Management of Multiple Sclerosis in Pregnancy and Postpartum

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Discolure

- I have no financial disclosures related to this topic.

Categories

- MS at the diagnosis phase
- Pregnancy and MS
- Management of MS symptoms during Pregnancy
- Post Partum Period

Ludwina of Scheidam

Saint Ludwina the Patron Saint of Ice Skaters

Jean Martin Charcot

Sylvia Lowry

MULTIPLE sclerosis. Will anyone recovered from it please communicate with patient. T378 Times.

MS Epidemiology

- MS is a disease that often occurs in reproductive age women
- Most common onset age 22-23
- Mean onset age 28
- Female : male ratio is 3:1

Heredity and MS

- MS risk has environmental and genetic factors
- Genetic factors typical for a polygenic disease
- In general population, risk is about 1 in 800
- Risk increases in first degree relatives of MS patients to 3-4% in a females and 2-3% in males
- If both sides of the family have MS, risk even higher

Bashinskaya et al. Human Genetics.
2015; 134(11): 1143-1162

MS at the diagnosis

Fertility and Pregnancy in MS

- Women with MS tend to have fewer children
- Little, if any, direct change
  - birthweight
  - fertility
  - miscarriage rate
  - malformations
- Prior cytotoxic chemotherapy agents such as mitoxantrone or cyclophosphamide and Teriflunamide may impair fertility

Infertility Treatment for Women with MS

- Women with MS undergo assisted reproductive techniques (ART) more frequently (Cavalla. Neurol Sci. 2006; 27: 231-239)
- If ART unsuccessful, relapse risk increases for 3 months (Michel. JNNP. 2012; 83: 796-802)
- May be increased relapse risk if gonadotrophin releasing hormone (GnRH) agonists are used for ART rather than GnRH antagonists (Hellwig et al. Euro Neurol. 2009; 61: 65-68)

Role of Vitamin D in Mom and Child

- Vitamin D intake may attenuate risk of getting MS
- Growing data shows increased relapse risk with vitamin D deficiency
- Some data suggest the mother's vitamin D intake/level may alter the future child's MS risk
  - Maternal vitamin D levels < 12 ng/mL during early pregnancy were associated with a nearly 2 fold increased risk of MS in the offspring
- It is prudent to make sure maternal vitamin D levels are adequate

Munger et al. JAMA Neurology. 2016; 73(5):515-519

Potential Fertility Issues for Fathers with MS

- MS and MS medications may cause difficulty with sexual function including erectile or ejaculatory dysfunction
- Fertility may be decreased by previous use of cytotoxic agents
- Fetal malformation risk may be increased by prior use of teriflunomide
  - Use in the previous two years by the father
  - Accelerated excretion protocols exist

Decisions of Conception

- Stability of MS and MS symptoms, including mood and cognition
- Disability level of parents
- Timing of possible MS treatment alterations
- Willingness and ability to alter MS treatment agents

Pre-Pregnancy Planning: Non- Pharmacological Symptom Treatment

- Bowel and Bladder
  - Pelvic floor rehabilitation
  - Botulinum toxic of detrusor may provide some relief for 6 or more months (Brin et al. Pharmacoepidemiology Drug Saf. 2016; 25(2): 179-187)
- Fatigue
  - OT
  - Physical activity “ Yoga”
- Ataxia
  - PT

MS course during Pregnancy

MS Disease Course and Pregnancy

- Exacerbation rate 1, 2, 3
  - Relapse rate decreases as pregnancy progresses
  - 80% decrease in third trimester
- Post-partum
  - risk increased for 3 or more months
- Exacerbation risks in previous pregnancies does not predict next pregnancy exacerbation risk

Confavreux et al. NEJM. 1998; 339(5):285-291

Symptomatic Changes During Pregnancy

- Anecdotally, many women with MS report a significant lessening of symptoms during the course of pregnancy
- I have not seen this “symptom holiday” reported in any journal articles but have heard it numerous times from women with MS
  - “I wish I could stay pregnant all the time”

Injectable Disease Modifying MS Medication Use During Pregnancy

- There is increasing evidence that neither Glatiramer acetate nor Interferon beta constitutes a major risk for prenatal developmental toxicity.
- Most publications including the 2016 Continuum (AAN) Journal still list stopping the medication 2 months or more before conception!
- Interferon beta may increase miscarriage rate; therefore, I suggest discontinuing it once attempts to conceive begin
- Glatiramer acetate appears safe to continue throughout pregnancy

Weber-Schoendorfer and Schafer. Mult Scler. 2009; 15: 1037-1042

Oral Disease Modifying MS Medication Use During Pregnancy

- Fingolimod: 2 months needed to eliminate, fetal anomalies (14.6% poor pregnancy outcome) including acrania, tetralogy of Fallot (Karlsson et al. Neurology. 2014; 82: 674-680)
- Teriflunomide: 2 year washout, associated with fetal abnormalities
- Dimethyl fumarate: rapid elimination, limited data, crosses placenta some abnormalities in animal studies

Amato and Portaccio. CNS Drugs. 2015; 29(3):207–220

Monoclonal antibody administration

- Human IgG is selectively transported across the placenta
- Serum concentrations equal to maternal at approximately 26 weeks gestation
- Fetal concentrations may exceed maternal concentrations at delivery

Chakravarty et al. Blood. 2011; 117(5): 1499-1506

Intravenous Disease Modifying MS Medication Use During Pregnancy

- Natalizumab: half life 11-16 days, possible increased risk for birth defects (Friend et al. BMC Neurology. 2016; 16:150-158), increased hematologic abnormalities with third trimester exposure (Haghikia et al. JAMA Neurology. 2014; 71: 891-5)
  Crosses the BPB in a measurable amounts in the fetal blood samples.
- Alemtuzumab: half life about 12 days, 193 pregnancies reported, no major issues but watch mother's thyroid tests
  (Vukusic and Marignier. Nat Rev Neurol. 2015; 11: 280-289)
- Rituximab: half life 18-22 days, some drug present beyond 24 weeks in some patients, 231 pregnancies with maternal exposure reported, many concomitant medications, data unclear Chakravarty et al. Blood. 2011; 117(5): 1499-1506)
- Ocrelizumab: No data available

Maternal MRI and Pregnancy

- Recent report of 1,737 first trimester MRI exposures and 397 gadolinium exposures (compared with over 1,400,000 non MRI pts)
- Exposure to MRI during the first trimester of pregnancy has not been associated with risk of harm to the fetus or in early childhood
- Gadolinium based contrast agent use at any time during pregnancy was associated with an increased risk of:
  - a broad set of rheumatologic, inflammatory, or infiltrative skin conditions
  - Stillbirth or neonatal death

Ray et al. JAMA. 2016; 316(9):952-961

Exacerbations During Pregnancy

- Rule out pseudo-exacerbations
  - Infection, medication interactions/toxicity, overuse
- Exacerbation treatment with high dose corticosteroids may shorten exacerbation duration but are not proven to decrease long term deficits, steroid treatment of exacerbations is not required

Management of Exacerbations During Pregnancy

- High dose methylprednisolone is an option
  - ACTH (Acthar Gel) has been shown to have an embryo-cidal effect per package insert
- IVIG is suggested for exacerbations in many reviews, but this is an ineffective exacerbation treatment in well controlled studies on non-pregnant patients Visser et al. Mult Scler. 2004; 10:89-91, Sorenson et al. Neurology. 2004; 63: 2028-2033
- Plasmapheresis can be performed for severe exacerbations
  - Should use an experienced team in this situation

Treatment of MS Exacerbations in Pregnancy

- High-dose methylprednisolone (500-1000 mg) daily for 3-5 days is the treatment of choice for MS relapses
- Recent report of breastmilk concentrations were well below doses given to neonates requiring methylprednisolone drug therapy (0.25 mg/kg)
- Theoretic effects could include growth suppression or interference with endogenous corticosteroid-production

Cooper et al. J Human Lactation. 2015; 31(2): 237-239

MS in the Postpartum

Labor and Delivery in MS

- Patients with greater disability, esp. motor dysfunction in lower body, may have impaired ability to deliver vaginally
- The symptomatic medication Dalfampridine (decreases weakness) has a seizure risk and should not be used during pregnancy or delivery
- Remember fatigue is a hallmark MS symptom
  - Prolonged labor may accentuate this symptom

Anesthesia, Cesarean Delivery

- Epidural anesthesia was not associated with a higher postpartum relapse rate or with disability progression.
- Cesarean delivery was not correlated with postpartum relapses or with disability progression.

Pasto et al. BMC Neurology. 2012; 12:165-171

Preventing Postpartum Relapses

- Methylprednisolone 1000 mg pulses for 6 months was associated with a normalization for relapse risk in a case control study (DeSeze et al. Mult Scler. 2004; 10:596-597
- Restarting DMD decision should be discussed before delivery
  - Take into account baseline disease activity, disease activity during pregnancy, patient preferences
  - Insurance reauthorizations may cause delays
- If restarting fingolimod, patient must be observed for cardiac conduction/rhythm changes

Breast-feeding Impact on MS

- Langer-Gould and others documented that exclusive breast-feeding and concomitant suppression of menses significantly reduced the risk of postpartum MS attacks
- Hellwig and others confirmed this finding of relapse risk decreasing from 38% to 24%

Langer-Gould et al. Arch Neurol. 2009; 66(8): 95
8-963 Hellwig et al. JAMA Neurol. 2015; 72(10): 1132-1138

Breast-feeding and MS Injectable Disease Modifying Therapy

- Interferon beta: no adverse events have been reported, probably compatible (very small amounts in breastmilk)
- Glatiramer acetate: probably compatible (amino acid polymer, likely degraded with digestion)
- Daclizumab: very limited data, avoid pending further data

Alams et al. Mult Scler Internat. 2016: 6527458, Vukusic and Marignier. Nature Reviews Neurology. 2015; 11:280–289

Breast-feeding and MS Oral Disease Modifying Therapy

- Fingolimod: secreted at 2-3 times higher concentrations in animal studies in breast milk, avoid due to risk of immunosuppression and initial cardiovascular side effects
- Teriflunomide: likely present in milk, long half-life, avoid
- Dimethyl fumarate: although rapid metabolism, avoid as likely to enter breastmilk

Alams et al. Mult Scler Internat. 2016: 6527458
Vukusic and Marignier. Nature Reviews Neurology. 2015; 11:280–289

Breast-feeding and MS Intravenous Disease Modifying Therapy

- Natalizumab: very limited data, small amounts in breastmilk, accumulation in breast milk increases over the first 24 weeks of use, safety unknown (Baker et al. J Human Lactation. 2015; 31(2): 233-236)
- Alemtuzumab: very limited data, short half-life, still classified as possibly hazardous
- Rituximab: very limited data, long half-life and in plasma for 3-6 months after last dose, possibly hazardous
- Ocrelizumab: no data, consider similar to rituximab

Alams et al. Mult Scler Internat. 2016: 6527458
Vukusic and Marignier. Nature Reviews Neurology. 2015; 11:280–289

Breast-feeding and Symptomatic MS Medications

- Dalfampridine: small molecular weight potassium channel blocker, likely high risk
- Baclofen: Probably compatible, although data limited
- Modafinil is excreted into breastmilk, avoid

Alams et al. Mult Scler Internat. 2016: 6527458

Care of Mom After Delivery

- Fear of falling with or dropping the baby is common
- Remember pre-existing deficits may increase fall risk
  - Fatigue, weakness, ataxia
  - Check gait safety, consider physical therapy screening
- Review plans, breast-feeding and resumption of:
  - Disease modifying medications
  - Symptomatic therapies

Resources for your questions

- National MS Society
  - NMSS.org can provide information with literature searches and clinical consultations with members of the National Medical Advisory Committee
  - Look under professional resources, resources for you and your practice
- Toxnet.nlm.gov LactMeds database
- Mothertobaby.org

Thank you