INTERNAL MEDICINE - PEDIATRICS

MULTIPLE SCLEROSIS AND PREGNANCY

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MULTIPLE SCLEROSIS AND PREGNANCY (Abstract): Multiple sclerosis is one of the main reasons for invalidation of young adults of both sexes. The disease is more common in women than in men. The illness begins most frequently in patients between the ages of 20 and 40 years, which is also the most fertile period for women. MS is an immune-mediated disease with chronic evolution marked by exacerbations and remissions that amplify the degree of disability. The most common clinical picture is the one with relapse and remission whose evolution is greatly improved after immunomodulatory treatment. We have revised the literature together with the data from the national multiple sclerosis society and the cases that are in the National Programme of Multiple Sclerosis, mainly the ones that are assigned to the regional center of Iaşi, at the Neurology Clinic inside the Clinical Rehabilitation Hospital Iaşi. Pregnancy is quite frequent in female patients with MS. Certain risks are present during pregnancy, birth and breastfeeding and certain protocols must be applied, such as interrupting the immunomodulatory treatment before the conception. Child delivery must be closely monitored and it must take into consideration the dysfunction that the patient has and be adapted to the existing deficits. There are some methods that may be used during delivery for female patients with multiple sclerosis in order to make this process smooth and reduce the risk of postpartum complications. Multiple sclerosis is an invalidating disease, with a high prevalence in women. Pregnancy in patients with MS is not such a natural phenomenon as in a healthy female and it requires a multidisciplinary team in order to ensure the safety of both the mother and the newborn. Keywords: MULTIPLE SCLEROSIS, PREGNANCY, BREASTFEEDING, BIRTH.

Multiple sclerosis is one of the main reasons for invalidation of young adults of both sexes. The disease is more common in women reports of 2:1 or even 3:1 being cited. The illness begins most frequently in patients between the ages of 20 and 40 years but can affect also children, adolescents and adults over 50 years (1). The prevalence is 30-150 cases per 100,000 inhabitants and depends on geographic location among others. Multiple sclerosis (MS) is a disease with increasing prevalence in temperate regions and also as we move away north or south of the 45th parallel.

MS is an immune-mediated disease with chronic evolution marked by exacerbations and remissions that amplify the degree of disability. The most common clinical picture is the one with relapse and remission whose evolution is greatly improved after immunomodulatory treatment (2). This form can go into secondary progressive form which requires changing the type of interferon therapy. There are primary progressive forms
which often do not respond to current immunomodulatory treatments. In the last years it was identified the so-called clinically and radiological isolated syndrome that can be treated effectively with some of the known immuno-modulatory therapies (3).

More than half of the female patients with MS are in their fertile period of life which means that while taking the treatment they resort to contraception methods. The efficacy of the disease-modifying therapy has made more and more female patients to want their first child in terms of a significant decrease in the annual rate of relapses and "relapse free" period. At several of the female patients with MS clinical and imaging stabilization was found and approaching or exceeding the age of 30 years has generated a desire for pregnancy which should develop in optimal conditions without adverse effects on the mother or newborn. There are risks related to the possibility of transmitting the disease, worsening health of the mother, the difficulties at birth, during breastfeeding and resumption of immunomodulatory therapy (4).

There were identified multiple genes that may negatively influence the risk of developing the disease in combination with certain environmental factors. Loci have been identified with the help of the major histocompatibility complex (MHC) and seem the most significant encoding IL2R and IL7R. If the mother or father has MS the risk for the children to develop the disease is 3-5% compared with the general population where the probability is only 0.2%. If both parents have MS risk increases to 29.5% (5). Among the environmental factors involved temperate climate, exposure to sunlight, disease prevalence in the geographical area of birth etc are involved. In the northern hemisphere the risk of disease is higher in offspring’s born in spring compared to those born in winter. The same phenomenon takes place in the southern hemisphere and it is related to sunlight exposure of pregnant patient. Reduction of exposure to sunlight may cause a vitamin D deficiency which would not exert immunomodulatory effect under the influence of the MHC (6).

The health of the mother may suffer some aggravation especially after birth, but therapeutic strategies to prevent and counteract undesirable events exist. We can expect the apparent worsening of pre-existing dysfunction or the appearance of new events.

Underlying dysfunction may be of motor type related to sphincters, digestive, sensory, fatigue and seem to be due to the state of pregnancy associated with weight gain. Excess weight can decrease motility already affected by demyelinization more or less extended to some fibers of the cortico-spinal tract. Existing spasticity and ataxic elements may contribute to gait problems.

The presence of demyelinating plaques localized in the spine and the impact of the pregnant uterus on thoraco-abdominal-pelvic cavity can generate or amplify urgency, constipation, mild ventilatory dysfunction. Some sensitive changes related to failure notification to the urinary passage through the urethra, the presence of paresthesia, constrictive or existing areas of hypoesthesia can be easily determined.

Depending on the effort and the temperature of the external environment, the increase in intensity and prolonged daily presence of the fatigue phenomenon can be present. Fatigue has among psychological components also motor ones that exacerbate when the body temperature or of the environment increase or by immersion in hot water. Fatigue can easily change bio-
rhythm prolonging the patients’ rest and sleep (7).

The main event announcing the unfavorable evolution both during pregnancy and beyond is the relapse. Although the effect of pregnancy on the evolution of MS is of protective type exacerbations can occur both during pregnancy and after giving birth. PRIMS study says the annual rate of relapse during pregnancy decreases from 0.6 relapses/year before conception to 0.2 relapses/year in the last weeks of gestation. The danger of relapse seems to outline and amplify after birth when the annual rate reaches 1.2 relapses/year interfering with breastfeeding (8).

The occurrence of a relapse during pregnancy requires differentiated treatment depending on the stage of pregnancy. In the first trimester of pregnancy methylprednisolone may not be administered because there were identified cases of children born with malformations of the palate and cataract. Depending on the extent of dysfunction there can be taken into account relapse therapy with methylprednisolone 500-1000 mg/day for 3-5 days in the second and third quarters of the pregnancy. It is known that methylprednisolone can pass through the placenta and can induce preeclampsia, gestational diabetes, venous thrombosis, low birth weight of the child, postpartum adrenal insufficiency. Immunoglobulin (0.2-0.4 g/kg/day, 5 days) seems to be more secure and hassle-free. It is considered as belonging to the same relapse the dysfunction that occur which extend to 30 days after onset. Plasma exchange can be practiced, similarities in the evolution of pregnant patients who have myasthenia (9).

In the first quarter after birth the risk of a new relapse increases, in which case we have to choose between treatment of relapse or discontinuation of breastfeeding.

There are therapeutic strategies using bolus methylprednisolone 3-5 days and evacuating the milk secreted after each injection.

The most important moment is the birth itself. The obstetrician and anesthetist must choose the safest solution for the mother and fetus taking into consideration the already existing neurological dysfunctions.

MS does not have any contraindications to vaginal birth or for cesarean. The decision for natural childbirth should take into account maternal age, existing neurological dysfunction at the time, the phenomenon of "fatigue", the fact that the mother is at her first pregnancy or not. The presence of a pyramidal syndrome with paraparesis requires special adaptation with a position in lateral decubitus with the lower limbs supported by a support. Labor and birth in water may be a solution with protective effect by the supporting force and push from the bottom up of the liquid and low body temperature of the pregnant patient in order to prevent fatigue.

Some studies of female patients with MS who gave birth vaginally say that forceps usage was more frequent in comparison with the healthy population. This maneuver would replace the motor and sensitive deficits of the mother with origin in the brain or spinal cord.

Caesarean operation is most commonly practiced type of birth in patients with MS being a deliberate choice that is practiced before the onset of labor in order to avoid possible complications (10).

There are some decisions to make about anesthesia. Most opinions converge towards the use of drugs such as Entonax, Pethidine or TENS machine. There is a preference for epidural anesthesia in comparison with the spinal one. The presence of the anesthetic in high concentrations in CSF is associated with increased annual
rate of postpartum relapse being suspected a potentiation of low spinal demyelination (11). There were described several cases in which after the anesthesia it was found the so-called autonomous dysreflexia which consists of hypertension spikes, headache, cold sweats and anxiety (12).

Breastfeeding should be encouraged because there is no risk of disease transmission through breast milk. If the mother should receive a drug, it will reach the baby. Planning pregnancy is one of the important moments in the life of female patients with MS. There is some risk of disease worsening if the immuno-modulatory treatment is stopped for at least 15 months. In the first three months the birth control and immuno-modulatory drugs should be stopped. For patients treated with glatiramer acetat only two months of interruption should be enough. At least three months after stopping natalizumab should the conception process begin. Fingolimod requires only two months distance to conceive from the moment of interruption. Special measures should be taken for patients who were treated with combined drugs or only with mitoxantrone. The aggressiveness of this product and its teratogenic impact requires initial contraceptive therapy 6 months after stopping administration (13).

Fertility in female patients with MS is under the influence of contraceptive medication and the modifying disease treatment. Interrupting them is the first step towards planning pregnancy. There are no reliable data on negative influence of immunomodulatory medication on fertility, the increased risk of miscarriage in patients undergoing treatment with interferon beta being cited. Animal studies have shown reduced fertility after treatment with Natalizumab, a phenomenon that is not met by the use of fingolimod. Mitoxantrone has negative effects on fertility which means stopping it long before conception. Reduced effect of contraceptives may be induced by concomitant administration of drugs such as Modafinil, Phenytoin and Carbamazepine. Mitoxantrone or cyclo-phosphamide medications may exert negative influences on spermatozoons and oocytes.

Spontaneous fertility appears to be influenced in MS patients in which the effect of the medication is combined with some couple problems. Sexual dysfunction is a consequence of erection problems, motor deficit, sensory deficit, sphincter deficit or psychological issues. Decreased libido is a phenomenon that applies to both sexes and reduced testosterone in male patients will affect fertility. To counter some of the aspects of the disease and the treatment some methods such as in vitro fertilization may be used. The risk is to increase the annual rate of relapses. Cryostorage or egg cryopreservation followed by selfgrafting may be another solution (14).

Fertility in men appears not to be negatively affected; the recommendations are between continuing the treatment and discontinuation for some time before conception.

Our experience covers a total of 450 patients of whom more than half are women. Most of the female population is at fertility age (18-40 years).

A significant number of patients had one or more children before being diagnosed with MS and treated. After starting treatment more patients expressed a desire to have children. Our recommendations supported starting immunomodulatory treatment and follow-up to stabilize the evolution of the disease. This stabilization occurred after a minimum of 3 years and maximum of 5 years. At this time some patients have given up the desire to have
off springs because of the disease. Until now they were born 28 healthy children of whom a pair of twins. Our patients had no relapse during pregnancy or breastfeeding. They restarted immunomodulatory treatment within four months after birth.

The EDSS (disability score) of the female patients who gave birth was 1.5. The largest EDSS was 4.5 in a person aged 33 years old with 9 years of disease with initial treatment with glatiramer acetate and after birth being switched to interferon beta. At this moment she continues with interferon beta. We have treated a person who has made a second child under treatment with interferon beta. The average age of those who gave birth was 30 years.

**CONCLUSION**

Multiple sclerosis is an invalidating disease, with a high prevalence in women. Pregnancy in patients with MS is not such a natural phenomenon as in a healthy female and it requires a multidisciplinary team in order to ensure the safety of both the mother and the newborn. More studies are needed in order to have a specific protocol in the future.

**REFERENCES**

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