

# Multiple Sclerosis: Pregnancy Management

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## Maria Houtchens – Disclosures and Conflict of Interest

I would like to disclose the following associations that could be perceived as a conflict of interest in the context of this presentation.

- Research grants from Genzyme Sanofi, Biogen Idec, Novartis
- Consultant engagements with Teva, Genzyme Sanofi, Questcor, Biogen Idec, Novartis

## Why are we here today?

- > 500,000.00 patients with MS in the US
- > 380,000.00 of patients are women with MS in the US
- Estimated 50% of all pregnancies in the US and 40% of all pregnancies world-wide are unplanned
- Women with MS should receive support and counseling from their MS specialist on issues of possible pregnancy.
- MS Health Care Providers should feel comfortable discussing:
  - the effects of pregnancy on MS course and MS influence on pregnancy outcomes
  - genetic risk of MS in offspring
  - optimal conception timing to minimize time off therapy
  - disease control before and during pregnancy, and post-partum including management of RRMS women desiring pregnancy with FDA and EMA approved medications
  - lactation

## Current challenges

- Comprehensive management programs for pregnant MS patients do not exist
- There are no evidence-based practice guidelines on clinical decision making and therapeutic choices for women with MS who choose to become pregnant or experience an unplanned pregnancy
- Level of care received by pregnant MS patients varies dramatically depending on the knowledge and comfort level of a provider
- While most pregnant MS patients are stable throughout pregnancy and post-partum, some patients will have attacks and serious symptoms intra-partum, and will require management
- Patients with aggressive and poorly controlled MS may also desire pregnancy and are at known increased risk for MS-related complications

## Helpful resource by – MS-CERCH

*Multiple Sclerosis Center of Excellence for reproductive and child health*

Obstet Gynecol. 2014 Dec;124(6):1157-68. Management of multiple sclerosis during pregnancy and the reproductive years: a systematic review.

[Bove R, Alwan S, Friedman JM, Hellwig K, Houtchens M, Koren G, Lu E, McElrath TF, Smyth P, Tremlett H, Sadovnick AD.](#)

To examine the evidence guiding management of multiple sclerosis (MS) in reproductive-aged women.

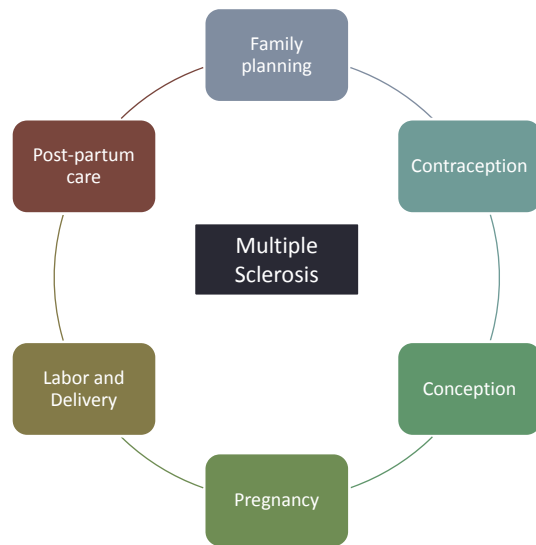
We conducted an electronic literature search using PubMed, ClinicalTrials.gov, and other available resources. The following keywords were used: "multiple sclerosis" and "pregnancy." We manually searched the reference lists of identified studies.

The risk of MS relapses is decreased during pregnancy and increased postpartum. Data are lacking regarding the risks of disease-modifying treatments during pregnancy. There may be an increased risk of MS relapses after use of assisted reproductive techniques.

There does not appear to be a major increase in adverse outcomes in newborns of mothers with MS.

Although there are many unmet research needs, the reviewed data support the conclusion that in the majority of cases, women with MS can safely choose to become pregnant, give birth, and breastfeed children. Clinical management should be

individualized to optimize both the mother's reproductive outcomes and MS course.



Our goal as physicians is to help women live lives to the fullest potential, with their disease that we can't yet cure. This includes experiencing motherhood.

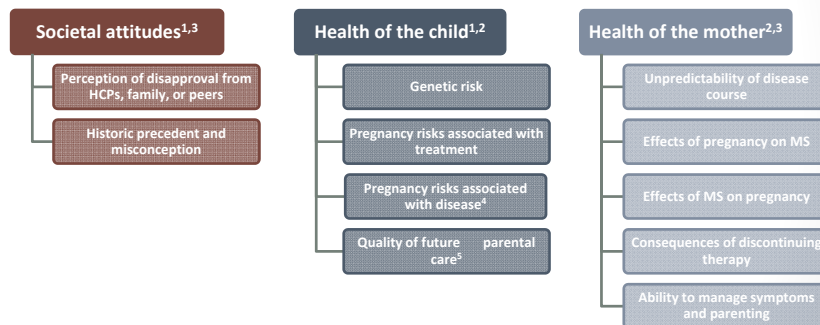
We should not discourage our patients from becoming pregnant, even our more active or disabled patients

# Deciding to be a Mother

## The Motherhood Decision

- The decision to start or enlarge a family can be complicated by chronic illnesses like MS
- MS has little impact on reproductive capacity
- In otherwise healthy mothers, pregnancy, labor, and delivery can generally be managed routinely

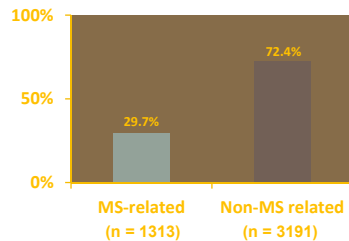
### Domains of Concern for Prospective Mothers With MS



# Parenthood Decisions Among Patients With MS

- In a survey of 4408 female\* patients with MS, 78% (n = 3446) stated that they had not become pregnant since being diagnosed with MS
- The most common contributing factor (n = 1698, 53.2%) across both MS-related and non-MS-related categories was the completion of families prior to an MS diagnosis

## Reasons Contributing to the Decision to Defer Pregnancy Post-MS Diagnosis\*\*



MS-Related Reasons That Contributed to Not Having Children	N = 1313
Symptoms interfering with parenting	75%
Burdening partner	51.3%
Finances	37.2%
Prescription interactions	34.5%
Children's MS risk	32.5%
Not stopping therapy	19.7%
Chronic pain	13.3%
Family support	12.3%
Worsening of symptoms post-pregnancy	7.8%
Interference of sexual function	7.7%
Medical professional advised against	6.0%

\*Respondents were instructed to select all reasons that applied; the MS-related and non-MS-related categories were not mutually exclusive.

# Fertility in MS

- There is no convincing data that there is an overall decrease in fertility in MS patients. However, several factors need to be considered:
  - Possibly, greater prevalence of endometriosis in patients with MS. Moderate to severe endometriosis is associated with decreased fertility
  - Altered reproductive decision making related to chronic illness
  - Sexual dysfunction, including decreased arousal, libido and unorgasmic intercourse, possibly delaying conception.
  - Higher prevalence of thyroid autoimmunity
  - Treatment-related temporary amenorrhea or premature ovarian failure
- One small (N = 61) prospective study reported that patients with MS were more likely to employ assistive reproductive techniques
  - 4.9% (n = 3/61) of patients with MS versus 0.9% (N = 55547\*) of the general population needed artificial insemination to conceive

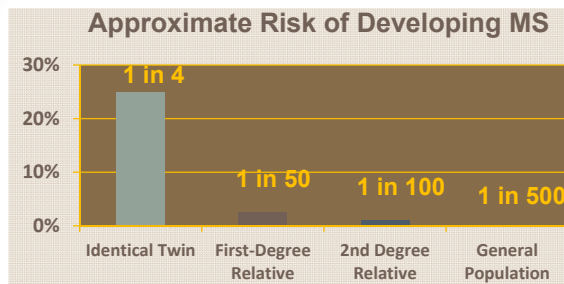
## Fertility in MS

- Hyperprolactinemia might occur
- LH and FSH increase and estrogen decrease are described
- 6–8% of MS patients have thyroid disorders
- ECTRIMS 2014:
  - Diane Ferraro.
  - 303 women with MS, 500 healthy controls
  - Higher rates of pregnancy terminations – 20% versus 12% (p<0.04)
  - Similar rates of miscarriages
  - 22% childless women with MS, 13% childless healthy controls (significant difference)
    - Lack of stable relationships (two fold increase compared to healthy women)
    - Similar socio-economic status, ethnicity, thyroid disease

## Fertility Effects of MS Therapies

- No known effects on fertility (male or female):
  - Glatiramer Acetate
  - Interferons (may cause transient amenorrhea)
  - Fingolimod
  - Teriflunomide (seen in seminal fluid in minute concentrations, no effect on fertility in males)
  - Fumarate
- BUT - No robust data on DMT and fertility relationship
- Possible effects on fertility:
  - Natalizumab (in preclinical studies, at 10 times human dose)
  - Mithoxanthrone (in preclinical animal studies and in humans: 30% permanent amenorrhea in women ages 35+)

## Genetic Counseling for patients with MS



- Monozygotic twins: 25% concordance
- Two parents with MS: 20-25%
- Dizygotic twins: 5% concordance
- 1 parent has MS: 2%-4%
- Lifetime risk of developing MS: 0.1%-0.2%

There is a ~98% chance that children of a patient with MS will *not* develop MS

Genetics are not the sole determinant of MS risk  
Currently, there is no genetic test for MS

**Clinicians should discuss this increased risk with patients who are planning a family as this is often a source of great concern for future parents**

## Contraception for Female Patients with MS

- Consider the patient's MS symptoms when discussing contraception methods.
  - Patients with decreased mobility and spasticity may have an increased risk of DVT associated with HRT and OCP use
  - Alternative methods (eg, diaphragms and sponges) may be difficult to use if the patient has symptoms of paresthesia or spasticity
  - IUDs and condoms can be a safe and effective method of contraception with similar failure rate if used correctly
- MS diagnosis is not a unique consideration is starting OCP.
- The data on prevalence of MS in OCP users is conflicting.
- There are studies to suggest that there may be a slight delay in MS onset in OCP users compared with non-users, but no conclusive evidence to date. Recent work by Dr. Hellwig, using data linkage analysis, however, suggests that there may be an increased risk of MS in ever OCP users.
- There are no formal drug-drug interaction studies between OCPs and MS DMTs, but no concerns have been reported.

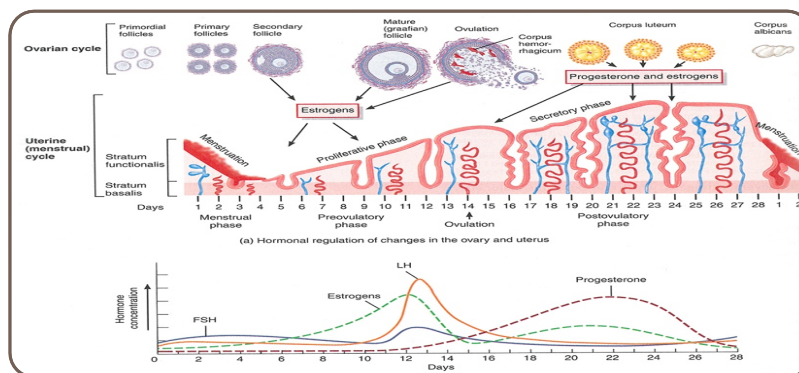
DVT = deep vein thrombosis; HRT = hormone replacement therapy; OCP = oral contraceptive; IUD = intrauterine device.  
1. Thorogood M et al. *Br J Obstet Gynaecol.* 1998;105:1296-1299; 2. Alonso A et al. *Arch Neurol.* 2005;62:1362-1365.



## How do we optimize chances of conception?

- OCPs need to be stopped 2-3 months prior to conception attempts, and patients should be advised to transition to mechanical birth control.
- “Fertility window” – 6 day period, ending with the ovulation day. This window can be estimated based on duration of menstrual cycle, cervical mucus and basal body temperature, as well as commercially available ovulation kits.
- Intercourse is most likely going to result in pregnancy if attempted within a 3 day period, ending with the ovulation day.
- Moderate alcohol consumption, smoking, drug use, vaginal lubricant use decrease the chances of conception.

## Family Planning for Women With MS



Traditional fertility awareness methods can be used to track fertility and improve chances of conception ([www.fertilityfriends.com](http://www.fertilityfriends.com))

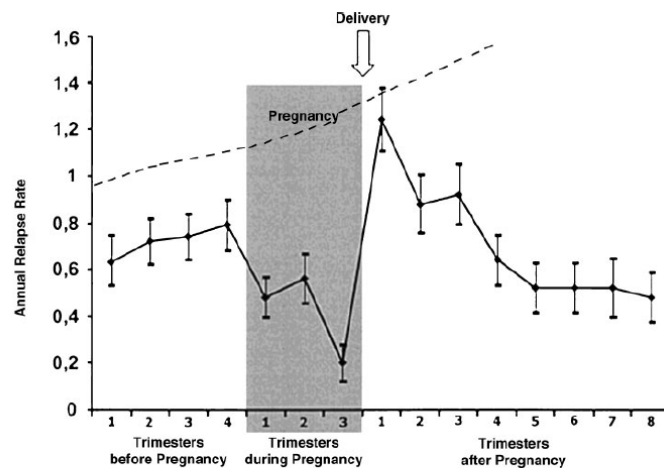
- Calendar
- Basal temperature
- Cervical mucus
- Symptothermal (combined)

## Effects of Pregnancy on the Course of MS - 1

- PRIMS was the first prospective study of 254 women with MS (269 pregnancies) who were followed for up to 2 years after delivery
- Results:
  - Prepregnancy rate of 0.7 relapses per year decreased to 0.2 per year in the third trimester (~70% reduction)
  - Relapse rate increased to 1.2 per year in the first 3 months postpartum; however, 72% of women did not experience any relapses during that period
  - Annualized relapse rate for the 21 month postpartum period did not differ significantly from the prepregnancy rate
  - Breastfeeding was not predictive of a subsequent relapse or of disability progression

PRIMS = Pregnancy in Multiple Sclerosis.  
 Vukusic S et al. *Brain*. 2004;127:1353-1360. Confavreux C et al. *N Engl J Med*. 1998;339:285-291.  
 Vukusic S et al. *Clin Neurol Neurosurg*. 2006;108:266-270.

## Effects of Pregnancy on the Course of MS - 2



Nº of patients	201	211	227	216	201	161
Mean DSS	1.1	1.3	1.6	1.7	1.8	2.0
Standard Deviation	1.3	1.4	1.5	1.5	1.6	1.7
95% Confidence Interval	[0.9-1.3]	[1.1-1.5]	[1.4-1.8]	[1.5-1.9]	[1.6-2.0]	[1.7-2.3]

Adapted from Vukusic S et al. *Brain*. 2004;127:1353-1360.

## Effects of Pregnancy on the Course of MS - 3

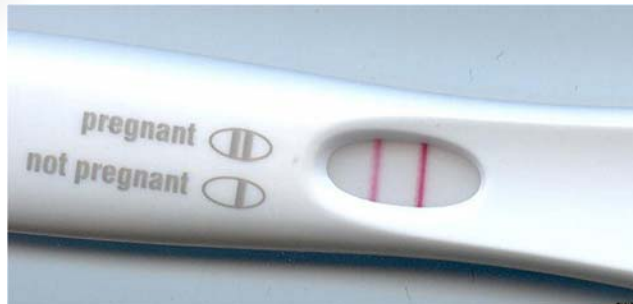
- Most studies failed to demonstrate negative effects of pregnancy on long-term MS outcomes, including disability progression.
- Several studies suggest that the rate of disability increase most rapidly in nulliparous women when compared to those with MS onset before, versus during or after pregnancy.
- Recent Canadian study looked at clinical and term pregnancy data from 2105 female MS patients
- Delay in reaching the Expanded Disability Status Score of 6 by patients having children after MS diagnosis could be explained by the age of MS onset rather than the number of term pregnancies.
- These results may suggest that pregnancy does not have an independent effect in reaching advanced disability levels.

## How do we chose the safest time to attempt conception?

- Pregnancy and motherhood is a personal decision (availability of a spouse or a partner, financial security, social support system, and health status of future parents)
- PRIMS showed significant correlation between pre-pregnancy ARR x 12 months preceding conception, and post-pregnancy relapse rate
- Need to consider potentially extended time off DMDs while attempting pregnancy.
- Probably helpful to stabilize an active patient with more effective therapies for 6-12 months prior to attempting conception
- Establish pre-pregnancy clinical and radiographic disease baseline

## Preconception Care

- Standard Prenatal Vitamins with 0.4mg – 1 gm of daily Folate
- Smoking, alcohol cessation
- Improved sleep hygiene
- Vitamin D3 supplementation
  - Low levels are associated with adverse pregnancy outcomes
  - Low levels are associated with poorer clinical and radiologic MS course
  - Low levels may be associated with increased MS susceptibility in offspring



## Pregnancy Test

Should be administered prior to EVERY treatment with chemotherapeutic or cytostatic agent in a woman of child-bearing age, EVEN IF HER PERIODS HAVE STOPPED AS A RESULT OF CHEMOTHERAPY TREATMENT

## MS and Pregnancy Outcomes

- Babies born to MS mothers are slightly smaller for gestational age by weight (OR 1.45).
- There is no difference in Apgar scores in babies of MS mothers
- There may be a slightly increased rate of operative deliveries in MS patients
- There is no increase in birth defects, perinatal mortality, or other adverse fetal outcomes.

## Labor and Delivery

- Method of labor and delivery does not impact the post-partum course of MS
- Cesarean section to be considered in a woman with paraplegia, pelvic floor weakness, decreased/absent pelvic floor sensation
- Epidural anesthesia or general anesthesia, if required, has no effect on post-partum course of MS
- Consider stress-dose steroids for a woman with extended exposure to corticosteroids in pregnancy or pre-partum

## Secondary MS Symptoms May be Affected by Pregnancy

- Women with MS experience symptoms of pregnancy similar to those observed in healthy women
- Pregnancy may exacerbate some symptoms of MS, including:
  - ▣ Fatigue
  - ▣ Bladder symptoms
  - ▣ Mobility difficulty due to increased weight

1. Multiple Sclerosis Trust Society, Pregnancy and Parenthood Fact Sheet. MS Trust Society, February 2011.  
2. Neuteboom RF, Janssens AC, Siepmann TA, et al. *J Neurol*. 2012;259(2):311-317.  
3. Burke J. MS Essentials. *MS Society*. March 2011.

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## How do we manage relapses in pregnancy?

## Treatment of Relapses in Pregnancy

- **Intravenous corticosteroids** are used widely to treat acute attacks in MS patients, as well as in obstetrics to speed fetal lung maturity.
- Steroids cross the placental barrier and may increase the risk of cleft palate when used in the first trimester or may cause low birth weight and they could in theory delay healing for the mother after birth.
- **Prednisone, prednisolone, and methylprednisolone can be administered with low levels of fetal exposure.** These agents are metabolized to inactive forms by  $11\beta$ -hydroxysteroid dehydrogenase in the placenta, allowing less than 10% of the maternal dose to reach the fetus.
- Betamethasone and dexamethasone, cross the placenta with minimal metabolism, leading to direct full-dose effects on the fetus

## Intravenous Immunoglobulin (IVIg)

- IVIg appears safe for post-partum use to either treat or prevent relapses. There are several anecdotal reports of efficacy and safety.
- The GAMmaglobulin Post Partum (GAMPP) study investigated two IVIg doses and concluded that IVIg application likely had beneficial effects, since the relapse rate did not increase post partum.
- Study of comparative efficacy of IVIg, treatment with other immunomodulatory compounds and no treatment on the postpartum relapse rate showed IVIg-treated patients to have fewer postpartum relapses than the untreated control group matched for disease activity before and during pregnancy (chi-square test,  $p = 0.013$ )

## Assisted reproductive techniques

- ART options:
  - **GnRH agonists:**  
Longer half life, higher affinity to GnRH receptors in the pituitary
  - **GnRH antagonists**
  - **Clomifene citrate:**  
anti-estrogen compound, neg. feedback in the pituitary gland → FSH increase (pre-ovulatory levels estrogen levels 2–3 times higher)
  - **Gonadotropins:** FSH, human Menopausal Gonadotropin (hMG), mixture FSH/LH, (pre-ovulatory levels estrogen levels 10 times higher 3000–3500 pg/ml)
  - **HCG:** induction of ovulation
  - **Progesterone** support of luteal phase

Slide courtesy of Dr. Hellwig

## Assisted reproductive techniques in MS

- French Study 1:  
6 MS women with 10 cycles of ART
  - After 5/6 cycles with GnRH agonists, a relapse occurred.
  - No relapses in GnRH antagonist cycles ( $p < 0.04$ )
- French Study 2:  
32 MS women with 70 cycles of ART
  - 19 had 26 relapses during the first 3 months following ART ( $p = 0.01$ )
  - GnRH agonists ( $p = 0.03$ ; vs GnRH antagonist) and IVF failure ( $p = 0.02$ ; vs ART pregnancy) associated with relapses
  - 21 pregnancies
- More pregnancies with GnRH agonists (40%) than with antagonists (10%)

Laplaud DA. Increase in multiple sclerosis relapse rate following in vitro fertilization. Neurology 2006 Apr 25; 66(8): 1280-1  
Michel L. Increased risk of multiple sclerosis relapse after in vitro fertilisation. J Neurol Neurosurg Psychiatry 2012 Aug; 83(8): 796-802

Slide courtesy of Dr. Hellwig



## Assisted reproductive techniques in MS: German data

- 23 women with MS undergoing 78 cycles of ART
  - insemination (n=32), IVF (n=15), ICSI (n=31)
- 14 (18% of cycles) pregnancies
  - 2 miscarriages, 12 healthy babies
- 4 patients with IVIG and 1 with glatiramer acetate during ART
- Relapse rate increased during the first 3 months after ART ( $p < 0.05$ )
- **Independent** from gonadotropin use and time interval between ART

Hellwig K. Increase in relapse rate during assisted reproduction technique in patients with multiple sclerosis Eur Neurol 2009; 61(2): 65-8

Hellwig K. Increased MS relapse rate during assisted reproduction technique J Neurol 2008 Apr; 255(4): 592-3

## Assisted reproductive techniques in MS in Argentina

- 16 patients with 26 cycles of ART, prospectively followed, all treated with GnRH agonists
- 12 /16 (75%) experienced relapses
  - 7-fold increased relapse risk
  - 9-fold increase of radiological disease activity
- Persistent EDSS increase in 7 of 12 patients
- 7 pregnancies (27%), 3 miscarriages

Correale, et al. Increase in multiple sclerosis activity after in vitro fertilization. Ann Neurol 2012

## Possible mechanisms for relapse

- GnRH-related:
  - Proliferation of immune cells
  - Increase in cytokine, chemokine and endothelial growth factor production
- Estrogens: increase in B-cell mediated factors
- Possible dose effect?
- Transmigration of immune cells through the blood–brain barrier
- Rapidly changing hormonal levels
- Stress
- (Absence of MS therapy?)

Slide courtesy of Dr. Hellwig

## Disease Modifying Drugs and Pregnancy

Generic (brand) name	Chemical structure	Indications(s)	T <sub>1/2</sub> (elimination)	FDA category <sup>a</sup>	Lactation category <sup>b</sup>
<b>GA (Copaxone®</b> , Teva Pharmaceutical Industries, Petach Tikva, Israel)	L-glutamic acid polymer with L-alanine, L-lysine, L-tyrosine molecular weight: 5–9 kDa	To reduce relapse frequency in patients with relapsing-remitting MS and patients who have experienced a first clinical episode and have MRI features consistent with MS	≈20 h	B	L3
<b>IM IFNβ-1a</b> (Avonex®, Biogen Idec, Weston, MA, USA) * Plegridy	166-amino acid (aa) glycoprotein molecular weight: 23 kDa	To slow accumulation of physical disability and decrease frequency of clinical exacerbations in patients with relapsing forms of MS and patients who have experienced a first clinical episode and have MRI features consistent with MS	≈10 h	C	L3
<b>SC IFNβ-1a</b> (Rebif®, Merck Serono, Geneva, Switzerland)	166-aa glycoprotein molecular weight: 23 kDa	To slow accumulation of physical disability and decrease frequency of clinical exacerbations in relapsing forms of MS	69 ± 37 h	C	L3
<b>IFNβ-1b (Betaseron®</b> , Bayer HealthCare Pharmaceuticals, Pine Brook, NJ, USA; Extavia®, Novartis, Basel, Switzerland)	165-aa protein product molecular weight: 19 kDa	To reduce the frequency of clinical exacerbations in patients with relapsing forms of MS and patients who have experienced a first clinical episode and have MRI features consistent with MS	8 min–4.3 h	C	L3

Generic (brand) name	Chemical structure	Indications(s)	T <sub>1/2</sub> (elimination)	FDA category <sup>a</sup>	Lactation category <sup>b</sup>
<b>Fingolimod (Gilenya™</b> , Novartis)	2-amino-2-[2-(4-octylphenyl)ethyl]propan-1,3-diol hydrochloride molecular weight: 344 kDa	To reduce frequency of clinical exacerbations and delay accumulation of physical disability in patients with relapsing forms of MS	6–9 d	C	L4
<b>Natalizumab (Tysabri®</b> , Biogen Idec)	Recombinant humanized IgG4k monoclonal antibody molecular weight: 149 kDa	As monotherapy for relapsing forms of MS; to delay accumulation of physical disability and reduce frequency of clinical exacerbations	11 ± 4 d	C	L3
<b>Teriflunomide (Aubagio)</b>	Active metabolite of leflunomide, inhibits pyrimidine synthesis	As monotherapy for relapsing forms of MS	2 weeks to 2 years	X	?
<b>Alemtuzamab</b>	monoclonal anti-CD52 Ab present on surface of mature lymphocytes	Third line therapy for treatment of refractory relapsing forms of MS	288 hours	C	?

<b>Mitoxantrone</b> (Novantrone®, EMD Serono)	Synthetic anthracenedione $C_{22}H_{28}N_4O_6 \cdot 2HCl$   molecular weight 517 kDa	To reduce neurologic disability and/or the frequency of clinical relapses in secondary (chronic) progressive, progressive relapsing, or worsening relapsing- remitting MS	23–215 h	D	L5
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## Corticosteroids during pregnancy (FDA Category C)

- Corticosteroids have weak teratogenic potential, but caveat before gestational week 12
- Cortisol and prednisolone are inactivated in the placenta (10% reach the fetus, 100% with dexamethasone)
- Caveat: closure of the soft palate between gestational week 8 and 11
- Cleft risk in animal studies 1:1000
- OR meta-analysis in humans 3.5 [95% CI 1.97, 5.69]
- With continuous steroids: premature rupture of the membranes, disturbances of electrolytes, hypoglycaemia

## Interferon-beta risk in pregnancies (FDA Category C)

- >1000 pregnancies tracked
  - No increased risk of miscarriage
  - No increased risk of malformations
  - Lower mean birth weight/lower mean birth length
  - Increased risk of preterm birth (OR 2.11)?
- No elective termination of pregnancy due to IFN exposure

Lu, et al. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology* 2012; 79(11): 1130-5

## Glatiramer acetate risk in pregnancies (FDA Category B)

- >300 pregnancies under GA tracked
- No increased risk of
  - Malformation
  - Abortions
  - Preterm birth
  - Reduced birth weight
- Recent data from Germany (ECTRIMS 2014, AAN 2015, K. Hellwig) suggested no increased risk in a large, prospective cohort, exposed to GA in early pregnancy

Lu, et al. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review *Neurology* 2012; 79(11): 1130-5

## Natalizumab risk in pregnancies (FDA Category C)

- Not teratogenic in animal studies/increased risk for miscarriage in one of several animal studies
- Preliminary data show no increased risk in humans (birth weight, malformation, abortion)
- During the 2nd quarter, transplacental transport of antibodies observed
- Caveat: if given during the last quarter of pregnancy, hematological screening of the newborn is necessary (10/13 exposed babies have thrombocytopenia at birth) – Data from German study of 17 pregnancies with 2/3 trimester exposures
- 40% of natalizumab-treated women have relapses during pregnancy if it is discontinued prior to pregnancy onset (AAN 2015).

## Fingolimod risk in pregnancies (FDA Category C)

- Teratogenic in animal studies
- Fertility is not reduced
- 280 pregnancies exposed to fingolimod tracked
- 65 healthy newborns
- 27 spontaneous and 49 induced abortions
- 6 malformations (Fallot's tetralogy, acrania, posteromedial bowing of the tibia, vesicouretral reflux, inguinal hernia, atrial septal defect)
- **2 months after last intake, sufficient contraception for women**
- Breastfeeding is contraindicated
- Worldwide pregnancy registry

## Teriflunomide risk in pregnancies (FDA Category C)

- 70 pregnancies (elimination procedure with (cholestyramine or activated charcoal))\*
  - Induced abortion, n=29
  - Spontaneous abortion, n=8;
  - Healthy newborn, n=26;
  - Ongoing pregnancy, n=7;
- So far no pattern of malformation in about 100 leflunomide-exposed pregnancies\*\*

\*Kieseier, et al abstract ECTRIMS 2012; \*\*Chambers, et al Arthritis Rheum 2010

## Alemtuzumab

- 139 pregnancies to date in 104 patients among 1486 study subjects
- 67 live births
- 17% miscarriage
- 133 of 139 pregnancies > 4 months after last Campath dose
- 3 pregnancies < 1 month
- Significant adverse events in 11 (7.9%) of infants
- 1 thyrotoxic crisis in one infant – nuchal cord, - mother w Graves disease in pregnancy
- cystic hygroma, hypoplastic left heart
- Pregnancy can be initiated 4 months after the last cycle

## Dimethyl fumarate risk in pregnancies (FDA Category C)

- No teratogenicity in animal studies
- No embryo and fetotoxicity
- Very short half-life
- 38 pregnancies in clinical MS trials
- 22 healthy newborns
- 3 (12%) spontaneous abortions
- 7 (28%) ETP
- 23 pregnancies in German TIS registry in psoriatic patients without a signal
- **delayed release fumarate** – no signal in rats and rabbits
- no impaired fertility; 135 human preg – no increase in sp abortions, no teratogenicity

Gold, et al. DMF and pregnancy – Poster P02-129 AAN San Diego 2013, [www.embryotox.de](http://www.embryotox.de)

## Resuming MS medications after delivery and lactation

- **IgG antibodies** (eg natalizumab) pass freely into breast milk, albeit at much lower concentrations than in serum; largely degraded by gut (infant serum levels low from nursing only) (information from humans)
- **Oral small molecules** at a lower fraction in breast milk than in sera (peak concentrations and half-life) but more likely to directly affect the infant's immune/neurological systems, little gastric degradation, slowed hepatic clearance in infants (eg dimethyl fumarate, fingolimod) (information from rats)
- **Beta-interferons** found at 0.006% of maternal dose in infant (even using the highest value measured in breast milk)

It is not well known whether **GA, IM IFN $\beta$ -1a, SC IFN $\beta$ -1a, or SC IFN $\beta$ -1b** are excreted in human milk. The molecular weight of these compounds may limit their transfer to maternal milk and they are likely to be depolymerized if ingested orally, so toxicity is unlikely.

*Probably safe to breastfeed on beta-interferons and glatiramer acetate, natalizumab and other non-depleting monoclonal antibodies but not on small molecules (dimethyl fumarate, fingolimod)*



## Lactation in MS

- Exclusive breastfeeding may be protective
  - Annette Langer Gould
  - Kirstin Hellwig
    - 201 MS patients, 12 months postpartum f/u
    - excl breastfeeding – 24% relapsed withi 6 m pp
    - non-exclusive or none - 38% relapsed,  $P=0.02$  and  $0.04$
    - independent effect – relapses in pregnancy and use of DMDs at time of conception – predicts foregoing exclusive breastfeeding

## Psychological Impact of Pregnancy on Women With MS

### Postpartum depression is common in mothers with MS

The lifetime prevalence of major depressive disorder in people with MS is estimated to be approximately 50%

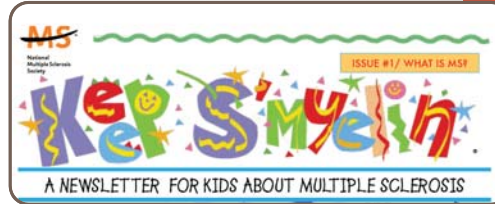
The rate of suicides among patients with MS is 7.5 times greater than that of the general population

In a survey of mothers with MS 1 to 6 months postpartum, symptoms correlated with increased depression and emotional distress

Postpartum depression can affect a woman's ability to care for herself or her child during a time already complicated by increased incidence of relapse and significant baseline stress

## Parenting With MS

- Prior to raising children, all parents must consider the subsequent emotional, social, and economic issues<sup>1</sup>
- Patients with MS must factor in the uncertainties of a chronic, unpredictable disease<sup>1</sup>
- Couples can employ strategies to alleviate disease-related parenting issues<sup>1,2</sup>
  - Consider available support system
  - Manage financial resources and contingencies
  - Assess both personal and family priorities
  - Create open dialogue with children
    - Age-specific disease information
    - Instill problem-solving, adaptation, coping skills



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## General Management Guidelines

--also detailed in earlier reference--

- For any woman with MS of childbearing age, begin with pre-conception counseling session.
  - Discuss family planning, including timing
  - Discuss genetic risks: family history, one or both parents affected, level of anxiety about “disease transmission” to offspring
  - Assess MS activity in pre-conception phase, and the risk of MS activity increase intra-partum, or post-partum
- Discuss cessation of treatment prior to attempting conception (1-4 weeks, depending on  $T_{1/2}$  of the medication)
- Discuss optimization of conception chances: charting, basal body temperature measurement, use of ovulation kits, with goal to decrease time off therapy while trying to achieve pregnancy
  - Referral to infertility clinic if no pregnancy achieved after 3-6 months of optimal conception attempts, as opposed to 12 months’ recommendation in a non-MS patient
- Consider stabilizing active patient with alternative therapy before starting conception attempts
- Consider monthly IV steroids timed to menses in an active MS patient off therapy, while attempting conception
- For a non-lactating patient, it is safe to resume MS therapy within 1 week after birth. Patient typically abstains from intercourse postpartum for up to 6 weeks. Thereafter, they should be advised to return to their preferred method of birth control.

- For a lactating patient with previously active disease, it may be safe to administer monthly steroids or monthly IVIG, instructing them to discontinue breastfeeding for 24 hours after treatment.
- MRI should be repeated within 6 months post-partum, to assess radiographic disease activity.
  - Compare to pre-partum MRI
  - Compare to clinical disease course post delivery
  - If marked worsening, consider changing therapy.
- Monitor for signs of post-partum depression
- Advise on community resources and assess for adequate social support system