Teaching Course 2

MS during pregnancy and post-partum

Chairs:  
K. Hellwig (Bochum, DE)  
A.M. Langer-Gould (Pasadena, US)

4 Family planning with MS general consideration/assisted reproductive techniques  
M.K. Houtchens (Brookline, US)

5 Pregnancy management: medications and lactation  
K. Hellwig (Bochum, DE)

6 MS and oral contraceptives: the effect on susceptibility and prognosis  
A.M. Langer-Gould (Pasadena, US)
MS and Pregnancy

Although data are not available on the prevalence of multiple sclerosis among women of reproductive age in the United States, estimates suggest that 135 persons per 100,000 in the United States have multiple sclerosis, which translates to roughly 435,000 people. As women are affected 2.4 times as often as men, we estimate that roughly 307,000 women in the United States have multiple sclerosis.

Our goal as physicians is to help women live lives to the fullest potential, with their disease that we can’t yet cure. This includes experiencing motherhood.

Prior to 1960s the message to MS patients was: “Avoid pregnancy”

In 2012 National Multiple Sclerosis website stated:

“There is no evidence that MS impairs fertility or leads to an increased number of spontaneous abortions, stillbirths or congenital malformations. Several studies of large numbers of women.. demonstrated that pregnancy, labor, delivery and the incidence of fetal complications are no different in women who have MS than in control groups... Over the past 40 years, many studies have been done in hundreds of women with MS, and they have… reached the… conclusion: that pregnancy reduces the number of MS exacerbations, especially in the second and third trimesters.”

Current challenges in the management of pregnant patients with MS:
• Comprehensive management programs for pregnant MS patients do not exist

• There are no evidence-based practice guidelines on clinical decision making and therapeutic choices for women with MS who choose to become pregnant or experience an unplanned pregnancy

• Level of care received by pregnant MS patients varies dramatically depending on the knowledge and comfort level of a provider

• While most pregnant MS patients are stable throughout pregnancy and post-partum, some patients will have attacks and serious symptoms intra-partum, and will require management

• Patients with aggressive and poorly controlled MS may also desire pregnancy and are at known increased risk for MS-related complications

**Motherhood decision**

• The decision to start or enlarge a family can be complicated by chronic illnesses like MS

• MS has little impact on reproductive capacity
  - In otherwise healthy mothers, pregnancy, labor, and delivery can generally be managed routinely

• Many women with MS will become mothers

• Domains of concern for prospective mothers with MS include the health of a child, the health of the mother, and perceptions of disapproval from society (health care providers, family, peers.)

• Women are specifically concerned about genetic risk of the disease in their offspring, pregnancy risks associated with the MS therapies, the disease itself, and the quality of
future parental care they can provide to their children. They are also worried about the consequences of stopping disease modifying therapies, the possible influence of pregnancy on worsening the course of their illness, and the unpredictable nature of MS.

Fertility in MS

There is no convincing data that there is an overall decrease in fertility in MS patients. However, several factors need to be considered:

1) Possibly, greater prevalence of endometriosis in patients with MS. Moderate to severe endometriosis is associated with decreased fertility
2) Altered reproductive decision making related to chronic illness
3) Sexual dysfunction, including decreased arousal, libido and un-orgasmic intercourse, possibly delaying conception.
4) Higher prevalence of thyroid autoimmunity
5) Treatment-related temporary amenorrhea or premature ovarian failure
6) One small (N = 61) prospective study reported that patients with MS were more likely to employ assistive reproductive techniques. 4.9% (n = 3/61) of patients with MS versus 0.9% (N = 55547*) of the general population needed artificial insemination to conceive

Fertility effects of MS therapies.

- No known effects on fertility (male or female):
  - Glatiramir Acetate
  - Interferons (may cause transient amenorrhea)
  - Fingolimod
  - Teriflunomide
• Fumarate

• Possible effects on fertility:
  • Natalizumab (in preclinical studies, at 10 times human dose)
  • Mithoxanthrone (in preclinical animal studies and in humans: 30%
    permanent amenorrhea is women ages 35+)

Genetic counseling for patients with MS.

There is no genetic test for multiple sclerosis. Inheritance is likely polygenic

There is a ~98% chance that children of a patient with MS will not develop MS

Approximate risk of developing MS:

- Monozygotic twins: 25% concordance
- Dizygotic twins: 5% concordance
- 1 parent has MS: 2%-4%
- Second degree relative: 1%
- Lifetime risk of developing MS: 0.1%-0.2%
How do we optimize the chances of conception for a patient with MS who has stopped disease modifying treatment and is trying to become pregnant?

- OCs need to be stopped 2-3 months prior to conception attempts, and patients should be advised to transition to mechanical birth control.
- “Fertility window” – 6 day period, ending with the ovulation day. This window can be estimated based on duration of menstrual cycle, cervical mucus and basal body temperature, as well as commercially available ovulation kits.
- Intercourse is most likely going to result in pregnancy if attempted within a 3 day period, ending with the ovulation day.
- Moderate alcohol consumption, smoking, drug use, vaginal lubricant use decrease the chances of conception.
- Traditional fertility awareness methods can be used to track fertility and improve chances of conception (www.fertilityfriends.com)
Assisted reproduction techniques (ART) and MS.

Infertility is defined as failure to achieve clinical pregnancy after regular unprotected intercourse over 12 months’ period. As many as one in six couples in the Western world encounter problems with fertility.

Center for Disease Control (CDC) in the United States defines ART as “all fertility treatments in which both eggs and sperm are handled.” In general, ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body or donating them to another woman.” ART, generally, does not include treatments in which only sperm are handled (i.e., intrauterine—or artificial—
insemination) or procedures in which a woman takes medicine (Clomiphene citrate) only to stimulate egg production without the intention of having eggs retrieved.

Several protocols are available for *in Vitro* Fertilization and Embryo Transfer. GnRH agonists and GnRH antagonists protocols are the ones that are most commonly used for IVF cycles. The GnRH antagonist protocols have become more common, due to with fewer side effects, shorter duration, and the absence of profound hypoestrogenemia. There is no difference in the live birth rates between protocols employing GnRH agonists or antagonists.

In MS, several studies reviewed disease outcomes following IVF protocols. **Although the studies are small, there appears to be a higher risk of relapse after a failed IVF attempt, if GnRH agonist protocol was used.**

Possible reasons for this effect could include GnRH-related proliferation of immune cells, increased cytokine, chemokine and endothelial growth factor levels, estrogen-dependent increase in B-cells and B-cell mediated immune factors, extended duration off disease modifying therapy, and rapid shifts in hormone levels.

While no definite specific recommendations can be given to patients about the safety of IVF techniques in MS, the general concept is that ART is possible in well-controlled MS patients. Patients need to be educated about possible increase of disease activity.

If possible, GnRH agonist protocols should be avoided, if GnRH antagonists can be safely used. Ultimately, the goal is to allow MS patient to achieve pregnancy, so the protocol most likely to result in viable pregnancy should be selected for an individual patient, based on recommendations of their infertility specialist.
Intravenous steroids or disease modifying treatment without known effects on fertility or embryo can be considered on individual basis, throughout pregnancy attempts, for a patient with particularly active disease course.

What is the safest time to consider pregnancy in the course of MS?

There is no published data to help answer this very important question. Pregnancy and motherhood is a personal decision that depends on availability of a spouse or a partner, financial security, social support system, and health status of future parents, among other matters. However, we know that Pregnancy in Multiple Sclerosis (PRIMS) trial showed significant correlation between pre-pregnancy annualized relapse rate in the 12 months preceding conception, and post-pregnancy relapse rate. Therefore, we may need to consider potentially extended time off DMDs while attempting pregnancy. It is probably helpful to stabilize an active patient with more effective therapies for 6-12 months prior to attempting conception. We also need to establish pre-pregnancy clinical and radiographic disease baseline, to refer to after labor is completed, and when we are considering a restart, or a change of the disease modifying therapy.

Pre-pregnancy care recommendations do no differ substantially from those given to healthy expectant mothers:

- Standard Prenatal Vitamins with 0.4mg – 1 gm of daily Folate
- Smoking, alcohol cessation
• Improved sleep hygiene
• Vitamin D3 supplementation
  • Low levels are associated with adverse pregnancy outcomes
  • Low levels are associated with poorer clinical and radiologic MS course
  • Low levels may be associated with increased MS susceptibility in offspring

What do we know about the effects of pregnancy on the course of multiple sclerosis? PRIMS was the first prospective study of 254 women with MS (269 pregnancies) who were followed for up to 2 years after delivery. The results of the study showed that pre-pregnancy rate of 0.7 relapses per year decreased to 0.2 per year in the third trimester representing approximately a 70% reduction. The relapse rate then increased to 1.2 per year in the first 3 months postpartum; however, 72% of women did not experience any relapses during that period. Additionally, annualized relapse rate for the 21 month postpartum period did not differ significantly from the pre-pregnancy rate. Breastfeeding was not predictive of a subsequent relapse or of disability progression.

Most studies failed to demonstrate negative effects of pregnancy on long-term MS outcomes, including disability progression. Several studies suggest that the rate of disability increase most rapidly in nulliparous women when compared to those with MS onset before, versus during or after pregnancy. A Canadian study looked at clinical and term pregnancy data from 2105 female MS patients; it showed that a delay in reaching the Expanded Disability Status Score of 6 by patients having children after MS diagnosis could be explained by the age of MS onset rather
than the number of term pregnancies. These results may suggest that pregnancy does not have an independent effect in reaching advanced disability levels.

**Pregnancy outcomes in MS:**

- Babies born to MS mothers are slightly smaller for gestational age by weight (OR 1.45).
- There is no difference in Apgar scores in babies of MS mothers
- There may be a slightly increased rate of operative deliveries in MS patients
- There is no increase in birth defects, perinatal mortality, or other adverse fetal outcomes.
- Method of labor and delivery does not impact the post-partum course of MS
- Cesarean section to be considered in a woman with paraplegia, pelvic floor weakness, decreased/absent pelvic floor sensation
- Epidural anesthesia or general anesthesia, if required, has no effect on post-partum course of MS
- Consider stress-dose steroids for a woman with extended exposure to corticosteroids in pregnancy or pre-partum

Women with MS experience symptoms of pregnancy similar to those observed in healthy women. These can include worsening of symptoms often associated with both MS and pregnancy, such as fatigue, bladder symptoms, mobility difficulty due to increased weight, sleep disturbances.
Postpartum depression and coping in MS

- The lifetime prevalence of major depressive disorder in people with MS is estimated to be approximately 50%.

- The rate of suicides among patients with MS is 7.5 times greater than that of the general population.

- In a survey of mothers with MS 1 to 6 months postpartum, increase in MS symptoms correlated with increased depression and emotional distress.

- Postpartum depression can affect a woman’s ability to care for herself or her child during a time already complicated by increased incidence of relapse and significant baseline stress.

- More research is needed to ascertain the prevalence of postpartum depression in MS so that effective preventive and treatment strategies and screening programs can be implemented.
References:


Multiple sclerosis management during pregnancy and postpartum

Kerstin Hellwig
Annette Langer Gould

Presentations

1. Multiple Sclerosis and Pregnancy: Family Planning with MS general consideration/assisted reproductive techniques (M. Houtchens, Boston, US)


3. Multiple Sclerosis and oral contraceptives: the effect on susceptibility and prognosis „Should I recommend my patients to take the pill to treat MS“ ? (A. Annette Langer-Gould, Pasadena, US)

Learning objectives

• Key elements required to counsel MS patients wanting to become pregnant
• Improve existing knowledge on the management of pregnancies in MS patients
• Improve existing knowledge on MS pregnancy and disease modifying treatments
• Improve existing knowledge on postpartum management
• Improve existing knowledge on how to prescribe exogenous hormones (e.g. oral contraceptives) in women with MS
Multiple sclerosis and Pregnancy
Medication and Lactation
Kerstin Hellwig
Bochum/Germany

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Outline

1. Pregnancy and immunotherapies in women with MS
   - available human data
   - recommendations for clinical practice
2. Fatherhood and MS and DMT
3. NMO, pregnancy and medication
4. Postpartum management
Safety of medication during pregnancy

+ =

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 size</th>
<th>Number of Events</th>
<th>Number of Pregnancies Needed</th>
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</thead>
<tbody>
<tr>
<td>Spontaneous Abortion</td>
<td>Live Births</td>
<td>3/100</td>
<td>296</td>
<td></td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>Low Births</td>
<td>12/139</td>
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<td></td>
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<tr>
<td>Fetal Death</td>
<td>Live births</td>
<td>3/100</td>
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<tr>
<td>Any major birth defect</td>
<td>Live Births</td>
<td>3/100</td>
<td>594</td>
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<td>Live Births</td>
<td>5/911</td>
<td>1919</td>
<td></td>
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<td>Diet for twin or without pains</td>
<td>Live births</td>
<td>1/980</td>
<td>97011</td>
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<tr>
<td>Distal syndrome (or other low birth defects)</td>
<td>Live births</td>
<td>1/100000</td>
<td>185893</td>
<td></td>
</tr>
</tbody>
</table>

Corticosteroids during pregnancy (FDA Category C)

- Corticosteroids have weak teratogenic potential, but caveat before gestational week 12
- Cortisol and prednisolone are inactivated in the placenta (10% reach the fetus, 100% with dexamethasone)
- Caveat: closure of the soft palate between gestational week 8 and 11
- Cleft risk in animal studies 1:1000
- OR meta-analysis in humans 3.5 [95% CI 1.97, 5.69]
- With continuous steroids: premature rupture of the membranes, disturbances of electrolytes, hypoglycaemia
Interferon-beta risk in pregnancies (FDA Category C)

- >1500 pregnancies tracked
- No increased risk of miscarriage
- No increased risk of malformations
- Lower mean birth weight/lower mean birth length?
- Increased risk of preterm birth (OR 2.11)?

No wash-out for IFN-beta
Stop contraception and IFN-beta
Monitor IFN-beta until pos. pregnancy testing

Glatiramer acetate risk in pregnancies (FDA Category B)

- >400 pregnancies under GA tracked
- No increased risk of
  - Malformation, Abortions
  - Preterm birth, Reduced birth weight

No wash-out of GLAT
Stop contraception and GLAT
Maintain GLAT until pos. pregnancy testing

Active transport of monoclonal antibodies

- Mabs are actively transported over the placenta
- Increasing during the course of pregnancy
- Differences for different subclasses
  - IgG1 > IgG4 > IgG3 > IgG2
- Rapid increase between gw 22 – 26
- During third trimester fetal concentration can exceed mothers

Haghikia ... et Hellwig, JAMA Neurol. 2014;71(7):891-5
Natalizumab risk in pregnancies (FDA Category C)

- Not teratogenic in animal studies/increased risk for miscarriage in one of several animal studies
- Preliminary data show no increased risk in humans (birth weight, malformation, miscarriage ?)
- During the 2nd quarter, transplacental transport of antibodies observed
- Caveat: if given during the last quarter of pregnancy, haematological screening of the newborn is necessary (10/13 exposed NB)
- At least 40% of natalizumab-treated women have relapses during pregnancy
- Natalizumab crosses into milk

Natalizumab clinical recommendations

Case by case decision according to pre natalizumab disease activity:

- Very conservative approach: Discontinue natalizumab before conception, maintain contraception for 2-3 additional months *
- Semiconservative approach: Discontinue natalizumab and contraception
- Semiactive approach: Stop natalizumab with positive pregnancy testing
- Active approach: Continue Natalizumab during pregnancy, extend infusion intervals on 6 weeks, stop natalizumab before gw 30, check newborn for hematological abnormalities, inform about potential anemia and thrombocytopenia

Alemtuzumab

- Monoclonal antibody against CD 52
- > 200 pregnancies
- Mainly 4 months after the second cycle
- No signs of increase in reproductive toxicity
- Caveat: One baby with thyreotoxic crisis after maternal development of hyperthyrosis
- Caveat: thyroid autoimmunity and interaction with fertility

Negative pregnancy testing before each cycle
Pregnancy ok 4 months after the last cycle
Daclizumab

- Monoclonal IgG1 antibody
- 150 mg every 4 weeks, half life time 21-25 days
- Animal studies no signs of reproductive toxicity
- About 40 pregnancies in humans no concerning signals (exposed defined as last DAC 6 months before pregnancy)

Conservative approach: Stop DAC 3 months prior to pregnancy
Semiconservative approach: Stop DAC with contraception
Active approach: Stop next DAC with pos. pregnancy testing

Fingolimod risk in pregnancies (FDA Category C)

- Teratogenic in animal studies
- Fertility is not reduced
- No interaction with EE-LNG Ocs
- Meanwhile several hundred pregnancies with some diverse malformations not following a certain pattern,
- The magnitude of a possible teratogenic potential is not known yet
- Breastfeeding not recommended

Discontinue FTY 2 months prior to conception
In case of accidental exposure, discontinue FTY, recommend organ screening ultrasound

Teriflunomide risk in pregnancies (FDA Category X)

- 70 pregnancies
  (elimination procedure: cholestyramine/activated charcoal)*
  - Induced abortion, n=29; spontaneous abortion, n=8;
  - Healthy newborn, n=26; ongoing pregnancy, n=7;
- So far no pattern of malformation in about 100 leflunomid-exposed pregnancies**

Stop Teriflunomide before conception
Recommend accelerated elimination with cholestyramine and control plasma level (should be < 0.02 mg/l) before conception or in case of accidental exposure during pregnancy
In case of accidental exposure recommend organ screening ultrasound
Dimethyl fumarate risk in pregnancies (FDA Category C)

- No teratogenicity in animal studies
- Embryo and fetotoxicity
- Very short half-life
- So far no signs of increase risk in reproductive toxicity in DMF exposed pregnancies (about 200 exposed pregnancies, most of them ongoing)

Stop DMF and contraception
In case of accidental exposure stop DMF after pos. pregnancy testing/ consider recommend organ screening ultrasound?

Fatherhood + MS medication

- No clinical evidence that MS medication alters male fertility
- None of the MS drugs has to be withdrawn in EU except:
  - Mitoxantrone, which should be interrupted in both sexes 6 months prior to pregnancy

To breastfeed or not to breastfeed?

- Possibly exclusive breastfeeding can reduce early postpartum relapses
- Additional benefit through IVIG?
- Additional benefit through DMT?
- It is not evident if early DMT reuptake is beneficial in postpartum relapse reduction
Breastfeeding vs non-breastfeeding


Kerstin Hellwig ECTRIMS 2016 Pregnancy Workshop

Resuming MS medications after delivery and lactation

- IgG antibodies (e.g. natalizumab) pass freely into breast milk, albeit at much lower concentrations than in serum; largely degraded by gut (infant serum levels low from nursing only)
- Oral small molecules at a lower fraction in breast milk than in sera (peak concentrations and half-life) but more likely to directly affect the infant’s immune/neurological systems, little gastric degradation, slowed hepatic clearance in infants (e.g. dimethyl fumarate, fingolimod)
- Beta-interferons found at 0.006% of maternal dose
- Glatiramer acetate unlikely, cannot be measured

Probable safe to breastfeed on beta-interferons and glatiramer acetate, but not on small molecules (dimethyl fumarate, fingolimod)

Safety of breastfeeding on natalizumab and other non-depleting mAbs unclear

MS and family planning: summary

1. Most women with MS will have healthy babies
2. Having MS does not increase the risk of pregnancy complications
3. More information on DMT-exposed pregnancies is needed
4. Most women with MS will not experience an increase in permanent disability from a postpartum relapse
5. Breastfeeding is not harmful – exclusive breastfeeding may be beneficial thus in women with more mild disease (low pregnancy relapse frequency and severity). Breastfeeding should NOT be discouraged in favour of resuming MS medications in most women
6. In women with highly active disease (controlled pre-pregnancy only by natalizumab, fingolimod, or cyclophosphamide) foregoing nursing, resuming medications as soon as possible may be necessary
Thank you for your attention!

- Dr. Sandra Thiel
- Annette Langer Gould
- Reinhold Rau
- Tanja Steiner
- Delia Kremer
- Ralf Gold
- DFG
- DSMG
- All the patients and referring physicians and nurses

Neuromyelitis optica and pregnancy

Azathioprine and Mycophenolatmophetile

- Azathioprine: 2000 pregnancies, most probably not teratogenic
- Reduced birth weight? Caveat confounders

Consider to continue AZA in stable patients with NMO, recommend organ screening ultrasound

- MMF: Abortifant (45%), teratogenic (26%), Mycophenolat Embryopathie (Microzy, clefts, cardiac defects, esophageal atresia)

Stop MMF, maintain contraception for 4 additional weeks in case of accidental exposure recommend organ screening ultrasound
Overview

• Background
• Oral Contraceptives: Can they prevent MS?
  – Hormonal content of oral contraceptives
  – Summary of studies
  – Biological plausibility of findings
• Oral Contraceptives as a treatment for MS
  – OC + Rebif randomized controlled trial
  – Summary of observational studies
• Pregnancy-dosed Hormones: Can they treat MS?
  – Estriol + glatiramer acetate trial
  – POPART MUS trial

Inspiration for 2 decades of research

- Stronger than any MS medication
- Can we uncover the mechanism and ‘bottle’ it
- Coupled with observation that MS is a female predominant disease that usually starts during reproductive years

Rising MS Prevalence in Women

Explanations:
- Improved life expectancy
- Obesity
- Smoking
- Oral contraceptive use?

Oral Contraceptives to prevent MS

Hormonal Content of OCs

- Estradiol low dose or very low dose + Progestin
  - High dose use discontinued due to thrombosis risk
- Biological properties of Progestins

<table>
<thead>
<tr>
<th>Androgenic*</th>
<th>Estrogenic</th>
<th>Progesteral*</th>
<th>Mineral-corticoid</th>
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<tr>
<td>Norethindrone</td>
<td>+</td>
<td>+ &amp; -</td>
<td>+</td>
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<tr>
<td>Levonorgestrel</td>
<td>++++</td>
<td>-</td>
<td>+++</td>
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<tr>
<td>Drospirenone</td>
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- Immunological effects of progestins not studied
- Most studies in MS did not examine potential differences in progestin effects
Oral Contraceptive Use and risk of MS

<table>
<thead>
<tr>
<th>Study</th>
<th>Study years</th>
<th>No. MS cases</th>
<th>OC use</th>
<th>RR/OR (95%CI)</th>
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- No study was able to demonstrate increasing risk with increasing duration of use
- Most likely, no significant effect on MS risk
- Even if, would need >25,000 women exposed to OCP for 1 additional case of MS

Does Progestin Content Matter?

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Does Progestin Content Matter?

Association between progestin content of combined oral contraceptives and risk of multiple sclerosis / clinically isolated syndromes

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<thead>
<tr>
<th>Incident Cases/Control Adjusted</th>
<th>N OR 95% CI p-value</th>
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<tbody>
<tr>
<td>None</td>
<td>224/2460</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>69/536 1.57 1.16 2.12 0.003</td>
</tr>
<tr>
<td>Levenorgestrol</td>
<td>69/471 1.75 1.29 2.37 &lt;0.001</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>22/253 1.02 0.64 1.62 0.950</td>
</tr>
</tbody>
</table>

- adjusted for parity, miscarriage, smoking, obesity

- Androgenic* Extragenic Pro-gestational* Mineral- corticoid
- Norethindrone ++ + & - + none
- Levenorgestrol +++++++++ - ++++ none
- Drospirenone ++ - ++++ none

- Does Progestin Content Matter?
- Maybe

Susceptibility: Oral Contraceptive Use

- Odds ratios adjusted for parity, smoking, obesity and miscarriages/abortions

- OCP use up to 10 years prior increases the risk of MS but longer use does not mean higher risk
- Most likely due to unmeasured confounder
Biological Plausibility

- Animal studies of MS (EAE)
  - High doses of progesterone, estradiol and estriol suppress
  - Low doses female sex hormones not studied
- High and low doses of estradiol different effects on PLP-specific T cells clones from MS patients*
  - High doses= IL-10 secretion
  - Low doses= IFNγ and TNFα secretion
- Low dose estrogen states are proinflammatory
  - Women of childbearing age more vigorous immunological response to vaccinations and infections than men**
  - Onset of autoimmune diseases coincides with estrous cycle and more common in women
- OC use associated with modest increased risk of inflammatory bowel disease***

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Oral Contraceptives as Treatment for MS

Oral Contraceptives

Randomized controlled trial of low and lower dose estrogen OC added to Rebif blinded EDSS assessor but not patient or treating physician

<table>
<thead>
<tr>
<th>Oral Contraceptives as Treatment for MS</th>
<th>Biological Plausibility</th>
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<td><em>Animal studies of MS (EAE)</em></td>
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<td>- High doses of progesterone, estradiol and estriol suppress</td>
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Primary Outcome: MRI

Pilot data supporting modest anti-inflammatory activity of OC on MRI measures only

Clinical outcomes: OCP RCT

Oral Contraceptive Use and Prognosis

- Inconclusive evidence: mixed results, studies not so good
  - Disability progression:
    - 1 study no effect on disability progression (Poser et al., Acta Neurol Scand 1979)
    - 1 study increased progression in progressive onset patients (Dhooghe et al., J Neurol 2012)
    - 1 cross-sectional study showed less SPMS among OC users (Gava et al., Fertility and Sterility 2014)
  - MS symptoms:
    - milder MS symptoms (Holmqvist et al., Eur J Contracept Reprod Health Care 2009)
  - MS Onset:
    - older age at onset of first MS symptoms (Holmqvist et al., Fertility and Sterility 2010).
Pregnancy Hormones as Treatments for MS

Estriol Study

- Objective: to determine whether pregnancy-levels of estriol reduce disease activity in RRMS
  - Double blind study randomized to copaxone+estriol (n=83) or copaxone+placebo (n=81)
  - Primary outcome ARR at 2 years not significantly reduced (p=0.16) nor was reduction MRI disease activity as presented at AAN 2014
  - 'positive' result on adjusted ARR at 2 years 0.25 and 0.37 (p=0.077 reported in Lancet)
  - Independent analysis of data by 2 biostatisticians revealed negative study on all endpoints (ARR at 2 yrs 0.17 vs. 0.25 p=0.302)

Voskuhl RR et al presented at April 29, 2014 AAN

POPART’MUS Study

- Objective: to determine whether sex hormones can prevent postpartum relapses
  - Double-blind placebo controlled study of progestins combined with low dose transdermal estradiol for the first 3 months postpartum (n=200; 100 placebo:102 P+E)
Immunobiology of Pregnancy

- Th1/Th2 shift, Fetal Allograft Story are out
- Complex state of simultaneous immunosuppression and hyper-vigilance
  - Intricate and coordinated responses from mother, fetus and placenta
  - Defend against pathogens and tolerate paternal antigens
  - Include pregnancy-associated glycoproteins, exosomes and
  - Maternal-fetal bi-directional microchimerism


What have we learned?

- Immunobiology of pregnancy more complex than single hormone (symphony not a solo)
- Increase in prevalence of MS in women probably not explained by OC use
- Future studies are needed
  - Progesterin content and effect on MS prognosis and susceptibility
  - Animal and in vitro studies of low dose combination hormones like those in OCs effects on immune system, neurodegeneration and cognitive function

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