Multiple Sclerosis and Pregnancy

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Abstract

Background:

Multiple sclerosis, a chronic neurological disease, has been proven to have an imbalance rate of incidence towards the female gender. As the onset age of the disease overlaps with the age of most pregnancies, concerns have arisen on the safety of the mother and the child, however, since not many pregnancies happen to be involved with MS, huge Cohort studies are needed to determine a certain fact regarding this issue.

Objective:

This article reviews the factors linking female sex, pregnancy and MS, for a better understanding of the matter. Indicating concerns regarding effect of: feminine hormones (pre-pregnancy/general); hormones that are produced while pregnancy; puberty and menopause; and breastfeeding on the mothers diagnosed with MS in increasing the incidence rate of the disease.

Methods:

We have searched PubMed and Google Scholar mostly, using search terms including the words 'MS' or "multiple sclerosis' in addition to the desired subject of understanding [e.g. ((Multiple Sclerosis) AND (prolactin))]. Then, each article was discussed and an abstract of the total information gathered during the process was provided, aiming easy understanding of the public.

Results:

We have chosen the best and most simply digestible information between approximately 35 NCBI articles, providing definition of five of the most repeated subjects-concerning the higher interest of those five topics. These five headings include: Menarche and Puberty, Pregnancy: Relapse/Disabilities, Breastfeeding, Fertility and sex hormones. (e.g. people diagnosed with MS are not seemingly less fertile than other participants of the society nor will they have a problem initiating a pregnancy).

Conclusion:

Pregnancy is clearly a major modifier in MS, but gender effect and the protective effects of pregnancy definitely need more clinical trials to be determined. However, there is one certainty; while breastfeeding, hormonal and other types of drugs for controlling the disease, if used by the mother, will have an effect on the child through the feeding.

Introduction

Multiple sclerosis (MS) commonly affects womenin childbearing years making pregnancy issues important forpatients with MS and their families. Pregnancy is a naturallyoccurring disease modifier of MS associated with a 70% reductionin relapse rates in the third trimester. This relapse ratereduction during the last trimester is roughly equal to the mosteffective disease-modifying treatments for MS. Given this efficacy,various pregnancy factors have been tested to determinewhich play a part in pregnancy's protection, and somehave been translated to completed and ongoing phase II clinicaltrials. In contrast to protective effects during pregnancy,the postpartum period entails increased relapse risk, whichmay be due to either abrupt removal of protective pregnancyfactors after delivery or to unique deleterious factors inherentto the postpartum period. The effect of breastfeeding on MSremains unclear. The best predictor for whether a patient willhave a postpartum relapse is the incidence of her having activerelapsing MS prior to pregnancy. The medical management ofMS during pregnancy and the postpartum period is challenginggiven the risks of medication exposure to the fetus in uteroand to the infant through breast milk. This review will focuson clinical aspects of pregnancy, including the effects of pregnancyon MS disease activity, as well as the medical managementof MS during pregnancy and postpartum.[1] Although its etiology is not clear, autoimmunity, influencedby environmental and/or genetic factors, is knownto play a major role in disease pathogenesis.Clearly more common in women, prevalence in femaleshas been rising, causing an increased gender bias with acurrent female to male ratio of 3: 1. Important genderdifferences in progression and inflammatory activity ofdisease have been observed. Women experience more frequentrelapses in relapsing–remitting (RRMS) forms,whereas men accumulate disability faster, reach disabilitymilestones more rapidly, and show poorer recovery after initial disease relapse. Hormonal and/or genetic factors are therefore presumablyinvolved in regulating the course of the disease, andsex hormones such as estrogens, progesterone, prolactin,and androgens probably play a role in these complexmechanisms.

Indeed, different hormone-related physiologicalconditions in women, such as puberty, pregnancy,puerperium, and menopause, significantly impact the frequencyand course of disease.In this review, we discuss clinical evidence of theimpact of hormonal factors in MS and attempt to elucidatethe complex hormonal and immunological mechanismspotentially underlying these effects. Understandingthese molecular mechanisms may contribute to the developmentof new and safer treatments for both men andwomen. [2] Contraception is an important consideration for women with multiple sclerosis (MS). MS is more prevalent among females, and the peak age of onset for women is during the childbearing years. MS does not seem to significantly impair fertility although there is emerging data on decreased ovarian reserve and higher prevalence of thyroid autoimmunity in MS patients, possibly affecting fertility. A chronic neurologic illness may also influence pregnancy intentions. Although some patients report having completed their families prior to MS diagnosis, one study found that among women with MS who did not become pregnant after diagnosis, nearly one-third cited MS-related concerns such as symptoms interfering with parenting, burdening their partner, and children inheriting MS. Many women with MS use disease modifying therapies (DMTs). DMTs are generally not recommended for women trying to become pregnant and there are known risks to the fetus associated with some treatments, and none are specifically approved for use in pregnancy. If a woman is on certain DMTs, a washout period before conception is recommended. Providers are always encouraged to review up-to-date product-specific information for their practice location and scope, prior to giving advice to their patients. The optimal time for a woman with MS to conceive should be considered individually, based on the activity of her disease, her response to treatment, and the availability of resources to manage the challenges of early motherhood. As such, family planning should be an essential part of any comprehensive treatment plan for women of reproductive age with MS, including regular counseling on the use of effective contraception to optimally time desired pregnancies and prevent unintended pregnancies. However, neurologists may not be well equipped to discuss contraception with patients. A survey of female neurologists from the United States and Canada found that most referred their patients to anobstetrician–gynecologist or internist for contraceptive counseling, and many were unsure whether their MS patients used contraception or the type of method used. Many methods of contraception are available to women and couples. When choosing an appropriate contraceptive method, factors to consider include safety, availability, acceptability, and effectiveness. For women with MS, additional issues may include difficulty swallowing pills or manual dexterity needed for placing vaginal rings and barrier methods. The effectiveness of a contraceptive method depends on the inherent effectiveness of the method itself and on how consistency and correctly the method is used. Whereas pregnancy rates during perfect use show how effective a method is in a hypothetical “perfect use” scenario, pregnancy rates during typical use show how effective a method is during actual use, including inconsistent and/or incorrect use. The most effective reversible methods of contraception during typical use are intrauterine devices (IUDs) and implants, collectively known as long-acting, reversible contraception (LARC). LARC methods are highly effective because once in place, they do not require regular user compliance. LARC methods provide pregnancy protection for 3–10 years depending on the device but can be removed at any time if the woman chooses to become pregnant (or for any other reason). Methods that are user-dependent, such as oral contraceptive pills and condoms, rely on consistent and correct use and, as a result, are less effective during typical use. When counseling women about contraceptive options, the full range and effectiveness of methods for which they are medically eligible should be discussed.Although several clinical reviews are available on the management of and therapeutic considerations for women with MS during the reproductive years, the focus of these reviews has largely been on issues around the time pregnancy. Topics have included the effect of pregnancy on the MS disease course; the management of MS during pregnancy, labor, and postpartum; and safety of breastfeeding while on DMTs. Safe and effective contraceptive choices for women with MS have not been included. This topical review will specifically focus on the safety of contraception being used for contraceptive purposes for women with MS; it does not consider the safety of contraception as primary or adjunct MS therapy. [3]

Differences in prevalence and clinical characteristics

Prevalence differences between genders occur in mostautoimmune disorders, with women generally more frequentlyaffected than men. In MS, gender prevalence biasmay be increasing. In the 1980s, female to male prevalencewas approximately 2: 13 but recent reports indicate levels up to 3: 1. This trend is noted primarily inRRMS forms and has been noted not only in westernsocieties but also in Iran6 and Latin America. Genderbias seems to be associated with a latitudinal gradient, asmore significant increases are observed

in northern latitudes, worldwide. Given that changes in MS prevalencehave occurred in a short time, they are most likely relatedto a combination of behavioral and/or environmental factorstogether with epigenetic mechanisms.Over the past 50 years, lifestyle changes in womenrelated to smoking habits, use of birth control, diet, obesity,and sunlight exposure could explain incidence differences.Also, women today tend to have fewer children, atan older age. Interestingly, there is evidence to suggest anassociation between parity and MS risk in women. Inone study, greater number of offspring was linked toreduced risk of first clinical demyelinating event; this, incombination with older maternal age at childbirth, mayhelp to explain the current increase in MS prevalence inwomen.Both MS symptoms as well as their severity alsoappear to differ between men and women, with womenexperiencing more frequent relapses, developing moreinflammatory lesions on magnetic resonance imaging(MRI) and presenting earlier onset. Men, on theother hand, show faster progression and worse outcomes with more cerebellar involvement, cognitionimpairment, gray matter atrophy, and T1 lesions. Clinical MS phenotypes have been recently reported todiffer with race/ethnicity, for example Hispanics andAfrican Americans are at risk of a more severe early disease course. Nevertheless, most of the sexualdimorphism findings have been replicated in nonwesternsocieties. Recently, an association was reported between genderidentity disorders and MS risk, in which adjusted relativerisk of MS in men with gender identity disorders wassignificantly increased, suggesting the influence of feminizinghormones or low testosterone levels on risk, providingfurther evidence of the importance of sexhormones in the pathophysiology of the disease. Intriguingly,gender differences like the ones described are notobserved in women with late-onset MS (diagnosed over50 years of age), suggesting that complex hormonalmechanisms related to menopause or aging might be atplay. [4]

Menarche and puberty

Gender bias is not seen in MS before puberty20 but thereis evidence that age at menarche may be related to age of disease onset, further linking sex hormones to MS riskduring childhood and adolescence.Menarche is currently occurring 1–4 months' sooneramong European women born since 1935 for each decademonitored, probably due to changes in nutrition, hygiene,and general health conditions in western populations. This finding coincides with an increase in MS incidenceand several studies have now shown that early menarcheis associated with increased risk of MS and earlier onset of disease. No differences were found in age ofpuberty between males with MS and controls. Conversely,age at menarche among women with MS was generallylower than in women not developing the disease, suggestingan inverse association between age at menarche andMS risk. For each year of age that menarche is delayed, MS risk falls 13%. In addition, puberty affects the course of MS, as relapserates increase in young girls during the peri-menarcheal period. There also seems to be association betweenolder age at menarche and reduced risk of reaching theEDSS 6 milestone in progressive MS. It is important to note that higher body weight hasbeen linked to earlier onset of puberty in girls. Hormonalpathways activated during puberty and in obese individualsimpact the immune system, with potentially differenteffects on MS triggers. A role for adiposity-related inflammatorymechanisms is also supported by reports of elevatedfat tissue markers in MS such as leptin. [5]

Pregnancy

Effect on MS relapses

Evidence for an effect of pregnancy on MS activity comesfrom studies reporting 70% decrease in relapse rates duringthe third trimester compared with pre-pregnancylevels, and increased relapse rates 3–6 months after delivery,to levels almost three times higher than pre-pregnancy ones. Normal pregnancy induces physiological changesincluding elevated cardiac output, increased lipid levelswith weight gain, as well as changes in estriol, progesterone,prolactin, a-fetoprotein, leptin, glucocorticoids,and insulin growth factor. Early during pregnancy,immune tolerance develops in order to protect the fetusagainst rejection, through regulatory T (Treg) cellelevation, reduction in T helper cells (Th)1/Th17 activityand increase in Th2 activity. Total number of naturalkiller (NK) cells falls, although the proportion ofCD56bright NK cells increases in late pregnancy.In the third trimester and during early postpartum,interleukin-12 (IL-12) production increases threefold andtumor necrosis factor-a (TNF-a) levels drop 40% comparedwith late postpartum values. A shift to a Th2 profilewith increased IL-10 and decreased CXCR3expression by CD4+ and CD8+ cells occurs, withincreased expression of the chemokine receptor CXCR4and the mRNA IL-10/interferon-c (IFN-c) ratio.30 Inaddition, there is elevation of proteins of the heat-shockfamily with immunomodulatory capacity, as well as oftolerance-promoting molecules, including HLA-G,CD200, Fas ligand, a-fetoprotein, and indoleamine 2,3-dioxygenase. Additional mechanisms that may play a role in MSamelioration during pregnancy include: production ofIFN-s by human placenta trophoblast

cells (structurallysimilar to IFN-b), and elevation of estrogen and progesteronelevels, which can induce changes in the IFN-c promoterregion, and in T-bet, FoxP3, programmed celldeath protein 1, and cytotoxic T-lymphocyte antigen 4transcription factors. These hormones also exert profoundeffects on B cells, increasing expression of different genessuch as cd22, shp-1, bcl-2, and vcam-1. Human chorionic gonadotropin (hCG) is a glycoproteinhormone synthesized by syncytiotrophoblast cellsimmediately after embryonic implantation, inducing profounddown-regulation of maternal cellular immunityagainst trophoblastic paternal antigens. There is increasingevidence indicating that hCG alters dendritic cellactivity through up-regulation of indoleamine 2,3-dioxygenase,reducing T-cell activation and cytokine production,as well as stimulating Treg cell recruitment to thefetal–maternal interface. These changes are critical in promotingmaternal tolerance, and may also ultimately influenceimmune responses in pregnant women with MS. Furthermore, up to 95% of CD19+ CD24hi CD27+ regulatoryB cells also express the hCG (LH/hCGR) receptor.Addition of human recombinant hCG to isolated CD19+B cells in vitro induces strong production of IL-10, apotent anti-inflammatory cytokine. Based on these findings,investigators believe that hCG may drive an expansionof IL-10-producing regulatory B cells during normalpregnancy, so controlling undesired immune activation(which would otherwise jeopardize fetal well-being), withthe added effect of contributing to control of MS during pregnancy. Little is known about the effects on MS of microchimerism(bidirectional trafficking of cells between motherand fetus), but it may play a role in disease pathogenesis.Of interest, risk of disability does not increase in womenwith MS having children with more than one partner, aswould be the case if the immune response to paternalgenes was harmful. [6]

Effect of pregnancy on disability

Effects of pregnancy on disability levels in MS remaincontroversial. Given the beneficial effect of pregnancy onrelapse rates and on inflammatory changes, it couldafford protection against relapse-related disability. In acohort of 2466 patients followed for 10 years, morepregnancies were independently associated with lower disability scores. However, although some studies show that womenwith MS who have been pregnant have less progression of disability and propose that these effects might even becumulative since multiparous women seem to have better outcomes, other studies have shown no effect onpermanent disability scores. Importantly, such observational studies are prone toselection bias given the fact that rigorous matching ofgroups at baseline is impossible. For example, youngwomen with severe disease at onset are less likely tobecome pregnant.Taken together, currently available data do not provideconvincing evidence that there is a significant beneficialeffect of pregnancy on long-term disability, although itdoes seem clear that pregnancy does not increase risk ofsecondary progression. [7]

Fertility treatments

There are no clear data to indicate that women experiencingMS suffer impaired fertility. Because general infertilityrates are 10–20% for couples in western countries, infertility in women with MS may represent co-occurrence,such that some may seek fertility treatments.Assisted reproductive technology (ART) has generated arise in the number of live births. This generally involvesthe use of hormone therapy including: gonadotropinreleasinghormone (GnRH) agonists or antagonists, follicle-stimulating hormone (FSH), luteinizing hormone(LH), hCG, and/or progesterone to induce ovulation orto assist implantation.Several studies have reported an increase in annualizedrelapse rates after ART use, especially in women treatedwith GnRH agonists, or when fertilization treatments failed. Mechanisms proposed include: cessation ofDMT, stressful events associated with infertility, andimmunological changes induced by GnRH, as well as augmentedimmune cell migration across the blood–brain barrier. It would seem prudent to recommend cautionwhen women with MS undergo ART and monitor carefullyfor intervention as necessary. [8]

Oral contraceptives

Because oral contraceptives (OCs) contain estrogens (orestrogen receptor regulators) and progestogens, theirinfluence on MS has been investigated, although moststudies did not specify OC combinations or type, suggestingthat differences in hormones and dosage are likely.Regarding risk of developing MS with OC use, somestudies failed to find an association, whereas othersshowed short-term reduction in risk of MS. In oppositionto these findings, a recent study on OC use inwomen with MS was associated with slightly increasedrisk of MS and clinically isolated syndrome (CIS)Concern over whether OCs could affect disease symptoms,activity and/or progression has also been expressed.In fact, one study reported that OC use was associatedwith a higher risk of reaching EDSS 6, even thoughmost epidemiological evidence has not found a negativeeffect on MS and some studies even suggest a positiveeffect, not only on symptoms66 but also on MRI activity(when used in combination with IFN-b1a) and on progressionof disability. [9]

Recommendations for women with MS

IUDs—IUDs include the copper-containing IUD (Cu-IUD) and the levonorgestrel-releasing IUD (LNG-IUD). For both the Cu-IUD and the LNG-IUD, there are no restrictions for use by women with MS(Category 1).

Progestin-only contraceptives-Progestin-only contraceptives include etonogestrel implants, DMPA, and progestin-only pills (POPs). For implants and POPs, there are no restrictions for use by women with MS. For DMPA, women with MS(Category 1) can generally use the method although careful follow-up might be required(Category 2) related to concerns about bone health. Women with MS might have compromised bone health from disease-related disability, immobility, or use of corticosteroids, and use of DMPA has been associated with small changes in bone mineral density.

Combined hormonal contraceptives-Combined hormonal contraceptives (CHCs) include low-dose combined oral contraceptives (containing ≤35 μg ethinyl estradiol), the hormonal patch, and the vaginal ring. Classifications for CHCs for women with MS differ based on immobility status. For women with MS without prolonged immobility, there are no restrictions for use of CHCs (Category 1).However, for women with MS with prolonged immobility, CHCs are usually not recommended unless other more appropriate contraceptive methods are not available or acceptable(Category 3). This is because of inferred concerns about VTE risk. Although no evidence was found examining the effect of CHCs on VTE among women with MS, women with MS are at higher risk than unaffected women for VTE, and CHCs increase VTE risk.

Barrier methods-Barrier methods include condoms (male and female), spermicides, and diaphragm with spermicide or cervical cap. For these methods, there are no restrictions for use by women with MS(Category 1).

Other methods-Other methods of contraception are included in the US MEC 2016 including fertility awareness-based methods, the lactational amenorrhea method, coitus interruptus (withdrawal), and female and male sterilization. None of these methods are restricted for women with MS.

Although a specific contraceptive method may be classified as a Category 1 (which means that the method can be used with no restrictions related to safety), it does not necessarily mean that the method is the best choice for the patient. When counseling women of reproductive age with MS about contraception, providers, including neurologists, should always consider the individual social, cultural, and clinical circumstances of the patient seeking advice. For example, for a woman with MS taking potentially feto-toxic DMTs, more effective methods such as LARC might be the best option to avoid unintended pregnancy or delay pregnancy until teratogenic medications are no longer needed. [10]

Drug interaction considerations

DMTs that were approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treatment of relapsing forms of MS prior to July 2015 were considered as related to drug interactions with contraception. Alemtuzumab, approved in the United States in 2014, was the most recently approved DMT considered. DMTs do not appear to decrease the effectiveness of hormonal contraception although formal drug–drug interaction studies are limited. However, all medications should be reviewed at every visit, as some therapies taken for MS symptom management may affect contraceptive efficacy. A number of medications used for management of specific MS symptoms and other common illness may have interactions with OCPs. These interactions may result in either decreased efficacy of oral contraceptives or a change in efficacy of the other medications. One notable example is modafinil, commonly used (off label) to treat MS fatigue. Oral modafinil has been shown to decrease the level of ethinyl estradiol by altering drug metabolism through the cytochrome P450-mediated oxidative pathways. Thus, efficacy of oral contraceptives may be reduced in MS patients taking modafinil, potentially leading to unintended pregnancy. Another example is anticonvulsant therapy. Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, and oxcarbazepine) lower the effectiveness of progestin-only contraception and CHCs. Women who are long-term users of these drugs should be encouraged to use another contraceptive method. Lamotrigine does not appear to affect the efficacy of progestin-only contraception, but pharmacokinetic studies have shown that levels of lamotrigine decrease significantly during the use of combined oral contraceptives. The US MEC includes recommendations for contraceptive use for select drug interactions. [11]

Conclusions

The observed increase in gender ratio suggests gender specificassociations between environmental and/or gene–environment interactions, and susceptibility to MS.Hence, some environmental factors such as D3 or themicrobiome may in turn affect endogenous sex hormonelevels, which then alter hormonal interaction with MSsusceptibility genes.Difficulties in fully

replicating the protective effects ofpregnancy in MS during clinical trials using sex hormones underscore just how difficult it is to attributegender effects in MS to a single biological factor.Furthermore, the effect of sex hormones during the agingprocess has not been well studied, and consequently theimpact of both variables on the immune response duringthe course of MS is severely limited. Future clinical andpreclinical studies should consider these variables in detail.Similarly, the development of suitable animal modelscould provide relevant information. Current clinical observationsreflect the complex interplay of genetic, epigenetic,hormonal, and environmental factors present in MS.Increasing use of bioinformatics approaches, in large andclinically well-characterized cohorts, will help to unravelthe molecular mechanisms involved and may identify newpathways for therapies that can be targeted in more sexspecificways, to halt autoimmune attacks and even promoteneuroprotection and repair in the CNS.Contraception is important for women of reproductive age with MS to optimally time desired pregnancies and prevent unintended pregnancies. In 2016, the US MEC published evidence-based recommendations for contraceptive use by women with MS to assist health-care providers, including neurologists, when counseling women about contraception. Most methods of contraception appear to be safe for women with MS based on current evidence—the only exception is use of CHCs by women with MS with prolonged immobility due to concerns about possible VTE risk. Although neurologists may frequently refer MS patients to other providers for contraceptive care, neurologists can play a key role in promoting reproductive health by routinely assessing their patients' pregnancy intentions and helping women make contraceptive choices that factor in their level of disability, immobility, and medication use. When counseling women with MS about contraception, the full range of methods for which they are medically eligible should be discussed in order for women to choose the best method for their personal circumstances. For women with MS taking potentially teratogenic medications, highly effective methods that are long-acting, such as IUDs and implants, might be the best option to avoid unintended pregnancy.

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