Pearls in Managing Skin Disease in Pregnancy

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March 1, 2019

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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

FDA Pregnancy and Lactation Label Ruling (PLLR)

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


Resource

- 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
Systemic steroids

- Teratogenicity of systemic cortisones (?)
  - Fraser and Fainstat (1951): systemic cortisone in pregnant mice caused cleft palate
  - Prospective studies → no evidence malformation
  - Epidemiologic studies → 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
Anti-histamines

1\textsuperscript{st} generation
- Anti-emetics for 1st tri
- Hydroxyzine \textit{slightly} higher increased risk of congenital malformations (5.8%)
- Diphenhydramine: 1974 Lancet case control study increase in cleft palate (?)

2\textsuperscript{nd} generation
- Loratidine 1\textsuperscript{st} line, Cetirizine 2\textsuperscript{nd} line

Avoid anti-histamines in last month of pregnancy

#1: Oxytocin-like effects: can stimulate uterine contractions (esp. IV/overdose)

#2: Reports of increased rates of retrolental fibroplasia in premature infants (22% vs. 11%) w/ anti-histamine use w/in 2 wks of delivery

Zierler S, Purohit D. Prenatal antihistamine exposure and retrolental fibroplasia, American Journal of Epidemiology 1986: 123 (1), 192-6,
Avoid anti-histamines in last month of pregnancy

- #3: Withdrawal symptoms: tremulousness, irritability, poor feeding, diarrhea [mother on 150 mg qd of hydroxyzine->infant tonic-clonic seizures]

Zierler S, Purohit D. Prenatal antihistamine exposure and retrolental fibroplasia, American Journal of Epidemiology 1986: 123 (1), 192-6,
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>Change in pregnancy</th>
<th>Change postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>55%</td>
</tr>
<tr>
<td>No change</td>
<td>21%</td>
</tr>
<tr>
<td>Worsen</td>
<td>23%</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 [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

Generalized pustular psoriasis (impetigo herpetiformis)

- “The fifth dermatosis of pregnancy” 3rd tri
  - Often lack previous or family history of PSO
- Hypocalcemia: seizures and tetany
- Can recur in future preg w/ increased severity; Fetal prognosis less predictable despite therapy

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

- Topical steroids and antihistamines are safe in pregnancy
- Biologics for psoriasis have mounting safety data showing safety of the anti-TNF class in pregnancy and breastfeeding
- IgG is an excellent choice for moderate-to-severe cases of pemphigus in pregnancy
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