Using Systemic Therapy in Pregnancy

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Disclosures

- **Disease State Management Speaker**
  - Regeneron (Atopic Dermatitis)
  - UCB (Psoriasis in Pregnancy)
- **Advisory Board**
  - Dermira
  - UCB
  - Genzyme/Sanofi
- **Dermatologic Consulting**
  - Ferndale
  - UpToDate
Objectives

- Discuss management of skin disease in pregnancy
  - Atopic dermatitis
  - Psoriasis
  - Pemphigus
Family planning should be addressed in all women of reproductive potential!!

- 50% of the pregnancies in the US population are not planned with a health care professional
- Development of major organs starts 3rd week after conception
- Most women discover they are pregnant 2-5 weeks after conception

International Classification

Three widely accepted classification systems

- Europe: FASS (Swedish Catalogue)
  - Additional: Netherlands, Denmark, Germany
- USA: FDA (Food and Drug Administration)
- Australian: ADEC (Australia Drug Evaluation Committee)

Only 26% (61) of 236 common medications were in same risk category

New FDA Pregnancy and Lactation Label Ruling (PLLR)

- New ruling December 2014
  - Contact info for registry
  - Narrative sections
  - Breastfeeding section
  - Females/males of reproductive age
- Effective as of June 30, 2015 (phase in)


Resources

- March 2014 Vol 70(3) Journal of the American Academy of Dermatology
  - CME Part 1 Safety of dermatologic medications in pregnancy
  - CME Part 2 Safety of dermatologic medications in lactation
- PLLR article in IJWD (www.wdsijwd.org, Chi 2019)
**Systemic steroids**

- **Teratogenicity of systemic cortisones (?)**
  - Fraser and Fainstat (1951): systemic cortisone in pregnant mice caused cleft palate
  - Prospective studies $\rightarrow$ no evidence malformation
  - Epidemiologic studies $\rightarrow$ incr risk of oral clefts
  - Meta-analysis: Oral cleft risk increases 3.4 fold (c/w animal studies)
- Betamethasone and dexamethasone cross placenta well; prednisone only to small extent
Topical steroids

- Only dermatologic topical in Cochrane

Reviewed all cohort and case controlled studies in 11 databases

- Mygind 2002: population cohort study, topical corticosteroid use in 2.9% of malformed cases (363) vs. 3.6% of control births (9263)

- Czeizel 1997: population case-control, topical corticosteroid use in 0.35% of malformed cases (20,830) vs. 0.33% of control births (35,727) [p=0.7]

- Kallen 2003: RR 2.0 [0.55-5.15], national register, 1044 orofacial cleft (576,873 controls)

- Pradat 2003: RR 0.6 [0.20-1.97], multi-country case control, 11,150 orofacial cleft

- Carmichael 2007: RR 0.9 [0.2-4.3], population case-control, 1141 cases with cleft lip/palate vs. 4143 controls
If possible, limit to 300 grams.
Population cohort study (Chi 2013)

- No associations of maternal topical corticosteroid in 2658 pregnant women (vs. 7246 controls)
  - Orofacial cleft
  - Preterm delivery
  - Fetal death
  - Apgar score
- Increased risk of low birth weight when the dispensed amount of potent exceeded 300 g
Immunosuppression

- **Mycophenolate mofetil**
  - Contraception at least 4 wks prior to therapy and 6 wks after completing therapy
  - Cannot use hormonal contraception alone

- **Azathioprine**
  - Cannot use IUD alone (multiple reports of pregnancies with IUD in place)

- **Dupilumab**: insufficient data, no safety issues
Psoriasis in Pregnancy and Postpartum

<table>
<thead>
<tr>
<th></th>
<th>Change in pregnancy</th>
<th>Change postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>55%</td>
<td>9%</td>
</tr>
<tr>
<td>No change</td>
<td>21%</td>
<td>26%</td>
</tr>
<tr>
<td>Worsen</td>
<td>23%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Dramatic improvement in pregnancy (80% BSA clearance)!

Light

- UVB generally considered safest form of therapy
- Photodegradation of vitamins (folic acid)
- PUVA decreases serum folic acid
- NBUVB studies examining folic acid levels
  - Definition of folate deficiency: $< 3.7 \text{ [ng/ml]}$

<table>
<thead>
<tr>
<th>Journal</th>
<th>Pts (Study vs. Control)</th>
<th>Exposure</th>
<th>Folate levels Baseline [ng/ml]</th>
<th>Folate levels s/p Exp [ng/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDOJ</td>
<td>20 S/20 C</td>
<td>42 tx</td>
<td>8.1 +/- 2.6</td>
<td>5.9 +/- 1.5</td>
</tr>
<tr>
<td>JAAD</td>
<td>35 S</td>
<td>18 tx</td>
<td>6.3 +/- 3.6</td>
<td>6.4 +/- 3.3</td>
</tr>
</tbody>
</table>

Oral systemic therapy for psoriasis: Cyclosporine

- Cyclosporine
  - No increase in malformation risk >1000 births
  - Growth restriction (?)
  - Cohorts of children followed 2-3 yrs: no neurodevelopmental, immunologic, or nephrogenic defects
Oral systemic therapy for psoriasis: Apremilast

- Pregnancy category C
- Dose dependent increase in abortions/fetal death in monkeys >2X human dose
- No malformations in mice in doses 4 x human dose
**Anti-TNF placental transfer**

- Maternal antibodies transported across villi by neonatal Fc receptor to provide immunity to the newborn
- IgG increase from early 2nd tri until delivery; most during the third trimester
- Infant serum up to 7 mo
Biologic placental transfer

- Infliximab, adalimumab, ustekinumab are IgG monoclonal antibodies
  - Large hydrophillic protein, use Fc receptor
- Etanercept is fusion protein
  - Cross placenta by simple diffusion
  - Transferred less in 3rd tri: cord blood 4-7% (vs. IFX 160% and ADA 153% maternal levels)

Mervic L. Acta DermVen (2014)
Fatal case of infant death in mother taking infliximab during pregnancy

- Mother received infliximab every 8 wks (10 mg/kg) for Crohn’s
- Infant healthy until BCG vaccine given at 3 months of age
- Widespread eczematous dermatitis, head lag, poor weight gain
- Died at 4.5 months

CRIB (Certolizumab Pegol During Pregnancy)

- Certolizumab is the only PEGylated anti-TNF without an Fc region; study of patients greater than 30 weeks pregnant
- CZP levels were below (<0.032 microgram/ml) in 13/14 infant samples at birth; one infant minimal CZP level (infant/mother ratio 0.0009)
- No safety signals

Biologics have low oral bioavailability due to their large molecular size and digestive system proteolytic environment.

Neonatal Fc receptor on intestinal epithelial cells may promote uptake of undigested IgGs.

Highest concentration of CZP in breast milk (0.0768 microgram/ml) is <1% of plasma trough.

Average daily infant dose (0-0.01014 mg/kg/day) and relative infant dose (0.15%) minimal with no safety signals.
Dermatologists comfort with prescribing anti-TNFs

- **Childbearing age:** 54% (EU) vs. 83% (USA)
- **Pregnant women:** 10% (EU) vs. 21% (USA)
- One third of providers agreed with the statement, “Women who are breastfeeding should not be prescribed an anti-TNF treatment”


Pemphigus in Pregnancy

- Fetal skin shares same desmoglein 3 profile as adult oral mucosa: neonatal pemphigus is more likely if mother has oral disease!
- Increased risk of fetal demise

Pemphigus in Pregnancy

- Transient neonatal pemphigus lasting a few weeks (transplacental passage of IgG4 abs)
- No direction correlation between the severity of the mother’s disease and extent of neonatal involvement!!

A Case of Pemphigus in Pregnancy

- 1st pregnancy
- Clobetasol and daily oral prednisone 40-60 mg
- IV Ig started 26 wks gestation
- Emergent C-section at 30 wks gestation (2 lbs)
- HELLP (Hemolysis, Elevated LFTs, Low Platelet count), Gestational diabetes, Intrauterine growth retardation
A Case of Pemphigus in Pregnancy

- 2nd pregnancy
  - IV Ig every 4 weeks (20 g, 0.5 g/kg)
  - Completely discontinued steroid therapy
  - 38 wks gestation (4 lbs 11 oz)
IV Ig

- IV Ig improves the chance of in vitro fertilization (antibody-mediated disease contributes to 10% of infertility cases)
- IgG antibodies begin to cross placenta around 32 wks gestation
- Literature to support efficacy/safety in pregnancy in pemphigus treatment

Pemphigus Therapy in Pregnancy

- **Therapeutic ladder**
  - Topical steroids
  - Systemic therapy with corticosteroids at lowest effective doses
  - If requiring more than 20 mg of prednisone a day consider IV Ig, Azathioprine, Dapsone, Rituximab

Take-home points

- **AD:** Offer a detailed fetal US when oral corticosteroids are rx'd 1\textsuperscript{st} trimester

- **Psoriasis:** Biologics have mounting safety data showing safety of the anti-TNF class in pregnancy and breastfeeding

- **Pemphigus:** IgG is an excellent choice for moderate-to-severe cases in pregnancy
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