When contemplating a pregnancy, women treated for multiple sclerosis (MS) with a disease-modifying drug must decide to discontinue their medication before conception or risk exposing their unborn child to potential drug toxicity. Few studies exist as reference for patients and physicians, and of those available, the majority are less than ideal due to real-world constraints, ethical issues and methodological shortcomings. The authors provide a brief summary of existing animal and human data with current recommendations regarding the safety of IFN-β, glatiramer acetate, natalizumab, mitoxantrone, fingolimod and teriflunomide during pregnancy and lactation in women with MS. We also assess the quality, strengths and limitations of the existing studies including challenges with study design. The investigation of outcomes such as spontaneous abortion and congenital anomalies are highlighted with potential methodological improvements for future studies on drug safety in pregnancy suggested. The authors explore the pharmacokinetics and pharmacodynamics of the MS disease-modifying drugs for their possible mechanistic role in fetal harm and discuss the potential role of clinical trials. Future pharmacovigilance studies should continue to pursue multicenter collaboration with an emphasis on appropriate study design.

**Keywords:** birth • breastfeeding • disease-modifying drugs • multiple sclerosis • pregnancy • safety
Learning objectives
Upon completion of this activity, participants will be able to:
• Describe general principles of DMD management during pregnancy for women with MS, based on a review
• Describe DMD management during breastfeeding for women with MS, based on a review
• Describe findings regarding safety of specific DMDs in pregnancy, based on a review

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Authors and Credentials
Ellen Lu, BSc
Department of Medicine (Division of Neurology), Faculty of Medicine, University of British Columbia, Vancouver, Canada.
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Bing Wei Wang
Department of Medicine (Division of Neurology), Faculty of Medicine, University of British Columbia, Vancouver, Canada.
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Colleen Guimond, MSc
Department of Medical Genetics, Faculty of Medicine, University of British Columbia, Vancouver, Canada.
Disclosure: Colleen Guimond, MSc, has disclosed no relevant financial relationships.

Anne Synnes, MDCM, MHSc
Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada.
Disclosure: Anne Synnes, MDCM, MHSc, has disclosed no relevant financial relationships.

A Dessa Sadovnick, PhD
Department of Medicine (Division of Neurology); Department of Medical Genetics, Faculty of Medicine, University of British Columbia, Vancouver, Canada.
Disclosure: Dessa Sadovnick, PhD, has disclosed receiving research support from the MS Society of Canada Scientific Research Foundation, and CIHR; speaker honoraria and/or travel expenses to attend conferences from: Biogen-Idec, Merck-Serono, Teva Neurosciences, Bayer and unrestricted educational funding to hold a workshop from CIHR, Biogen-Idec and Teva Neurosciences.

Leanne Dahlgren, MD, MHSc
Department of Obstetrics and Gynecology, Faculty of Medicine, University of British Columbia, Vancouver, Canada.
Disclosure: Leanne Dahlgren, MD, MHSc, has disclosed no relevant financial relationships.

Anthony Traboulsee, MD
Department of Medicine (Division of Neurology), Faculty of Medicine, University of British Columbia, Vancouver, Canada.
Disclosure: Anthony Traboulsee, MD, has received honoraria from EMD Serono, Teva Neurosciences, Bayer, Biogen Idec, Chugai Pharmaceuticals and Roche.

Helen Tremlett, PhD
Department of Medicine (Division of Neurology), Faculty of Medicine, University of British Columbia, Vancouver, Canada.
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Sophia, aged 29 years, was diagnosed with multiple sclerosis (MS) 4 years ago. Her symptoms began with unilateral optic neuritis and transverse myelitis. Since the beginning of IFN-β therapy 2 years ago, she has experienced a decrease in relapse frequency (from two per year before treatment to <1 per year on treatment). Sophia wishes to start a family and has been advised by her neurologist to discontinue her disease-modifying drug (DMD) at least 3 months before conceiving. She is concerned about the risk of relapse following discontinuation of disease-modifying therapy as well as the conflicting findings regarding the potential harm to her unborn child of using a DMD during pregnancy.

MS is an autoimmune disease of the CNS that commonly first presents in men and women of childbearing age [1]. Although considered a progressive disease, the severity and rate of progression is highly variable; some patients may only experience occasional relapses of MS disease interspersed with periods of relatively stable

### Table 1. Disease-modifying drugs for multiple sclerosis during pregnancy and breastfeeding: summary of current evidence and recommendations.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Animal studies</th>
<th>Human studies</th>
<th>Breastfeeding</th>
<th>Current recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IFN-β</strong></td>
<td>Pregnancy loss observed in monkeys with 100x human dose of IFN-β&lt;sub&gt;1a&lt;/sub&gt; [101] and 2.8–40x human dose of IFN-β&lt;sub&gt;1b&lt;/sub&gt; [102] Decreased fetal growth: unknown Teratogenicity not observed in monkeys with 100x human dose of IFN-β&lt;sub&gt;1a&lt;/sub&gt; [101] or 2.8–40x human dose of IFN-β&lt;sub&gt;1b&lt;/sub&gt; [102] Decreased newborn survival: unknown</td>
<td>Pregnancy loss: conflicting findings (observed in n = 23 [25] and n = 69 [IFN-β&lt;sub&gt;1b&lt;/sub&gt; only [13]], but not in n = 88 [12]) Decreased fetal growth: conflicting findings (observed in n = 88 [12] and n = 69 [13], but not in n = 78 [59]) Teratogenicity not observed (n = 88 [12], n = 78 [59] and n = 69 [13]) Impaired development of newborn not observed (n = 88 [12])</td>
<td>Minimal excretion of IFN-β&lt;sub&gt;1b&lt;/sub&gt; in human milk, even at the highest recommended human dose [58] Excretion of IFN-β&lt;sub&gt;1b&lt;/sub&gt; in human milk: unknown [102]</td>
<td>Pregnancy category C (risk shown in animal studies [101,102]) Women should be cautioned about the abortifacient potential of IFN-β&lt;sub&gt;1b&lt;/sub&gt; [102] Recommend discontinuation prior to conception or once pregnancy is known [7,8] with some suggesting a washout period of at least 1 month prior to conception [60] for women with mild MS Recommend continuation until conception or through pregnancy [6] for women with severe or highly active MS Use not recommended in breastfeeding [6,8,10]</td>
</tr>
<tr>
<td><strong>Glatiramer acetate</strong></td>
<td>Pregnancy loss: unknown Decreased fetal growth not observed in rats with 18–36x human dose [110] Teratogenicity not observed in rats or rabbits with 18–36x human dose [110] Decreased newborn survival: unknown</td>
<td>Pregnancy loss not observed (n = 31 [13], n = 46 [61] and n = 17 [62]) Decreased fetal growth not observed (n = 31 [13] and n = 17 [62]) Teratogenicity not observed (n = 31 [13], n = 46 [61] and n = 17 [62]) Impaired development of the newborn not observed (n = 11 [16])</td>
<td>Excretion in human milk: unknown [110] Breastfeeding not observed to harm newborn (n = 10 [16])</td>
<td>Pregnancy category B (no risk shown in animal studies; no adequate human studies [110]) Recommend discontinuation prior to conception or once pregnancy is known [7,8] with some suggesting a washout period of at least 1 month prior to conception [60] for women with mild MS Use until conception or into pregnancy may be recommended for women with severe or highly active MS [6] Use not recommended in breastfeeding [6]</td>
</tr>
<tr>
<td><strong>Natalizumab</strong></td>
<td>Pregnancy loss: unknown Decreased fetal growth: unknown Teratogenicity: unknown Decreased newborn survival observed in guinea pig with 7x human dose [106]</td>
<td>Pregnancy loss: unknown Decreased fetal growth not observed (n = 35 [17]) Teratogenicity not observed (n = 35 [17]) Impaired development of newborn: unknown Preliminary data of the Tysabri Pregnancy Exposure Registry (expected study end date: June 2016) suggests no increased risk of pregnancy loss or teratogenicity (n = 277 [63,103])</td>
<td>Detected excretion in human milk [106] Breastfeeding: unknown effect on newborn [106]</td>
<td>Pregnancy category C (risk shown in animal studies; no adequate human studies [106]) Contraception required for women with childbearing potential; recommend discontinuation at least 3 months prior to conception [6] Use not recommended in breastfeeding [6,11]</td>
</tr>
</tbody>
</table>

MS: Multiple sclerosis.
Table 1. Disease-modifying drugs for multiple sclerosis during pregnancy and breastfeeding: summary of current evidence and recommendations (cont.).

<table>
<thead>
<tr>
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<th>Human studies</th>
<th>Breastfeeding</th>
<th>Current recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone</td>
<td>Pregnancy loss: unknown</td>
<td>Decreased fetal growth observed in rats and rabbits with &lt;0.01x human dose</td>
<td>Restricted fetal growth in one case report</td>
<td>Pregnancy category D (positive evidence of human fetal risk)</td>
</tr>
<tr>
<td></td>
<td>Decreased fetal growth observed in rats or rabbits with &lt;0.01x human dose</td>
<td>Teratogenicity not observed in rats or rabbits with &lt;0.01x human dose</td>
<td>Fetal malformation in one case report</td>
<td>Negative pregnancy test prior to each dose required in women with childbearing potential</td>
</tr>
<tr>
<td></td>
<td>Decreased newborn survival: unknown</td>
<td></td>
<td></td>
<td>Use NOT recommended in breastfeeding</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Pregnancy loss observed in rats with &lt;1x and rabbits with &gt;20x human dose</td>
<td>Decreased fetal growth observed in rabbits with &gt;20x human dose</td>
<td>Preliminary data from the Multi-National Gilenya Pregnancy Exposure Registry in Multiple Sclerosis (expected registry completion date: August 2017) suggests no increased risk of teratogenicity (66,104)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Teratogenicity observed in rats with &lt;1x human dose</td>
<td>Teratogenicity observed in rats and rabbits with &lt;1x human dose</td>
<td>Detected excretion in rat milk, but unknown for human milk (108)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased newborn survival observed in rats with &lt;1x human dose</td>
<td>Decreased newborn survival observed in rats with &lt;1x human dose</td>
<td></td>
<td>Pregnancy category C (risk shown in animal studies; no adequate human studies)</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Pregnancy loss observed in rats and rabbits with &lt;1x and rabbits with &gt;1x human dose</td>
<td>Decreased fetal growth observed in rats with &lt;1x human dose</td>
<td>A clinical trial database revealed no increased risk of spontaneous abortion, lower birthweight, lower gestational age or congenital malformation (n = 43 (67))</td>
<td>Contraception required for women with childbearing potential; 2 months contraception recommended after discontinuation</td>
</tr>
<tr>
<td></td>
<td>Teratogenicity observed in rats and rabbits with &lt;1x human dose</td>
<td>Teratogenicity observed in rats and rabbits with &lt;1x human dose</td>
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<td></td>
</tr>
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<td></td>
<td>Decreased newborn survival observed in rats with &lt;1x human dose</td>
<td>Decreased newborn survival observed in rats with &lt;1x human dose</td>
<td></td>
<td>Pregnancy category X (fetal malformation reported in animal studies)</td>
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<td></td>
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<td></td>
<td>Negative pregnancy test and contraception required for use in women with childbearing potential</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Accelerated elimination procedure recommended for discontinuation of therapy in men wishing to father a child</td>
</tr>
</tbody>
</table>

MS: Multiple sclerosis.

...disease [1]. Nonetheless, patients with relapsing–remitting disease are encouraged by some clinicians to start DMDs early to reduce the frequency of relapse with the hopes of slowing disease progression [2], although actual evidence is mixed [3,4]. IFN-β and glatiramer acetate (GA) are currently considered as first-line therapies, whereas natalizumab, fingolimod, mitoxantrone and teriflunomide are typically reserved as second-line options [5]. Patients with MS are generally recommended to discontinue DMDs before conception [6]; however, for those with severe or highly active disease, some recommend GA or IFN-β be continued throughout pregnancy (clinical opinion) [6]. Natalizumab, mitoxantrone, fingolimod and teriflunomide are not recommended and do not play a major role in the management of a planned pregnancy because the known (or potential) risks currently outweigh the benefits [7,8]. Although the risk of a relapse is decreased during pregnancy, particularly in the third trimester [9], some risk remains and relapse rates can increase immediately postpartum, such that some patients and physicians may be reluctant to stop DMD therapy. In other cases, women with MS may have an unplanned pregnancy while taking a DMD. In either situation, there is a real need for clear information regarding the safety of DMD exposure in pregnancy. Women who intend to breastfeed are typically advised to not take a DMD [8,10]; nonetheless, those with highly active disease may opt to reinitiate DMD therapy and forego breastfeeding [6,11]. Here, the authors discuss the evidence from studies exploring DMD safety during pregnancy and highlight major challenges and key considerations for future studies of drug safety in pregnancy.

Summary of findings from the existing literature

Prospective cohort studies appear to be the best way to assess the risk of adverse perinatal outcomes in patients with MS, as clinical trials of pregnant women pose significant ethical issues (discussed later). The authors recently systematically reviewed the literature (2005–2012) surrounding DMD safety during pregnancy in MS [7]. With data from 15 studies and 893 pregnancies in MS women with in utero DMD exposure, we were able to examine perinatal outcomes such as spontaneous abortion...
(i.e., miscarriage), cesarean delivery, birthweight, birth length, gestational age and congenital anomaly (i.e., birth defects). The best evidence from one prospective cohort study suggested that IFN-β exposure was associated with preterm birth, shorter mean birth length and lower mean birthweight [12]. However, the growth of newborns exposed to IFN-β still fell within the normal expected general population range [12]. IFN-β exposure was not associated with low birthweight (<2500 g), cesarean delivery, congenital anomaly or spontaneous abortion [12]. Fewer studies (with limited sample size) were available regarding the safety of GA [13–16] or natalizumab [17]. Therefore, while GA exposure was not associated with lower mean birthweight, congenital anomaly, preterm birth or spontaneous abortion [13], and natalizumab did not appear to increase the risk of shorter birth length, lower birthweight or lower gestational age [17], conclusive statements surrounding safety cannot be made. There were also no reported cohort studies of mitoxantrone, fingolimod or teriflunomide exposure during pregnancy in MS. Since women with MS are at an increased risk of relapse during the postpartum period [18,19] and breastfeeding has been found in some studies (although not all [20,21]) to reduce postpartum relapses [19,22], a discussion of the potential (and wider-known) benefits of breastfeeding versus reinitiation of a DMD would be appropriate. Table 1 shows a summary of pregnancy and breastfeeding outcomes following DMD exposure in animals and humans with current recommendations.

### Strength & limitations of existing studies

At the time of our systematic review, few studies were considered of high quality when evaluated using internationally accepted criteria [23]. However, these criteria must be balanced against the real-world limitations inherent in research involving pregnant women [24]. Nonetheless, most studies were susceptible to recall, voluntary participation, surveillance or reporting bias. Furthermore, studies with small sample size are often unable to adjust for potential confounders including family history, maternal age, previous obstetric history, comorbid illnesses, or exposure to other medications or recreational drugs. There was also considerable heterogeneity in methodology. For example, when classifying DMD exposure, some defined in utero DMD exposure as within 1 month prior to conception, whereas others used the estimated time of conception. All these issues outlined here could contribute to the differences in reported findings between studies – with some studies reporting harm [12,13,25–27] and others not [24–27,33].

Some of the best available studies are prospective, which, by their nature, minimize reporting and recall bias (a common challenge in pregnancy-related pharmacovigilance studies). Three such cohort studies have been published to date and all examined IFN-β exposure [12,13,25]. Of these, two had relatively large sample sizes (n = 69 [13] and 88 [12]), which also allowed for adjustment of important confounders (including gestational age, parity, socioeconomic status and smoking or alcohol use) to better estimate the true effect of IFN-β exposure. In addition, some studies investigated DMD exposure late in pregnancy; three small studies (n = 9 [14], 11 [16] and 12 [15] pregnancies) reported on GA exposure up to the third trimester of pregnancy, whereas others followed long-term developmental outcomes beyond the immediate perinatal period in offspring exposed to GA [16] or IFN-β [12,26] in utero. Individual studies have also investigated maternal natalizumab exposure during pregnancy [17] and paternal DMD use around conception [28] – both represent the first cohort studies published on these topics. These studies did not find evidence of harm; however, given their relatively small sample sizes, further studies should seek to confirm these findings.

### Challenges with ascertainment of specific outcomes

Perhaps one of the biggest challenges to date when examining pregnancy outcomes in MS relates to study power, because small sample sizes limit the ability to examine many important outcomes. Most studies of DMD exposure in pregnancy have involved relatively few women. From our own experience in British Columbia (Canada), this related largely to good clinical practice, with women following advice to discontinue DMDs before conception [30]. In addition, given the relatively short period of time that some of the recently approved DMDs have been licensed for MS, especially fingolimod and teriflunomide, there are limited long-term postmarketing data available to assess safety. Consequently, many studies have been unable to adequately assess rarer outcomes such as specific birth defects or syndromes. Other outcomes, such as spontaneous abortion, are difficult to ascertain. These are discussed in more detail below.

### Spontaneous abortion

IFN-β has been found to cause spontaneous abortion in animals [101,102]; however, there was mixed evidence from human observational studies [12,25,29]. Spontaneous abortions are difficult to detect in practice, especially those that occur early enough in gestation to avoid routine detection by patient or clinician. The symptoms of early pregnancy can be vague and easily confused with transitory illnesses (e.g., viral illnesses) or normal menstrual cycle variability [34]. If pregnancy is not recognized, a spontaneous abortion may be mistaken for heavier-than-normal menses or a passed clot – underestimating the true risk of spontaneous abortion. Prospective enrollment through pregnancy registries as well as regular use of objective pregnancy detection methods, such as home pregnancy kits and/or serum β-human chorionic gonadotropin levels, may improve ascertainment of spontaneous abortions.

### Congenital anomalies & related rare outcomes

Roughly 260 DMD-exposed pregnancies are needed for a study to achieve 80% power, with a type I error of 5%, to identify a 5% absolute increased risk of congenital anomaly from a baseline risk of 3% in the general population [35]. Consequently, most studies to date have lacked a sufficient sample size to investigate these rarer outcomes. In addition, since the majority of identified cases of in utero DMD exposure occur within the first trimester, the risk of congenital anomalies (or other adverse outcomes) associated with exposure beyond the first trimester remain largely unknown [30].
One potential solution to improve ascertainment of rare outcomes is the creation of universal standardized research templates to investigate drug safety in pregnancy. Multicenter pregnancy registries with prospective recruitment of women initiated on DMD therapy may be the ideal platform to investigate newly licensed drugs using these standardized forms; presently, there are some drug-specific worldwide registries, including those for natalizumab [103] and fingolimod [104], that are actively recruiting patients. Such an approach would permit future meta-analyses because these templates would include key demographic, obstetrical and medical data using common definitions. These standardized forms should also capture key developmental outcomes such as gross and fine motor milestones, intellectual development and behavioral measures among children exposed to DMD during pregnancy or breastfeeding – all of which are important and largely understudied. Another approach is through data linkage where population-based registries and/or data sources (often collated for purposes other than research, e.g., health administrative data) are linked together to create powerful, comprehensive datasets [36–39]. Data on confounders are also crucial because drugs are estimated to be responsible for only 1% of birth defects [105] – albeit an important preventable cause.

**Potential confounding factors**

Data from population-based studies suggest that some diseases including epilepsy, migraine, irritable bowel syndrome, systemic lupus erythematosus, depression, anemia and rheumatoid arthritis are more prevalent among individuals with MS compared to the general population [40,41]. These comorbid medical conditions, or the medications used to treat them, may have effects on the unborn child. Lifestyle factors such as smoking, alcohol intake, exercise and obesity may also play a role; for example, there is evidence that individuals with MS may be more likely to engage in behaviors that are known to be harmful to developing fetuses including smoking and alcohol consumption [42]. These potential confounders should be considered in any analysis of birth outcomes of individuals with MS. In addition to the well-established contribution of maternal factors on birth outcomes, it is recognized that paternal ethnic origin, height and birthweight and the degree of paternal involvement during pregnancy may influence birth outcomes [43,44]. Furthermore, as most women with MS and their clinicians would take precautions to avoid DMD exposure in planned pregnancies [30], it is very likely that a higher proportion of unintended pregnancies make up the DMD-exposed cohort relative to the DMD-unexposed cohort. Planned pregnancies are associated with significantly less fetal and maternal morbidity and mortality [6], potentially due to increased parental precaution regarding recreational substance use, better nutrition, as well as better management of comorbid medical conditions. Hence, births in a DMD-exposed cohort may be biased toward a greater risk of adverse birth outcomes.

**Potential biological mechanism(s)**

Both IFN-β and GA are large macromolecules [45] that are unlikely to cross the placenta to directly affect the developing fetus [46]. However, indirect effects are possible. For instance, IFN-β is a cytokine that has immune, antiproliferative and antiviral effects [47]. It is known to increase transcription of over 100 different genes [48]; hence, IFN-β and its metabolites could trigger downstream production of maternal cytokines that affect the developing placenta or cross the placental barrier to affect the fetus. This could disrupt the complex, sequential pattern of chemical signals required for normal fetal growth and development [49].

Natalizumab is an antibody that crosses the placenta to cause in utero exposure, leading to reduced platelet counts and decreased survival of offspring in animals [106]. Mitoxantrone is toxic to DNA, causing inhibition of topoiso sterease II and DNA strand breakage, with a cytotoxic effect on cells [50]. It is known to cause growth retardation and preterm birth in animals [107]. Spontaneous abortion and decreased fetal growth were observed in newborns of women with in utero

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**Figure 1. A conceptual timeline of pharmacokinetic and pharmacodynamic effects of drugs on pregnancy and potential methodological improvements to study design.** *All or none* refers to the time from conception until implantation when insults to the embryo are likely to result in either death or intact survival of the embryo. The ‘critical period’ refers to early organogenesis, during which all the major organ systems of the body are being formed; drug exposure during this period can result in significant congenital anomalies (although exposure at any time during pregnancy has the potential for adverse effects). DMD: Disease-modifying drug; MS: Multiple sclerosis.
mitoxantrone exposure for cancer treatment [51]; women using mitoxantrone may also have secondary amenorrhea [107]. In men undergoing cancer chemotherapy, mitoxantrone may cause azoospermia with a return to normospermic levels 3–4 months after chemotherapy for most patients [52]. Fingolimod binds to the sphingosine 1-phosphate receptor that is involved in vascular formation during embryogenesis in animals [108]. Teriflunomide is known to cause fetal death and malformations in animals [109]; the putative mechanism of harm is suspected to involve the inhibition of dihydroorotate dehydrogenase, an enzyme involved in pyrimidine synthesis [109].

The relationship between DMD exposure and adverse birth outcomes is obscured by our limited understanding of the pharmacokinetic and pharmacodynamic properties of these agents. On the basis of studies of healthy human subjects, IFN-β has a half-life of hours to days (depending on the specific formulation) [101,102], whereas the half-life of GA is unknown, although most of the drug appears to be hydrolyzed locally at the injection site [100]. Natalizumab has a half-life of 11 ± 4 days [106], mitoxantrone 3 days [107], fingolimod 6–9 days [108] and teriflunomide 18–19 days [109]. One commonly studied biomarker of IFN-β bioactivity, the protein MxA, remains in circulation for days to weeks after administration [53]. Even when the drug is no longer detectable in the body, the biochemical and physiological effects of drugs on the body may persist such that harm to the fetus is still possible. In utero exposure at different stages of pregnancy with the same drug can result in different outcomes [54]. Pregnancy loss occurs most commonly during the first 2 weeks after conception, whereas congenital anomaly and impaired brain or growth development often occur later in pregnancy [54].

Proposed methodological improvements as well as pharmacokinetic and pharmacodynamic considerations for future observational studies of drug exposure in pregnancy have been summarized in Figure 1. In addition, substantial physiological changes occur during pregnancy [55], which can affect the pharmacokinetic/dynamic properties of drugs. However, these physiological changes may not be as relevant in women with DMD exposure since most cases of DMD exposure (based on studies to date) have occurred early in gestation when these physiological effects may be not as prominent.

Potential role of clinical trials
The active recruitment of pregnant women (or those actively planning pregnancy) into a randomized controlled trial of a drug for MS is typically considered unethical. Nonetheless, women enrolled in clinical trials [29,31] do occasionally become pregnant accidentally. Collectively, these data can be invaluable as they often represent the first human exposures to drugs during pregnancy. However, these women represent a specific MS subpopulation that may not be generalizable to the wider MS population. Nonetheless, increasingly, there has been debate about the merits of including a limited number of pregnant women in clinical trials [56]. There are some situations where the use of drug therapy during pregnancy may be justifiable. For example, a woman with very active MS may remain on DMDs during pregnancy to minimize the risk of a relapse. Likewise, a woman with epilepsy may be safer continuing anticonvulsants throughout pregnancy rather than risk experiencing significant hypoxic events due to seizures that could be life-threatening to her and her child [57]. When clinically justified, a smaller scale clinical trial with regular, close follow-up of mothers has been suggested – especially if drug therapy during pregnancy is unavoidable due to the mother’s medical condition [56].

Expert commentary & five-year view
Future research on drug safety in pregnancy should strive to minimize methodological limitations and fully consider pharmacokinetic and pharmacodynamic factors. One potential solution to improve ascertainment of rare outcomes is the creation of universal standardized research templates to investigate drug safety in pregnancy. In addition, pharmacovigilance studies in pregnancy highlight the necessity for international, multicenter collaboration. It is encouraging to find several active pregnancy registries with prospective recruitment of women initiated on DMD therapy (including the newer agents natalizumab, fingolimod and teriflunomide); these international multicenter pregnancy registries may be the ideal platform to investigate newly licensed drugs using standardized forms. Such an approach would permit future meta-analyses because these templates would include key demographic, obstetrical and medical data using common definitions. It is also promising to find recent studies investigating longer-term developmental outcomes in offspring associated with in utero drug exposure [12,26] as well as the potential effects of paternal drug use on pregnancy [28]; future studies should continue to expand on these areas of research. The potential benefits of clinical trials involving a limited number of pregnant women warrant further consideration as a viable approach to investigating drug safety in pregnancy.

Key issues
- Women with multiple sclerosis should discontinue disease-modifying drugs (DMDs) before conception; those with severe or highly active disease may consider continuing with glatiramer acetate or IFN-β during pregnancy (clinical opinion).
- Women intending to breastfeed are advised to remain off DMD therapy; those with severe or highly active disease may choose to reintiate therapy and forgo breastfeeding (clinical opinion).
- Future studies should strive to account for pharmacodynamic and pharmacokinetic considerations as well as investigate the risk of spontaneous abortion and the safety of breastfeeding associated with DMD therapy, ideally with large, multicenter collaborations.
- Confounding factors including maternal obstetrical history, lifestyle factors, comorbidities and medication use should be assessed and accounted for in future studies.
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Papers of special note have been highlighted as:
• of interest
•• of considerable interest


•• Discusses the use of disease-modifying drugs (DMDs) during pregnancy and lactation.


•• Discusses animal and human data on the safety of DMD use in pregnancy and lactation.


•• Discussed controversies of clinical trials involving women and their offspring.


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Safety of disease-modifying drugs for multiple sclerosis in pregnancy

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   (Accessed 10 June 2012)

109 Sanofi Aventis US. Aubagio® (teriflunomide).
   www.accessdata.fda.gov/drugsatfda_docs/label/2012/202992s000lbl.pdf
   (Accessed 30 December 2012)

110 Teva Pharmaceuticals. Copaxone® (glatiramer acetate).
   (Accessed 10 June 2012)
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### Activity Evaluation

Where 1 is strongly disagree and 5 is strongly agree

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<tbody>
<tr>
<td>1. The activity supported the learning objectives.</td>
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<td>2. The material was organized clearly for learning to occur.</td>
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<td>3. The content learned from this activity will impact my practice.</td>
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<td>4. The activity was presented objectively and free of commercial bias.</td>
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1. Your patient is a 28-year-old woman with highly active multiple sclerosis (MS) who plans to become pregnant. Based on the review by Dr. Lu and colleagues, which of the following statements about disease-modifying drug (DMD) management is most likely correct?

- **A** Many studies support the safety of continuing her current treatment with DMDs
- **B** Risk of MS relapse is increased during pregnancy
- **C** Clinical opinion is that women with severe or highly active MS may consider continuing glatiramer acetate or interferon beta during pregnancy
- **D** There is high-quality evidence available regarding the risks of spontaneous abortion and congenital anomalies associated with DMD use in pregnancy

2. The patient described in question 1 continued interferon beta therapy and had an uneventful pregnancy and delivery of a healthy boy. Based on the review by Dr. Lu and colleagues, which of the following statements about use of DMDs during breastfeeding is most likely correct?

- **A** She should continue interferon beta therapy while breastfeeding
- **B** Clinical opinion is that women with severe or highly active disease may choose to reinitiate DMD therapy and forgo breastfeeding
- **C** Natalizumab is not excreted in human milk and is therefore safe to use during breastfeeding
- **D** Use of glatiramer acetate while breastfeeding has been proven to harm the nursing infant

3. Based on the review by Dr. Lu and colleagues, which of the following statements about use of specific DMDs during pregnancy would most likely be correct?

- **A** In 1 prospective cohort study, use of interferon beta in pregnancy was associated with preterm birth, shorter mean birth length, and lower mean birth weight
- **B** Use of interferon beta in pregnancy was associated with cesarean delivery, congenital anomaly, and spontaneous abortion
- **C** Many large studies have proven that use of glatiramer acetate in pregnancy is not associated with lower mean birth weight, congenital anomaly, preterm birth, or spontaneous abortion
- **D** Findings of cohort studies of exposure to mitoxantrone during pregnancy have been inconclusive