• Disclosure:
  – Nil

  – Presentation not backed by RCT’s
    • Only Small Studies and Observational Data
• Multiple Sclerosis – Is an autoimmune demyelinating disease of the CNS affecting the brain and the spinal cord.

• Incidence and prevalence varies according to the geography
  – 60 cases per 100,000 population (Highly prevalent including Australia)
    • Ebers et al. Lancet 2008;7(3):268-77
    • Simpson et al. JNNP 2011;82(10):1132

• Females > Males (~2:1)
  • Alonso et al. Neurology 2008;71(2):129

• Onset in 3\textsuperscript{rd} and 4\textsuperscript{th} decades of life
  – Mean age of onset early for Women than Men
    • Van Der Mei et al. Neurol Clin 2011;29(2):207-17

• MS affects over 23000 Australians and 2 Million worldwide
  • MS Australia
Overview

- MS in Offspring's
- Impact of MS on Pregnancy
- Impact of Pregnancy on MS
- Changes during Pregnancy
- Contraception in MS
- DMT’s and pregnancy
- Postpartum and MS
Overview

• MS in Offspring's
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There is a 98% chance that children of a patient with MS will not develop MS

- Monozygote twins: 25% concordance
- Dizygote twins: 5% concordance
- 1 parent has MS: ~2%
- 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

- M Houtchens et al. TC04 Boston ECTRIMS 2014
Overview

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Impact of MS on Pregnancy

• Fertility
  – No direct impact of MS on fertility
  – Sexual dysfunction delay conception
  – Higher incidence of endometriosis in MS patients
  – Small (n=61) prospective study reported that patients with MS were more likely to employ assistive reproductive techniques (ART)
    • 4.9% (n=3/61) vs 0.9% (n=55547)
Impact of MS on Pregnancy

• Pregnancy
  – Maternal MS is associated with an increased rate of caesarean delivery and lower infant birth weights.
  – Database with an estimated 15 million deliveries in US
    • 4730 in women with MS.
    • MS was associated with a small but statistically significant increase in the risk of IUGR (OR 1.7, 95% CI 1.2-3.3) and cesarean delivery (OR 1.3, 95% CI 1.1-1.4)
  – There is no increase in birth defects, perinatal mortality, or other adverse fetal outcomes.
    • Finkelsztejn et al. BJOG 2011;118(7):790-7
MS and Pregnancy

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Impact of Pregnancy on MS

• ART
  – Although no definitive data
  – ART (GnRH agonists) increase the risk of MS relapses during pregnancy
    • Hellwig et al. J Neurol 2008 Apr;255(4):592-3
    • Hellwig et al. Eur Neurol 2009;61(2):65-8
    • Michel et al. JNNP 2012 Aug;83(8):796-802
  – Prospective study of 16 women
    • 7-fold increase in the risk of MS relapses
    • Nearly 9-fold increase in the risk of new brain lesions by MRI in the three months following ART
Impact of Pregnancy on MS

• **Effect on clinical activity:**
  - 70% reduction in ARR during third trimester compared to pre-pregnancy
  - Rebound to 70% above pre-pregnancy level during first 3 months post-partum

There was no acceleration in the rate of disability or disease progression postpartum.

- Confavreux et al. NEJM1998;339(5):285
Impact of Pregnancy on MS

• A meta-analysis of 13 studies with 1221 pregnancies
  – pregnancy is associated with a significant decrease in MS disease activity
  – postpartum period is associated with an increase in MS activity

  • Finkelsztejn et al. BJOG 2011;118(7):790-7
Impact of Pregnancy on MS

- **Effect on MRI:**
  - New or enlarging lesions detected as soon as 4 weeks after delivery in half of the patients
  - Significant *increase* in the number of T2 lesions and Gadolinium-enhancing lesions

Impact of Pregnancy on MS

- **Effect on disability progression:**
  - Patients who had children after MS onset when compared with women who did not; longer time for disability progression
    - D’Hooghe et al. JNNP; 2010(81):38-41
  - Cross-sectional study of 973 women with MS, two or more pregnancies were less likely to reach EDSS 6, which means that a cane is required to walk 100 meters
Impact of Pregnancy on MS

• **Susceptibility to develop MS:**
  – a large Australian study looked at CIS patients and matched controls
    • reported a cumulative benefit of pregnancies to decrease risk for CIS.
      • Ponsonby et al. Neurology 2012;78(12):867-74
  
  – A small study of RIS patients ($n = 60$) found that pregnancy ($n=7$)
    • Associated with increased risk for subsequent clinical attack in the postpartum period, and MRI disease activity
      • Lebrun et al. Mult Scler 18: 1297–1302
• PRISMS study showed significant correlation between post-partum exacerbation of MS
  – the number of relapses in pre-pregnancy year
  – the EDSS at pregnancy onset
  – the number of relapses during pregnancy

  • Vukusic et al. Brain. 2004;127(Pt 6):1353
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• Pregnancy = Immunotolerant state

• Important biological changes occur during pregnancy
  – Hormone level increase
  – Immune cell shift
  – Fetal antigens interact and modulate the maternal immune system

Hormonal Changes

- Cortisol
- Progesterone
- dOH Progesterone
- Estradiol
- Estriol
- Prolactin
- Hormones have potent immunomodulatory and neuroprotective properties
  - Shift in cytokines production
  - Downregulation of adhesion molecule expression
  - Decrease antigen presentation
  - Induction of regulatory T cells
  - SNC protection and remyelination promotion


Role of Estrogen in MS

• Phase I clinical trial of Estriol (8mg daily) in females with RRMS
  – decreased Gd enhancing lesions on brain MRI
    • Sicoteel et al. 2002

• Phase II clinical trial in 164 females with RRMS – Estriol (8mg od) + Copaxone vs Placebo
  – At 12months Estriol group had a 47% reduction in confirmed relapses compared to placebo group. No difference in relapse rate reduction at 24 months
    • AAN 2013
• Phase III clinical trial (POPARTMUS) examining the effects of progestin and estradiol vs placebo on post-partum relapse in RRMS (3 months post-partum)
  – no significant results for ARR and MRI outcomes at 12 and 24 post-partum
  • ECTRIMS 2012

• Estrogen levels induced by oral contraception and HRT do not seem to be protective.
Immune swift during pregnancy
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Contraception in MS

• No published data

• Pregnancy is a personal decision

• Probably helpful to stabilize an active patient with more effective therapies for 12 months prior to attempting conception

• OCPs need to be stopped 2-3 months prior to conception attempts, and patients should be advised to transition to mechanical birth control.
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<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies show no risk.</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk in humans; the chance of fetal harm is remote.</td>
</tr>
<tr>
<td>C</td>
<td>Risk not excluded. Adequate studies lacking. Chance of fetal harm but benefits outweighs risks.</td>
</tr>
<tr>
<td>X</td>
<td>Contraindicated.</td>
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</table>
## DMT’s and Pregnancy

<table>
<thead>
<tr>
<th>DMT</th>
<th>FDA category</th>
<th>Pregnancy effects</th>
<th>Washout</th>
<th>Placental transfer</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-β</td>
<td>C</td>
<td>Animal models: dose-dependent abortocentric activity</td>
<td>0 – 1 month</td>
<td>Unlikely</td>
<td>Minimal levels (0.006%) detected</td>
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<tr>
<td></td>
<td></td>
<td>Humans: some reports of lower birth weights/birth lengths; preterm births</td>
<td></td>
<td></td>
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<tr>
<td>Glatiramer acetate</td>
<td>B</td>
<td>No evidence for negative effects</td>
<td>Not necessary</td>
<td>Unlikely</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>C</td>
<td>Animal models: decreased female fertility, pup survival, fetal hematologic</td>
<td></td>
<td>Crosses by 2nd trimester</td>
<td>Low levels; avoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>abnormalities</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Humans: hematologic issues at birth</td>
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<tr>
<td>Mitoxantrone</td>
<td>D</td>
<td>Animal models: growth retardation, premature birth</td>
<td>6 months</td>
<td>Limited</td>
<td>Present; avoid</td>
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<tr>
<td>Fingolimod</td>
<td>C</td>
<td>Animal models: fetal malformations, death, growth retardation</td>
<td>2 months</td>
<td>Crosses</td>
<td>Present; avoid</td>
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<tr>
<td>Teriflunomide</td>
<td>X</td>
<td>Animal models: fetal malformations</td>
<td></td>
<td>Unknown</td>
<td>Avoid</td>
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<tr>
<td>Dimethyl fumarate</td>
<td>C</td>
<td>Animal models: embryo-fetal toxicity</td>
<td>0 – 1 month</td>
<td>Unknown</td>
<td>Avoid</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>C</td>
<td>Unknown</td>
<td>3 – 4 months</td>
<td>Crosses by 2nd trimester</td>
<td>Present; avoid</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>C</td>
<td>Animal models: prenatal loss</td>
<td>4 months</td>
<td>Crosses by 2nd trimester</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
Interferon Beta

• Beta – 1a (Avonex); Beta – 1a (Rebif); Beta – 1b (betaseron)

• Category C

• > 1000 pregnancies under IFN
  – No increase risk of:
    • Miscarriages
    • Malformation
  – Lower mean birth weight / lower mean birth length
  – Increased risk of preterm birth

• Washout period: 0-1 months
Glatiramer Acetate (Copaxone)

• Category B

• > 300 pregnancies under GA
  – No increase risk of:
    - Malformations
    - Abortions
    - Preterm birth
    - Reduced birth weight

• Washout period: not necessary

• Can be given whilst breast feeding
Fingolimod (Gilenya)

- Category C

- Fingolimod exposure
  - 33/83 known outcomes from the Gilenya Pregnancy Registry; the prevalence of major congenital malformations in live births in the pregnancy registry was 3.8%.
  - 349/879 known outcomes in Novartis safety database; Prevalence was 5.4%
    - Geissbuhler et al. ECTRIMS 2015

- Washout period: 2 months
Teriflunomide (Aubagio)

- Category X

- 70 pregnancies
  - 29 induced abortions
  - 8 spontaneous abortions
  - 26 healthy newborns
  - So far no pattern of malformation

- Formal washout to lower drug level
  - Cholesteryamine (4 or 8gms TDS) x 11 days
  - Activated charcoal (50gms BD) x 11 days
  - Decreased level by ≥ 98%
    - Aubagio prescribing information 2012
Dimethyl Fumarate (Tecfidera)

- Category C

- Embryo and foeto-toxicity at very high doses in rats

- 38 pregnancies in clinical trials
  - 22 healthy newborns
  - 3 spontaneous abortions
  - 7 elective abortions
    - Gold et al. AAN 2013

- Pregnancy registry ongoing

- Washout period: 0-1 months
Natalizumab (Tysabri)

• Category C

• > 369 patients with pregnancy exposure to NTZ
  – Abortions 9%
  – Birth defects 5.05%

• 9 patients treated during pregnancy Mild to moderate hematologic abnormalities in 8 children (thrombocytopenia, hypogammaglobulinemia and haemolytic anaemia)
  • Haghikia et al. AAN 2013

• Washout period: 3 months
Alemtuzumab (Lemtrada)

- Category C

- 72 pregnancies (Genzyme registry)
  - 10 after the first cycle: 4 healthy babies, 2 miscarriages, 4 abortions
  - 62 after second cycle: 28 terms newborns, 3 preterm, 14 miscarriages, 5 abortions, 1 stillbirth, 11 unknown

  - Houtchens, Management during pregnancy, TC04 Boston ECTRIMS 2014

- Washout period: 3-4 months after last cycle
Relapse management during pregnancy

• Intravenous CS are probably safe in the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester.

• Should be avoid during 1\textsuperscript{st} trimester because of risk of cleft palate and lower birth weight

• CS should be reserved for treatment of serious relapse.
Relapse management during pregnancy

• No fetal effect of MRI during pregnancy documented.

• However guidelines are precautionary and recommend MRI only if essential.

• Contrast is not recommended as Gadolinium compounds cross the placenta.
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Postpartum and MS

• Breast Feeding
  – Meta analysis > 1500 pregnancies
    • decreased risk for post-partum relapse in women who breastfeed
      • Pakpoor et al. J Neurol. 2012;259(10):2246-8
Postpartum and MS

• Predictors of postpartum relapses should influence the decision to breastfeed or not.

• Methylprednisolone levels in breast milk may be as high as 1.45% of maternal dose, but are much lower with a 2- to 4-hour delay following the intravenous infusion
Postpartum and MS

- DMT (IFN and GA) have delayed onset of efficacy beyond the peak of the postpartum exacerbations

- GAMmaglobulin Post Partum (GAMPP) study
  - lower postpartum relapse risk in IVIg group
    (10g following delivery/ 10g every 4 weeks of 6 months)
• Although there are many unmet research needs, the reviewed data support the
  – 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.