# Safety of Biologics for Psoriasis in Pregnancy

Sylvia Hsu, M.D.
Professor and Chair
Department of Dermatology
Temple University School of Medicine

## 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

## Pregnancy

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

## Biologics for psoriasis

- 2013
  - 25% of psoriasis patients on biologics
    - adalimumab
    - etanercept

Armstrong et al. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. JAMA Dermatol 2013;149(10):1180-5.

## Biologics during 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

## 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
    - all others - recommended to continue anti-TNF throughout the pregnancy

Levy RA, et al. Critical review of the current recommendations for the treatment of systemic inflammatory rheumatic diseases during pregnancy and lactation. Autoimmun Rev 2016;15:953–63.
van der Woude CJ et al. IBD: Exposure to anti-TNF agents in utero: Controlling health risks. Nat Rev Gastroenterol Hepatol 2016;13:387–8.
Nguyen GC, et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. Gastroenterology 2016;150:734-57.

## 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
    - 495 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

Weber-Schoendorfer C, et al. Pregnancy outcome after TNF-α inhibitor therapy during the first trimester: A prospective multicentre cohort study. Br J Clin Pharmacol 2015;80:727–39.

## Chronic 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

Bröms G, et al. Low risk of birth defects for infants whose mothers are treated with anti-tumor necrosis factor agents during pregnancy. Clin Gastroenterol Hepatol 2016;14:234.e1-5–41.e1–5.

## Birth outcomes

- link between psoriasis severity and development of adverse birth outcomes

Bobotsis R, et al. Psoriasis and adverse pregnancy outcomes: A systematic review of observational studies. Br J Dermatol 2016;175:464–72.

## TNF-alpha inhibitors

- Review of 105 articles on anti-TNF agents in patients with IBD and pregnancy
  - anti-TNF agents - safe during pregnancy (Khan 2014).
- 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 (Clowse 2010).

Khan N, Asim H, Lichtenstein GR. Safety of anti-TNF therapy in inflammatory bowel disease during pregnancy. Expert Opin Drug Saf 2014;13:1699–708.
Clowse ME. The use of anti-TNFα medications for rheumatologic disease in pregnancy. Int J Womens Health 2010;2:199–209.

## TNF-alpha inhibitors

- PIANO (Pregnancy in IBD Neonatal Outcomes) registry
  - *in utero* IBD drug exposure and developmental milestones to age 4 yrs -- 1,039 live births
    - immunomodulators (AZA or 6-MP) n = 215
    - TNF blockers (adalimumab, infliximab, certolizumab) n=364
    - combination therapy (immunomodulators and anti-TNF) n=137
    - unexposed n=323
  - Infants exposed to drug(s) achieved equivalent scores for all developmental milestones compared with unexposed infants

Mahadevan U, Martin CF, Chambers C, et al. Achievement of developmental milestones among offspring of women with inflammatory bowel disease: the PIANO Registry [abstract 1]. *Gastroenterology.* 2014b;146( 5 )( suppl 1 ):S. 1.

## 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

## 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

Carter JD, et al. Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. J Rheumatol 2006;33:2014–7.
Carter JD, et al. A safety assessment of tumor necrosis factor antagonists during pregnancy: A review of the Food and Drug Administration database. J Rheumatol 2009;36:635–41.
Koren G, Inoue M. Do tumor necrosis factor inhibitors cause malformations in humans? J Rheumatol 2009;36:463–6.
Verstappen SM, et al, BSRBR Control Centre Consortium BSRBR. Anti-TNF therapies and pregnancy. Outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:823–6.

## 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

- embryo-fetal 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

Burmester et al. Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2017; 76(2): 414-417.

## 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

Johnson et al. Pregnancy outcomes in women exposed to adalimumab: an update on the OTIS Autoimmune Diseases in Pregnancy Project [poster]. Poster presented at: 75th Annual Scientific Meeting of the American College of Rheumatology, November 4-9, 2011, Chicago, IL.

## 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

Götestam Skorpen C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016;75:795–810.

## 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
  - 8% (7/87) drug exposure in all 3 trimesters
- Percentages of congenital anomalies, spontaneous abortions, and preterm births are consistent with rates in U.S. general population

Naurekas S et al. Pregnancy outcomes in women with psoriasis and psoriatic arthritis exposed to ustekinumab. Poster P3106 presented at: 74th Annual Meeting of the AAD; March 4-8, 2016, Washington, DC.

## 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

Warren R, et al. 25th Congress of EADV, 28 September–2 October 2016, Vienna, Austria. Poster P2134.

## 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 unrelated to drug (maternal neglect, trauma)
  - 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

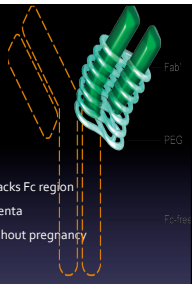
## ixekizumab

- 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

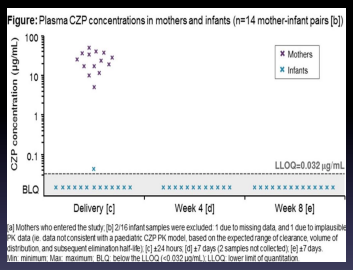
- FDA approval: PsA, ankylosing spondylitis
- TNF-alpha inhibitor
- Multiple studies (cohorts, case control, case reports/ series) of >300 pregnancies show no increase in miscarriage or congenital malformation
- low levels in cord blood, suggesting minimal active transplacental transport

# certolizumab




- 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

Förger et al. Certolizumab treatment during late pregnancy in patients with rheumatic disease. Low drug levels in cord blood but possible risk for maternal infections. A case series of 13 patients. Joint Bone Spine 2016; 83(3): 341-3.




**certolizumab**

Mariette et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, multicenter, pharmokinetic study. Ann Rheum Dis 2017; 76 (Supp 2): OP0017

# certolizumab - 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 1st half of pregnancy
- TNF-alpha inhibitors should be considered over IL-12/23 and IL-17 inhibitors due to more long-term data

# Biologic safety in pregnancy

- 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 x 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.

Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. Am J Gastroenterol. 2013;108(9):1426-38.
Clowse ME. The use of anti-TNFα medications for rheumatologic disease in pregnancy. Int J Womens Health 2010; 2:119-209.

## 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!

sylvia.hsu@tuhs.temple.edu