS. Therefore, pre-pregnancy genetic screening should be performed on suspected FXS patients, necessary genetic counseling should be given, and a reasonable fertility plan should be formulated to prevent the birth of children with FXS. This paper summarizes the first patient carried full mutation of the *FMR1* gene diagnosed and treated in our hospital that successfully got pregnant and delivered a male offspring with normal genotype by means of human assisted reproductive technology, it also discusses pregnancy mode of FXS patients and the effective method of blocking the birth of children with FXS.

Case Presentation

The 34-year old patient, who had not been pregnant for 8 years due to bilateral fallopian tube obstruction and asked for assisted reproductive technology treatment on May 4, 2019. Mensuration was usually regular. On June 9, 2011, after full-term of pregnancy, she delivered a female baby naturally by natural pregnancy, and the girl is in good health now. On April 2, 2019, salpingography (HSG) examination was performed, indicating bilateral fallopian tube obstruction; karyotype: 46, XX. Her husband's karyotype is 46, XY. The sperm concentration was 10.51 × 106/ml, the ratio of sperm forward movement was 7.98%. Preliminary diagnosis: 1. Secondary infertility; 2. Obstruction of bilateral fallopian tubes; 3. Male oligoasthenospermia. It is found that the patient has language communication disorder during communication, according to the description of her family members; patient also has autistic and aggressive behavior. It is recommended to perform relevant genetic testing. After signing the informed consent, the patient's peripheral blood was drawn for examination. On May 24, 2019, the gene test results showed that the number of CGG repeats in the *FMR1* gene was: 30/>200, suggesting the patient was a carrier of full mutation in the *FMR1* gene. We informed the couple that they were at risk of having children with FXS and should accept Preimplantation Genetic Testing (PGT), but the couple refused PGT due to economic reasons. Therefore, we informed the couple that prenatal diagnosis should be performed in the second trimester, and if the fetus affected by *FMR1* gene, pregnancy should be terminated. The patient and her husband signed the consent form after being informed.

According to the routine Scheme [4] of our center, the follicular phase long-acting long protocol was adopted. On the second day of menstruation, triptorelin (diphereline, Huiling pharmaceutical) was given 3.75 mg for pituitary suppression. After reaching the pituitary down-regulation standard, urinary follicle stimulating hormone (Urofollitropin injection, 75 IU, Lizhu pharmaceutical factory of Zhuhai Lizhu group, China) was given to promote follicle

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development. When the follicle developed to mature, 10,000 IU of human chorionic gonadotropin (hCG, Lizhu pharmaceutical factory of Zhuhai Lizhu group, China) was injected intramuscularly. After 36 hours, 18 oocytes were taken, and 11 oocytes were injected by Intracytoplasmic Sperm Injection (ICSI). According to Gardner embryo quality scoring standard, there were 5 embryos with 8 cells (8/I) and 1 embryo with 7 cells (7/I) on the third day, and 2 embryos with 8/I were transplanted in the fresh cycle. After 35 days, color Doppler ultrasonography showed that a gestational sac of 15 mm × 13 mm × 19 mm could be seen within the echo, but no fetal bud and fetal heart beat were found. The diagnosis was early pregnancy, but the embryo stopped to develop, so uterine curettage was performed.

On December 17, 2019 (the third day of menstruation), the patient asked for freezen-thawing embryo transfer, and was given 6 mg of 17β-estradiol (Fimton, Abbott, USA) per day for 14 days. Ultrasound showed that the thickness of the endometrium was 13 mm. Progesterone needle (60 mg/d, im) was given to transform the endometrium for 3 days. Two 8/I embryos were thawed and transplanted. 14 days later, the blood β-HCG level was 700 IU/L. On the 35th day after transplantation, the ultrasound showed that the echo of the gestational sac of 25 mm × 13 mm × 19 mm was seen in the uterus, and the fetal heart was visible. Prenatal diagnosis by amniocentesis at 15 weeks of gestation showed that the fetal *FMR1* gene was normal. On September 16, 2020, a male full-term baby was born, weighing 3.6 kg and 50 cm in length. The umbilical cord blood was kept for gene verification. The results showed that the number of CGG repeats of the *FMR1* gene was 30 times.

In order to trace the distribution of the family's *FMR1* mutation gene, with the informed consent of the patient and his family, the peripheral blood of the patient's father, brother, daughter, and husband was collected for examination, and the results of the *FMR1* gene test were all normal. The patient's mother was deceased (samples could not be obtained), and it was described that she had the same symptoms of mental retardation and abnormal behavior as the patient before her death. It is speculated that the patient's fully mutated chromosome may be derived from her mother (Figure 1).

Discussion

FXS is an X chromosome linked incomplete dominant genetic disorder. More than 99% of FXS are caused by translation products of the *FMR1* gene due to hypermethylation of *FMR1* 5'-terminal (CGG) n of X chromosome (Xq 27.3) (i.e. n ≥ 200, full mutation) and the high methylation of its upstream promoter Island [5,6]. FMRP is a transcription level regulator, which exists in a large number in neurons and can be involved in the regulation of brain function as Messenger RNA (mRNA) [7]. The lack of FMRP can affect the development of brain and nervous system at various levels, causing the disorder of nerve cell development and electrophysiological activity, and showing a series of neurological symptoms: mental retardation, language and behavior abnormalities, autism and mental illness, so it is the core of the pathogenesis of FXS. (CGG) n is highly polymorphic, which is varying between 26-38 in the general population [8]. When n ≥ 200, it is called "full mutation". It is best to perform PGT or prenatal diagnosis in the second trimester of pregnancy.

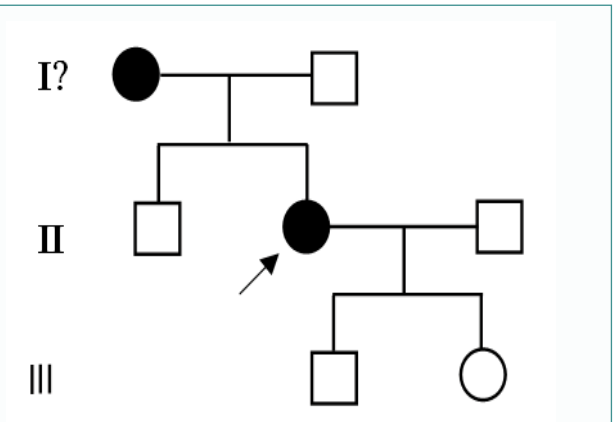

Figure 1: A pedigree of the investigated families affected by *FMR1* gene variants. In the second line, family pedigree with black fills denoting *FMR1*-affected female patient. The arrowhead indicates the proband. The question mark indicates the proband's mother could be a carrier (but was dead).

Men with *FMR1* full mutations are generally FXS patients, because they have only one X chromosome, while women have two X chromosomes, and the degree of mental retardation ranges from normal to severe [9], which is one of the reasons why middle-aged women are more likely to miss the detection and diagnosis in the population. In 2019, Mayinan [10] screened 11,819 individuals during or before pregnancy, and the results showed that the *FMR1* gene full mutation carrier rate was 1/3940 (CI: 1/11765-1/1351). However, due to people's limited awareness of the value of genetic testing and limited laboratory testing conditions, only a small number of hospitals or companies in China carry out FXS molecular genetic testing, resulting in the failure of most FXS patients to be diagnosed. A study [11] reported that 50% of the patient's families were pregnant again before the pro band was diagnosed clearly, and 43% of them gave birth to child affected by *FMR1* gene again.

The incidence rate of FXS is high, the clinical manifestations are complex, and there is no effective treatment to it. Therefore, pre-pregnancy *FMR1* gene screening, PGT and prenatal diagnosis are effective means to prevent the birth of *FMR1*-affected children. Xi Hui [12] and others conducted *FMR1* gene screening on six family members with unexplained mental retardation, and confirmed two family members with positive cases. They performed genetic diagnosis and prenatal diagnosis for family 1 to prevent the birth of a child with full *FMR1* mutation. Luo Shikun [13] reported a female who was *FMR1* full mutation carrier, chose PGT combined with prenatal diagnosis and gave birth to one normal male offspring. In this study, we also performed *FMR1* screening on the relatives of the patient and help them eliminate the concern of having sick children. The second trimester prenatal diagnosis confirmed that the fetal's genotype was normal. The patient only underwent ICSI-ET and FET without PGT due to economic reasons, but fortunately, the *FMR1* was performed again on the newborn to confirm the normal genotype, excluding the possibility of vertical transmission of the mutant gene. Although the patient did not heridity the abnormal X chromosome to the offspring after two pregnancies, if she gave birth again, she is still at risk of having a child carring a full mutation in the *FMR1* gene. Half of her male offspring will be born with FXS, and half of the female offspring will carry the full mutation of *FMR1* alleles, therefore, there can be no fluck.

Conclusion

For patients with positive family history or suspected FXS, pre-pregnancy gene screening should be carried out in advance to determine the presence and type of *FMR1* mutation, and necessary pre-pregnancy genetic counseling and risk assessment should be carried out for full mutation carriers. It is recommended that PGT

is the first choice for assisted pregnancy. For those who have not performed PGT, prenatal diagnosis must be carried out through amniotic fluid cells in the second trimester. Once abnormalities are found, pregnant and their families should be informed in time to terminate pregnancy as soon as possible to prevent the birth of *FMR1*-affected child.

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