Safety of Biologics for Psoriasis in Pregnancy

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Psoriasis
• chronic, immune-mediated disease
• 2% worldwide
• 7.2 million in the U.S.
• age of onset: age 28
• Th17-mediated disease
  – some Th1 involvement

Psoriasis
• Th2 response - up-regulated
• Th17 and Th1 - down-regulated
  – psoriasis
    • 55% improve
    • 21% no change
    • 23% worsen

Pregnancy
• pregnant women are commonly excluded from clinical trials
• limited data
  – animals, case reports or case series, small retrospective studies
  – most data come from GI and rheum literature
  – surveillance registries
  – biased because those with adverse outcomes are more likely to report

Biologics for psoriasis
• 2013
  – 25% of psoriasis patients on biologics
  • adalimumab
  • etanercept


Biologics during pregnancy
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FDA pregnancy categories
• A, B, C, D, X
• Biologics - Pregnancy Category B
  • animal studies did not show increased risk to fetus
  • no well-controlled trials in humans
  • benefits of the drug may be acceptable despite potential risks
• In 2015, this 5-letter system was changed due to concerns that it was too simple and did not accurately assess risk.
FDA

- Pregnancy and Lactation Labeling Rule
  - provides more detailed information in 3 categories:
    - Pregnancy
      - data from pregnancy registries
    - Lactation
      - amount of drug is breast milk
    - Females and males of reproductive potential
      - need for pregnancy testing, contraception recommendations, infertility information

Fetal exposure to biologics during pregnancy

- IgG -- the only antibody class transported across placenta
- Fetal IgG low in 1st 2 trimesters
- Fetal IgG may surpass maternal levels in 3rd trimester
  - active transport of IgG across placenta
- IgG1 is the most effectively transported
  - adalimumab and infliximab are both IgG1
  - etanercept - fusion protein with IgG1 Fc - less transplacental transport

TNF-alpha inhibitors in pregnancy

- minimal placental transport of maternal antibodies in 1st 2 trimesters
- rheumatology literature
  - continue drug up until week 30
- inflammatory bowel disease literature
  - Canadian Association of Gastroenterology (March 2016)
    - low-risk of IBD relapse and a compelling reason to stop TNF inhibitor - should stop at weeks 22–24
    - otherwise - recommended to continue anti-TNF throughout the pregnancy

Biologics in pregnancy

- Patients who continue biologics throughout pregnancy
  - potential for an impaired immune response in their newborns
    - live vaccinations should be avoided in newborns with exposure to biologics for at least 6 months

TNF-alpha inhibitors

- prospective, observational, multicenter cohort study
  - European Network of Teratology Information 1993 – 2013
    - 455 pregnancies exposed to TNF-alpha inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab)
    - 1532 control subjects - without disease
    - patients exposed to TNF-alpha inhibitors had:
      - moderately increased risk of birth defects
      - increased risk of preterm birth and low birth weight
    - could not attribute these findings to disease vs. medication

Bi慢性 inflammatory disease and pregnancy

- 2 population-based health registries - infants born to mothers with chronic inflammatory disease
  - birth defects were slightly more common in those infants who were born to mothers with chronic inflammatory disease regardless of whether they were treated with anti-TNF agents

Birth outcomes

- Link between psoriasis severity and development of adverse birth outcomes


TNF-alpha inhibitors

- Review of 105 articles on anti-TNF agents in patients with IBD and pregnancy
  - anti-TNF agents - safe during pregnancy (Khan 2016)
  - Effect of infliximab, adalimumab, etanercept on pregnancy compared with the general population
  - no significant differences in the number of live-born infants, miscarriages, terminations, or congenital abnormalities (Closeau 2010)


PIANO (Pregnancy in IBD Neonatal Outcomes) registry

- In utero IBD drug exposure and developmental milestones to age 4 yrs of 1,039 live births
  - Immunomodulators (AZA or 6-MP) n=215
  - TNF blockers (infliximab, adalimumab) n=364
  - Combination therapy (immunomodulators and anti-TNF) n=337
  - Unexposed n=323

Infants exposed to drugs achieved equivalent scores for all developmental milestones compared with unexposed infants


etanercept

- TNF-alpha inhibitor
- Multiple studies (cohorts, case controls, registry data, case reports/series) of >300 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls

Carter et al. 2006 proposed a causal relationship between TNF-alpha inhibitors and VATER abnormalities - mother was receiving etanercept

Carter et al. 2009 proposed a causal relationship between TNF-alpha inhibitors and VATER based on review of FDA database of birth defects
- Methodology was controversial
- Further evaluation of larger registries failed to confirm this association


etanercept

- Case report (Carter, et al. 2006) - vertebral, anal, tracheal, esophageal, and renal (VATER) abnormalities - mother was receiving etanercept
- Carter et al. 2009 proposed a causal relationship between TNF-alpha inhibitors and VATER based on review of FDA database of birth defects
- Methodology was controversial
- Further evaluation of larger registries failed to confirm this association


adalimumab

- TNF-alpha inhibitor
- Multiple studies (cohorts, case controls, registry data, case reports/series) of >500 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls


adalimumab – animal data

- Embryofetal perinatal development study conducted in monkeys
- No fetal harm or malformations with IV adalimumab during organogenesis and later in gestation, at doses up to 373 times maximum human SQ dose 40 mg

Pregnancy and Newborn Outcomes adalimumab

- OTIS prospective, observational, exposure cohort study
- Pregnant RA exposed to drug (n=74) compared with pregnant women with RA not exposed to drug (n=80), and with a healthy pregnant women cohort (n=219)
  - 74 pregnant women in drug group
    - 40% used drug during 1st trimester only
    - 16% used drug for 2 trimesters
    - 44% used drug throughout pregnancy
  - No significant differences in frequencies and relative risk (RR) of major birth defects between the drug-exposed RA group, unexposed RA group, and healthy cohort

adalimumab

- OTIS prospective cohort study
  - 114 women with Crohn’s exposed to drug 1st trimester
  - 13 pregnant women with Crohn’s not taking drug
  - 141 pregnant healthy women
- No difference in the rate of pregnancy outcomes after controlling for maternal disease activity

infliximab

- TNF-alpha inhibitor
- Multiple studies (cohorts, case controls, registry data, case reports/series) of > 1000 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls

ustekinumab

- IL-12/23 inhibitor
- Limited data in pregnant women from observational studies
- Few published case reports, limited registry data – insufficient to inform a drug associated risk
  - No increased risk of congenital defects or miscarriage

ustekinumab

- Janssen safety database through July 8, 2015 (clinical trials and post-marketing data)
- Maternal exposure to ustekinumab for PsO or PsA during pregnancy or < 2 months before conception
  - 87 patients (86 PsO, 1 PsA)
    - 53% (46/87) drug exposure during the 1st trimester only
  - No increased risk of congenital defects or miscarriage
- Percentages of congenital anomalies, spontaneous abortions, and preterm births are consistent with rates in U.S. general population


secukinumab

- FDA approval: PsO, PsA, ankylosing spondylitis
- IL-17 inhibitor
- No human studies
- Studies in mice and monkeys show no embryo-fetal toxicity

secukinumab

- Novartis global safety database (clinical trials and postmarketing data through Dec. 25, 2015)
  - 21,500 patient-years
- All cases of pregnancy with either maternal or paternal exposure to secukinumab
  - 84 pregnancies

secukinumab

- 65 (77.3%) pregnancies after maternal exposure
- 19 (22.6%) pregnancies after paternal exposure
- In all cases after maternal exposure, drug was discontinued
- Of 19 cases of paternal exposure
  - 9 cases continued drug
  - 10 cases -- information not available
- Median exposure to drug before conception -- 186 days
- Median time to discontinuance of drug after conception -- 26 days

secukinumab

- All cases carried to term led to delivery of a normal neonate -- no reports of congenital malformation
- Rate of spontaneous abortion -- within expected range, with all cases occurring within the 1st trimester

ixekizumab

- IL-17A inhibitor
- No human studies
- ixekizumab crosses the placenta in monkey
- 1 study in monkeys shows no effect on fetus when drug was given during the 1st 20 weeks of gestation
  - Exposure from week 20 - birth showed an increase in neonatal deaths
  - Due to circumstances considered drug (maternal neglect, premature)
  - No effects on infants’ immune system or maturation at age 6 months
- Drug exposure during pregnancy showed no effects on fetal or infant development, including immune function

ixekizumab

- Lilly Safety Systems database
  - 1359 female pts were exposed to ixekizumab in 7 clinical trials
    - 18 pregnancies
    - All maternal exposures to drug in 1st trimester
    - No congenital abnormalities
  - 2850 male pts were exposed to ixekizumab in 7 clinical trials
    - 40 pregnancies
    - No congenital abnormalities
- Pregnancy outcomes with drug exposure consistent with US epidemiologic data
certolizumab

- FDA approval: PsA, ankylosing spondylitis
- TNF-alpha inhibitor
- Multiple studies (cohorts, case control, case reports/series) of >300 pregnancies show no increase in miscarriage or congenital malformation
- Low levels in cord blood, suggesting minimal active transplacental transport

- PASI 75 at week 16
  - 400 mg, 76%
  - 200 mg, 67%
- Pegylated antigen-binding fragment (Fab) antibody that lacks Fc region
- Cannot be actively transported by Fc receptor on placenta
- Case series of 13 pts with rheumatic dz on drug throughout pregnancy
- Cord blood in late pregnancy between 0–1 μg/ml
- Maternal levels of 33 μg/ml
- Suggests that certolizumab may be used during pregnancy without exposure to newborn


- Breast milk
  - 18 mothers
  - Patient at least 6 weeks postpartum
  - Highest concentration of drug in breast milk ~ 1% of expected plasma trough concentration of a therapeutic dose
  - Daily dose ingested by infants is minimal.
  - AEs in infants comparable to untreated population of same age

Clowse et al. Evaluating transfer of certolizumab pegol into breast milk: results from a prospective, postmarketing, multicenter pharmacokinetic study. Poster AAD 2017

**Biologic safety in pregnancy**

- No well-controlled trials have studied the effects of biologics during pregnancy
- Literature suggests that biologics can be used for psoriasis during pregnancy and breastfeeding
  - TNF-alpha inhibitors can be used during the first half of pregnancy
  - TNF-alpha inhibitors should be considered over IL-12/23 and IL-17 inhibitors due to more long-term data
- Longer-term use of TNF-alpha inhibitors during pregnancy can be considered depending on psoriasis severity
- If biologics are required throughout the pregnancy, certolizumab should be considered because it does not cross the placenta in significant amounts
- Etanercept may also be a reasonable alternative because its placental transfer is less than adalimumab or infliximab
- Babies born to mothers who are continually receiving biologics should not receive live vaccinations ≤ 6 months due to increased risk of infection
Breastfeeding and biologics

- very little to no risk to breastfed infant
  - minimal amounts of TNF-alpha inhibitors in breast milk
  - infant gastric digestion
- This safety profile is likely generalizable to IL-12/23 and IL-17 inhibitors.

Summary

- TNF-alpha inhibitors are safe in the 1st half of pregnancy
  - if biologics are given throughout pregnancy, certolizumab can be considered because it does not cross placenta in significant amounts
  - etanercept may also be a reasonable alternative because its placental transfer is less than adalimumab or infliximab
- if TNF-alpha inhibitors are given throughout pregnancy, baby needs to avoid live vaccines for 6 months
- Biologics are safe during breastfeeding

Thank you!

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