Case Report

Favorable outcome of r-FSH treatment in male with homozygous Ser680ASN variant in FSHR gene: a case report demonstrating pharmacogenomic implication in male infertility

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Abstract

Treatment of impaired spermatogenesis with recombinant follicle-stimulating hormone (r-FSH) has heterogenous response among patients. FSH receptor (FSHR) gene polymorphisms are known to be associated with male infertility with varied phenotype presentation. The presence of Serine 680 Asparagine (Ser680Asn) polymorphism is also linked to response to r-FSH when treating impaired spermatogenesis. We present a case of an Indian male with severe oligoasthenoteratozoospermia carrying homozygous Asn680Asn FSHR genotype, who responded favorably to r-FSH treatment, demonstrating significant improvement in seminal parameters and reduction of sperm DNA fragmentation index. Ser680Asn polymorphism of FSHR gene may serve as a clinically useful pharmacogenomic marker in identification of good responders to r-FSH treatment.

Keywords: FSH, FSHR polymorphism, r-FSH treatment

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INTRODUCTION

Infertility affects 10% to 12% of couples with male factor in 40% to 50% of cases.[1] Male infertility with abnormal sperm parameters affects about 7% of general male population.[2] With multiple etiologies are reported, 50% of spermatogenic failure cases remain unexplained or idiopathic. Having said that, is it worth stating that more often reason is unexplained because reason is unexplored as further investigations are not always offered or done? One of the known treatments for improvement of seminal parameters is administration of exogenous recombinant follicle-stimulating hormone (r-FSH). FSH activates its cognate receptor, FSHR, facilitating Sertoli cell function and spermatogenesis in males.[3]. r-FSH therapy for at least 3 months in idiopathic infertile men with normal FSH levels was shown to promote a quantitative and qualitative improvement of semen parameters and pregnancy rate. Mean duration of FSH administration is 11.77 ± 2.59 weeks and the mean cumulative r-FSH dose used is 7168.75 ± 4815.47 IU.[4] Additionally, reduction in sperm aneuploidy[5] and DNA fragmentation index (DFI)[6] were demonstrated by r-FSH treatment.

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The FSHR gene polymorphisms are reported to influence male fertility by affecting the receptor sensitivity and expression.[3] The Serine 680 Asparagine (Ser680Asn) polymorphism is widely studied and reported in various ethnic groups.[7] In women, it influences the ovarian response to FSH. In males, the role of polymorphism, although not associated with FSH levels, is linked to phenotypic expression and severity of spermatogeneic impairment.[8] Inability to predict responsiveness to treatment with r-FSH remains a great limitation to the relatively expensive r-FSH therapeutic approach today. FSHR gene polymorphisms were proposed as promising, predictive, pharmacogenetic markers for FSH response.[9,10] Men with homozygous Asn of Ser680Asn were reported to have better response to r-FSH treatment not only in improving seminal parameters but also resulting in favorable assisted reproductive technology (ART) outcome and spontaneous conception.[11] Few studies proposed role of combinations of genotypes in response to r-FSH and some showed contradictory results.[12] In this context, we present a case of severe Oligoathenoteratozoospermia (OATS) with favorable response to r-FSH treatment, which may be attributed to the pharmacogenomic marker on FSHR gene. To our knowledge, this is the first case presented in Indian population.

CASE REPORT

Clinical presentation

Primary infertility couple, married for 8 years with two unsuccessful ovulation induction cycles attended clinic for fertility treatment. Male partner showed severe OATS with a count of 3 million/mL, total motility 7% (progressive A 2% and nonprogressive B 5%), and morphology 2% (Kruger classification). Acrosome intactness was 15% and DFI was high at 27%. Scrotal Doppler was normal. Hormonal tests showed normal FSH at 5.77 IU/L (1.5–12.4 IU/L), luteinizing hormone at 6.49 IU/L (1.8–8.6 IU/L), testosterone 15 ng/mL (<300 ng/dL), and prolactin at 6.9 ng/mL (<20 ng/mL). The patient was a nonsmoker, 73.2 kg, 1.65 m height [26.6 body mass index (BMI) kg/m^2], nondiabetic, nonhypertensive, had no erectile dysfunction, no injuries to groin or scrotum, no history of mumps or TB, and no history of major surgeries except a left varicocelectomy for grade III varicocele 3 years ago. Female partner was 27 years, BMI 20.2 kg/m^2, Anti-Mullerian Hormone (AMH) 1.71, appropriate for the age, normal pelvic ultrasound scan. No relevant medical or surgical history. Family history was unremarkable and both partners had normal karyotypes.

Genomic fertility analysis

A comprehensive genomic fertility analysis was performed using next generation sequencing technology to sequence multiple male fertility-associated genes. One hundred nanograms of genomic DNA obtained from blood and was used to process the custom designed multigene panel (Ion AmpliSeq™, Intas, India) using ion semiconductor technology (Ion Gene Studio S5 Sytem; Thermo Fisher Scientific, USA). Sequencing data was aligned to hg38, and variant caller was used to detect clinically relevant variants. The analysis revealed presence of a clinically correlating, missense, homozygous FSHR gene polymorphism, Ser680Asn at c.2039G>A. We ruled out AZF gene deletions, CFTR mutations, and other gene variants associated with male infertility by polymerase chain reaction (SimpliAmp, Applied Bio systems, Thermo Fisher).

r-FSH treatment and outcome

Following counseling regarding the genomic variation and pharmacologic treatment with r-FSH, recombinant human FSH (Follitropin Alfa, Intas, India) injection Folisurge 100 IU (INTAS, Ahmedabad, Gujarat, India) administered subcutaneously was commenced twice a week along with vitamins C and E and antioxidant supplements. Sperm count improved to 10 million/mL and motility improved to total motility 15% (progressive A 5% and nonprogressive B 10%) after 8 weeks of treatment. Folisurge was continued for another 4 weeks, and a repeat semen analysis after 3 months showed drastic improvement in seminal parameters with count going up to 25 million/mL, and total motility 25% (progressive A 10% and nonprogressive B 15%) and most importantly, significant improvement in DFI to 15% (normal range). There were no side effects in the index period. Controlled ovarian stimulation was performed with long downregulated antagonist cycle with 11 retrieved oocytes and 9 MII matured oocytes. Post-intracytoplasmic sperm injection (ICSI), seven embryos fertilized, three cleavage embryos transferred (fresh embryo transfer), and rest were cultured to blastocyst. Two blastocysts were frozen and rest discarded due to arrested growth. Pregnancy test was positive after 2 weeks. Initial ultrasound scans showed triamniotic trichorionic pregnancy. Fetal reduction was performed after nuchal translucency scan at 12 weeks and reduced to diamniotic dichorionic pregnancy, and is currently 19 weeks gestation.

DISCUSSION

In the absence of a rational pharmacologic treatment in these cases, clinicians attempt to stimulate spermatogenesis with various protocols. Spermatogenesis is a gonadotrophin-dependent process and the administration of r-FSH is one of the treatments known to improve sperm parameters in men with idiopathic infertility[13] and improves pregnancy rate, both spontaneous and by ART.[4] High heterogeneity to response, high costs, poorly understood pharmacodynamic effects of r-FSH, lack of clinical data on outcome, and bias based on female factor are some of the current challenges.[14] Indeed, data from the clinical studies indicated that the use of r-FSH would not be beneficial in about half of the patients. In such a situation, clinical evaluations should be corrected for confounding factors, such as pharmacogenetic markers.[3] Individual specific genotype-based pharmacologic approach can optimize the pharmacogenetic potential of r-FSH for infertility treatments resulting in successful outcomes.

The case demonstrates that r-FSH treatment significantly improves seminal parameters and reduces DFI in infertile men carrying Asn homozygous Ser680Asn polymorphism. Regarding the duration, treatment for at least two spermatogenic cycles is recommended[14] and we have shown positive results in 3 months with a dosage of Folisurge 100 IU twice a week. One study showed that men with Ser680Asn showed notable improvement in sperm hyaluronic acid-binding capacity with 1 month r-FSH treatment, emphasizing that viable r-FSH treatment is an available option prior to IVF/ICSI.[15] Large-scale studies on Indian population are needed to identify good responder group, optimize dosage and duration, and facilitate evidence-based Individualized FSH treatment for male infertility.

CONCLUSION

This study demonstrates that r-FSH administration in a man with idiopathic infertility and severe OATS carrying homozygous N680N FSHR genotype resulted in improved sperm quality and reduced sperm DFI, eventually leading to conception in first cycle of ICSI. We therefore propose that FSHR Ser680Asn genotype may serve as a clinically useful pharmacogenomic marker to identify good responders to r-FSH treatment.

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Conflicts of interest
There are no conflicts of interest.

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