Pregnancy, Breastfeeding and MS: Evolving Evidence

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Overview

• How women with MS who get pregnant now are different than 20 years ago
  – Change in diagnostic criteria
  – Highly effective treatments
• Infant and Maternal Health Benefits of Breastfeeding
  – Summary of general health literature
  – Emerging data in MS
• How this influences MS counseling recommendations
  – Pregnancy, Risk of Postpartum Relapse
  – Breastfeed or Resume DMTs?
  – Preventing their children’s risk of MS
2 clinical scenarios: MS & pregnancy

Both want to get pregnant and breastfeed, but worried about risk of relapse and ability to care for their baby

Case 1:
- 26 y/o woman had optic neuritis age 20 and met McDonald criteria for MS by brain MRI
- started on injectable DMT stopped after 6 months, no further relapses, no new lesions on MRI, normal neurological exam

Case 2:
- 34 y/o woman diagnosed with RRMS age 26, 2-3 relapses/year, multiple myelopathic relapses and new lesions on MRI on injectable and oral DMTs until age 32
- for the last 2 years stable on highly effective DMT. No further relapses, no new lesions on MRI; improved neuro exam EDSS=3.0 (was 4.0 at time started highly effective DMT)
Evolving Evidence 1980s-present

**MS**
- **1980s**
  - Clinical Dx Criteria
  - No DMTs
- **2000s**
  - New Dx Criteria with MRI
  - Modestly effective DMTs
- **2010-present**
  - Highly effective DMTs
  - Small molecules (pills)

**Pregnancy & MS**
- **1980s**
  - Is pregnancy bad for women with MS?
- **2000s**
  - Healthier ♀ getting pregnant
  - Fewer breastfeeding to resume DMT
- **2010-present**
  - Sicker ♀ able to get pregnant
  - Rebound dz activity during pregnancy
  - ?safety of pills??

**Infant & maternal health**
- **1980s**
  - Infant health benefits of breastfeeding
- **2000s**
  - Maternal and long-term infant health benefits and of breastfeeding emerge
- **2010-present**
  - Strong evidence
  - Plethora of infant and maternal health benefits of longer duration of breastfeeding

Is pregnancy bad for women with MS? Healthier ♀ getting pregnant Fewer breastfeeding to resume DMT Sicker ♀ able to get pregnant Rebound dz activity during pregnancy ?safety of pills?? Infant health benefits of breastfeeding Maternal and long-term infant health benefits and of breastfeeding emerge Strong evidence plethora of infant and maternal health benefits of longer duration of breastfeeding
Is pregnancy bad for women with MS?


NO, but postpartum relapse risk is real and in most women unpredictable

- Predictors of Postpartum Relapse:
  - Relapse during pregnancy but this was RARE
  - Relapse Rate prior to Pregnancy

- Breastfeeding no influence

- 1993-1995
- High Relapse Rate (0.7)
- 28% had PP relapse within 3 months
- 59% breastfed
Postpartum Relapses in Modern Treatment Era
Postpartum Relapses Now

- Majority of Women getting pregnant on MS DMTs
  - ~60% in community-based settings
  - ~90% in referral center populations

- Highly Effective Treatments
  - Women who were too sick to get pregnant are now well-controlled and having babies

- What is the risk of postpartum relapses now?

- How relevant is pre-pregnancy relapse rate?
  - Does the type of DMT needed to control their disease activity matter more?
## Patient Characteristics, Major Cohorts

<table>
<thead>
<tr>
<th>Country</th>
<th>Study Period</th>
<th>Size</th>
<th>Pre-pregnancy relapse</th>
<th>Pregnancy relapse</th>
<th>Postpartum relapses</th>
<th>DMTs prior to preg</th>
<th>DMTs early PP period</th>
<th>% breastfed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>France</strong></td>
<td>1993-1995</td>
<td>227</td>
<td>50% 1yr</td>
<td>27%</td>
<td>28%, 0-3 mo</td>
<td>0</td>
<td>2%, 6mo</td>
<td>59%</td>
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<tr>
<td>Confavreux et al</td>
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<tr>
<td><strong>Italy</strong></td>
<td>2002-2008</td>
<td>302</td>
<td>mean= 0.4, 1yr</td>
<td>mean 0.12</td>
<td>~20%, 6mo (from 37%, 1yr)</td>
<td>46%</td>
<td>21%, 3mo</td>
<td>35%</td>
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<td>Portaccio et al</td>
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<tr>
<td><strong>Germany</strong></td>
<td>2008-2012</td>
<td>201</td>
<td>77%, 2yr</td>
<td>21%</td>
<td>30% 6mo 47%, 1yr</td>
<td>87% (11% high)</td>
<td>15%, 1mo</td>
<td>60%</td>
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<tr>
<td>Hellwig et al</td>
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<tr>
<td><strong>MSBase</strong></td>
<td>1967-2010</td>
<td>893</td>
<td>mean= 0.32, 2yr</td>
<td>nr</td>
<td>14%, 0-3 mo 37%, 1yr</td>
<td>39%</td>
<td>nr</td>
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<td>Hughes et al</td>
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## Predictors of PP Relapses

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>n</th>
<th>Pre-preg relapse</th>
<th>Preg relapse</th>
<th>DMTs early PP period</th>
<th>Any bf</th>
<th>Exclusive breastfeeding?</th>
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</thead>
<tbody>
<tr>
<td>France</td>
<td>1993-1995</td>
<td>227</td>
<td>yes</td>
<td>yes</td>
<td>NA</td>
<td>No effect</td>
<td>Not studied</td>
</tr>
<tr>
<td>Confavreux et al</td>
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<tr>
<td>Italy</td>
<td>2002-2008</td>
<td>302</td>
<td>yes</td>
<td>yes</td>
<td>By 3mo, not significant</td>
<td>No effect</td>
<td>Not studied</td>
</tr>
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<td>Portaccio et al</td>
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<tr>
<td>Germany</td>
<td>2008-2012</td>
<td>201</td>
<td>no</td>
<td>yes</td>
<td>by1mo, No effect</td>
<td>No effect</td>
<td>Yes, protective</td>
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<td>MSBase</td>
<td>1967-2010</td>
<td>893</td>
<td>yes</td>
<td>no*</td>
<td>Not studied</td>
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<td>Not studied</td>
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</table>
7 studies examined effect of breastfeeding

Primary hypothesis in only 1 study (Hellwig et al)

Breastfeeding associated with either no effect*†** or beneficial effect¶‡ ††.

* No study reported a harmful effect

Studies that found no effect measured breastfeeding crudely and did not distinguish between exclusive and non-exclusive breastfeeding †*

Studies that measured breastfeeding carefully found a protective effect ††

† Nelson et al. JAMA 1988;259
‡ Gulick and Halper. Intl Jrnl MS Care 2002
†† Langer-Gould, Archives of Neurology, 2009

* Confavreux et al. NEJM 1998;339
¶ Haas and Hommes. MS 2007
‖ Portaccio E, Neurology 2011
Distinct Hormonal Effects of Exclusive Breastfeeding

**Exclusive BF**
- Frequent & intense suckling
- prolactin↑↑↑↑
- FSH, LH
- progesterone
- estradiol
- anovulation & amenorrhea

**BF + formula**
- Lack of frequent or intense suckling
- prolactin↓↓
- FSH, LH
- progesterone
- estradiol
- ovulation & return of menses

**formula only**
- Immunological effects of anovulation

Howie PW et al, Clin Endocrinol, 1982
Exclusive breastfeeding for ≥ 2 months reduces risk of postpartum relapse

HR=1.8 95%CI (1.09-2.99) unadjusted, P=0.02

HR=1.7 95%CI (1.02-2.85) adjusted*, P=0.04

*adjusted for age and measures of disease severity

Hellwig et al JAMA Neurol 2015
Disease activity is resuming in both groups after the introduction of supplemental feedings

HR = 1.13 95% CI (0.72-1.78)
adjusted*, P=0.60

*adjusted for age and measures of disease severity

Hellwig et al JAMA Neurol 2015
Exclusive breastfeeding appears to reduce the risk of postpartum relapses in the first 6 months.

Once regular supplemental feedings are introduced, relapses return.

*Exclusive breastfeeding acts as a treatment with a natural end date.*
Infant and Maternal Health Benefits of Breastfeeding
1980s

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Strong evidence
plethora of infant and maternal health
benefits of longer duration of breastfeeding

Infant health benefits of breastfeeding emerge

Maternal health benefits of breastfeeding emerge

Infant & maternal health

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Evolving Evidence 1980s-present
Infant Health Benefits

- Breastmilk contains antibodies, enzymes, hormones
  - antibacterial, antiviral, anti-parasitic and antifungal effects

- Primary Infant health benefits: infection prevention
  - dose- response reduction diarrhea and URI
  - 6mo exBF= 53% for diarrhea and 27% URIs, hospitalizations
  - partial BF=31% and 25% reduction*

- Prolonged infant health benefits
  - Reduced risk of DM1 (autoimmune) and DM2 (metabolic)
  - Reduced risk of overweight or obesity; dose-response
  - MS??: 4 studies all methodologically flawed but all with reduced risk of MS; ever, never (Tarrats 2002, Conradi 2012, Magyari 2013; Langer-Gould 2017)

- Some bf is better than nothing

- More bf is better for prolonged benefits but not necessarily for infections

Maternal Health Benefits of BF

- **Reset Hypothesis (best evidence for metabolism)**
  - Maternal adiposity, lipid and glucose homeostasis is disrupted during pregnancy (fat accumulation, insulin resistance, high triglyceride levels)
  - Breastfeeding, particularly exclusive BF, reverses these changes quickly

- **Maternal Health Benefits**
  - Reduced risk of DM2 (particularly if no gestational DM)
  - Breast and ovarian cancer
  - Metabolic syndrome (immediate and delayed) and CV dz
  - MS?

- **Longer duration = more benefit for mom**
Among women who had children, breastfeeding for 15 months or longer decreased the risk of later developing MS by 23-53%.

MS Sunshine Study: 830 women, incident cases with matched controls

*Langer-Gould et al 2017*
Do DMTs reduce the risk of Postpartum Relapses?
DMT Use and Postpartum Relapses

- **Take DMT**
  - **Start within 2 weeks**
  - **Start within 1 month (n=29)**
  - **Start within 3 months**
  - **Later in PP year**
  - **No benefit n=55**
  - **No benefit n=81**
  - **Hint of benefit in later in postpartum year (n=35, p=0.08)**

- **Do not take DMTs**

- **Breastfeed exclusively (no early DMT use)**

DMT restart slightly worse than exBF

Q1: Beaber BE et al 2014 Permanente Jnl
Q2&3: Hellwig et al JAMA Neuro 2015
Q4: Portaccio E et al J Neurol Neurosurg Psychiatry 2014
DMT Use and Postpartum Relapses: Women who do wish to breastfeed

Women who do not wish to breastfeed

- Resuming treatment within the first 2 weeks postpartum does not protect against postpartum relapses compared with women who did not breastfeed and resumed treatment later in the postpartum year (HR=1.2 95% CI 0.6-2.5 PS-adjusted; p=0.6) Beaber BE et al 2014

- Resuming within 1 month does not protect against risk of PP relapses (HR 1.36, 95% CI:0.63-2.94 p=0.42) (Hellwig et al 2015)

Those who restart DMT vs exBF

- higher risk of postpartum relapses compared with women who breastfed exclusively adjusted HR 2.02, 95% CI: 1.03-3.99 p=0.04 (Hellwig et al 2015)

Those who restart within 3mo vs all other women

- Inconclusive: may reduce relapse risk later in the postpartum year (adjusted OR=0.7 95%CI 0.4-1.0; p=0.08) or disability progression in the postpartum year Portaccio E et al 2014
Conclusions

1) **Strong evidence**: breastfeeding, particularly prolonged, exclusive bf has significant infant and maternal health benefits

2) **Moderate evidence**: breastfeeding, even in lieu of DMTs does NOT increase risk of postpartum relapses
   - Exclusive breastfeeding may reduce risk of postpartum relapses

3) **Low quality evidence**: DMTs do NOT reduce the risk of postpartum relapses

4) **Anecdotal only**: to guide treatment decisions in women who have DMT-rebound disease activity during pregnancy is lacking

5) **Unknown**: clinical impact of postpartum relapses
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  - Margaret Chi
  - Sonu Brara

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