MODE OF DELIVERY IN MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system, affecting women of childbearing age. Little is known about the possible association between mode of delivery and the risk of MS in offspring. Delivery represents a unique event in a woman's lifetime, with complex mechanisms controlling human parturition. Concurrent with the trend of increasing numbers of caesarean deliveries (CD), there has been an increasing frequency of autoimmune diseases such as MS. Several theories have emerged suggesting that environmental influences are contributing to this phenomenon. The data available in literature seem reassuring for women with MS, suggesting that the disease is not associated with adverse pregnancy or birth outcomes. On the other hand, there is little information in the literature regarding the role of mode of delivery in predicting the post-partum disease activity, pregnancy, and birth outcomes in women with MS. The aim of our review is to provide a brief summary of the available data on the role of mode of delivery in MS, and the eventual correlation with disease outcome.

Keywords: Multiple sclerosis, pregnancy outcome, delivery.

INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system and, together with epilepsy, the most common neurologic disorder affecting women of childbearing age.[1] Several prenatal and perinatal factors have been investigated in MS, founding modest associations with subsequent risk of MS for late initiation of prenatal care, lack of parental cohabitation at birth, elevated maternal pre-pregnancy body mass index, and maternal diabetes. In the past, there has been speculation about the possible role of pregnancy, together with other stressful life events, in the risk of developing a relapse, and the course of the disease.[2] Pregnancy involves a relative state of immunosuppression as the foetus carries paternally-derived antigens. It is likely that hormonal and cytokine changes during pregnancy are linked to a Th2-type immune response. In fact, a pathophysiological hypothesis, to explain the spontaneous remission of MS during pregnancy, is that pregnancy is associated with a decrease in cellular immunity and an increase in humoural immunity, and with a shift away from Th1 to Th2 responses; on the contrary, delivery is associated with an inversion of this balance and a shift from Th2 to Th1 response. Based on these assumptions, pregnancy is beneficial in patients with autoimmune inflammatory conditions such as MS.[3] With regards to the influence of pregnancy in modifying the disease-activity (i.e. the relapse rate and the progression of the disease), the large Pregnancy In Multiple Sclerosis (PRIMS) study reported that pregnancy status does not affect long-term prognosis in women with MS.[4] Little attention has been given to the possible association between mode of delivery and the risk of MS in offspring and in disease progression. It is well known that delivery represents a unique event in a woman's lifetime, with complex mechanisms controlling human parturition involving mother, foetus, and placenta. To this regard, we sought to review the current understanding of the putative role of the parturition in the risk of developing MS and in the modulation of the disease course. We believe

that gaining further knowledge on this topic might provide insight into additional treatment strategies for patients with MS.

PARTURITION AND MULTIPLE SCLEROSIS

The influence of pregnancy in median and long-term effects of MS is out of the scope of this review. Nonetheless, we have to underline that counselling women with MS about pregnancy has long been a matter of controversy. Until the late 1950s and 1960s, women were discouraged from considering pregnancy, which was believed to worsen the course of the disease, based on isolated case reports and small retrospective studies subject to many biases, such as recall bias for cases with a tragic outcome naturally.[5] Later, the PRIMS study[4] reported that the rate of relapses decreases during the pregnancy, increases during the first trimester of postpartum, then returns to the pre-pregnancy rate after delivery, leading to a major change in the counselling of women with MS. Only three factors seem independently predictive of an increase of relapses in the 3 month post-partum period: the number of relapses in the year before pregnancy, the number of relapses during pregnancy, and the duration of MS.[4] The possible role of breastfeeding is still under discussion.[6] Previously, it was described that maternal MS is more frequently associated with operative deliveries (caesarean section, use of forceps or vacuum extractor), but these data were not confirmed in a retrospective cohort study (analysing data from the British Columbia MS Clinics' database), which made comparisons between births to 432 women with MS and to a frequency-matched sample of 2,975 women without MS, and it found that maternal MS is generally not associated with adverse neonatal and delivery outcomes.[7] In the United States, the rate of vaginal delivery (VD) has reduced since 1996, reaching a level of 68.2% in 2007.[8] This trend is reflected in many parts of the world. Although a significant number of caesarean deliveries (CD) are performed for obstetric indications, some are simply because of maternal request. Concurrent with the trend of increasing CD numbers, the frequency of autoimmune diseases has increased, such as MS.[9] The occurrence of these diseases seems to be higher in more affluent, Western, industrialised countries, even if data from non-industrialised country are limited.

MODE OF DELIVERY

Disease Development

Several theories have emerged suggesting that environmental factors may contribute to the development of the disease. Among them, the hygiene hypothesis suggests that an exposition to clean environment, especially in early childhood, may contribute to the development of an abnormal immune system.[10] The interplay between the emerging microbial ecology of the gastrointestinal tract and the developing mucosal immune system serves as a backdrop for a relationship between CD and the emergence of autoimmune diseases. With the highly immunoreactive intestine serving as the largest surface area of the body that is exposed to a number of infective agents, especially a vast array of luminal microbes and antigens, it is intriguing to speculate that the intestinal environmental interaction during early development of the immune system may relate to these diseases. One intriguing component of this speculation relates to the early development of the intestinal microbiota, the developing immune system, and the early influence of CD versus VD on these phenomena. It has been suggested that different initial exposures depend on mode of delivery (VD versus CD). The microbes that develop in the intestine during either CD or VD may lead to changes in long-term colonisation and subsequent altering of immune development. Most current literature suggests that the gastrointestinal tract of a normal foetus is sterile. During birth, and rapidly thereafter, bacteria from the mother and the surrounding environment colonise the infant's gut. The long-term sequelae or impact of this difference in exposure on the child has yet to be determined. Although there is an increasing body of evidence that the intestinal microbiota play an essential role in the postnatal development of the immune system, the mechanisms remain poorly understood.[10] A case-control study (based on 449 MS cases recruited from the Isfahan MS Society database and 900 of their healthy siblings) reported a 2.3 to 2.7-fold increased risk of MS among the persons delivered by caesarean section, as compared to their VD siblings.[11] Information about mode of delivery and other perinatal characteristics were collected; however, they were based on self-reports.[11] Later, in a nationwide register-based cohort study

that included all individuals born in Denmark from 1973 to 2005, the association between being delivered by caesarean section and the risk of developing MS later was assessed.[12] The cohort of individuals, born from 1973 to 2005, consisted of 1,727,747 persons of whom 86.2% were born vaginally and 12.4% by CD. During follow-up, 645 women and 285 men were diagnosed with MS. Overall, the effect of CD on the subsequent risk of MS (RR = 1.17; 95% CI: 0.92–1.46) was not observed, when adjusted for age, calendar period, birth order, birth weight and gestational age.[12]

The role of mode of delivery in modulating various endocrinological axes in mother and offspring was scarcely studied. Concentrations of epinephrine (EP), norepinephrine (NOR), adrenocorticotropic hormone (ACTH), cortisol (CORT), prolactin (PRL), corticotropin-releasing factor, and beta-endorphin (BE) were investigated. It seems that CD is associated with significantly lower maternal concentrations of EP, NOR, ACTH, CORT, PRL, and BE, and lower newborn levels of EP, NOR, and CORT compared with all other modes of delivery. In a prospective observational study, concentrations of EP, ACTH and BE differed significantly in newborns delivered by normal VD, VD with epidural anaesthesia, and ventouse extraction. Since the role of hormones in the pathogenesis of MS has been widely studied, we may postulate that mode of delivery can influence hormone levels, increasing the risk of developing MS.[13] Data regarding a possible enhanced risk of MS in the offspring born from CD has to be confirmed in different epidemiological settings (e.g. population-based studies) and, the hypothesis that the intestinal microbiota and stress hormone levels could play an essential role in the postnatal development of the immune system and, as such, in the risk of MS, needs further attention.

Disease Progression

Regarding the influence of mode of delivery in predicting the postpartum disease activity, the data provided so far seem to show a lack of association between CD and worsening of the disease.[14] A recent Italian prospective study, collecting data on 423 pregnancies in 415 women with MS, found that 44.4% of patients underwent CD and 18.5% epidural analgesia (EA).[15] In the multivariate analysis, CD was not associated with a higher risk of postpartum relapses or disability progression (assessed by Expanded Disability Status Scale).[15] Regarding the EA, no controlled studies exist to assess any negative or positive associations with MS. It was described that the relapse incidence in women who received EA for VD did not significantly differ from that in women who received local infiltration analgesia,[16] and in the PRIMS,[4] women with or without EA did not differ in their risk of postpartum relapses. Also, no effect on disability progression has been found.[4] In the Italian cohort study, EA was performed in 18.5% of the patients, and it did not significantly affect postpartum relapses or disability progression.[15]

Several studies have investigated the role of mode of delivery on disease activity and pregnancy outcomes. Amato et al.[17] showed, in a large cohort of MS women, that CD together with IFNβ exposure were the only predictors of preterm delivery. Mode of delivery can also be influenced by disability. In a retrospective multicentre study, the authors found no factors can predict the risk of relapse during or after pregnancy, although they reported CD is associated with higher Expanded Disability Status Scale (EDSS) at conception and that SPMS patients are more likely to need a CD.[18] A recent study investigated the role of EA and CD in postpartum relapse. They found no correlation between EA, CD and postpartum relapse and disability.[19] An old study pointed to an increased risk of relapses after the administration of bupivacaine greater than 2.5 mg/ml.[20] However, this finding was not confirmed in more recent investigations.[21] With regards to the role of breastfeeding in the disease's progression, only conflicting data are provided to date. One hormone that is elevated during breastfeeding, but falls rapidly in the absence of breastfeeding is prolactin, suggesting a possible beneficial effect of prolactin postpartum, although several studies have correlated hyperprolactinemia with relapses of MS.[22]

In Table 1 we summarise the percentages about mode of delivery in the most relevant studies investigating pregnancy outcome in MS patients.[17-19,23-28]

CONCLUSION

In planning a pregnancy, women with MS usually want to know both the impact of a potential pregnancy on the disease, as well as the impact

Table 1. A summary of delivery mode data presented in studies investigating pregnancy outcomes in MS patients.

Author (date)	Study design	Therapy	Number of pregnancies	Caesarean delivery (%)	Vaginal delivery (%)	Relapse before pregnancy	Relapse during pregnancy	Relapse post pregnancy
De Las Heras et al. (2007)[18]	Retrospective, cohort	DMD	62*	10 (17.9%)	46 (82.1%)	N/A	N/A	N/A
Patti et al. (2008)[23]	Restrospective, cohort	IFN beta	36	28 (77%)	8 (22%)	N/A	N/A	N/A
Fernandez Liguori et al. (2009)[24]	Restrospective, cohort	IFN beta, GA	103	41 (39.8%)	62 (60.2%)	0.22° (0.12-0.32)	I 0.31° (0.10-0.52) II 0.19° (0.03-0.36) III 0.04° (0.00-0.12)	I 0.82° (0.42-1.22) II 0.50° (0.22-0.79) III 0.19° (0.03-0.36)
Amato et al. (2010)[17]	Prospective, cohort	IFN beta	75	34 (45.3%)	41 (54.7%)	N/A	N/A	N/A
Fragoso et al. (2010)[25]	Case series	GA	11	6 (54.5%)	5 (45.5%)	1.6±0.8**	0.4±0.9**	0.6±0.7**
Salminen et al. (2011)[26]	Case series	GA	14 (2 miscarriages)	2 (16.6%)	10 (83.3%)	N/A	N/A	N/A
Hellwig et al. (2011)[27]	Prospective, cohort	Natalizumab	35 (6 miscarriages)	14 (48.3%)	15 (51.7%)	0°°	I 1°° II 5°° III 2°°	6°°
Lu et al. (2012)[28]	Restrospective, cohort	IFN beta, GA	18	2 (11.1%)	16(88.9%)	N/A	N/A	N/A
Pastò et al. (2012)[19]	Prospective, cohort	DMD	349	155 (44.4%)	194 (55.6%)	0.4±0.7**	0.12±0.4**	0.45±0.7**

*See page 36 for abbreviations

I: first trimester; II: second trimester; III: third trimester;
*6 data about delivery method not available;
** mean ± standard deviation;
° annualised relapse rate (95% CI);
°° number of relapse.

of the disease on pregnancy and birth outcomes. Furthermore, the impact of therapy on pregnancy should be always discussed with patients. Women seeking to achieve pregnancy should generally discontinue therapy prior to attempting conception as current evidence has not reached a general consensus.[29] The data available in the literature seem to be reassuring for women with MS, suggesting that the disease is not associated with adverse pregnancy or birth outcomes. However, in detail, there is little information regarding the role of the mode of delivery in predicting the postpartum disease activity, pregnancy and birth outcomes in women with MS. Recent data about the putative role of mode of delivery and risk of developing MS in the offspring are conflicting. Two large studies investigated the association between mode of delivery and the risk of developing MS later;[11,12] due to the different design, a case-control and a nationwide cohort study, a comparison is difficult. Moreover, limitations due to chance, bias or methodological approach have to be considered in interpreting the results. Pregnancy is a stressor event and the modifications on the neuro-endocrine axis occurring during this event are well known.[13] Gaining more insight about the different profiles of risk regarding disease progression and risk of developing MS for the offspring, is a great opportunity to provide transparent, evidence-based information to both inquiring patients and to physicians who may be providing concurrent care.

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