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MS and Pregnancy

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Multiple Sclerosis (MS) is a chronic neurologic illness affecting adults at the time in their lives when they are most likely to consider starting a family. It affects women disproportionately more frequently than men. Therefore, issues of conception, pregnancy, childbirth and child rearing become critically important in the overall management strategies of MS patients and have been of great interest to neurologists and reproductive specialists. Pregnancy has a variety of immunologic and clinical effects on women with MS.

Immunologically, MS is known to be a major histocompatibility complex (MHC)-class-II-associated autoimmune disease where T-cell mediated responses depend on MHC class II antigens on the surfaces of antigen-presenting cells. Pregnancy induces changes in the maternal immune system, including both immunosupression on a local level and a heightened state of immunocompetence on a global level. The serum of pregnant women contains high levels of biologically active substances. Some of them have known anti-inflammatory and immunosuppressant effects in humans, and others have been shown to be effective in experimental allergic encephalomyelitis (EAE) models. In addition, female sex steroids estriol and progesterone, particularly in late pregnancy, inhibit production of nitric oxide (NO) thus decreasing the rate of synthesis of proinflammatory cytokines TNF-α and IFN-γ. In the postpartum period, secretion of pro-inflammatory cytokines INF-γ, IL-12 and TNF-α is increased compared to the pregnant state, offering a possible explanation for observed increased clinical disease activity postpartum.

Clinically, Pregnancy in Multiple Sclerosis (PRIMS) was the first prospective study to assess clinical effects of pregnancy on MS in 254 women (269 pregnancies), who were followed for up to two years after delivery. Annualized relapse rate was the primary outcome measure, and was assessed throughout the study period. In the cohort, pre-pregnancy rate of 0.7 relapses per year decreased to 0.2 per year in the third trimester. The relapse rate increased again to 1.2 per year in the first 3 months post-partum. Despite this increased risk, 72% of women did not experience any relapses during that period. For the 21 months post-partum, the annualized relapse rate did not differ significantly from pre-pregnancy rate. Three variables correlated significantly with occurrence of a post-partum relapse: an increased relapse rate in the year before pregnancy, an increased relapse rate during pregnancy, and a higher EDSS score at the onset of pregnancy. Neither relapses nor disability progression were predicted by method of anesthesia, or subsequent breast-feeding state. Disability at the two-year mark was not influenced by pregnancy, delivery or post-partum period.

Some studies suggest a significantly lower risk of conversion to a progressive course of MS in women who became pregnant after the onset of the disease, suggesting a possible beneficial effect of pregnancy on the risk of developing MS. For each year of observation, a risk of entering a progressive course was 3.2 times higher in a non-pregnant state compared with that after pregnancy (P = 0.0029). In addition, the risk of disease onset at the time of pregnancy was reduced compared to post-partum and non-pregnant times, where the risk of MS onset was the same. A prospective five-year study compared the rate of progression in disability between childless women, women who had onset of MS after childbirth, and women who had onset before or during their pregnancy. The rates of disability increased most rapidly in nulliparous women.

There are no contraindications to Caesarean section or vaginal delivery in MS patients. Effects of the disease on pregnancy outcomes, risk of malformations, fetal birth weight or duration of pregnancy are not consistent. Some groups report no increased risk in incidence of pregnancy and labor and delivery-related adverse events in MS patients. However, some reports indicate higher rates of operative deliveries and induced labor as well as greater numbers of neonates with low birth weight or being small for gestational age in mothers with MS. MS-related symptoms such as neuromuscular perineal weakness and spasticity in addition to fatigue and exhaustion may be important contributing factors. Alterations in the tubes and uterine function due to neuronal dysfunction in pelvic organs could produce suboptimal intrauterine conditions and influence fetal growth.

Medication Safety. Table 1 details the common FDA approved and off-label immunomodulatory therapies used in MS and their FDA pregnancy category designations. While there is no consensus on management of MS patients throughout pregnancy, the general standard of practice among neurologists is to discontinue MS medications prior to the time of conception and to not restart them throughout the time of pregnancy and lactation period. Decision to breastfeed an infant post delivery should be based on the estimated risk of post-partum relapse and severity of MS prior to conception. There is no definitive evidence that breastfeeding is uniquely protective against post-partum relapse, and conflicting results have been recently reported in the literature.

Conclusions. Pregnancy is not associated with adverse outcomes in MS patients. Some evidence suggests possible beneficial effects of pregnancy on subsequent course of MS, although clear prospective data is limited. There is a consensus supporting the observation that the second and third trimesters of pregnancy are associated with a reduction in the frequency of relapses, which is followed by an

increase in the relapse rate postpartum. However, long-term relapse rates or disability progression do not seem to be affected by pregnancy in MS patients. The use of immunosuppressive or immunomodulatory agents in pregnancy is not routinely advisable due to limited available evidence for their safety for the developing fetus.

Women should be aware of specific risks of relapse in the postpartum period when planning a pregnancy, as well as of particular issues related to conception, labor and delivery and follow-up care. Young women with MS who desire children can be informed that there is no clear evidence of increased risk of malformations, preterm delivery, low birth weight, or infant death due to maternal illness.

Table 1. **Medication safety during pregnancy**. Adapted from Simone Ferrero, Stefano Pretta, Nicola Ragni. Multiple Sclerosis: management issues during pregnancy. Eur Journal of Obstetrics & Gynecology and Reproductive Biology 115 (2004) 3-9

Immunosuppressant Agents

Medication and FDA class	Placental transfer	Fetal and maternal risks
Cyclosporin A, Class C	Yes	Fetal growth restriction, prematurity; maternal risk of hepatic and renal toxicity
Cyclophospha-mide Class D	Yes	Impaired fetal growth, axial skeleton, limbs, eyes and cranio-facial malformations;
Methylpredniso-lone, Class C	Yes * (in metabo-lized form)	Rare newborn immunosupression; probably not safe in the first trimester but may be used in second and third trimesters
Dexamethasone, Class C	Yes	Neonatal leukocytosis
Azathioprine, Class D	Yes	Premature birth, respiratory distress, intrauterine growth restriction, lower birthweight, cases of neonatal immunoglobulin deficiency (few isolated reports)
Methotrexate, Class X	Yes	Craniofacial and limb defects, CNS abnormalities (anencephaly, hydrocephalus, meningomyelocele), maternal risk of miscarriage
Mitoxantrone, Class D	Unknown	Animal data only: low birth weight, developmental kidney anomalies; increased premature birth rate

Immunomodulating Agents

Medication and FDA class	Placental transfer	Fetal and maternal risks
Interferon β-1-b and β-1-a, Class C	Unknown	Spontaneous abortions
Glatiramer acetate, Class B	Unknown	None reported
Intravenous immunoglobulin, Class C	Yes	Probably safe in pregnancy
Fingolimod (Gilenya), Class C	Unknown	Not safe in pregnancy
Natalizumab (Tysabri) Class C	Unknown	Unknown. Should not be used in pregnancy; It is secreted in breast milk and should be avoided in lactation

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