Pregnancy in patients with multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune disorder that affects ~2.5 million people globally. Women of reproductive age are highly susceptible to this disease. This study aims to explore the association between MS and pregnancy. Articles related to the topic under investigation were identified; the search terms included "pregnancy", "multiple sclerosis", "MS", and "women". Only articles published between 2010 and 2020 were included in the review. This review shows that researchers have attempted to explore the link between pregnancy and MS, and the results from previous studies indicate that pregnancy reduces the risk of MS relapse. However, evidence suggesting that pregnancy can affect the long-term progression of MS is lacking. The research results also indicate that MS does not increase the risk of maternal and fetal complications. MS remains a serious autoimmune disorder that affects many women worldwide. The data gathered during this review indicate that a significant correlation exists between pregnancy and MS relapse rates. The findings presented in this review can aid in the management of MS during pregnancy. Furthermore, these research results provide vital insights that caregivers can use to monitor patients with MS during pregnancy.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disorder that affects the central nervous system[1–3]; it is an inflammatory disease that occurs when T cells and antibodies attack and damage the fatty myelin sheath found on brain and spinal cord axons, leading to demyelination and axonal and neuronal loss.[1] Importantly, MS manifests as numerous focal neurological and other generalized signs and symptoms, such as inefficient communication with different body parts, fatigue, locomotion issues, impaired vision, and loss of sensitivity.[4–8] The early diagnosis of MS is important as it allows caregivers to initiate treatment and develop effective management strategies.[9–11] Usually, MS is diagnosed according to the revised McDonald criteria.

Approximately 80% of patients diagnosed with MS are aged between 20 and 45 years, and women are more susceptible than men.[1] As pregnancy is an attribute specific to women, it could be crucial to examine its impact on the symptoms and severity of MS or the effects of MS on pregnancy outcomes and children's development.[12–14] Currently, definitive data regarding the rate of pregnancy among women who have MS, as well as conclusive data showing the prevalence of MS among pregnant women, are lacking. However, research suggests that women with MS are twice as likely to be hospitalized within the first 3 months after delivery compared with their counterparts without the disease.[13] This systematic review aimed to review up-to-date research evidence regarding the risks and challenges that women with MS may experience during pregnancy.

MATERIALS AND METHODS

The current study involved performing a systematic literature review to understand the current knowledge concerning the impact of MS on pregnancy. This process required analyzing studies that focused on the subject of MS and pregnancy. Articles were obtained from the PsycINFO, PubMed, Web of Science, and Cumulative Index of Nursing and Allied Health Literature databases. The search terms were "pregnancy", "multiple sclerosis", "MS", and "women" and the search was limited to articles published between 2010 and 2020. The abstracts of the available articles were carefully reviewed to determine their quality and appropriateness for the study.

The aims, research design, results, and conclusions of each selected article were examined. The strategy used for article selection was consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (figure 1).[15] From all the available studies, 12 of the most relevant studies were selected and analyzed, as shown in online supplemental table 1.

RESULTS

The final list of articles obtained through the systematic search of the databases consisted of retrospective studies, clinical trials, cohort studies, experimental studies, and systematic reviews. An analysis of the studies showed that MS, a demyelinating condition, affects approximately 2.5 million people worldwide (eg, in Norway, the prevalence is 240/100 000, and the incidence is 8/100 000). Moreover, the clinical course of this disease is highly variable. Most studies focused on the factors predisposing individuals to the development of MS, while minimal attention has been paid to the factors that may control or affect the progression and course of this disease.

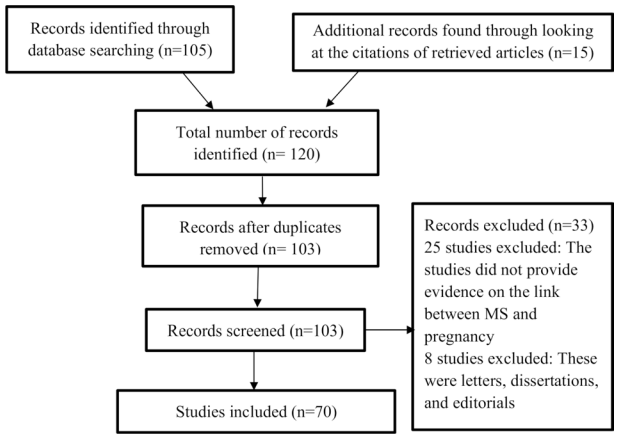

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. MS, multiple sclerosis.

The available evidence also revealed that >70% of people diagnosed with MS are of childbearing age. As a result, attempts have been made to explore the possible link between MS and pregnancy. MS is an isolated antibody-mediated disease and involves T cell dysfunction and genetic conditions.[3 5] The findings of this systematic review are divided into different sections, and the results culminate in a greater understanding of the impact of MS on pregnancy and the management of this disorder during pregnancy.

Onset of MS during pregnancy

Some of the studies reviewed showed that the chances of a pregnant woman contracting MS are quite minimal and that exacerbations tend to be reduced during pregnancy.[16–18] This finding implies that theoretically, the onset of MS should be reduced during pregnancy. However, the effects of pregnancy on the onset of MS remain unclear. Nonetheless, exacerbations may still manifest for approximately 30 days after a flare-up and last for at least 24 hours.

One study reviewed evidence from previous studies exploring the impact of MS on pregnancy and the optimal management techniques that can be used to improve the well-being of women.[16] These authors reported that an increasing volume of research has shown that the onset of MS decreases during pregnancy. However, the severity of this disorder and the risk of relapse may increase after pregnancy, along with the possibility of peripartum complications such as hemorrhage, embolism, or hypertension.[17] Despite such findings, an underlying immunological mechanism is still linked to delayed disease onset, and this mechanism is not well understood.[17–20] Particular studies have linked the delayed onset to the immunological alterations that occur during pregnancy to protect the unborn baby from the maternal immune system.[16] Furthermore, researchers have stated that changes from T-helper 1 to T-helper 2 cells and shifts in the production of natural killer cells, interleukin-8 serum, and interferon-gamma-producing $CD4^+$ T cells may hinder the onset and progression of MS during pregnancy.[21–24]

Effects of pregnancy on MS relapse

Pregnancy is normally considered a stabilizing period during the course of MS, and researchers have found that the rate of MS relapse is often reduced during pregnancy.[25 26] A review of retrospective studies has shown that pregnancy normally has a beneficial impact on the clinical development of MS.[24 27] Research has also revealed that women who report high disease activity before and during pregnancy have a greater risk of relapse during the postpartum period than those who experience low rates of disease activity.[28 29] However, the pathways underlying such reduced relapse rates have not been elucidated, and some uncertainties in various areas remain, such as the most effective practices for successful family planning among young women with MS.

MRI can be used to assess the progression of MS during pregnancy. MRI has become an important diagnostic and prognostic tool, as it allows caregivers to monitor the condition of patients who suffer from MS.[29 30] Furthermore, MRI is a prognostic tool that can be used to evaluate the condition of those experiencing the first signs of demyelination. Although conclusive data regarding the safety of MRI use during pregnancy are lacking, no fetal abnormalities as a result of MRI use have been reported previously.[30] Therefore, healthcare practitioners continue to use MRI as a tool to diagnose maternal and fetal problems after the first trimester to avoid potential risks from its use during the first trimester.

Evidence from MRI studies has suggested that pregnancy may be associated with an increase in lesions on T2-weighted and diffusion-weighted imaging.[24 31–33] In this case, lesions refer to a particular area of focal hyperintensity on a T2-weighted or proton density-weighted sequence.[34] Although there are different types of lesions, this review focused on active lesions, which show sharply bordered demyelination with macrophages.[35]

As a result, a review of postpartum scans from previous studies revealed the presence of T2 activity and active lesions.[36–38] The results of previous studies also showed that the activation of MS normally occurs during the early postpartum period.[39 40] In addition, researchers have suggested the possibility of immune system alterations occurring during the late stages of pregnancy in preparation for delivery; these changes have been found to be accompanied by an increase in MS disease activity in these patients.

MS and pregnancy outcomes

Many women are concerned about their ability to conceive and successfully progress through the stages of pregnancy. Furthermore, pregnancy remains a significant concern for women suffering from MS, as some of them fear that they will be unable to bear a child due to the disease.[40] Nonetheless, scholars have shown that MS does not compromise fertility[23]; it is essential for women with MS who wish to conceive to undergo counseling to help them understand their condition.

A successful pregnancy usually depends on the ability of the mother's immune system to tolerate a genetically incompatible fetus. The fetomaternal unit created during pregnancy has been shown to cause immune reactions and responses in the mother.[23 24] The main adaptation that contributes to immunotolerance is the shift from helper T cell 1 to helper T cell 2 dominance. The appropriate dominance of helper T cells during pregnancy allows the fetus to develop normally and ensures that no complications are

encountered during development. Therefore, unsurprisingly, MS and helper T cell 1 dominance-related diseases do not affect the development of the fetus.[41] Notably, placenta-derived hormones can influence the normal functioning of immune cells in the body. This process entails direct interaction with progesterone and estrogen receptors during pregnancy.

As the fetus develops, level of placenta-derived estriol increases. While these changes affect how MS progresses, they have no significant impact on the development of the child.[42] The realization that estrogen seems to show a dose-dependent biphasic impact on the immune system has also been used as the basis for exploring why MS does not affect fetal development. Research has revealed that increased estrogen levels hinder cell-mediated immunity; this trend is reversed in the case of low estrogen levels, which have been linked to high cell-mediated immunity. These changes are used as the basis for explaining how MS may affect pregnancy outcomes. For instance, reduced levels of estrogen have been considered beneficial since they enhance pregnancy outcomes and ensure that the child develops normally. As a result, it can be deduced that pregnant women with MS do not experience complications that affect fetal development compared with healthy women.[1 24]

The link between MS and pregnancy outcomes has been examined in retrospective and prospective studies. Thus far, evidence suggesting that patients with MS are at a higher risk of experiencing delivery or pregnancy complications than their counterparts who do not suffer from demyelinating conditions is lacking.[43 44] The complications that researchers have considered include pre-eclampsia, miscarriage, prolonged labor, and ectopic pregnancy. Furthermore, there is no research evidence that children born to mothers with MS suffer from problems such as low birth weight or congenital abnormalities.[45 46] Notably, no research has indicated that MS can increase the risk of fertility or congenital problems among women.[47 48] Even in cases in which the mothers require operative delivery, the issue cannot be linked directly to MS; instead, it may be due to factors such as exhaustion, fatigue, and neuromuscular perineal weakness.

In other instances, researchers have focused on delivery methods among mothers with MS and the need for anesthesia use.[49 50] In most instances, it may be prudent for caregivers to plan for the possibility of an operative delivery with any patient, including those with MS, and the decision to undergo elective cesarean section (CS) should be made only after meeting the existing obstetric criteria of the healthcare facility.[51 52] Mothers with MS who have a significant functional disability may face problems during delivery because of exhaustion and fatigue. Notably, the use of epidural anesthesia during the delivery process has not been linked to an increased risk of disability or any sign of postpartum flare among patients with MS.[53 54]

However, concerns have been raised regarding the dangers faced by patients with MS when receiving spinal anesthesia during delivery. In particular, spinal anesthesia has been reported to potentially increase the risk of postoperative relapse among mothers with MS. Regarding local anesthesia, although minimal research has been conducted, limited clinical evidence has shown that it may adversely affect demyelinated axons in patients with MS.

The use of certain immunosuppressive agents such as cyclophosphamide and mitoxantrone has also been linked to reproductive toxicity and reduced levels of fertility in women. Currently, a significant volume of research and clinical evidence has suggested that assisted reproduction techniques can escalate the risk of relapse. In addition, assisted reproductive techniques usually increase the number of T2 lesions during the initial 3 months after conception.[2 41 55] This trend occurs regardless of the hormonal method used during the treatment process. Recent evidence from other clinical studies also suggests that gonadotropin-releasing hormone (GnRH) agonists could cause a wide range of immunological effects that influence the development of the child and fertility levels among those with MS.[23 56] Some factors affected by GnRH agonists include endothelial growth factor production and estrogen levels. Notably, however, the use of GnRH antagonists appears to have a minimal risk of causing pregnancy complications among those diagnosed with MS.[42 57 58] Nevertheless, there is a need to carry out further prospective studies to confirm these results. In addition, further research is necessary to determine whether such medicines can affect the chances of relapse and the ability of the mother to successfully progress through the stages of pregnancy.

MS management during pregnancy

The disabling effects of MS can adversely affect the physical health of patients and make it difficult for women to carry a pregnancy to term. In particular, MS can result in coordination challenges and muscle weakness, thus increasing the risk of falls. In some cases, women may become dependent on a wheelchair and develop urinary infections.[40 59] Despite this situation, research evidence proving that pregnancy, birth defects, and deliveries differ between women with MS and their counterparts without this disease is insufficient.[60] During pregnancy, it is important for caregivers to closely monitor patients who are receiving treatment for MS. Furthermore, tracking the progression of the disease and the development of the fetus is critical.

The increasing incidence of MS among women implies that caregivers must understand the potential impact of disease-modifying therapies (DMTs) on pregnancy and the well-being of the mother. DMTs refer to medications and therapies that can be used to reduce the progression and activity of MS.[61] The current approach of withdrawing DMTs before conception may cause patients to experience severe symptoms if the disease remains untreated for a long duration.[61–63] Therefore, some experts and researchers have recommended DMT cessation after the patient becomes pregnant. Some of the main therapies used to treat MS include interferon beta-1a/b, mitoxantrone, glatiramer acetate (GA), and natalizumab (see table 1). In some instances, expectant women fail to stop DMT, thereby exposing the fetus to the medication used to manage the symptoms of MS, and research has shown that interferon-beta exposure during pregnancy may increase the risk of a low birth weight and miscarriage.[60 64 65] In addition, exposure to the drug during pregnancy has been linked to adverse outcomes such as fetal defects, congenital abnormalities, and miscarriages.[1 66] The frequency of these problems tends

Table 1 Approved MS DMTs and pregnancy ratings

DMT	Type of DMT	Pregnancy ratings	Use in pregnancy
Interferon-beta	Injectable DMT	Category C	Should not be used since adverse effects were reported in animal reproduction studies.
Glatiramer acetate	Injectable DMT	Category B	Can be used safely and routinely.
Peginterferon-beta 1a	Injectable DMT	Category C	Should not be used since adverse effects were reported in animal reproduction studies.
Fingolimod	Oral DMT	Category C	Should not be used since adverse effects were reported in animal reproduction studies.
Dimethyl fumarate	Oral DMT	Category C	Should not be used since adverse effects were reported in animal reproduction studies.
Teriflunomide	Oral DMT	Category X	These drugs have serious adverse effects that outweigh the potential benefits.
Alemtuzumab	Infusion DMT	Category C	Should not be used since adverse effects were reported in animal reproduction studies.
Natalizumab	Infusion DMT	Category C	Should not be used since adverse effects were reported in animal reproduction studies.
Mitoxantrone	Infusion DMT	Category D	Not advised since it has adverse effects on the fetus.

Category B drugs: these drugs can be used safely and routinely during pregnancy.
Category C drugs: their adverse effects on the fetus have been shown in animal reproduction studies.
Category D drugs: these drugs were analyzed using data from investigational and human studies.
Category X drugs: their adverse effects have been proven through animal and human research models.
DMT, disease-modifying therapy; MS, multiple sclerosis.

to differ depending on the stage of pregnancy in which the fetus is exposed to the medication.

Several reports have illustrated how the use of GA and azathioprine to manage MS among pregnant women affects their health and the development of the fetus. Currently, the existing body of literature indicates that GA use does not increase the risk of fetal abnormalities, birth defects, or pregnancy complications. The use of azathioprine in the management of MS during pregnancy is a common practice.[66–68] This drug and its main metabolite, i.e., 6-mercaptopurine, can cross the placenta when used by expectant women.[30] Nevertheless, although the concentrations of the metabolites in the fetus are usually low, concerns have been raised regarding the possibility of 6-mercaptopurine resulting in growth-restricted babies. More therapeutic options are available than those listed here.

None of the available DMTs are curative or capable of offering neuroprotection for patients with MS, and these therapies may have diverse effects on patients depending on their disease stage. Category B drugs refer to treatments that can be used safely and routinely during pregnancy.[69]

However, there are no adequate clinical or human studies indicating that the treatments adversely affect the development of the fetus. Therefore, the potential benefits of the drugs may warrant their administration in pregnant mothers.[69] Examples include alemtuzumab, peginterferon beta-1a, and natalizumab. In contrast, category D drugs have been analyzed using data obtained from investigational and human studies and have shown to cause adverse effects on the fetus. However, DMTs can still be used despite the potential risks.[69]

One example is mitoxantrone, which can be administered to reduce the risk of MS relapse. Finally, Category X drugs have serious adverse effects that outweigh the potential benefits. Adverse fetal abnormalities linked to Category X drugs have been proven through animal and human research models.[69] One example is teriflunomide, which can cause embryo-fetal toxicity.

DISCUSSION

Perhaps the most critical area of interest in exploring the link between MS and pregnancy is how MS can influence the pregnancy course. Currently, the actual effect of MS on pregnancy remains highly debated. In addition, this area continues to attract the attention of researchers with the goal of generating evidence that may be used to improve the well-being of patients with MS during pregnancy. A review of previous studies showed that women who conceive after developing MS seem to have a lower disease progression rate than nulliparous women. Furthermore, studies have revealed that term pregnancies have a minimal impact on the time required for the condition to progress to a level that causes disability. Overall, no clinical or research evidence is available to support the conclusion that pregnancy or the number of children to which a woman gives birth can affect the long-term progression of MS and lead to disability.[23] Regarding the question of whether pregnancy can influence the risk of patients developing MS with isolated signs, it has been suggested that the risk of MS is linked to increased parity and gravidity. The same argument has been used to show that childbirth before the onset of MS lowers the risk of disabling symptoms of the disease.

Finally, researchers have explored how postpartum rebound affects the development and progression of MS in women.[23 37] To date, studies have shown that a significant link may exist between postpartum rebound and disease activity.[23] In particular, MS has been associated with increased T2 gadolinium-enhancing brain lesions postpartum. The evidence from such studies seems to suggest that better postpartum outcomes can be achieved by minimizing the relapse frequency among women. However, further investigations are required to provide information that can be used to draw valid conclusions regarding this topic. From a practical point of view, women need to be counseled about MS and informed of how the disease may affect them. These discussions should revolve around the link among MS, conception, pregnancy, and pregnancy outcomes. Women should be reassured that this condition can be managed even when they are pregnant.

Patients with MS need help coping with the signs and symptoms of this disease during pregnancy. Against this background, studies have explored how MS can be managed among such women. Multiple DMTs are usually used for managing MS; therefore, researchers have strived to explore how such interventions may affect MS progression and pregnancy. Overall, significant improvements have

been made in our understanding of how different DMTs affect pregnancy outcomes and fetal development. Furthermore, the number of studies performed to explore how DMTs can affect the course of pregnancy in women with MS has increased.[64] Although these interventions seem to have a minimal effect on fetal development, there is also the possibility that they may have an adverse effect on immune system development in the fetus. Furthermore, the natural course of MS among pregnant women renders the use of DMTs questionable since the risk of disease progression or relapse is low.[68]

The standard form of care in such cases is to avoid multiple DMT use during pregnancy. In addition, DMTs should be stopped immediately once pregnancy has been detected. Patients who have MS should be encouraged to participate in a formal pregnancy registry. Some DMTs used to manage this disorder include interferon beta, GA, and natalizumab,[70] but other treatments are available, too. Evidence from previous studies has suggested that these drugs are safe for managing MS,[23] but for pregnant women with MS, they should be used only after exploring their benefits and risks. In addition, the patient should make an informed decision regarding the type of treatment or medicine that will be used to manage her condition during pregnancy. Therefore, caregivers must carefully assess the need for DMTs and the potential impact they may have on the health of both the mother and fetus.

CONCLUSION

MS is a serious neurological disease that affects many women worldwide and is common among those of reproductive age. Research has indicated that MS is caused by a wide range of genetic and environmental factors. This study aimed to explore the link between MS and pregnancy. A review of previous research results has shown that pregnancy can slow the progression of MS and reduce the risk of relapse. However, conclusive research data regarding a direct association between MS and pregnancy outcomes, such as miscarriages, fetal malformations, fertility, or birth weight, are lacking. Further investigations are warranted to assess ways in which MS symptoms can be managed among pregnant women and adverse effects can be avoided.

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