Pregnancy in multiple sclerosis: influence on disease trajectory

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Abstract
The implications of pregnancy on multiple sclerosis (MS), and vice versa, is of great concern to female MS patients of child-bearing age. There is no evidence of worsening of MS-related long-term disability associated with pregnancy and breast-feeding, and there may even be some long-term benefits, although reverse causation remains an important confounder. Patients with more active disease have more to consider in terms of continuing disease-modifying treatment during pregnancy and immediately postpartum. Furthermore, tailored breastfeeding advice is recommended.

Multiple Sclerosis (MS) is more common in females than males, and tends to first present in early to mid-adulthood, meaning that many people with MS are women of child-bearing age. Evidence suggests that the disease itself has no negative impact on pregnancy outcomes or fertility.[1] There is, however, increasing interest in the impact of pregnancy on short and long-term disease outcomes in terms of relapse rates and disability. The mechanisms linking pregnancy and MS disease outcomes are relatively poorly understood, but likely result from a complex interplay between hormonal, immune and genetic factors. Understanding the implications of MS and its treatment on pregnancy and vice versa is an area of great concern to patients.

Pregnancy results in a reduction in MS relapse rate, followed by a transient increased risk in the immediate postpartum period. The reduction in relapse risk is most marked in the third trimester with a risk reduction of approximately 70%.[2] Large claims database studies have confirmed this finding; demonstrating that the risk of MS relapse declines during pregnancy (OR 0.62) and increases markedly three months postpartum to a higher level than pre-pregnancy (OR 1.71) before declining over the ensuing 12 months postpartum (OR=1.22).[3] Predictors of postpartum relapses include the number of pre-pregnancy relapses indicating highly-active disease, relapse rate during pregnancy and a higher disability score at conception (Kurtzke's Expanded Disability Status Score).[2]

Not all MS patients experience a disease rebound postpartum; approximately 28% of women experience a relapse in the 3 months postpartum.[2] A greater proportion of patients show radiological evidence of active MS in the postpartum period, with new or enlarging lesions present in 14/28 of patients on postpartum MRI and gadolinium-enhancing-lesions in 8/13 in a small case series.[4] However, the consequence of these observed changes on longer term MS outcomes beyond the pregnancy year remains uncertain.

Several mechanisms have been proposed to explain the improved MS relapse rate in pregnancy. Oestrogen and progesterone levels increase in pregnancy, which may have both anti-inflammatory and neuroprotective effects based on animal models of experimental allergic encephalomyelitis.[5] Oestrogen is thought to aid remyelination through mediating oestrogen receptors alpha and beta, expressed on T cells, regulatory B cells and dendritic cells through ligands in astrocytes and microglia.[6] Progesterone is involved in axonal protection and remyelination. There is believed to be suppression of the maternal immune system in pregnancy to prevent rejection of the foetus reflected by an increased anti-inflammatory Th2 response, reduced Th1 and Th17 responses. Furthermore, there are increases in the levels of regulatory T cells, as reflected by increased FoxP3 expression; as well as increased regulatory B cells.[7,8] In the postpartum period there are increased proinflammatory cytokines including IFN-gamma, IL-12 and TNF-alpha,[6] which may be associated with the precipitous decline in oestrogen and progesterone levels after birth.

In the last decade, there have been an increasing number of pregnant women exposed to disease modifying therapies (DMTs) early in their pregnancy (27% in 2006 vs 62% in 2016); additionally, a significant number of DMTs have rapidly become available over this period. A study using MSBase data demonstrated that pre-conception DMT exposure appears to protect against postpartum relapses.[9] However, managing patients who fall pregnant on newer high-efficacy treatments such as Natalizumab, which clinicians may consider using during pregnancy, particularly in the first and second trimesters, presents challenges due to pharmacodynamic considerations and the potential for rebound on cessation, particularly if no alternative DMT is commenced. The "protective effect of pregnancy" is not sufficient in at least some of these patients, who may suffer disabling relapses during pregnancy if therapy is withdrawn;[1] drug withdrawal may result in long term disability in at least some.[10]

Breastfeeding itself has neutral or potentially even protective effects on the risk of multiple sclerosis relapse post-partum.[11] Exclusive breastfeeding results in a rise in prolactin and its role in neurogenesis is controversial. Data suggests that prolactin is both neuroprotective supporting remyelination

and neurogenesis, and proinflammatory by stimulating T and B lymphocytes and macrophage cytokine release, thereby promoting the autoimmune process.[12] There have been some studies suggesting that earlier return of menses postpartum is associated with higher rates of disease relapse and lactational amenorrhoea can reduce this risk. Breastfeeding for greater than 15 months has been associated with a reduced risk of a recent diagnosis of MS/CIS compared to age matched controls (OR 0.47).[12] More recent data from population-based studies show that even breastfeeding for at least two months results in an over 60% reduction in the relapse risk in the early postpartum period, and this applies for women with more active MS prior or during pregnancy.[12]

However, population-based studies cannot fully overcome the role of individual choice as a potential confounder. The observation that breastfeeding protects against postpartum relapses is potentially confounded by the likelihood that patients with less active disease pre-pregnancy may be more likely to choose to delay restarting DMT for breastfeeding. Currently Beta-interferon and Copaxone can safely be resumed during breastfeeding; however, it takes three months following commencement of these therapies to reach peak efficacy. Corticosteroids for relapses are also safe in breastfeeding. Natalizumab, rituximab and ocrelizumab do cross into breast milk, but at low concentrations into the GI tract of the infant, resulting in very low maternal-infant transfer of these drugs.[13,14] Despite this, and understandably, due to the limited safety data available, many women choose not to recommence DMT during lactation. As it stands currently, there is no evidence that breastfeeding negatively impacts MS disease course aside from the potential of delaying highly active DMT recommencement.[1]

The effect of pregnancy on modulating MS course in the long term has been a topic of intense interest. A Danish MS register study[15] showed that in both men and women, parenthood correlates with a lower risk of MS implying it is a protective factor. In the AusImmune Study,[16] higher offspring number was associated with a lower risk of a first clinical demyelinating event risk among women but not in men, although this finding is not consistent.[8] Interestingly, one retrospective cohort showed that women with one or two pregnancies had earlier MS onset compared to nulliparous women or women with three or more children.[17] MS risk may be inversely associated with parity, age at first childbirth and proximity in time since most recent birth,[8] although reverse causality may be a cause for these observations as patients with established and more active MS may choose not to have children or to have less children, and the impact of an "MS prodrome" may change reproductive behaviour for some time prior to clinical MS development. It has been speculated that societal trends towards older maternal age and reduced offspring number may account for the increasing female incidence of MS over time.

Data from MSBase has suggested that pregnancy is independently associated with lower EDSS scores over 10 years of observation, and may be up to 4.5 times more potent than first-line DMTs (interferon- beta and glatiramer acetate).[18] These findings may imply that parenthood or pregnancy itself could be protective through epigenetic changes. There is mounting evidence that environmental factors, including hormonal factors associated with pregnancy, could lead to epigenetic changes influencing DNA methylation. This may account for the cumulative effects of pregnancy process on MS disease course in the long-term. It has been found that Th17 and Treg cells in pregnant MS patients have a particular epigenetic profile (cell-type-specific regulatory regions) that is regulated by the oestrogen receptor.[7]

Current guidelines do not support routinely deferring DMT in women with MS who wish to start a family due to the risk of early myelin, white matter, neuronal and axonal damage and progressive brain atrophy from untreated neuroinflammation, which is largely irreversible. Pre-pregnancy disease activity can aid clinicians to decide whether complete cessation of DMT or selecting either induction treatment, or highly active treatment with relative safety in pregnancy is appropriate. These decisions must always be taken in conjunction with individual patients, and with a thorough evaluation of risks and benefits associated with possible approaches. The introduction of new DMTs is rapidly changing the landscape for MS disease trajectory and needs to be taken into account in pregnancy. Some highly active DMTs, namely Natalizumab, are now deemed to be compatible with pregnancy.[1] Thus, women living with MS can be relatively assured their disease can be safely managed during pregnancy in most cases, under suitable expert advice.

What does this mean in terms of advice for patients? Breastfeeding does not increase relapse risk and in fact may be protective, but deferring DMT in a patient with highly-active disease to allow breastfeeding may be harmful. Thus, those women with relatively mild disease can, and should, be encouraged to breastfeed if they wish to do so. Women with more active MS will require individualised advice, which should be based on their desire to breastfeed along with their prior and future DMT preferences. Overall the effects of pregnancy on MS disease trajectory is not clear, but it seems that there is no large effect in the short and long-term. We can advise women that there is no evidence of worsening of MS-related long-term disability associated with pregnancy, and there may even be some long-term benefits of pregnancy over 10 years, although reverse causation remains a major confounder. As increasing numbers of registry studies report pregnancy outcomes with and without DMT exposure, and provide longer term data, our ability to help women with MS make the best decision for their individual situation can only improve.

MS, pregnancy and COVID-19 *Dr Ruth Dobson*

Concerns around infection with the novel Coronavirus SARS-COV-2 causing COVID-19 are particularly marked for both people with MS and pregnant women. People with MS who are also pregnant are thus likely to be doubly concerned regarding the current global pandemic. Pregnancy affects an individual's immune system, and responses to viral infections may differ in pregnant women. Much of the limited available data around COVID-19 infection and pregnancy derives from the obstetric literature, and as such, neurologists may not be familiar with the current advice.

Previous novel Coronavirus infections (SARS, MERS) were associated with increased risks of adverse outcomes including pregnancy loss and preterm birth, with case fatality rates up to 25% in pregnant women. Fortunately, this pattern has not been replicated thus far in COVID-19, and there does not appear to be more severe disease in women who are pregnant. However - the impact of critical illness during pregnancy on pregnancy-related outcomes is not insignificant, regardless of underlying aetiology. Physiological changes during pregnancy place additional strain on the cardio-pulmonary system, in addition to increasing susceptibility to infections; as such an increased risk of respiratory failure in the context of infection in pregnancy is of significant concern.

Emerging evidence suggests that vertical transmission (i.e. transmission between mother and baby) is possible, although the proportion of pregnancies affected and the significance for the neonate has yet to be determined. To date, viral RNA (indicating active viral infection) has not been detected in amniotic fluid, vaginal secretions, or breastmilk, although there have been case reports of SARS-COV-2 IgM detected in neonatal serum at birth. IgM is a large molecule, and does not cross the placenta, meaning that this is likely to represent a neonatal immune response to in utero infection. In addition, droplet spread between mother and baby during the neonatal period is highly plausible. COVID-19 appears to be a relatively mild illness in young infants, who may be asymptomatic. However, this may not be the case in preterm or immune compromised infants, and the longer-term implications of neonatal infection with COVID-19 are currently unknown.

The number of currently pregnant women with MS is relatively small, and so clinical experience with this group is limited, but gradually increasing. Pregnant women do not appear to be more likely to contract COVID-19 than the general population. In general, women with MS who are also pregnant should be advised to follow appropriate social distancing measures and/or shielding measures depending on their immunosuppressant exposure and additional clinical co-morbidities. They should be reassured that obstetric services are continuing to operate, with appropriate efforts to minimise the risk of infection for women under their care.

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Investigation of hereditary muscle disorders in the genomic era

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Abstract
Identifying the genetic basis of inherited muscle disease is the single most important step to accurately guide patient care. A timely and accurate diagnosis is crucial for patients with neuromuscular disorders and their families. Advances in genomics are transforming the way we diagnose and treat many inherited diseases and their integration into clinical practice has reduced the diagnostic odyssey for patients with limb-girdle muscular dystrophies and myopathies. This review proposes a new, less invasive diagnostic algorithm that incorporates next generation sequencing (NGS) into neuromuscular clinics, reserving muscle biopsies for the "difficult to diagnose" patients. We discuss the importance of accurate history taking and detailed phenotyping, followed by initial screening investigations and exclusion of the common neuromuscular disorders. Once sufficient clinical and screening information has been obtained, NGS would be considered an appropriate next step, with a targeted neuromuscular panel usually favoured in view of the lower cost and less difficulties with variant data compared to whole exome and whole genome sequencing. Using this diagnostic paradigm will enable a greater number of patients to achieve an accurate and timely diagnosis, receive appropriate disease-specific treatments and gain access to informed family planning.

Introduction

Many patients with limb-girdle muscular dystrophies and inherited myopathies often remain undiagnosed or are misdiagnosed for long periods of time due to the phenotypic heterogeneity of these disorders. The traditional diagnostic pathway has relied on a stepwise process of clinical assessment and multiple investigations that are performed prior to proceeding to a muscle biopsy. Histologic and biochemical assessment of a muscle biopsy has remained the historical "gold-standard" for diagnosing the muscular dystrophies and myopathies.[1,2] Based on the muscle biopsy findings and the clinical phenotype, Sanger sequencing of candidate genes would be subsequently performed, usually one gene at a time. A lack of clear genotype-phenotype correlation meant many genes often needed to be sequenced to identify the causative gene and pathogenic variants. Sanger sequencing a large number of individual genes is time consuming, laborious and prohibitively expensive. Moreover, often large genes such as titin (*TTN*) with 363 exons, were not entirely Sanger sequenced routinely due to its size and complexity. Thus, only a few *TTN* mutations were reported prior to the advent of next generation sequencing (NGS).[3]

Using this traditional sequential pathway, the diagnostic rate for the limb-girdle muscular dystrophies remained low as reported in a review of a large Australasian limb-girdle muscular dystrophy (LGMD) cohort for whom 65% of families remained without a genetic diagnosis, despite numerous investigations at an expert neuromuscular centre.[4]

Integration of NGS technology into clinical practice for the diagnosis of Neuromuscular Disorders: *Benefits and Ongoing Challenges*

Implementation of NGS into clinical practice has transformed how we investigate and deliver health care to myopathy and muscular dystrophy patients. NGS, also known as massively parallel sequencing, enables high-throughput DNA sequencing of large numbers of genes simultaneously. There are three methods of DNA sequencing technologies available; Neurogenetic Subexomic Supercapture (NSES), also known as targeted neuromuscular panel, whole exome sequencing (WES) and whole genome sequencing (WGS).[5,6]

NGS has been shown to be efficacious[4,7,8] and also cost-effective.[9] NGS has also facilitated the discovery of novel disease genes[10] and allowed us to expand the phenotype of known disease genes.[11-13] In a cohort of Australasian LGMD patients that had been previously extensively investigated, the use of NSES or WES had enabled a diagnosis to be achieved in 45% of these families. Other studies have shown a similar diagnostic rate for the limb-girdle muscular dystrophies, myopathies and the congenital myopathies.[7,14] The inclusion of family members or "trios" for WES yielded a better diagnostic rate of 60% compared to 40% diagnosis in cases where the proband was only included for WES.[4] The inclusion of 'trios' allows filtering and stratifying identified variants based on familial segregation with disease. Moreover, including family members highlights variants that might have been interpreted as unlikely candidates or simply overlooked when a large amount of data is generated with the initial bioinformatics analysis.[4]

Despite our best efforts to improve the diagnostic yield of neuromuscular patients using