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SHORT COMMUNICATION

The effects of liraglutide on male fertility: a case report



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Paula Fontoura got a biology degree from the State University of Rio de Janeiro in 2008. In 2009 she developed a specialization thesis on the "Relationship between oxidative stress, sperm DNA fragmentation and male fertility" at Sapietiae Institut of Fertility Clinic, Sao Paulo, Brazil. She continued her research career by getting a Master degree in Science from the State University of Rio de Janeiro in December 2011. After that she began a PhD project on the 'Correlation between sperm quality and IVF success: leptin's role on sperm function', a collaboration between the State University of Rio de Janeiro and the clinic VIDA, Fertility Center in Rio de Janeiro, Brazil.

Abstract Liraglutide is an agonist of the glucagon-like peptide I receptor, and is commonly recommended as a treatment for obesity and type 2 diabetes mellitus. Adverse effects related to liraglutide include acute pancreatitis and polyarthritis. No studies, however, have reported an adverse effect of liraglutide on male reproduction. This case report shows a deleterious effect of liraglutide on male reproductive function. 

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KEYWORDS: liraglutide, male infertility, male reproduction, spermatozoa

Introduction

Liraglutide is an agonist of glucagon-like peptide I (GLP-I), and is commonly recommended for the treatment of obesity and type 2 diabetes mellitus. Glucose-induced insulin secretion is stimulated by GLP-I agonists, which inhibits glucagon secretion, reduces gastrointestinal motility, and in turn reduces appetite and food intake, leading to weight loss (Ishøy et al., 2013; Marathe et al., 2013). Adverse effects of liraglutide treatment include acute pancreatitis (Famularo et al., 2012;

Knezevich et al., 2012) and polyarthritis (Ambrosio et al., 2013). This is a case report showing an adverse effect of liraglutide on male fertility.

Case report

A 35-year-old man experiencing primary and idiopathic infertility for one year presented to the clinic in November 2011. He had no previous family history of infertility and was seeking

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Table 1 Patient's spermiogram values.

Date	Semen volume (ml)	Sperm concentration ($\times 10^6$ /ml)	Sperm motility (% A+B)	Sperm morphology (%)	Leucocyte concentration ($\times 10^6$ /ml)
November 2011	2.5	51.6	55.6	8	0.8
March 2012	3.0	0.2	0.0	-	-
March 2012	1.1	0.0	0.0	-	-
May 2012	3.0	0.01	0.0	-	0.6
July 2012	2.7	8.7	48.1	2.5	0.1
August 2012	3.2	28	32.1	-	-
Reference values ^a	≥ 1.5	≥ 15	≥ 32	≥ 4	≤ 1.0

Dash means not evaluated.

^aReference values according to World Health Organization, 2010.

infertility treatment for the first time. He previously had surgery for myopia correction. He reported social drinking, physical activity twice a week and normal sexual function; his scrotal Doppler ultrasound was normal. His wife was also investigated and presented a normal blood screening and hormonal levels, no infectious serologies and no alterations in pelvic ultrasound screening, hysterosalpingography and hysteroscopy examinations. The patient's first spermiogram was carried out in November 2011, and showed normal parameters of semen volume, sperm concentration, motility, morphology and leucocyte count according to the sperm classification established by the World Health Organization (World Health Organization, 2010). The patient returned 4 months later for an intrauterine insemination. The semen analysis showed a 0.2×10^6 sperm/ml concentration and no sperm motility (100% type D spermatozoa) (Table 1). To confirm this result, the sperm collection was repeated after 6 h, and no spermatozoa were found, and the clinic doctors cancelled the intrauterine insemination procedure. At this time, the patient reported that he was taking a 0.6 mg dose of liraglutide, and that this was the only medication he was taking. He reported no changes in his lifestyle, nor any flu or fever. He also reported that he had no history of infertility in his family, and that the only family history of disease he had was his father's obesity. He began taking liraglutide in October 2011 (1 month before the first and normal sperm analysis) because of a slight increase in his glucose levels and his high weight (100 kg). Because liraglutide was the only medication he was using at that time, the patient was advised to make an appointment with his doctor to consider the possibility of interrupting the drug treatment. The patient used liraglutide for 5 months and lost 2 kg during this period.

Two months after the medication was interrupted, a new spermiogram was carried out for the patient. The results showed normal semen volume, normal leucocyte concentration, a sperm concentration of 0.01×10^6 sperm/ml, and no sperm motility (100% type D spermatozoa). The sperm morphology could not be assessed owing to the low sperm concentration. Two months later (4 months after liraglutide interruption), a new spermiogram showed normal volume, normal leucocyte concentration, an 8.7×10^6 sperm/ml concentration, normal motility and 2.5% normal morphology (Table 1). Although the motility was recovered and the sperm production was increased, the sperm concentration was not normal. This sample was frozen as a precaution, and the couple

started an IVF treatment. One month later (5 months after liraglutide interruption), on the day of the oocyte retrieval, the semen analysis showed normal values for all parameters (Table 1). Therefore, the doctors decided to use this fresh sample for oocyte fertilization. Of the four oocytes retrieved, three were mature, and were used for the intracytoplasmic sperm injection (ICSI) procedure, resulting in 100% fertilization. Two class A embryos (according to the ASEBIR classification, (ASEBIR, 2008)) were transferred on day 2 of embryo development, and the remaining embryo was vitrified at the blastocyst stage. The couple had a successful pregnancy and gave birth to twins after 36 weeks. This study had the patient's written consent.

Discussion

Liraglutide has been shown to have adverse effects, such as acute pancreatitis (Famularo et al., 2012; Knezevich et al., 2012) and polyarthritis (Ambrosio et al., 2013). In this case report, liraglutide use was found to cause interrupted sperm production, which was completely restored after 5 months of liraglutide interruption. Because spermatogenesis is a continuous process and germ cells take 72 days to complete their maturation, it would take approximately this time to recover normal sperm production after a complete halt of spermatogenesis. Unfortunately, the patient had a new sperm evaluation only 4 months after drug interruption. At this time, his spermiogram showed normal sperm motility and a sperm concentration of 8.7×10^6 sperm/ml. One month later, the patient had all normal sperm parameters. The US Food and Drug Administration (FDA communication, unpublished data <http://www.ehealthme.com/ds/victoza/sperm+count+decreased> accessed date: november 15, 2013) reported that, among 11,308 people with different adverse side-effects taking liraglutide, two of them reported having a decreased sperm count. It was not clear, however, how many patients were tested for fertility, the amount of time of drug treatment, or the values of the sperm parameters before and after liraglutide treatment.

Although the laboratory policy is to carry out one-half conventional IVF and one-half ICSI in the oocytes, it was decided that all the oocytes should be injected by ICSI for several reasons. First, there was a risk of total fertilization failure, because the patient's wife was 28 years old and showed a poor

ovarian response; furthermore, it was not known whether the medication would have an effect on sperm function. The patient did not exhibit any other adverse effects that have been previously described in the literature.

The first evidence for a role of GLP-1 in reproduction came from knockout mice. Pubertal delay occurred in female GLP-1 receptor knockout mice and reduced gonadal weight occurred in male GLP-1 receptor knockout mice had reduced gonadal weight despite normal steroid hormone levels in both sexes (MacLusky et al., 2000). In men, GLP-1 infusion reduced the frequency of testosterone pulses, suggesting an inhibitory effect on testosterone secretion that is independent of changes in LH levels (Jeibmann et al., 2005). In healthy men, 6-h GLP-1 infusion resulted in no change in LH levels or LH pulse frequency and amplitude (Jeibmann et al., 2005). Frequency of testosterone pulses in the 6-h time course in men is also reduced by GLP-1 infusion (Jeibmann et al., 2005).

Furthermore, the relationship between GLP-1 and male reproduction still needs to be clarified. The current data on GLP-1 and reproduction are scarce and controversial. No clear mechanism by which liraglutide affects the reproductive system can be provided. As this is a case report, it was not possible to carry out additional analyses. Therefore, it is not possible to indicate the potential effect of liraglutide on spermatogenesis. The only thing we can assume is that the drug influences the reproductive system, which leads to an arrest in spermatogenesis, probably by affecting the hormones and factors that regulate the gonads, such as gonadotropins, leptin, insulin and others. To our knowledge, this is the first report of a detailed case of adverse effects on male reproduction associated with liraglutide use. Further experimental studies should be conducted to clarify the mechanism of liraglutide's effects on the male reproductive system. Caution should be taken with liraglutide treatment in male partners of couples who are attempting to become pregnant.

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