Sex related issues and Multiple Sclerosis
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Learning Objectives
- Describe epidemiological differences in MS for men vs women
- Discuss presentation and natural history of MS disease differences in men and women
- Learn how MS affects pregnancy and vice versa
- Discuss medication management considerations
  - Fertility
  - Pregnancy
  - Breastfeeding
Epidemiology of MS

- Why do women develop MS at a ratio of currently 3:1?
- Why is this ratio rising over the last century?
- Theories center on the fact that men and women differ in many ways including chromosomally, immunologically, socially and hormonally.

Sex genetics and MS

- MS has been linked to HLA-DRB*15
- But more risk of MS is transmitted through mother than father to offspring (more mother-daughter pairs seen).
- X chromosome itself may confer some susceptibility to MS as seen in transgenic mice.
- Females with autoimmune disease can display skewed X inactivation.
Immune differences

- One theory on why MS is more common in women is that the immune systems of women are more active than men.
- For example, women have stronger responses to vaccinations and more resistance to infections than men.
- This is probably evolutionarily beneficial as women bear and nurse the offspring.

Hormonal Differences

- Men tend to be diagnosed later in life (age 30-40) with MS than women, coinciding with their natural decline in testosterone. But this could be multifactorial.
- Although men transition to SPMS more quickly than female patients, both sexes develop SPMS around the same age of 40-45.
- Animal studies seem to indicate neuroprotective and anti-inflammatory effect of testosterone in MS.
- Interestingly, PPMS, a less inflammatory condition than RRMS, still has a 1:1 male: female ratio.
Environmental Differences

- Men tend to have more sun exposure and use less sunscreen according to population data, which may explain their higher Vitamin D levels.
- Low vitamin D levels have been associated with an increased risk for developing MS.

How do sex hormones affect MS?

- All sex hormones are lipophilic and cross the blood brain barrier.
- When testosterone crosses into brain it becomes aromatized to estrogen.
- In the mouse model of MS (EAE): males are less susceptible than females, but castrated males have an increased risk.
- EAE mice show lower levels of testosterone during relapses.
- Male MS patients in some studies show lower levels of testosterone compared to controls and are less responsive to GnRH injections (indicating probable central dysfunction).
Female sex hormones

- Women have three different types of estrogen: estradiol, estriol, and estrone
- Estradiol: produced by the ovaries and regulates menstruation
- Estriol: made by the fetal placental unit during pregnancy
- Estrone: created by the body’s fat cells
- High doses of estrogen are known to augment Th2 responses while low levels augment Th1 responses
- In MS, causing a shift towards a Th2 immune response is beneficial for disease modification

Menstrual cycle and MS

- Early age of menarche has been associated with increased risk of developing MS
- Delayed menarche after 13 seems to be associated with delayed progression on EDSS in PPMS.
- MS patients do not experience menstrual irregularity or early menopause more than the general population.
- In one study, MRI lesions in MS were seen more frequently during luteal phase of cycle when progesterone outweighs estrogen
- There may be an increase in MS symptoms perimenstrually
Oral contraceptive pills (OCPs), Hormone replacement therapy (HRT) and MS

- No protective effect seen in MS with OCPs but no deleterious effect seen either thus far.
- In fact if MS patients had early use of OCPs as a teen they progress to EDSS 6 more quickly.
- Menopause may increase MS symptoms but no benefit seen from HRT on progression of disease.
- Could it be that different types of estrogen may be more beneficial than others? Or that there is an ideal amount or ratio?

Fertility and MS

- No significant impact of MS on fertility and reproductive health for males or females.
- Small studies have shown limited evidence than MS exacerbations can be seen with IVF failure or use of GnRH agonists to aid fertility.
Fertility and MS Medications

- Although MS does not effect fertility itself, there are many DMT medications or treatments for symptoms that may effect either current/future fertility or a developing fetus.
- Biggest consideration for future fertility is the use of chemotherapy agents which can cause sterility. Hence sperm and egg banking should be discussed with the patient as an option.

FDA Pregnancy Risk Category Definitions

- A: No evidence of fetal harm in human studies
- B: No evidence of fetal harm in animal studies
- C: Evidence of fetal harm in animal studies or no data available
- D: Evidence of fetal harm in humans; use may be justified in some circumstances
- X: Evidence of fetal harm in humans; not indicated for use in pregnancy
Pregnancy categories of DMTs in MS

**TABLE 1: DISEASE MODIFYING THERAPIES—PREGNANCY SAFETY CATEGORIES**

<table>
<thead>
<tr>
<th>First line therapies</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-interferon 1-b</td>
<td>C</td>
</tr>
<tr>
<td>Beta-interferon 1-a</td>
<td>C</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>C</td>
</tr>
<tr>
<td>Gilanipir acetate</td>
<td>B</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>C</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>X</td>
</tr>
<tr>
<td>Second line therapies</td>
<td>Pregnancy Category</td>
</tr>
<tr>
<td>Azathioprine**</td>
<td>D</td>
</tr>
<tr>
<td>Cytoxosulphamide**</td>
<td>D</td>
</tr>
<tr>
<td>IVIG**</td>
<td>C</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>C</td>
</tr>
<tr>
<td>Methotrexate**</td>
<td>X</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>D</td>
</tr>
</tbody>
</table>


Symptom management medications and pregnancy safety categories

**TABLE 2: SYMPTOM MANAGEMENT MEDICATIONS—PREGNANCY SAFETY CATEGORIES**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>SYMPTOM</th>
<th>PREGNANCY RISK CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid</td>
<td>Acute exacerbation*, Spasticity</td>
<td>C</td>
</tr>
<tr>
<td>Redudokin</td>
<td>Acute exacerbation*, Spasticity</td>
<td>C</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Spasticity, anxiety</td>
<td>D</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Spasticity</td>
<td>C</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Seizure, pain*, spasticity*</td>
<td>C</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Fatigue*</td>
<td>C</td>
</tr>
<tr>
<td>Modafnil</td>
<td>Fatigue*</td>
<td>C</td>
</tr>
<tr>
<td>Oxycetine</td>
<td>Overactive bladder</td>
<td>B</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Overactive bladder</td>
<td>C</td>
</tr>
<tr>
<td>Dalfraafine</td>
<td>Improve walking</td>
<td>C</td>
</tr>
</tbody>
</table>

Goals for symptom management during pregnancy

- Ideally should use lifestyle changes and non-pharmacologic aids (timed voiding, stretching, yoga) as most medications contraindicated during pregnancy.
- Energy conservation important for fatigue.
- Be careful to see if new symptoms are relapses vs. pseudoexacerbation from UTI etc.

Contraceptive and Family Planning concerns in MS

- There are no guidelines for or against the use of any particular type of contraception (estradiol, progestins, IUDs, surgical) as it relates to MS and disease exacerbation or protection.
- Family planning issues will relate to the timing and use of DMTs as there are no DMTs that are recommended for use during pregnancy.
- Before starting DMTs, caregivers should discuss patient’s desire to have children and in what timeframe so that ideal medical decisions can be made.
Contraceptive and Family Planning concerns in MS: general guidelines for DMTs

- Advice is based on known half-lives of DMTs and general experience
- Interferons and glatiramer acetate should be discontinued 1-2 menstrual cycles before trying to become pregnant.
- Stop fingolimod at least 2 cycles before
- Natalizumab should be discontinued 3 cycles prior to conception
- Teriflunomide is category X and has a long half-life (can be found in patient’s serum for up to 2 years). Do not recommend use in child-bearing age patients unless strict contract for contraception.

What if patient takes more than 3 months to become pregnant and is off DMT?

- No current guidelines for care but should keep in close contact and have frequent visits to neurologist
- Keep in mind certain types of IVF induction therapies may exacerbate MS
- If patient anticipates long duration off DMT, could consider use of monthly IVIG which is safe if she becomes pregnant unexpectedly
What if patient becomes pregnant while on DMT?

- Stop DMT immediately, for all but teriflunomide no further action is required other than usual prenatal care.
- For Teriflunomide, would recommend rapid wash out of medication per protocol with activated charcoal
- Consider PLEX if patient on Natalizumab
- In general, recommend all patients take folate and Vitamin D during pregnancy and should start during pregnancy planning stage

Does MS itself affect pregnancy and developing fetus?

- Short answer is no, it does not.
- A national pregnancy registry showed that MS patients displayed higher incidence of intrauterine growth restriction and caesarean delivery than controls.
- Main risk to fetus is a higher risk of developing MS in life of 20-50x that of the general population. Roughly 3% overall lifetime risk.
- There are no prenatal tests for genetic risk for MS in fetus
How does pregnancy affect MS?

- We now know that pregnancy can be protective in many ways in regards to the development and progression of MS.
- This makes sense scientifically because MS is thought to be a cell-mediated autoimmune disease.
- During pregnancy there is a shift from Th1 (cell-mediated) to Th2 (humoral) immune responses that is beneficial in MS.
- This immune shift is thought to be mainly due to estriol produced by the placental unit.

Pregnancy and MS epidemiology

- Women who have had children take longer to reach an EDSS of 6 than those who are nulliparous.
- AusImmune study examined first clinical demyelinating event (FCD). An increasing number of offspring was associated with a dose-response trend towards a later age of developing an FCD for women but not men. Corrected for sun index, Vitamin D levels, smoking, BMI, HLA DR-15 risk.
- Interestingly, in 1961 average age of first birth in Australia was 23.2. In 2008 it was 31.9. Some theorize this may be a small part behind the rising incidence of MS.
Pregnancy and relapses: The PRIMS study

Relapses during pregnancy

- Would avoid IV methylprednisolone during the first trimester but a short course is safe in second and third trimester
- IVIG may be used in any trimester of pregnancy to treat relapses
- MRIs can be performed at any time during pregnancy but preferably after first trimester. But use of gadolinium is discouraged as fetal safety is unproven
- Evoked potentials and lumbar punctures safe throughout pregnancy if indicated
Management of labor

- Patient’s obstetrician may make decisions guided by patient without regard to MS.
- All types of anesthesia or delivery method are safe in regards to MS.
- No need for pulse steroids unless patient chronically on steroids for some reason.

Risk factors for postpartum relapses in MS in PRIMS

- More frequent rate of relapses year before pregnancy.
- Higher rate of MS related disability pre-pregnancy.
- No relation to epidural use, previous number of pregnancies, gender of fetus, age of MS or pregnancy onset, disease duration, total number of relapses prior or breastfeeding (54% of patients).
Postpartum management

- Patients who are not breastfeeding are encouraged to start DMTs within two weeks of delivery as they can take several months to reach full protective effect.
- If poorly controlled MS prior to pregnancy, this can be ideal time to try new DMT
- POPARTMUS trial using progestin and estradiol postpartum awaiting results
- IVIG in some trials given preventively may reduce risk of postpartum relapses, needs confirmation

Breastfeeding and MS management

- It is possible exclusive breastfeeding may protect against relapses but larger studies needed to confirm.
- Currently no DMTs are recommended for use during nursing as the transmission via breastmilk is unclear for many.
- I do not advise my patients against breastfeeding so they can start a DMT, but suggest starting DMT if they are unable to breastfeed exclusively for two months.
- Steroids are contraindicated for relapses while breastfeeding but IVIG may be considered safe.
- If MRI needed with gadolinium then recommend “pump & dump” for 24 hrs
Estriol as a possible neuroprotective agent for MS

- Interesting evolution: clinical observation led to bench research which led to clinical trials.
- Recent phase II study at 16 sites across US, randomized, double-blind, placebo controlled.
- 158 women with RRMS given 8 mg of estriol every day with Copaxone vs Copaxone with placebo.
- Treatment group saw 47% reduction in relapses after one year of treatment and scored higher on cognitive testing.
- After two years placebo group began to improve as well.
- Could be a good add-on therapy given its low cost, comes in pill form, and has a good safety profile for women. Phase III study needed.

Female cancers and MS

- Traditionally female MS patients had been seen in population studies to have a slightly lower incidence of cancers compared to general population.
- With advent of DMTs and immunosuppressant therapies, this protection may be counteracted and even trend to higher cancer rates in MS patients.
- Male cancer risk about the same as general population.
Male sex hormones and concerns for male patients

- Males develop MS less often and later in life than females.
- No decrease in fertility, but sperm count and motility may be lower in MS. More research is needed in this area.
- Remember to ask male MS patients about erectile dysfunction or decreased libido and consider a referral to urology.
- One pilot study (n=10) may indicate testosterone supplementation aids cognition, slows brain atrophy.

References