

Pregnancy in MS: Balancing the Risks CME

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Goal

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Learning Objectives

Upon completion of this activity, participants will:

Have increased knowledge regarding the

- Data on the use of disease-modifying therapies (DMTs) in MS during pregnancy

Have greater competence related to

- Development of a treatment plan for MS during pregnancy

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Pregnancy in MS

Balancing the Risk

| | |
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Pregnancy in MS: Balancing the Risk

Patricia K. Coyle, MD: Hello. I am Dr Patricia Coyle, director of the Multiple Sclerosis (MS) Comprehensive Care Center and professor of neurology at Stony Brook University Medical Center in Stony Brook, New York. Welcome to this program titled *Pregnancy in MS: Balancing the Risk*.

Joining me today is Dr Bianca Weinstock-Guttman who is professor of neurology and director of the Jacobs Comprehensive MS Center at the University of Buffalo in Buffalo, New York. Welcome, Bianca.

Bianca Weinstock-Guttman, MD: Thank you.

*This program will include
a discussion of off-label treatment and
investigational agents not approved
by the FDA for use in the US.*

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This program will include a discussion of off-label treatment and investigational agents not approved by the Food and Drug Administration (FDA) for use in the United States.

MS and Pregnancy: *Pregnancy Is Not a Negative Prognostic Indicator*

- MS is more common in young women
 - Female-to-male ratio: about 3:1^[a]
 - Hormones may make women more susceptible^[b]
 - Clinical onset often in childbearing years
- Impact of pregnancy on disease activity
 - Decreases during third trimester^[a]
 - Relapse rate up to 70% lower than before pregnancy
 - Increases after delivery
 - First 3 mo post partum are high risk for relapse^[c]
 - Pregnancy may be protective against long-term disability progression^[d]

a. Airas L, et al. *Obstet Med.* 2012;5:94-97.
 b. National Multiple Sclerosis Society website. Who gets MS? 2018.
 c. Coyle PK. *Ther Adv Neurol Disord.* 2016;9:198-210.
 d. Teter B, et al. *J Mult Scler.* 2014;1:101.

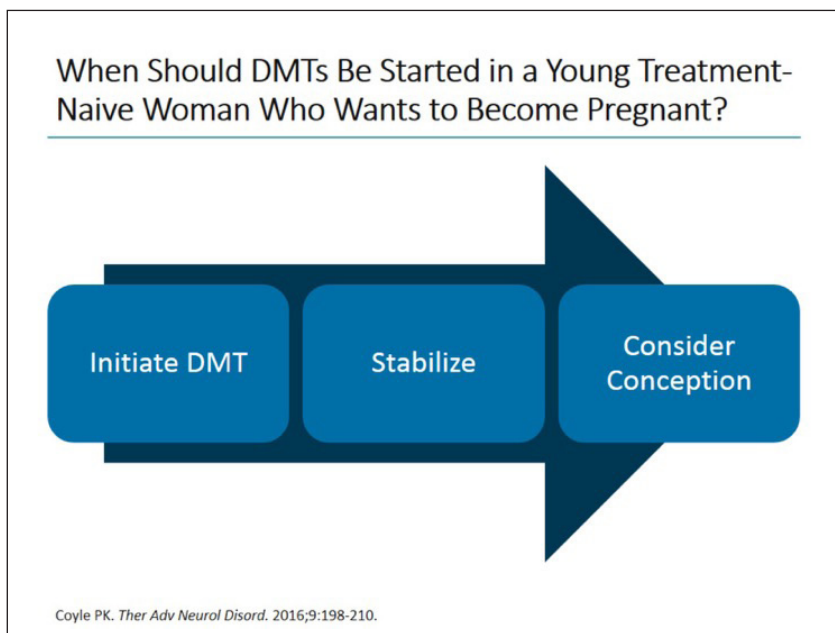
MS and Pregnancy: Pregnancy Is Not a Negative Prognostic Indicator^[1-4]

Dr Coyle: Today, we are going to be talking about pregnancy in MS. MS is a young person's disease, and MS is a predominantly female disease, currently 3-to-1, and it is increasing among young women. Therefore, we can really consider that the prototypic MS individual is a young woman of childbearing age. Hormonal states, and particularly pregnancy, are a major topic of interest. We are going to be talking about the latest thinking on pregnancy in MS disease activity, disease-modifying therapy (DMT) washouts, what are we currently doing, treating MS during pregnancy, and the use of long-lasting induction therapy and how that might fit into pregnancy planning in MS.

Let us begin with the impact of pregnancy on disease activity. Bianca, what do we know about the impact of pregnancy on MS prognosis both short-term and long-term?

Dr Weinstock-Guttman: Generally, it is well-known. We have an increased number of observational studies providing information on pregnancy and MS. We know that the number of relapses during pregnancy is decreasing primarily in the last trimester and is increasing after delivery, after the term of the pregnancy. However, in the long-term, relapses after pregnancy do not have a long-term effect on disability. Actually, there are observational studies suggesting that patients who became pregnant during their disease may actually have a better outcome than the ones who do not have any pregnancy during their disease.

Dr Coyle: That is certainly very helpful that we can counsel our patients with MS that we are not aware of any negative prognostic indicators with regard to pregnancy on their disease course.



When Should DMTs Be Started in a Young, Treatment-Naive Woman Who Wants to Become Pregnant?^[3]

Dr Coyle: I know a question that often comes up in a newly diagnosed young woman who may be recently married, is thinking about starting a family, how do you balance whether to recommend starting a DMT or not doing that and letting them try to become pregnant first?

Dr Weinstock-Guttman: In general, we recommend having the disease stable for at least 1 year. Therefore, we recommend to initiate therapy, stabilize the disease, and then consider conception. It is also very important to discuss the different DMTs. It will be much easier to consider discontinuation or continuation during the pregnancy.

Dr Coyle: I think that is a very important point, that you would really favor in a treatment-naive newly diagnosed treating them first to control the disease and then electively thinking about subsequent pregnancy. I think that is very important.

Primary Progressive MS

- Insufficient data about PPMS in pregnancy
 - Only ~ 15% of those with MS have PPMS^[a]
 - Disability may make conception difficult



a. National Multiple Sclerosis Society website. PPMS overview 2018.

Primary Progressive MS^[5]

Dr Coyle: I do know that most of the pregnancy series in MS involve relapsing MS patients who are really not disabled at all. We have much more limited data on progressive MS, which is the more disabling form. What would you comment about what we know about pregnancy in progressive MS?

Dr Weinstock-Guttman: Indeed, the data are mostly in patients with relapsing-remitting MS (RRMS). In patients with progressive MS, we do not have sufficient data, which will be important to evaluate further in prospective studies. However, there is a consideration that patients with progressive MS may already have disability and becoming pregnant may have a more difficult outcome.

Dr Coyle: Clearly, that is an area where we do not have enough information. It might really drive multicenter cooperation to try to get better data on the impact of pregnancy in progressive MS.

MS ≠ High-Risk Pregnancy



NIH website. High-risk pregnancy 2017.

- May have to treat additional comorbidities associated with high-risk pregnancy
 - Maternal age < 20 or ≥ 35
 - Carrying more than 1 fetus
 - Overweight or obesity
 - Health conditions
 - Diabetes
 - HIV
 - Hypertension

MS ≠ High-Risk Pregnancy^[6]

Dr Coyle: I have heard people say, if you have MS and you get pregnant, that is by definition a high-risk pregnancy. Is that correct?

Dr Weinstock-Guttman: No. I do not think that data support that MS itself is a high risk. However, many of our patients may have additional comorbidities that usually are associated with high-risk pregnancy, which have to be treated accordingly.

Treating Relapse During Pregnancy

- MS relapses occur^[a]
 - In 15% to 22% of women during pregnancy
 - In 14% of women during postpartum period
- MRI imaging without contrast acceptable^[b]
 - Gadolinium prohibited because it crosses the placenta
- Corticosteroids for acute relapses^[b]
 - Methylprednisolone sodium succinate IV
 - Dexamethasone contraindicated
- Severe relapses
 - IVIG^[c] or plasmapheresis

a. Alroughani R, et al. *Neurology*. 2018;90:e840-e846.
 b. Coyle PK. *Ther Adv Neurol Disord*. 2016;9:198-210.
 c. Bove R, et al. *Obstet Gynecol*. 2014;124:1157-1168.

Treating Relapse During Pregnancy^[3,7,8]

Dr Coyle: MS is an immunotolerant state. Certainly, MS disease activity can occur during pregnancy, but what do you counsel your patient with MS who is getting pregnant with regard to expectations of disease activity during their pregnancy period? Are there times when it really should be affected?

Dr Weinstock-Guttman: As mentioned before, it is well known that the number of relapses are actually decreasing during pregnancy, primarily during the last trimester and may, however, increase after delivery. We have to be prepared and mitigate the different periods.

Dr Coyle: Yes, I think that the current series have suggested maybe 14% of MS patients will relapse in that 3-month postpartum period. Relapses do occur during pregnancy, we know that. Some series have suggested 15% to 22%. Can we do imaging during pregnancy, and can we use steroids during pregnancy if our patient has an acute attack?

Dr Weinstock-Guttman: Yes, we can. Usually, we do use magnetic resonance imaging (MRI) but without contrast, without the gadolinium that may go through the placenta. We can use steroids for acute events; we can use intravenously administered immunoglobulin (IVIG) for very severe relapses, even plasmapheresis.

Dr Coyle: Are there any particular steroids that you might use or avoid?

Dr Weinstock-Guttman: Usually, I use intravenously administered [methylprednisolone], but dexamethasone is contraindicated.

Is DMT Washout Necessary Before Considering Conception?

| Medication | Washout |
|--------------------|--|
| Teriflunomide* | Accelerated elimination using oral cholestyramine until blood level is < 0.02 µg/mL ^[a] |
| Interferon | Unnecessary ^[a] |
| Glatiramer acetate | Unnecessary ^[a] |
| Dimethyl fumarate | Probably not necessary ^[a] |
| Natalizumab | Unnecessary (concern for rebound if discontinued) ^[b] |
| Fingolimod | 2 mo (concern for rebound if discontinued) ^[c] |

*Teratogenic in animals.
 a. Coyle PK. *Ther Adv Neurol Disord.* 2016;9:198-210; b. Portaccio E, et al. *Neurology.* 2018;90:e832-e839; c. Meinl I, et al. *Mult Scler J.* 2018;24:991-994.

Is DMT Washout Necessary Before Considering Conception?^[3,9,10]

Dr Coyle: Let us turn into the consideration of DMT washouts prior to trying to become pregnant. I think there is particular concern with regard to one of the orals, teriflunomide, that has been teratogenic at least in animal models. There is a so-called accelerated elimination. Do you use that? How does that actually work if somebody is on teriflunomide and wants to get pregnant?

Dr Weinstock-Guttman: Yes, we do use the teriflunomide accelerated elimination. It is usually for 11 days. It is looking for a decrease in the level of the teriflunomide to 0.02 mg/L for the pregnancy. Sometimes, we do accelerate for different switching of medication, but for pregnancy, it has to be less than 0.02 mg/L.

Dr Coyle: You monitor the blood levels?

Dr Weinstock-Guttman: The blood level can be obtained from the company.

Dr Coyle: Yes, I think that is an important point because sometimes, we have seen, it takes a little bit more than 11 days to get the level low. Are there any DMTs where we do not need to do a washout and a patient with MS could continue to take it up until they got pregnant?

Dr Weinstock-Guttman: After 20 years or more of available information on interferon and glatiramer acetate, it appears that these 2 medications can be continued until the time of conception with no harmful effects on the fetuses. Because the half-life being of dimethyl fumarate is so short, 2 weeks may be sufficient and a clear-cut washout may not be necessary.

Dr Coyle: There was a recent series that reported that women who were coming off natalizumab or fingolimod, if there was a washout, appeared to be at increased risk of disease activity during their pregnancy. These are the 2 DMTs that interfere with cell trafficking and in both of them concerns, in a minority, about rebound activity have been raised. What do you think about washouts with regard to natalizumab and then fingolimod?

Dr Weinstock-Guttman: It is well known that discontinuation of these 2 medications, natalizumab and fingolimod, results in reactivation of the disease. It is expected and seen in patients who become pregnant. Therefore, it is really recommended to not have any washout on natalizumab and eventually different interventions to decrease the risk for reactivation of the disease for natalizumab. For fingolimod, probably, we will have to wait for at least 8 weeks to consider conception. Other interventions are less clearly known and again eventually used every other day. It is not sufficiently considered to be controlling the disease.

DMT Use During Pregnancy

| Medication | Use During Pregnancy |
|--------------------|--|
| Teriflunomide | Contraindicated |
| Interferon | Acceptable |
| Glatiramer acetate | Acceptable |
| Dimethyl fumarate | Contraindicated |
| Natalizumab | Can be used in patients with active disease; increase interval between infusions |
| Fingolimod | Contraindicated |

Coyle PK. *Ther Adv Neurol Disord.* 2016;9:198-210.

DMT Use During Pregnancy^[3]

Dr Coyle: Let us turn to the topic of treating during pregnancy, using a DMT during pregnancy. Both the American Academy of Neurology practice guidelines and theECTRIMS/EAN (European Committee for the Treatment and Research in Multiple Sclerosis/European Academy of Neurology) treatment guidelines suggest that we typically do not use a DMT if somebody is pregnant or trying to become pregnant. Particularly, the European guidelines were a little bit more liberal. How do you think about that? Are there DMTs where you would feel comfortable if it is what the patient wanted, in particular, using them during pregnancy?

Dr Weinstock-Guttman: Both recommendations make it clear that the information has to be included as part of shared decision making with the patient. The data are increasingly suggesting the safety of maintaining glatiramer and interferon during the pregnancy with no consistent negative impact on the baby, on the fetus.

Dr Coyle: I think that is a very important point because generally we want to have at least 1000 human pregnancy exposures to be able to talk about safety. We have way more than that with glatiramer acetate—greater than 7000—and way more than 1000 with the interferon beta interferons collectively. You feel pretty confident that if a patient really wanted to continue their glatiramer acetate or interferon beta during the pregnancy, you would feel pretty okay about that.

What about natalizumab? We know there are articles where natalizumab has been used during pregnancy. What would you say about the use of natalizumab in pregnancy and what are the concerns and who might be the optimal agents to really talk about doing that and how would you handle it?

Dr Weinstock-Guttman: Patients on natalizumab usually having very active disease. If this drug were discontinued during pregnancy, the patients would be at increased risk for relapses during pregnancy, thereby affecting the mother and affecting the child. What we usually recommend is to continue natalizumab during the pregnancy but increase the time of the interval between the infusions. We do this also for prepregnancy, including every 6 weeks, every 8 weeks, and eventually at 10-week intervals for the last trimester when certain hematologic abnormalities may occur. We may give only 1 treatment during the third trimester.

Covering Medication Gaps: *Bridging Strategies*

- Consider bridging patient from a medication contraindicated for pregnancy to a safer medication
 - Interferon
 - Glatiramer acetate



Covering Medication Gaps: Bridging Strategies

Dr Coyle: If we have a woman with MS who is on treatment and she comes off treatment, be it natalizumab or fingolimod or dimethyl fumarate, and we expect her to get pregnant quickly, but she does not, we now have a patient whose MS is untreated, which may continue literally for months. Do we ever think about any bridging strategies? Are there such things and what are the data to support that?

Dr Weinstock-Guttman: We do not have yet any data on the benefit of bridging, but it theoretically should be very helpful. It is known that conception takes time and the conception date is not known. It may be around 7 or 8 months. A consideration of bridging to a safer medication that you can get pregnant on, glatiramer acetate or interferon, may be a consideration.

| Long-Lasting Induction Therapies: Pregnancy Planning | | |
|--|--|--|
| Alemtuzumab^[a] | Cladribine^{[b],*} | Ocrelizumab^[c] |
| <ul style="list-style-type: none"> Consider pregnancy no earlier than 4 mo after last infusion Treatment course: 2 y Infusions: 5 d in y 1 and 3 d in y 2 | <ul style="list-style-type: none"> Consider pregnancy no earlier than 6 mo after last dose Treatment course: 2 y 2 treatment wk/y | <ul style="list-style-type: none"> Consider pregnancy no earlier than 6 mo after last infusion Infusions administered every 6 mo |
| <small>a. Coyle PK. <i>Ther Adv Neural Disord.</i> 2016;9:198-210. b. Cladribine PI 2017. c. Vaughn C, et al. <i>CNS Drugs.</i> 2018;32:161-178. *Not available in the United States.</small> | | |

Long-Lasting Induction Therapies: Pregnancy Planning^[3,11,12]

Dr Coyle: Let us turn to our last topic, which is long-lasting therapies, so-called induction therapies. We have a humanized monoclonal against CD52, alemtuzumab. We have an oral agent that is not available yet in the United States but is approved in Europe, oral cladribine, and that may wind up being available here in the United States. We have another monoclonal, the anti-CD20 ocrelizumab that also gives a fairly long-lasting, at least in terms of months, impact on circulating B cells. What is the role of such long-lasting so-called induction therapies in pregnancy planning?

Dr Weinstock-Guttman: I think that they are very helpful. We are looking forward to eventually having more information on patients becoming pregnant after using these monoclonal antibodies. They do have a specific timing to consider trying to conceive: approximately 4 months for alemtuzumab, cladribine probably 6 months, and for ocrelizumab also 4 to 6 months. It is helpful knowing that long-term effectiveness and efficacy of these medications may control the MS much better during the period that patients are off medication.

Dr Coyle: Certainly, I think it sounds like, in particular, alemtuzumab and something like cladribine, if it were available, where you can have long-lasting effects, in terms of a couple of years, might be very reasonable agents to consider when planning a pregnancy.

Thank you

I want to thank you, Bianca. That was great, this discussion of pregnancy in MS, a very, very topical issue. I want to thank you for participating in this activity. Please continue to answer the questions that follow and complete the evaluation.

Abbreviations

DMT = disease-modifying therapy

ECTRIMS/EAN = European Committee for the Treatment and Research in Multiple Sclerosis/European Academy of Neurology

FDA = US Food and Drug Administration

IM = intramuscular injection

IV = intravenous

IVIG = intravenous immunoglobulin

MS = multiple sclerosis

PPMS = primary progressive multiple sclerosis

RRMS = relapsing-remitting multiple sclerosis

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