Pregnancy and MS

Stacy Donlon, M.D.
Immune changes in late Pregnancy: promoting maternal tolerance
• hCG alters dendritic cell activity through up-regulation of indoleamine 2,3-dioxygenase
  • Reduction in T-cell activation and cytokine production
  • Promotes T-reg cell recruitment to the fetal–maternal interface
  • Addition of human recombinant hCG to isolated CD19^+ B cells in vitro induces strong production of IL-10, a potent anti-inflammatory cytokine
    • expansion of IL-10-producing regulatory B cells

• Placenta produces INF-t (similar to INF-B)
• Regulatory T (T-reg) cell elevation
• Reduction in T helper cells (Th)1/Th17 activity
• Increase in Th2 activity
• Decrease in number of natural killer (NK) cells
  • Increased proportion of CD56^{bright} NK cells (later in 3^{rd} trimester)
Post-partum

• Possible increased risk of relapse and disability progression post-partum

  • Immune reconstitution Inflammatory Syndrome?

    • Abrupt reduction in levels of estrogen, progesterone, glucocorticoids, and activated vitamin D
    • Loss of possible protective INF-t
Historical Predictors of Post-partum Relapse

• number of relapses during the year before pregnancy

• number of relapses during pregnancy

• disability score at pregnancy onset
Is Pregnancy Safe in MS?

• PRIMS study (Confavreux et al., 1998) followed 227 women with MS diagnosis for at least 1 year prior to conception, prospectively through pregnancy and into first 1 year postpartum and a percentage of patients were followed for 2 years postpartum

• Study showed a significant decline in relapse rate during pregnancy (lowest in 3rd trimester) and a rebounded increase of relapse in first postpartum trimester that returned to pre-pregnancy baseline by month 4
• Higher numbers of relapses in the year prior to pregnancy and numbers of relapses during pregnancy were predictive of relapse risk in postpartum

• Patients with higher DSS had greater risk of relapse postpartum

• Despite increased risk of relapse, no apparent acceleration of disability in first 6 weeks postpartum

• EDSS worsened by 0.7 point during 33 months of follow-up
Houtchens et al., 2018 conducted a retrospective database analysis of 2158 MS patients with pregnancies between 1/1/2006 to 6/30/2015

- Performed using the IQVIA Real-World Data Adjudicated Claims-US database (commercial patients only)

- Patients were included if there was sufficient data available for the year leading up to pregnancy, pregnancy, and 1 year following live birth

- The date of live birth was used to estimate date of conception to determine the date of conception and the pregnancy trimesters

- Relapse was defined as an encounter that led to corticosteroid script (IV or oral) within 7 days of the visit
  - MS-related hospitalization, MS related ER visit, or MS related outpatient visit

- DMT initiation post-birth was analyzed (patients were required to have no DMT claims in pregnancy to be considered a DMT start)
<table>
<thead>
<tr>
<th>Time period, n (%)</th>
<th>Any DMD</th>
<th>Self-Injectable DMD</th>
<th>Oral DMD</th>
<th>Infusion DMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>9–12 mo prepregnancy</td>
<td>442 (20.5)</td>
<td>400 (18.5)</td>
<td>5 (0.2)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>6–9 mo prepregnancy</td>
<td>463 (21.5)</td>
<td>416 (19.3)</td>
<td>6 (0.3)</td>
<td>1 (0.05)</td>
</tr>
<tr>
<td>3–6 mo prepregnancy</td>
<td>445 (20.6)</td>
<td>398 (18.4)</td>
<td>7 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>3 mo prepregnancy</td>
<td>383 (17.7)</td>
<td>343 (15.9)</td>
<td>4 (0.2)</td>
<td>1 (0.05)</td>
</tr>
<tr>
<td>First trimester</td>
<td>260 (12.0)</td>
<td>231 (10.7)</td>
<td>4 (0.2)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Second trimester</td>
<td>41 (1.9)</td>
<td>37 (1.7)</td>
<td>2 (0.1)</td>
<td>1 (0.05)</td>
</tr>
<tr>
<td>Third trimester</td>
<td>64 (3.0)</td>
<td>62 (2.9)</td>
<td>2 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Puerperium (6 wk postpartum)</td>
<td>180 (8.3)</td>
<td>164 (7.6)</td>
<td>3 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>7–12 wk postpartum</td>
<td>279 (12.9)</td>
<td>235 (10.9)</td>
<td>14 (0.6)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>3–6 mo postpartum</td>
<td>474 (22.0)</td>
<td>392 (18.2)</td>
<td>34 (1.6)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>6–9 mo postpartum</td>
<td>528 (24.5)</td>
<td>418 (19.4)</td>
<td>52 (2.4)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>9–12 mo postpartum</td>
<td>550 (25.5)</td>
<td>422 (19.6)</td>
<td>66 (3.1)</td>
<td>5 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviation: DMD = disease-modifying drug.
• Proportion of patients using DMT was low throughout all time periods
  • 20% had a claim for DMT at 9-12 months pre-pregnancy
  • <7.5% received DMT at any time during pregnancy
  • <2% during the second trimester
  • 25% initiated DMT 9-12 months postpartum

• 3 or more relapses in the year prior to pregnancy was associated with higher likelihood of starting DMT in first year postpartum
  • ½ of patients initiated within 90 days, ¾ within 6 months
  • Breastfeeding led to 90+ day delay in starting treatment

• Majority of DMT were injectables (<3.1% oral and infusion therapies)

• Relapse rates decreased during pregnancy, increased in puerperium, and decreased 6-12 months postpartum
Langer-Gould et al., 2019 “Pregnancy-related Relapses in a Large, Contemporary Multiple Sclerosis Cohort: No Increased Risk in the Postpartum Period”

- Prospective study of 466 pregnancies in 375 MS patients between 2008-2016
- 38% were not on any treatment in the year prior to conception
- 14.6% CIS
- 8.4% relapsed during pregnancy
- ARR reduced from 0.39 pre-pregnancy to 0.14- 0.07 during pregnancy (p<0.0001)
- ARR remained somewhat suppressed in the first 3-months postpartum (0.27, p=0.02)
- ARR returned to pre-pregnancy rates at 4-6 months (0.37)
- Pregnancy was not associated with worsening of disease
Langer-Gould prospective study continued

• In the postpartum year: 26.4% relapsed, 87% breastfed, 35% breastfed exclusively and 41.2% resumed DMTs

• Exclusive breastfeeding reduced the risk of postpartum relapses (adjusted HR=0.58, p=0.01) but resuming modestly effective DMTs had no effect on relapse rate (time-dependent covariate, p=0.86)
Points to Keep in Mind

• Placental-maternal circulation is not fully formed/does not function until 5 weeks gestation

• Large molecules are unlikely to cross placental barrier in first trimester and are likely not teratogenic

• Patients who stop high efficacy medications are more likely to relapse with drug cessation (NTZ>FTYb)

• With use of higher effective therapy, pre-pregnancy relapse rate may not adequately predict pregnancy and post-pregnancy risk of relapse
More Points to Keep in Mind

• Excessive fear can lead to insufficient treatment of pregnant women

• Perform individual risk evaluation and counseling

• Estimated risk of major birth defects in US is 2-4%

• Estimated risk of spontaneous abortion in US is 15-20%
How many exposures before we understand if medication is safe?

Sample Sizes Necessary to Detect a Two Fold (100%) Increase In Selected Adverse Pregnancy Outcomes (80% power, 5% Level of Significance)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Denominator</th>
<th>Population rate</th>
<th>Number of Exposed Pregnancies Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Abortion</td>
<td>Enrolled Pregnancies</td>
<td>15/100</td>
<td>266</td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>Live Births</td>
<td>10/100</td>
<td>261</td>
</tr>
<tr>
<td>Fetal Death</td>
<td>Live births plus fetal deaths</td>
<td>3/100</td>
<td>684</td>
</tr>
<tr>
<td>Any major birth defect</td>
<td>Live Births</td>
<td>3/100</td>
<td>684</td>
</tr>
<tr>
<td>Cardiovascular defect</td>
<td>Live Births</td>
<td>1/115</td>
<td>2196</td>
</tr>
<tr>
<td>Cleft lip with or without palate</td>
<td>Live births</td>
<td>1/930</td>
<td>17311</td>
</tr>
<tr>
<td>Stickler syndrome (or other rare birth defect)</td>
<td>Live births</td>
<td>1/10000</td>
<td>185,539</td>
</tr>
</tbody>
</table>
What do we know about DMT safety in pregnancy?
FDA Pregnancy Categories

• Category A: adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)

• Category B: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women

• Category C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

• Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

• Category X: studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience
Relapse Treatments and Pregnancy

• High dose prednisone, prednisolone, and methylprednisolone are commonly used to treat relapse events

• Evidence about steroid exposure during pregnancy and possible side effects (low birth weight, preterm birth, cleft palate) to fetus is limited and sometimes conflicting

• A systematic review of steroids (Bandoli et al., 2018) suggests that 1st trimester use may confer a small increased risk of cleft palate but little evidence to link with other safety side effects (pre-eclampsia, gestational DM, low birth weight, preterm labor)

  • Information for risk of gestational DM related to steroid use is lacking
Injectable Treatments and Pregnancy

- Avonex half-life: 19 hr
- Betaseron half-life: 8 min-4.3 hr
- Plegridy half-life: 78 hr
- Rebif half-life: 69 hr
- Copaxone: unknown
Glatiramer acetate

• May use during pregnancy

• Risk of fetal harm not expected based on limited human data and animal data at 18x and 36x human doses
<table>
<thead>
<tr>
<th>Outcome of pregnancy, n (%)</th>
<th>Before conception (n=90)</th>
<th>1st Trimester n=573</th>
<th>2nd Trimester n=23</th>
<th>3rd trimester n=8</th>
<th>Timing unknown n=254</th>
<th>Total n=948</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopic</td>
<td>0</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0</td>
<td>3 (1.2)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>SA</td>
<td>2 (2.2)</td>
<td>53 (9.2)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>45 (17.7)</td>
<td>101 (10.7)</td>
</tr>
<tr>
<td>EA (defects)</td>
<td>2 (2.2)</td>
<td>4 (0.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>EA (no defects)</td>
<td>2 (2.2)</td>
<td>23 (4.0)</td>
<td>0</td>
<td>0</td>
<td>15 (5.9)</td>
<td>40 (4.2)</td>
</tr>
<tr>
<td>Stillbirth (defects)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Stillbirth (no defects)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (4.3)</td>
<td>0</td>
<td>0</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>LB with anomaly</td>
<td>2 (2.2)</td>
<td>8 (1.4)</td>
<td>1 (4.3)</td>
<td>0</td>
<td>6 (2.4)</td>
<td>17 (1.8)</td>
</tr>
<tr>
<td>LB normal</td>
<td>82 (91.1)</td>
<td>482 (84.1)</td>
<td>21 (91.3)</td>
<td>7 (87.5)</td>
<td>185 (72.8)</td>
<td>777 (82.0)</td>
</tr>
</tbody>
</table>

SA=spontaneous abortion; EA=elective abortion; LB=live birth
Interferons

• There are no adequate studies in humans

• No teratogenic or other effect on fetal development in INFβ treated pregnant monkeys given 100 times recommended dose

• Majority of human data known is on first trimester exposure

• Compared to general population, the prevalence of spontaneous abortions and live births with congenital anomalies is similar

• No evidence that INFβ exposure in pregnancy adversely affects outcomes
Monoclonal Antibodies

• Majority of MAB treatments are IgG1

• Human IgG is selectively transported across the placenta into the fetal circulation in a time-dependent fashion, most probably by Fc receptors in the placenta

• Fetal concentrations of IgG1 exceed those of other IgG subclasses at all time points

• Very little IgG is seen in fetal circulation during the first trimester of pregnancy

• Levels slowly rise during the second trimester and reach maternal serum concentrations by ~ 26 weeks of gestation

• Maximum IgG transfer across the maternal-fetal interface occurs during the last 4 weeks of gestation, and fetal concentration often exceeds maternal concentration at term delivery
Anti-CD20 MABs

- Rituximab half-life: 18-32 days
- Ocrelizumab half-life: 26 days
Anti-CD20 monoclonal treatments

• Rituximab and Ocrelizumab can cause adverse developmental outcomes (i.e., B cell lymphocytopenia)
  • B cell lymphocytopenia generally lasts 6 months
  • Rituximab was detected postnatally in serum of infants exposed
  • Animal models show that exposure during organogenesis caused B cell depletion

• Pregnancy should be avoided for 12 months from the last RTX infusion, 6 months from last Ocrelizumab infusion

• Observe infants with history of exposure for signs of infection and manage accordingly
Anti-CD20 monoclonal Treatments

- Vukosic et al. 2017 described pregnancy outcomes of women exposed to Ocrelizumab in clinical trial and post-marketing
  - Based on 3811 patients in clinical trials and >39000 patients post-marketing
  - Maternal exposure defined as having greater or equal to 1 infusion at any time prior to conception and/or during pregnancy
  - Fetus considered exposed if last infusion occurred during pregnancy, within 3 months of conception, or if date of infusion was unknown

- 68 maternal-exposures pregnancies
- 51 pregnancies considered to have fetal exposure
Pregnancy outcomes in 51 fetal Ocrelizumab exposures

• 8 healthy newborns (full term- 6, unknown gestation 2)
• 11 elective terminations
• 2 live preterm births
  • 32 weeks’ gestation due to pre-eclampsia
  • 34 weeks’ gestation with genetic disorder (trisomy 21)- not considered treatment related
• 1 stillbirth of unknown gestational age
• 1 nonviable pregnancy
• 16 pregnancies ongoing at time of report
• 12 unknown outcomes
Pregnancy outcomes without fetal Ocrelizumab exposure (n17)

- 9 healthy newborns
- 1 elective termination
- 1 live preterm birth (34 weeks with low birth weight, jaundice, respiratory disease)
- 4 pregnancies ongoing at time of report
- 2 unknown outcomes
Rituximab and Pregnancy

Chakravarty et al., 2011 reviewed reports of pregnancy following RTX through 11/2009

- 253 reports of pregnancy, 153 known outcomes
  - 90 (60%) resulted in live births
    - 68 (76%) full term
    - 22 (24%) premature (before 37 weeks but no extreme premature)
  - 1 neonatal death at 6 weeks (unknown cause- mother with SLE and DM- dose of RTX 14 months prior to conception)
  - 1 neonatal death at 6 weeks from multisystem organ failure (unknown cause)
  - 2 congenital malformations (clubfoot in 1 infant set of twins; ventral septal defect, patent foramen ovale, patent ductus arteriosus)
  - 11 infants with hematologic abnormalities (peripheral B cell depletion, neutropenia, lymphopenia, thrombocytopenia, and anemia)
  - 1 cerebral hemorrhage (mother treated with RTX during 3rd trimester because of ITP)
  - 4 neonatal infections (suspected viral infection, CMV hepatitis, bronchiolitis, chorioamnionitis)
- 33 (21%) first trimester miscarriages
- 28 (18%) elective terminations
Considerations with anti-CD20 meds

• Avoid treatment during pregnancy (especially later than first trimester)

• Very unlikely to cross placenta in first trimester

• Given half-life of drug and limited time for drug to be detected in serum, could consider conception 1-2 months after last dose for higher risk patients?
Natalizumab

• Half life: 11 days
• In animal model studies, there have been no effects on embryofetal development when administered during organogenesis but abortions were increased two-fold when compared to controls
• Hematologic abnormalities noted at highest doses (data from animal models)
  • Mild anemia
  • Reduced platelet counts
  • Decreased lymphocyte counts
Natalizumab

• Global TYSABRI Pregnancy Registry for MS and Crohn’s disease
  • Completed in July 2012
  • Included 466 pregnancy reports (376 prospective, 90 retrospective) with 355 exposed pregnancies

• Spontaneous abortion reporting rate was 9% (32/355)

• Preterm deliveries (defined as prior to 37 weeks): total of 48 preterm deliveries, data suggests no effect

• Adjusted rate of birth defects was 5.05% (based on criteria from Metropolitan Atlanta Congenital Defects Program)

• Rate of major structural or chromosomal defect was 7.9% (slightly higher than 2.67% published by MACDP but the nature of birth defects did not suggest a drug-related pattern)
Natalizumab

• A prospective database study was established in Germany in 2006

• Pregnancies were studied until at least 6 months postpartum

• Natalizumab exposure was defined as administration at least 8 weeks prior to last menstrual cycle or during pregnancy

• Exposed women were enrolled into a prospective observational study and compared with disease matched (DM) controls and healthy controls (HC) to investigate fetal outcomes from first trimester Natalizumab exposure

• Numbers of patients: Exposed (101), DM (78), HC (97)
## Results from German Study

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Natalizumab exposed</th>
<th>DM group</th>
<th>HC group</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>All abnormalities</td>
<td>4/77 (5.2%)</td>
<td>3/69 (4.3%)</td>
<td>5/92 (5.4%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Major birth defects</td>
<td>3/77 (3.9%)</td>
<td>1/69 (1.4%)</td>
<td>2/92 (5.4%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Premature (37wks)</td>
<td>6/76 (7.9%)</td>
<td>10/67 (14.9%)</td>
<td>9/92 (9.8%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Low birth weight (&lt;5.5 lbs)</td>
<td>6/77 (7.8%)</td>
<td>5/68 (7.4%)</td>
<td>7/92 (7.6%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Natalizumab Summary

• Women who stop natalizumab prior to and early in pregnancy are at risk for relapse

• Risk of hematologic abnormalities in fetus are higher when exposed later in pregnancy (≥34 weeks)

• Could consider continuing natalizumab during pregnancy with high disease activity and extend dosing interval to limit exposures

• Consider stopping natalizumab before 30 weeks gestation as less risk of hematologic abnormalities
Alemtuzumab

• Half life: 2 weeks

• In humans, alemtuzumab is low or undetectable within 30 days

• It is recommended that women of childbearing potential use contraception during and for 4 months following treatment

• Given treatment protocol (2 years), it is recommended that patients avoid pregnancy until 4 months after second course
Alemtuzumab Pregnancy Data

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>n=972</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnancies, n</td>
<td>248</td>
</tr>
<tr>
<td>Completed pregnancy with known outcome (%)</td>
<td>218 (87.9)</td>
</tr>
<tr>
<td>Ongoing (as of 4/2017)</td>
<td>14 (5.6)</td>
</tr>
<tr>
<td>Outcome unknown</td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>Known outcomes in completed pregnancies, n</td>
<td>218</td>
</tr>
<tr>
<td>Live births, n (%)</td>
<td>147 (67.4)</td>
</tr>
<tr>
<td>Spontaneous abortion (&lt;20 week’s gestation)</td>
<td>48 (22)</td>
</tr>
<tr>
<td>Elective abortion</td>
<td>22 (10.1)</td>
</tr>
<tr>
<td>Stillbirth (&gt;20 week’s gestation)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>
Pregnancy outcomes by time since last alemtuzumab dose to pregnancy onset

# of months from last dose of Alemtuzumab to pregnancy onset

<table>
<thead>
<tr>
<th># of months from last dose of Alemtuzumab to pregnancy onset</th>
<th>≤1 month</th>
<th>&gt;1 to ≤4 months</th>
<th>&gt;4 to ≤12 months</th>
<th>&gt;12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies, n</td>
<td>5</td>
<td>11</td>
<td>31</td>
<td>201</td>
</tr>
<tr>
<td>Outcome, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live births</td>
<td>2</td>
<td>6</td>
<td>22</td>
<td>117</td>
</tr>
<tr>
<td>Ongoing (as of 4/2017)</td>
<td>1</td>
<td>----</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Elective abortions</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Spontaneous abortions</td>
<td>----</td>
<td>3</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>----</td>
<td>----</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>
• Out of 248 pregnancies, 232 occurred >4 months after last alemtuzumab dose

• 16 pregnancies occurred ≤4 months:
  • 8 live births without defect
  • 3 spontaneous abortions (1 ectopic pregnancy)
  • 4 elective abortions
  • 1 infant with respiratory distress syndrome
  • 1 infant with grade 4 thyrotoxic crisis 3 weeks after birth
Alemtuzumab and Spontaneous Abortions

• Spontaneous abortion rate was 22%

• Rate of SA was not increased if pregnancy occurred <12 months (11%) rather than >12 months (25%), p value insignificant

• Maternal age was associated with SA rate
  
  • Patients <35 years, 15% (22/148); (general population 15-23%)
  
  • Patients ≥35 years, 37% (26/70); (general population 23-86%)
Alemtuzumab live births

• Out of 147 live births
  • No congenital anomalies

• 5 infants born premature (range 31-36 weeks)
Alemtuzumab and Pregnancy

• Complete both doses of Alemtuzumab (year1/2) and wait 4 months to attempt pregnancy

• Possible increased risk of autoimmune disorders in infants

• Possible risk of immunosuppression depending on time of exposure

• Mothers who develop autoimmune complications should be monitored closely during pregnancy
Fingolimod and Pregnancy

• Animal studies with fingolimod suggest a risk of fetal toxicity, including fetal loss and organ defects

• Sphingosine 1-phosphate receptor affected by fingolimod is known to be involved in vascular formation during embryogenesis

• All women of childbearing potential are recommended to use effective contraception during and for at least 2 months following discontinuation of fingolimod treatment

• If a woman becomes pregnant during treatment, discontinuation of fingolimod is recommended
Gilenya and Pregnancy

Keep in mind:

• There is a risk for disease progression and mom is at risk for relapse upon discontinuation of Gilenya
Fingolimod and Pregnancy

• As of February 2018, 1397 prospective cases documented fingolimod exposure during pregnancy in the Novartis database (NSDB) (including 135 cases from Registry and 843 cases from PRegnancy outcomes Intensive Monitoring program (PRIM))

• 868 cases with known outcomes

• live births were 607 (69.9%) (Registry [n=94] and PRIM [n=318])
  • Prevalence of major congenital malformations among live births in the Registry and PRIM was 5.3% and 1.89% (0.70; 4.06), respectively
• Overall proportion of spontaneous abortion for NSDB, Registry, and PRIM were 8.4%, 6.3%, and 13.9%, respectively, which were within the expected range observed in the general population (14.2%-20.9%).

• No unique patterns or clusters of similar defects were reported

• The prevalence of major congenital malformations in live births following fingolimod exposure was similar to that observed in the general population

• Study is ongoing and full risk is not known
Teriflunomide and Pregnancy

• Teriflunomide is contraindicated in pregnancy based on embryo-fetal toxicity in rats and rabbits at doses similar to those used clinically.

• No signal for human teratogenicity has been observed in leflunomide-exposed pregnancies (>100 cases).

• Females and males of reproductive potential should use effective contraception during therapy as use of teriflunomide during pregnancy is contraindicated.
Teriflunomide and Pregnancy

• A total of 231 pregnancies were reported (62 were from the clinical study program and 169 were from the post-marketing setting)

• In pregnancies with known outcomes, the last dose of teriflunomide was administered at pre-conception or in the first trimester for all but 4 cases. The 4 cases of second/third trimester exposure all occurred in post-marketing cases (3 cases involved exposure in the second trimester and one case in the third trimester)

• Outcomes are known for 62 pregnancies in the clinical study program and 67 in the post-marketing setting

• Among the 129 pregnancies with known outcomes, 99 (including all cases from the clinical trial program) were reported prospectively whereas 30 were reported retrospectively
• For the 99 prospectively reported pregnancy outcomes there were
  • 42 live births
  • 38 elective abortions
  • 17 spontaneous abortions
  • 2 ectopic pregnancies

• 30 retrospectively reported outcomes
  • 10 live births
  • 9 elective abortions
  • 10 spontaneous abortions
  • 1 fetal death (≥20 gestation weeks)

• Among the 52 live births, 2 structural abnormalities were reported (1 case of Ureteropyeloectasia, 1 case of congenital hydrocephalus in full term infants)

• No malformations/abnormalities were reported with elective abortions
• Accelerated elimination for teriflunomide was used in 81.8% of live births in patients from the clinical trial program and 60.0% of live births in patients from post-marketing settings

• The rate of spontaneous abortion was comparable to that reported in the general population of 17%–22%

• These observations are consistent with the 20 years of post-marketing experience of the parent compound, leflunomide, in which no teratogenic signal has been seen to date

• Despite these findings, accelerated elimination of teriflunomide is recommended prior to trying to conceive or as soon as an unplanned pregnancy is discovered
Dimethyl fumarate and Pregnancy

• In rats administered DMF orally (25, 100, 250 mg/kg/day) throughout organogenesis, embryofetal toxicity (reduced fetal body weight and delayed ossification) were observed at the highest dose tested. This dose also produced evidence of maternal toxicity (reduced body weight).

• Terminal half-life of MMF is approximately 1 hour and no circulating MMF is present at 24 hours in the majority of individuals. Accumulation of MMF does not occur with multiple doses of DMF.
• From March 2013 to March 2018, there have been 2,643 cases of pregnancy with a total of 3,463 events involving maternal exposure to DMF

• 102 cases of paternal exposure

• There is no evidence of adverse effect of DMF on pregnancy outcomes
Cladribine

• Half-life: 5.4h

• Given in pulse cycles

• Potentially genotoxic

• Avoid pregnancy until 6 months after last cycle for both men and women

• Recommend double contraception for women in first 4 weeks after the cycle
Cladribine Clinical trial

- 64 pregnancies occurred among 57 women
  - 44 pregnancies were in 38 women with exposure to cladribine
  - 20 were in 19 women who had received placebo
- Eighteen (41%) pregnancies in the cladribine group and 9 (45%) in the placebo group resulted in live births
- 14 of those in the cladribine-treated group and 4 in the placebo group were terminated by induced abortion on the patient's decision
- There were 9 spontaneous abortions in women treated with cladribine, and 5 in women who had received placebo (which is consistent with epidemiological data on pregnancy outcomes)
- 3 medically indicated abortions were reported for 2 women treated with cladribine (2 were due to ectopic pregnancy and 1 to choriocarcinoma)
- 1 for a placebo recipient (Dandy-Walker congenital malformation with placental abruption)
Cladribine treated Men

• The female partners of 9 cladribine-treated males experienced 10 pregnancies
  • 9 of which resulted in live births (there was 1 unknown outcome)
  • The female partners of 2 placebo-treated males experienced 2 pregnancies (each outcome unknown)
Cladribine Pregnancy Outcomes

• In this limited population of pregnancies with potential exposure to cladribine, no congenital malformations were identified.

• Because of the potential for teratogenicity, further study is warranted to better understand any risks that might be associated with cladribine in pregnancy.
Symptomatic Treatments in MS

• Consider using lowest possible dose

• Use monotherapy when possible
Spasticity Treatments

• Baclofen FDA: C; teratogenic in animal studies when used in first trimester; can be used in 3rd trimester

• Tizanidine FDA: C; possible risk of harm based on animal data at 0.5x human doses- avoid during pregnancy

• Tetrahydrocannabinol (THC) FDA: C; very small molecules that can easily cross placenta- should be avoided

• Non-pharmacologic treatments should be used whenever possible (physiotherapy, avoidance of triggers, etc)
Pain

- Gabapentin FDA:C, there is evidence of placental transfer of gabapentin, avoid in pregnancy unless benefit greatly outweighs risk

- Pregabalin FDA:C, contraception recommended and should be avoided, possible signal for risk of major birth defects after first trimester exposure (Winterfield et al, Neurology 2016)

- Oxcarbazepine FDA:C, possible risk of low birth weight and teratogenicity based on animal data and conflicting human data

- Carbamazepine FDA:D, risk of teratogenicity based on human data

- Tricyclic antidepressants (amitriptyline, Imipramine) FDA:C, have caused harm in neonates when taken in last trimester
Fatigue

- Recommend exercise, PT, yoga

- Modafinil FDA:C, no adverse events in pregnant women treated for narcolepsy but risk of fetal toxicity in animal models at less than recommended human dose

- Amantadine, category not assigned, animal models show risk of toxicity; women should consider use of highly effective contraception during treatment and for 5 days after last dose

- Stimulants (methylphenidate, amphetamine/dextroamphetamine) FDA:C, premature delivery and low birth rate in humans, case reports of cardio-respiratory toxicity; animal studies have shown risk; avoid use during pregnancy unless benefit significantly outweighs risk
Depression

• Consider cognitive behavioral therapy

• Selective Serotonin reuptake inhibitors (SSRIs): absolute risk of teratogenicity is small

• Serotonin-norepinephrine reuptake inhibitors (SNRIs): no known risk of congenital malformations but potential increase risk of bleeding if used in 3rd trimester
Urinary Dysfunction

- Incontinence pads
- Intermittent catheterization
- Oxybutynin FDA:B
- Tolterodine FDA:C
- Desmopressin FDA:B
Bowel dysfunction

• High fiber diet, fiber supplement, increased fluid intake can help with regularity and reduce fecal urgency

• Commonly used during pregnancy for constipation:
  • Lactulose
  • Glycerin suppositories
  • Bisacodyl
Gait impairment

• Physiotherapy should be recommended first line

• Dalfampridine FDA:C, animal studies have revealed adverse effects on fetus
Resources for Clinicians

• Pubmed.org (search “name of drug” and “pregnancy”)

• Toxnet.nlm.nih.gov (LactMed)

• www.drugs.com

• Briggs G, Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. 11th ed; 2017

• http://otispregnancy.org
Questions?

Thank you!!!!