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Contraception and *In Vitro* Fertilization in Young Women with Multiple Sclerosis: Review

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Multiple sclerosis (MS) is a chronic neurological disorder characterized by myelin sheaths damage, focal inflammation, gliosis and axonal degeneration. It affects predominantly women and the onset of the disease is at their child-bearing age. Myelination, a form of neural plasticity represents an important but poorly understood step to the process of repair. Unfortunately, cells that produce myelin can also be damaged which limits the ability of the brain to recover affected areas. The risks and benefits of using disease-modifying therapy during the various stages of a woman's reproductive life are topics that need attention. Since MS predominantly affects young women and is a hormone-dependent disease, then hormonal methods of contraception should be carefully discussed. Additionally, *in vitro* fertilization that also uses hormonal agents should be avoided. For that reason the pursuit of personalized medicine requires development of reliable biomarkers to predict the course of the disease and the response to therapies of this socially significant disease.

Key words: multiple sclerosis, contraception, contraceptives, *in vitro* fertilization, sex hormones.

Multiple sclerosis (MS) is the most common autoimmune inflammatory demyelinating disease of the central nervous system (CNS). Many young individuals are affected. Although the basic pathology of MS was already recognized in the 18th century, its causes and pathogenesis remain elusive. Relapsing-remitting multiple sclerosis (RRMS) accounts for approximately 80-85% of all MS cases. It affects 3 to 4 times more women than men, and many of these women are of child-bearing age. MS is characterized by intermittent or chronic damage to the myelin sheaths, focal inflammation, gliosis and axonal degeneration. The disease is both related to age (decreasing in elderly patients) and to sexual dimorphism [4]. Myelination, the process in which oligodendrocytes coat CNS axons with a myelin sheath, represents an important but poorly understood form of neural plasticity that may be sexually dimorphic in the adult CNS [6]. In response to demyelination oligodendrocyte precursor cells (OPCs) also considered as a type of adult neural stem cell, become activated. They proliferate, migrate and fill up the demyelinated lesions causing remyelination.

Addressing the reproductive concerns of women with MS is vital for comprehensive care [1]. Contraception, pregnancy, and breast-feeding remain disturbing questions to the woman with MS. The risks and benefits of using disease-modifying therapy dur-

ing the various stages of a woman's reproductive life are topics of great importance. Although physician's primary duty is to the patient, it is vital also to consider the fetus and later the child. Thus, the medical decisions that the patient is making should be guided by the physician after taking into account the patient's motivation for those decisions, including family obligations, cultural norms, and patient values [11]. Nowadays, it is considered that oral contraceptives are capable of offering health benefits beyond contraception. Some studies were designed to test the hypothesis that hormonal contraception brings certain health benefits. These were documented for several medical disorders including rheumatoid arthritis, multiple sclerosis, menstrual migraine and in perimenopause. Despite the benefits though, it is still outside the product license to use them in the majority of cases.

Recently, it has been suggested that hormones, including sex hormones, can affect and be affected by the immune system. Sex hormones have been linked to the disease activity in multiple sclerosis. Since they have major influence on brain and spinal neurons possible effect of the hormonal treatments used during assisted reproductive techniques may trigger some short-term disease processes. There is an increasing body of evidence that estrogen, progesterone, and testosterone provoke immune responses and influence damage repair in the nervous system and play an important role in neuroprotection following brain injury both *in vivo* and *in vitro* [3]. Estrogens and progestin may be the basis for such a new therapeutic approach and could help protect against myelin loss. Both types of hormones have been shown to promote the viability of neurons and the formation of myelin [5]. Sex steroids (particularly estrogen, androgen, and progesterone) also play an important role in neuroprotection following brain injury both *in vivo* and *in vitro* [9]. Moreover, hormones such as prolactin, vitamin D, leptin and gherlin may be used to modulate the immune response and may also influence the course of MS [12]. On the other hand, the role of male steroids in neuroprotection is less clear. For example, higher estradiol levels in men with MS were linked to a greater degree of brain tissue damage whereas testosterone proved to exert a protective role. Higher levels of testosterone in men may partially account for the fact that women with MS outnumber men. Apart from the protective role of testosterone a protective role of the pregnancy hormone estriol in pregnant women has been reported [14].

Infertility and MS might coincidentally come together and, therefore, these women might undergo assisted reproductive treatment (ART). Exogenous sexual steroids together with pregnancy have been shown to influence the risk of relapses in MS. Treatments used during assisted reproductive techniques may consequently influence the short-term evolution of MS by modifying the hormonal status of the patient thus increasing the risk of developing relapses or exacerbations in women with MS after *in vitro* fertilization (IVF) [10]. Other mechanisms involved in the worsening include temporary interruption of disease modified therapies, stressful events associated with infertility, and immunological changes induced by hormones such as increase in pro-inflammatory cytokines, as well as an increase in immune cell migration across the blood-brain-barrier. Women with MS who undergo IVF via hormonal injections may have an increased risk for relapse, a new study suggests. It is proposed that the increased risk is correlated with the use of GnRH (gonadotropin-releasing hormone) agonists leading to IVF failure [2]. The increased risk of relapse is particularly if the procedure does not result in a pregnancy. Furthermore, because there is a reasonable doubt that gonadotropin-releasing hormone agonists may make patients more prone to such an increase in relapse rate, gonadotropin-releasing hormone antagonists might be preferred for IVF protocols [10]. Prolactin (PRL) is a neuroendocrine peptide with potent immunomodulatory properties. Hyperprolactinemia enhances several autoimmune disorders and may play a role in the pathogenesis of MS. Significantly higher prolactin levels in serum

and cerebrospinal fluid (CSF) were found in female RRMS patients compared to males. The elevated PRL levels could be the result of an increased predisposition of females to synthesize and release PRL [3].

It is known that in women the artificial termination of pregnancy and childbirth leads to new attacks of the disease. Therefore, for women suffering from multiple sclerosis it is important to choose appropriate contraception on the advice of a gynecologist. Contemporary medicine has gained sufficient knowledge in the treatment of multiple sclerosis, unfortunately there are still no radical methods to treat it.

Women with MS or clinically isolated syndrome (CIS) were more likely to have used oral contraceptives in the 3 years before their diagnosis than women who did not have MS or CIS, the results of a new case-control study show. Independent of age, smoking status and obesity, there was a link between the use of oral contraceptives and the development of the first symptoms of MS. These findings suggest that using hormonal contraceptives may be contributing at least in part to the rise in the rate of MS among women. Hormones play an important role in many diseases, and it is known that pregnancy – which is associated with high estrogen levels – is protective against relapses in women who already have MS, so hormones appear to be involved in some way in this disease. Hughes noted that one idea is that low estrogen levels may trigger autoimmune disease, but there is no information on possible thresholds necessary for a protective or harmful effect. The researchers did not measure other factors associated with the lifestyle of modern women, such as diet, activity levels, or how long they spent outside, so several potential confounders were probably not accounted for [8].

The roles of progesterone (Pg), an immunomodulatory sex steroid, are poorly understood. Pg's immunomodulatory effects differ from those of estrogens and androgens. At pregnancy levels, Pg may suppress disease activity in MS [7].

POP (progestin only pills) is usually preferred during the postpartum period for its minimally suppressive effect on lactation. Considering the effect of progesterone on the myelin sheaths, it can be argued that POP can be an effective choice of contraception for MS patients during the postpartum period [13]. Because MS is usually observed among women of the reproductive age, the question about the most reliable contraceptive option for these patients will always be the first one for clinicians to answer. While in earlier studies the idea of using hormonal contraceptives in MS patients was not opposed, a recent study suggested that certain hormonal methods may increase the risk of developing MS or MS-like symptoms. Angiogenesis in MS causes neovascularization and a rise in the vascular supply of nutrients and migration of inflammatory cells to demyelinating lesions. Based on recent findings, it is recommended that clinicians should prescribe selective nonhormonal contraceptives such as copper-containing intrauterine devices (IUDs) in all phases of MS disease to be on the safe side. Those IUDs release free copper and copper salts into the uterine cavity without increasing serum copper levels in women with IUDs. Early analyses suggested that IUDs cause pelvic inflammatory disease (PID) in women. However, more recent studies have found no increased risk of PID in monogamous women with IUDs. It can be assumed that MS attacks can be triggered by the presence of infection in the genital tract. Based on the data in literature, it can be concluded that copper-containing IUDs can be safely used by MS patients. Additionally, the use of diaphragms increases urinary tract infections in women and can induce MS symptoms with mechanisms similar to those mentioned above. Additionally, when counseling about contraception methods for MS patients, each case should be individually evaluated on the basis of the severity of the disease and patient' s lifestyle. It proves logical that further studies are needed to come to a definitive conclusion regarding the identification of potential adverse effects of various hormonal and nonhormonal contraceptive methods [13].

In conclusion, all these findings can help establish a differential therapeutic concept in MS, which would allow treating MS women selectively according to their pathogenetic subtype and disease status. Advances in the understanding of the diagnostic significance of woman with multiple sclerosis may lead to novel therapeutic strategies in the future. Since MS is a hormone-dependent disease, then in the choice of contraceptive methods for young women diagnosed with MS should be carefully chosen.

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