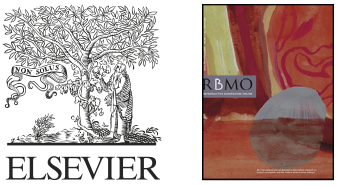
RBMO



COMMENTARY

Safe and successful use of oocyte in-vitro maturation in two infertile women with multiple sclerosis

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ABSTRACT

There is evidence to support an impact of ovarian stimulation with gonadotrophin-releasing hormone analogues on the progression or recurrence of multiple sclerosis. In addition, there is no universally acknowledged approach toward ovarian stimulation in patients with multiple sclerosis. This report describes two patients at a large tertiary university hospital who underwent an in-vitro maturation protocol in order to avoid a risk of exacerbating their multiple sclerosis by ovarian stimulation. Both patients were referred to the infertility clinic because of the concern of exacerbation of multiple sclerosis during or after ovarian stimulation treatment. The patients underwent the in-vitro maturation protocol to avoid ovarian stimulating agents. Both patients gave birth to healthy babies at term. They did not suffer any relapses of multiple sclerosis during their treatment or during pregnancy. Exacerbation of disease related to ovarian stimulation encourages the search for a safer approach to these patients. To the authors' knowledge, these are the first babies described in the literature who were born after in-vitro maturation to mothers suffering from multiple sclerosis. In-vitro maturation can thus be recommended as an alternative in suitable women with multiple sclerosis.

INTRODUCTION

In-vitro maturation (IVM) is an assisted reproductive technology (ART) involving the maturation in special culture environments of immature oocytes retrieved without ovarian stimulation from ovaries carrying follicles of less than 10–12 mm in diameter. The first live births using IVM in infertility practice were reported in the 1990s (*Cha et al., 1991*). Since then, this approach has been successfully used in particularly high responder infertile patients.

Multiple sclerosis is the most common neurological condition and mainly affects women during their reproductive years (*Niedziela et al., 2014*). Studies analysing the effects of ART in multiple sclerosis have shown a significant increase in the annualized relapse rate after IVF (*Hellwig et al., 2008*). This increase was particularly observed in those patients using gonadotrophin-releasing hormone (GnRH) agonists. In the current literature, it is suggested that many complex interactions between hormonal and immune factors may be associated with increased disease activity.

This report describes two patients who were eager to participate in IVM treatment. The authors therefore aimed to investigate whether IVM of immature oocytes from unstimulated cycles could be an alternative treatment option for patients suffering from multiple sclerosis. The group's clinical pregnancy rate for IVM among patients with polycystic ovarian morphology/polycystic ovary syndrome (PCOS) has previously been reported as 30% (*Gulekli et al., 2011*).

MATERIALS AND METHODS

The first patient (aged 28 years) was diagnosed with multiple sclerosis and had been suffering from primary infertility for 3 years. Her neurologist (E.I.), who was responsible for her treatment,

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KEYWORDS

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referred her and recommended against using GnRH agonists. The patient's comorbidities were not limited to multiple sclerosis; she had survived acute lymphocytic leukaemia more than 20 years previously, was wearing an insulin pump for type 1 diabetes and had hypothyroidism. Her husband's sperm analysis was normal (normozoospermic, 40 × 10^6/ml, with 4% normal morphology according to Kruger's criteria). Ultrasonographic examination of her ovaries was performed at the beginning of the woman's menstrual cycle, and a human chorionic gonadotrophin (HCG) trigger (250 µg subcutaneously) was administered on the ninth day of the cycle (when the diameter of one follicle had reached 10 mm). An oocyte retrieval procedure was performed 35.5 h later.

Ten immature oocytes were retrieved from an unstimulated cycle. The oocytes were placed in an IVM medium (MediCult IVM System Maturation Medium, CooperSurgical Fertility & Genomic Solutions, Denmark) at 37°C, 6% CO_2 and 95% humidity for 24 h and went under a hyase procedure. On the first day, five metaphase II (MII), three metaphase I (MI), one germinal vesicle (GV) and one degenerated oocyte were observed. Intracytoplasmic sperm injection (ICSI) was performed on the five MII oocytes. On the following day, two of the five oocytes were fertilized (producing two 2-pronuclear [2PN] zygotes). The three MI oocytes had matured and ICSI was performed on these three MII oocytes. The last oocyte remained arrested at the germinal vesicle stage. On the third day, one of the 2PN zygotes had developed to a 4-cell grade 1 embryo. Two of the three oocytes that had undergone the ICSI procedure on the second day had produced 2PN zygotes. One day later, one of them had developed into a 4-cell grade 2 embryo, while the other embryo had developed into an 8-cell grade 1 embryo. The 8-cell grade 1 embryo was transferred on day 3.

The second patient (aged 29 years) had a history of 8 years of primary infertility. She had been diagnosed with multiple sclerosis approximately 5 years before her admission to the clinic. She also had PCOS. After being unable to conceive for 3 years, she had visited another clinic and undergone ovarian stimulation for an intrauterine insemination cycle but suffered from partial loss of vision, which was shown to be an episode of multiple sclerosis with optic neuritis. Later, a hysterosalpingogram showed bilateral tubal occlusion and she was advised to visit an IVF clinic. She did not have any comorbidity except multiple sclerosis, and her neurologist (E.I) advised against ovarian stimulation with GnRH analogues. Her husband's sperm analysis was normal (normozoospermic, 55 × 10^6/ml, 4% normal morphology according to Kruger's criteria). Ultrasonographic examination of the patient's ovaries was performed at the beginning of her menstrual cycle, an HCG trigger (250 µg subcutaneously) was administered on the 11th day of the cycle (when the diameter of one follicle had reached 10 mm) and the oocyte retrieval procedure was performed 35.5 h later.

Twenty-six immature oocytes were retrieved from this unstimulated cycle. The oocytes were preserved in the same IVM medium as above (MediCult IVM System Maturation Medium, at 37°C, 6% CO_2 and 95% humidity) for 24 h and then subjected to a hyase procedure. At the end of the first 24 h, 11 MII, four MI, seven germinal vesicle and four degenerated oocytes were observed. The 11 MII oocytes underwent ICSI. On the second day, all 11 oocytes had developed into 2PN zygotes. All the MI and one of the germinal vesicle oocytes (five oocytes in total) had advanced to MII oocytes and ICSI was performed on these. On the third day, 10 of the 11 2PN zygotes had developed into embryos, while three of the later five MII oocytes produced five 2PN zygotes. These three developed into embryos 24 h later. At the end 13 embryos had been obtained in total. On day 2 after oocyte retrieval, three embryos (one 6-cell grade 1, and one 8-cell grade 2) were transferred, and six embryos were frozen for future use.

According to the policy of Institutional Review Board (IRB) at the study institution, published on 9 November 2019, IRB approval is not required for case reports. Informed consent was obtained from both patients for publication before the beginning of their treatment.

RESULTS

In the first woman, clinical pregnancy was achieved after embryo transfer. She developed no gestational complications until the last weeks of pregnancy. No new multiple sclerosis episode occurred, and her glycaemic regulation was normal with regularly adjusted insulin regimens. She was diagnosed with gestational cholestasis shortly before delivery. Her condition was stable after administration of ursodeoxycholic acid, and her symptoms reverted after delivery. She gave birth to a baby girl via Caesarean delivery, at a gestational age of 38 weeks and 3 days. The baby's birthweight was 4240 g, and mother and baby were discharged without any complications.

The second patient underwent a transfer of three embryos and was later diagnosed with a dichorionic diamniotic twin pregnancy. No gestational complications were observed. There were no new episodes of multiple sclerosis. She gave birth to two girls at a gestational age of 38 weeks 0 days via Caesarean delivery (birthweights 3090 g and 2620 g). The mother and babies were discharged without any complications.

The follow-up periods were 3 years for the first patient and 1 year for the second. Both women are regularly examined by the neurology department of the study institution.

DISCUSSION

Despite many studies having already been performed on it, IVM is not currently a conventional treatment, and in many centres focusing on ART is seen as an substitute treatment. Nevertheless, the literature has indicated that it is possible to use IVM in nearly all areas where IVF is used and it has a solid position in fertility preservation and the management of ovarian hyperstimulation syndrome (OHSS). After human menopausal gonadotrophins (HMG) had become available in the IVF industry, either alone or in combination with clomiphene citrate, HMG became a popular drug for ovarian stimulation protocols (*Lopata et al., 1978*). Down-regulation with a GnRH agonist or antagonist is frequently performed to down-regulate the hypothalamic–pituitary gland axis and prevent an uncontrolled LH surge and ovulation. Although HMG increased the number of oocytes and enhanced the chances of pregnancy, they can also cause OHSS, which can lead to fatal complications for even normally healthy women (*Delvigne and Rozenberg, 2003*). This is among the many reasons why IVM won popularity as an alternative in the

1990s. According to a worldwide review analysis, more than 5000 babies have been born using IVM (*Sauerbrun-Cutler et al., 2015*).

The current status and controversies relating to IVM have recently been reviewed (*Gulekli and Olgan, 2016*). Although the classic indication for IVM is PCOS or polycystic ovaries PCO, there are now also other indications: use in poor responders, for fertility preservation in cancer patients, for normal responders with a history of poor oocyte/embryo quality, and in oocyte donation. The growing concern among neurologists regarding the potential for exacerbations of multiple sclerosis from ART is encouraging the search for safer approaches in these patients. As ovarian stimulation is often considered inevitable for ART procedures, many patients with multiple sclerosis are exposed to GnRH agonists or antagonists during their treatment. Michel and colleagues observed an increased relapse rate of multiple sclerosis after IVF (*Michel et al., 2012*). Their data demonstrated that relapses were associated with use of GnRH agonists and IVF failure. In a recent study from Argentina (*Hellwig and Correale, 2013*), a cycle of ART was associated with a sevenfold increase in risk of clinical relapse.

Fortunately, pregnancy reduces the risk of relapse in patients with multiple sclerosis. According to a study by Houtchens and co-workers, adjusted monthly rates of total multiple sclerosis relapses are lowest during pregnancy (*Houtchens et al., 2018*). Increased oestrogen concentrations are among other changes that seem to help the immunomodulation that provides the protection against multiple sclerosis during gestation (*Voskuhl and Momtazee, 2017*). Throughout the puerperium, however, the relapse rate is expected to be higher than during the pre-pregnancy period (*Houtchens et al., 2018*). Fortunately, the women presented in the current study did not suffer any relapses during the puerperium.

The two women reported in this article are successful examples of a different approach to patients with multiple sclerosis. The literature regarding a risk of relapse of multiple sclerosis following ovarian stimulation is still far from determining a safe ovarian stimulation protocol. An unstimulated cycle is a striking alternative for infertile women with multiple sclerosis. This reports presents two patients who underwent an IVM protocol only because their comorbidity was multiple sclerosis, and they successfully gave birth to three children between them. To the authors' knowledge, this is the first report in the literature of three babies born by IVM to mothers suffering from multiple sclerosis. The suggestion is therefore made that IVM can be recommended for suitable women with multiple sclerosis as an alternative to IVF. In the authors' opinion, multiple sclerosis can be considered as an indication for IVM.

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