Reproductive safety of MS treatments

- Assisted reproduction technology and MS course
- Effect of DMT on fertility
- Effect of DMT in fathers on pregnancy outcome
- Safety of MS therapies during pregnancy/breastfeeding

Disclosures

- Grants from the National MS Society, the Nancy Davis Foundation, the Marcled Foundation, the NIH/NIAID
- Three educational lectures for physicians (Roche, Biogen Idec)
- Research grant from Roche
- Free medication for clinical trials from Sanofi Aventis and Biogen Idec
- Ad-hoc consultant for Actelion, Roche, Chugai, Sanofi Aventis
- Ongoing pharmaceutical clinical trials: Roche, Biogen Idec

Pregnancy and pregnancy product: Time and length of exposure and observation

- Pre-conception
- Pregnancy
- Post-partum
- Mother
- Father
- Childhood
- Birth
Risk compared to control population

- Control groups:
  - Other pregnancies in MS patients
  - Other pregnancies in the general population
- Controls should have:
  - Similar age when pregnant
  - Similar rate of risk factors that can affect pregnancy outcome such as smoking, HBP

Additional limitations

- Risks reported in animal models do not necessarily translate to humans
- Studies reporting outcomes after pregnancy exposure are often small, short and women typically have discontinued exposure within a few weeks of conception
- Studies often do not capture rate of miscarriage that can in part reflect teratogenicity
- Heterogeneous data: case reports, registries, prospective cohorts

Effect of assisted reproduction technology on MS

- Debated based on earlier studies.
- Recent small (n=16) prospective study: GnRH agonists and recombinant FSH may increase relapse risk (x7) and new MRI Gd+ lesions (x9)

Fertility and MS drugs

- In animal and humans:
  - No effect of interferon, glatiramer acetate
  - Mitoxantrone: amenorrhea
  - Cyclophosphamide: decreased fertility
- In animals:
  - Natalizumab decreases fertility in female guinea pigs (3 fold human regimen)
  - Slight decrease of fertility with fingolimod

Correale 2012
Paternal use of disease-modifying therapies

- 46 pregnancies fathered by 32 men with MS who conceived while on DMT:
  - 30 interferon beta,
  - 12 glatiramer acetate,
  - 2 natalizumab,
  - 1 methotrexate,
  - 1 azathioprine + interferon beta
- No effect on gestational age or birth weight vs. the general population.

Drug safety: pregnancy categories

- **Category A**: controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote
- **Category B**: no risk shown in animal studies; no adequate human studies
- **Category C**: risk shown in animal studies; no adequate human studies, but the benefits may outweigh the risks
- **Category D**: positive evidence of human fetal risk, but the benefits may outweigh the risks
- **Category X**: studies in animals or humans have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.

EMA pregnancy risk statements

- 1) Based on human experience (specified), Drug X is suspected to cause congenital malformation (specified), when administered during pregnancy
- 2) Drug X should not be used during pregnancy (trimester specified), unless the clinical condition of the woman requires treatment with Drug X
- 3) A moderate amount of data on pregnant women (between 300 and 1,000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity for Drug X
- 4) No effects during pregnancy are anticipated, since systemic exposure to Drug X is negligible

Lactation risk

- L1 (safest)
- L2 (safer)
- L3 (moderately safe)
- L4 (possibly hazardous)
- L5 (contraindicated)
### Symptomatic therapies

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drugs</th>
<th>Safety pregnancy</th>
<th>Safety breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatigue</strong></td>
<td>Amantadine (Symmetrel), Modafinil (Provigil), Methylphenidate (Ritalin), Dextroamphetamine-amphetamine (Adderall)</td>
<td>C</td>
<td>?</td>
</tr>
<tr>
<td><strong>Bladder dysfunction</strong></td>
<td>Oxybutinin (Ditropan), Trospium (Sanctura), Solifenacin (Vesicare)</td>
<td>B</td>
<td>?</td>
</tr>
<tr>
<td><strong>Spasticity</strong></td>
<td>Baclofen, Tiabinedine (Zanaflex)</td>
<td>C</td>
<td>?</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>Sertraline (Zoloft), Paroxetine (Paxil), Duloxetine (Cymbalta), Venlafaxine (Effexor), Fluoxetine (Prozac), Bupropion (Wellbutrin)</td>
<td>C*(D second half)</td>
<td>?</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>Gabapentin (Neurontin), Pregabalin (Lyrica), Amitriptyline (Elavil)</td>
<td>C</td>
<td>?</td>
</tr>
</tbody>
</table>

### Relapse therapy

- **IV methylprednisolone:**
  - Category C for pregnancy as teratogenicity in animals but no good data in human.
  - Possible increased risk of oral cleft when used during the first trimester of pregnancy and low birth weight.
  - Metabolized to inactive forms by 11-betahydroxysteroid dehydrogenase in the placenta, allowing <10% of maternal dose to reach the fetus.

- **PO dexamethasone:**
  - Crosses placenta with minimal metabolism, leading to likely direct full-dose effects on the fetus.

- **Steroids and breastfeeding:** Eliminated in about 4 hours

### Imaging

- **MRI:**
  - Possible teratogenic effect during first trimester

- **Gadolinium:**
  - Category C (avoid during pregnancy). Teratogenic in animals at repeated high doses
  - Breastfeeding? less than 0.04% of the maternal dose of IV gadolinium passes into the breast milk. Recommendation: discard breast milk for 24h post-gadolinium

### Disease-modifying therapies for MS

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>EMA</th>
<th>Pregnancy category</th>
<th>Breastfeeding</th>
<th>Minimum time between treatment discontinuation and conception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta</td>
<td>C</td>
<td>2</td>
<td>L3</td>
<td>L3</td>
<td>&gt;2 weeks</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>B</td>
<td>2</td>
<td>L3</td>
<td>L3</td>
<td>?</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>C</td>
<td>2</td>
<td>L3</td>
<td>L3</td>
<td>?</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>C</td>
<td>2</td>
<td>L4</td>
<td>L4</td>
<td>&gt;2 months</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>D</td>
<td>2</td>
<td>L5</td>
<td>L5</td>
<td>&gt;1 month</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>X</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>&gt;8 months or cholestyramine</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>C</td>
<td>1</td>
<td>L4</td>
<td>L4</td>
<td>?</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>C</td>
<td>1</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Kubik-Huch 2000, Okuda 1999
### Off-label disease-modifying therapies for MS

<table>
<thead>
<tr>
<th></th>
<th>Pregnancy category</th>
<th>Breastfeeding</th>
<th>Minimum time between treatment discontinuation and conception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>D</td>
<td>1</td>
<td>L3</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>D</td>
<td>1</td>
<td>L4</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>D</td>
<td>1</td>
<td>L5</td>
</tr>
<tr>
<td>Rituximab</td>
<td>C</td>
<td>1</td>
<td>L3</td>
</tr>
</tbody>
</table>

Modified from Houthens 2012

### Pregnancy and DMT

- 50% pregnancies are not planned
- Discussions about risks with DMT should occur:
  - at time of DMT initiation
  - regularly during treatment

Henshaw in Fam Plann Perspect 1998

### Systematic review: DMT exposure vs. no exposure

- **15 studies:**
  - 4 prospective,
  - 5 retrospective,
  - 6 case series

- **Exposed pregnancies:**
  - 761 interferon beta,
  - 97 glatiramer acetate,
  - 35 natalizumab

Lu 2012

### Interferon beta exposure

- Crosses very poorly the placental barrier
- No teratogenicity in animals but abortifacient activity at doses 2-100 times equivalent to human dose
- Compared with data for unexposed pregnancies, fair- to good-quality prospective cohort studies reported that IFNB exposure was associated with:
  - lower mean birth weight,
  - shorter mean birth length,
  - preterm birth (<37 weeks).
- But not low birth weight (2,500 g), cesarean delivery, congenital anomaly (including malformation), or spontaneous abortion.

Glatiramer acetate exposure

- Does not cross the placental barrier
- No risk reported in pregnant rabbits and rats, even at very high doses (up to ×36)
- Pregnancy outcome: fair-quality level 3 evidence:
  - No association with lower mean birth weight, lower mean gestational age, preterm birth (<37 weeks), congenital anomaly, or spontaneous abortion
  - One case of hypospadias reported in 22 live births
- Developmental outcome: 1/11 babies exposed in utero to GA (mean = 7 months) with inadequate language performance
- Manufacturer’s safety database: 5 cases of congenital malformations in 215 pregnancies

Natalizumab exposure

- In animals:
  - No teratogenic effect (up to ×7)
  - Decreased guinea pig pup survival (7x human dose)
  - Fetal hematologic effect in monkeys (2.3x human dose)
  - Decreased fertility in female guinea pig (2.3x human dose)
- In humans:
  - IgG can cross the placental barrier mostly 2nd/3rd trimesters
  - One fair-quality level 3 evidence study
  - Exposure (n=35) not associated with shorter mean birth length, lower mean birth weight, or lower mean gestational age
  - In trials, incomplete follow-up
  - In Crohn’s disease: 102 pregnancies of which 55 live births (all normal)
**Natalizumab exposure**

- Ongoing observational exposure registration study:
  - 277 exposed pregnancies to mothers with MS
  - 31 spontaneous abortions (11.2%, consistent with US rate)
  - 23 congenital anomalies in 21 women (no obvious drug-related pattern: malformations of the male genitalia, umbilical hernias, plagiocephaly, hemangioma, and cardiovascular defects (ventricular septal defect, patent ductus arteriosus, and tetralogy of Fallot))

  *Cristiano 2012*

**Fingolimod exposure**

- Crosses the placenta
- In rats and rabbits, developmental toxicity, including teratogenicity (rats) and embryolethality.
- In rats, the highest no-effect dose < human dose of 0.5 mg/day on a mg/m² basis. Most common fetal visceral malformations include persistent truncus arteriosus and ventricular septal defect.
- Data from ongoing registry:
  - 76 exposed pregnancies,
  - 27 normal births,
  - 27 elective abortions,
  - 3 malformations (tibial malformation, tetralogy of Fallot, acrania)
  - 8 spontaneous abortions

  *Collins AAN 2011*

**Mitoxantrone exposure**

- Limited placental transfer
- In animals:
  - Fetal growth retardation at doses >0.1 mg/kg/day (0.01 times the recommended human dose on a mg/m² basis)
  - No teratogenic effects, but maximum doses tested well below recommended human dose
- Fetal development: problems with related agents in humans
- 3 cases of live births exposed to mitoxantrone (1 normal, 1 small size, 1 Pierre Robin sequence)
- In trials: 9 pregnancies (3 unknown outcomes)

**Teriflunomide exposure**

- Crosses placenta
- In animals: teratogenicity (craniofacial, axial, appendicular skeletal defects)
- Upon discontinuing, all women of childbearing potential should undergo an accelerated elimination procedure and verification of [plasma] < 0.02 mg/L. [Human plasma] <0.02 mg/L should have minimal risk.
- Without accelerated elimination procedure on average 8 months to reach [plasma] < 0.02 mg/L, but up to 2 years
- Elimination can be accelerated by the following procedures:
  - Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
  - Administration of 50 g oral activated charcoal powder every 12 hours for 11 days.
**Terifunomide exposure**

- In RA with leflunomide, data do not support a substantial increased risk of adverse pregnancy outcomes among women who undergo cholestyramine elimination procedure early in pregnancy (mean 3.1 week post conception)
- Ongoing study with MS teriflunomide trials:
  - 10 pregnancies on drug (6 terminated, 3 miscarriages, 1 healthy live birth)
  - 53 pregnancies (17 healthy, 19 terminated, 9 miscarriages, 8 ongoing)

Chambers 2010, Cassina 2012, Stuve AAN 2012

**Alemtuzumab exposure**

- No animal reproduction studies
- Category C
- Cross placental barrier mostly 2nd/3rd trimesters
- Unknown how much crosses in breast milk (but IgG can)

**Fumaric acid exposure**

- In guinea pigs: no teratogenicity
- In rats: doses > 178 mg/kg associated with malformations in organs, coccyx, skull bones
- 15 pregnancies exposed to Fumaderm: 1 spontaneous abortion, one stillbirth, others normal outcome

Reviewed in Cree 2013

**Anti-CD20 monoclonal antibodies**

- Crosses placental barrier mostly during 2nd/3rd trimesters
- In monkeys: no malformations up to 100 mg/kg ofutumumab
- B cell depletion in fetuses
Recommendations

- 50% pregnancies are not planned --> discussions about risks during pregnancy should occur at time of DMT initiation
- Women should discontinue DMT before conception, unclear for how long
- If patients are pregnant on DMT, they should discontinue DMT asap
- There is no recommendation for pregnancy termination based on current knowledge
- Active participation in ongoing registries is recommended