MS and Pregnancy: A Case Review

Multiple sclerosis (MS) is challenging to manage from many perspectives. One patient population that is receiving increased attention is the women of childbearing age who either want to begin a family or add to the family. The debate surrounding this scenario is occurring more frequently as new data on the impact of disease modifying therapies (DMTs) becomes clearer. But it is not a level playing field for all DMTs. As an example, let's look at Jen's particular situation.

Jen is 34 years old and was first diagnosed with MS when she was 27. She and her husband Tom have a 9-year-old son. Initial discussion for Jen included consideration of interferon-beta or glatiramer acetate as first line injectables; Jen was subsequently started on interferon-beta but was switched to dimethyl fumarate, or DMF, at age 29 due to a relapse with evidence of two new gadolinium-enhancing lesions and an increase in her EDSS to 3.5 from 1.5. At age 31, she was switched to fingolimod as she had developed persistent GI upsets with DMF. Tom and Jen had put off having a second child but decided it was perhaps now or never. What advice would you provide to Jen and Tom as they begin the family "growing" discussion?

MS is common in women of childbearing age, and concerns related to the impact of DMTs on the growing fetus and infant subsequent to birth are well founded. For Jen, there are a number of considerations since her MS has recently been relatively active, so concerns are heightened should she go off her medication as she and Tom try to conceive. But let's take a closer look at the various DMTs used by Jen in the management of her MS. Much of this information derives from a 2018 breakdown by Vaughn and colleagues[1] in CNS Drugs as well as from the 2019 UK consensus on pregnancy in MS from the Association of British Neurologist.[2]

Interferon-beta and glatiramer acetate (injectables):

Interferon-beta and glatiramer acetate do not interact with hormonal contraception, and there is no evidence in humans of a reduced fertility in men or women, increased congenital malformation, or miscarriage rate associated with either. Previous concerns with interferon-beta related to spontaneous abortion have not been observed in larger registry studies. A range of studies and other accrued data suggest that both interferon-beta and glatiramer acetate are safe to continue up until conception if not into the first trimester. In a recent interview with Maria Houtchens, MD, she stated that:

"There is accumulating evidence that we currently have that having been exposed to any of the injectable medications, specifically interferon-betas or glatiramer acetate, is not detrimental or harmful to the developing fetus or to mother. This is quite different from what we would be discussing should the woman been on some of the other DMTs we have available today."

Lastly, for women contemplating a pregnancy and who wish to stop taking either interferon-beta or glatiramer acetate prior to conception, they should undergo a washout period of about 1 month for interferon-beta and 1 to 3 months for glatiramer acetate.

Dimethyl fumarate:

Dimethyl fumarate (DMF) does not reduce the effectiveness of hormonal contraception. One side effect of DMF is gastrointestinal upset, which Jen encountered. There is no evidence that DMF reduces fertility or increases congenital malformation or miscarriage rates. There are limited data about the safety of

DMF in pregnancy, and women with MS should use effective contraception while receiving this therapy. If they do become pregnant, they should only continue treatment if the potential benefit justifies the potential risk to the fetus. DMF has a very short half-life (about 1 hour), so a woman on DMF may not need a washout period before attempting to conceive.

Fingolimod

Fingolimod, as with DMF and the injectables, does not interact with hormonal contraception. There are no data if fingolimod reduces fertility in humans but conflicting data whether it increases congenital malformation rates. Further, there is limited data on the safety of fingolimod during pregnancy. Women with MS planning to become pregnant should stop fingolimod at least 2 months before conception and/or consider an alternative MS treatment. It should be noted that pregnancies in women on fingolimod should be treated as high risk.

Now that we've reviewed these DMTs, let's go back to our patient case.

Jen and Tom returned home to think about their "growing family" decision. You had explained to them that there are real concerns since Jen has already had a serious relapse, and even though her disease is currently under control, being off medication during the washout and conception phase, or even subsequently placed on a less effective medication (such as returning to interferon-beta or started on glatiramer acetate), has certain risks that will continue into pregnancy and the postpartum period.

Two weeks later, Jen and Tom are back to discuss their decision to either try for another child or to consider their family set and continue with Jen's current MS therapy strategy. With some concern, they have decided to move ahead with trying to grow the family but at the same time wonder if there is any way to possibly decrease the higher risk for relapse and further disability, as well as putting the growing fetus at risk.

At this time, you explain to Jen and Tom the different therapy approaches to treating MS. Jen is currently on escalation therapy in which there is an early start on a DMT, such as interferon-beta or glatiramer acetate, and if ineffective or partially effective, or if the patient is intolerant, moved to a somewhat more effective DMT. In Jen's case, she was moved to DMF following a relapse that resulted in increased disability and is currently on fingolimod. For patients with more active disease, usually earlier in the time course, induction therapy is a possible consideration. Induction therapy potentially comes with a more effective and longer lasting relapse-free outcome but at increased risk. Induction agents tend to reset the immune system in a manner that for many patients results in long[er] relapse-free periods. As an example of what Jen and Tom might face should they choose an induction strategy, you describe the possible use of one of the newer treatments for MS: *cladribine*.

You explain that cladribine in an oral pill. The dosing is unique in that cladribine is taken initially over two months, 5 sequential days each month, and then repeated a year later. Cladribine is incorporated into DNA strands and inhibits DNA synthesis and repair. Due to its mechanism of action, it poses a serious risk to the fetus, so conception should not be attempted for at least 6 months following a course of cladribine. This means that Tom and Jen would likely need to wait about 19 months before trying to conceive.

Jen and Tom both think the opportunity to grow the family and at the same time possibly reduce Jen's long-term risk of relapse and decrease the burden of treatment she faces is worth serious consideration.

They ask to think about the new option presented as they want to consider the benefits and risks of such a decision. They want to talk with their obstetrician and primary care physician and make an appointment for the following month to discuss their choice.

Although this is a hypothetical patient case, growing numbers of women with MS are faced with these same difficult decisions during their childbearing years, and as this case shows, there is much to consider.

References

1. Dobson R, et al. UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines. *Pract Neurol.* 2019;0:1–9. doi:10.1136/practneurol-2018-002060.
2. Vaugh C, et al. An update on the use of disease-modifying therapy in pregnant patients with multiple sclerosis. *CNS Drugs.* 2008;32:161–178.