SKIN HEALTH INSTITUTE

Pregnancy & Biologics

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Friday 23 April 2021

DISCLAIMER: The presenter declares that any potentially identifying patient information has been obtained with patient consent for the purposes of this presentation.

SPECIALIST TREATMENT EDUCATION & RESEARCH

Disclosure

- Advisory Boards – Janssen, Novartis, Sun-Pharma, Abbvie, Leo-Pharma

- Speaker/Chair for Novartis, Janssen

Australasian Journal of Dermatology

REVIEW ARTICLE

Psoriasis in those planning a family, pregnant or breast-feeding. The Australasian Psoriasis Collaboration

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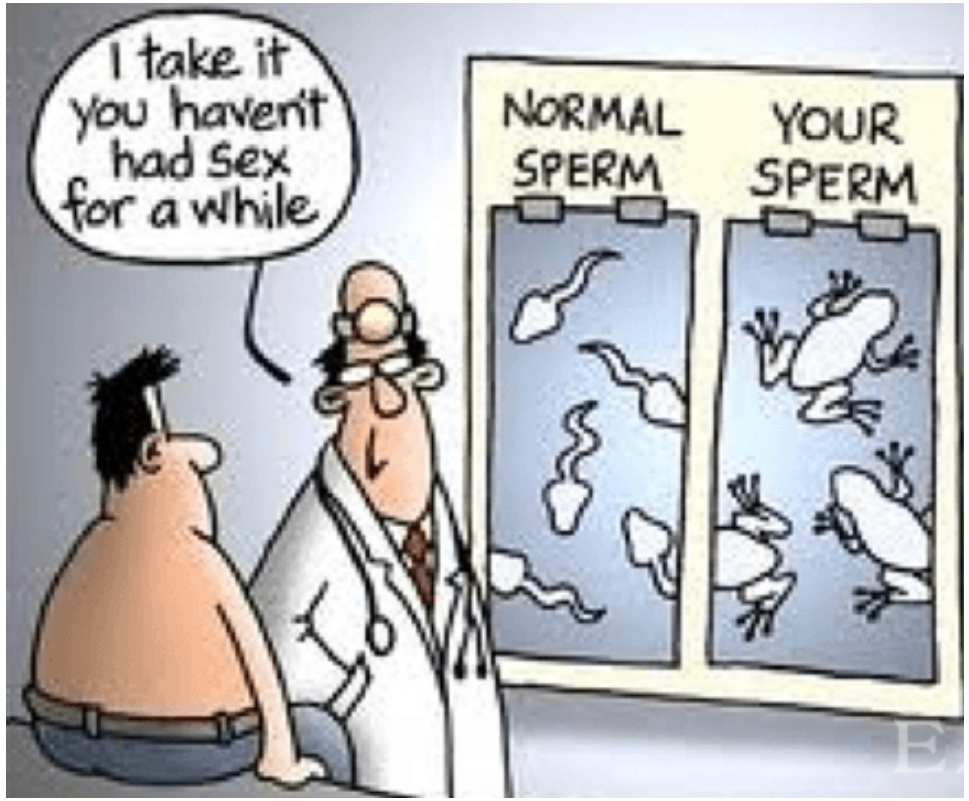
FROM THE ACADEMY

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics

Psoriasis, Systemic Therapies and Pregnancy / Lactation

- Peri-conception
- Early pregnancy
- Mid-late pregnancy
- Breast feeding
- Effects on the neonate



Background

- Psoriasis is not known to have a significant impact on fertility, either male or female

- 50% pregnancies are unplanned

Background

- Limited evidence available suggests that psoriasis usually improves significantly during pregnancy:
  - 55% improve (range 33–60%)
  - 25% report no change, and
  - 25% worsen
  - Conversely after childbirth, psoriasis is likely to flare over the subsequent weeks:
  - 65% worsen (range 40–88%)
  - 25% no change
  - 10% improve
  - For patients with psoriatic arthritis, 80% improve or remit during pregnancy, while 70% flare post-partum

Effect of psoriasis on pregnancy

- The data on pregnancy outcomes are conflicting
- Some studies have suggested there is a possible increase in preterm and low birthweight babies along with spontaneous and induced abortions
- However, other studies in psoriasis show no significantly increased risks of birth defects or other adverse pregnancy outcomes

Context

- Baseline risk for a live born baby to have a major birth defect is 3%
- Risk of a significant neurodevelopmental problem, which may not become apparent until later in life, is 5% of all live births
- In half of these the cause is unknown, 25% are multifactorial, over 10% are chromosomal, 8% are single gene disorders, 3% are maternal illness, including infection, and only 2–3% are attributable to medications or chemicals

Drugs and pregnancy

Category A	The safest drugs to take during pregnancy. No known adverse reactions.
Category B	No risks have been found in humans.
Category C	Not enough research has been done to determine if these drugs are safe.
Category D	Adverse reactions have been found in humans.
Category X	Should never be used by a pregnant woman.

Drugs and pregnancy

ADEC

Category A	Large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed
Category B1	Limited number of patients but no effect Animal studies – no effect demonstrated
Category B2	Limited number of patients but no effect Animal studies – inadequate or lacking, but no effect demonstrated
Category B3	Limited number of patients but no effect Animal studies - evidence of an increased occurrence of fetal damage, but significance uncertain in humans
Category C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.
Category D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. May have adverse pharmacological effects.
Category X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy

Outcomes

Unfavourable Global Pregnancy Outcome	• Spontaneous or elective abortion • Pregnancy ending before gestational week 37 • Presence of obstetric complications • Low birth weight • ICU admission • Congenital malformations • Death
Unfavourable Pregnancy Outcomes	• Onset of complications during pregnancy
Unfavourable Neonatal Outcomes	• Low birth weight • ICU admission • Congenital malformations • Death

Evidence-based obstetric drug information

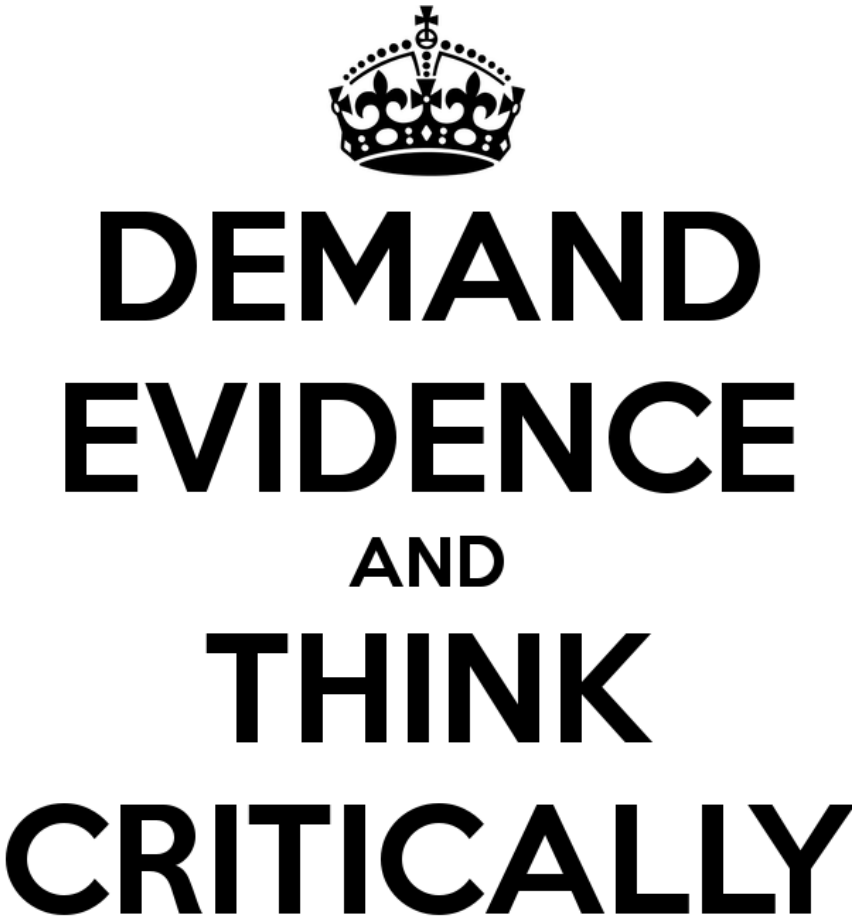
- MotherSafe - www.mother safe.org.au
- www.motherisk.org
- www.mother tobaby.org
- www.toxnet.nlm.nih.gov)

New drugs in pregnancy/lactation

- No clinical trials (strict contraception)
  - Animal studies
  - Post-marketing reports
- Case reports
  - Don’t capture denominator
  - Under-report
  - Selective reporting
- Registry data

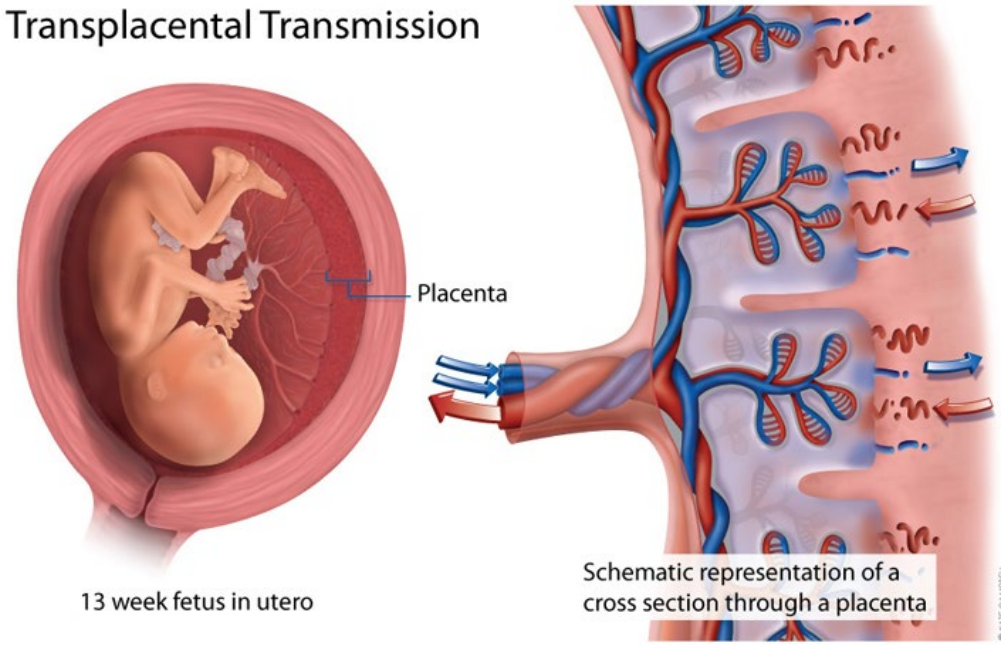
Evidence

- Most evidence is in gastroenterology and rheumatology use
- In psoriasis – most just small case series and some registry data



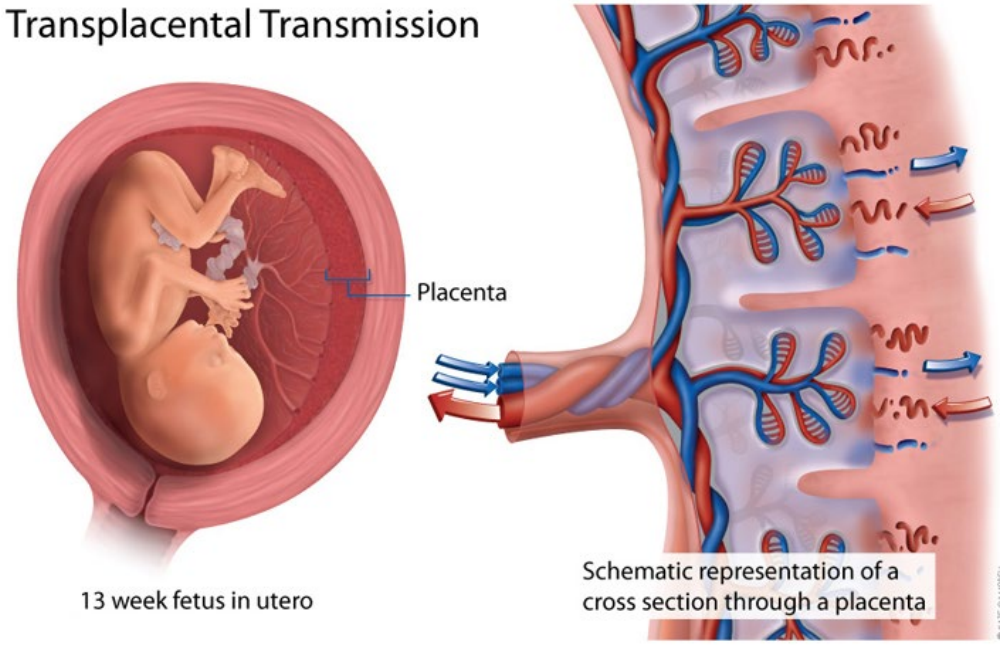
Transplacental transfer

- Antibodies >100kDa
  - Simple diffusion of monoclonal Abs unlikely to occur
- Maternal IgG Ab cross the placenta
  - Majority of Ab in a newborn are of maternal origin
  - Levels often exceed maternal levels



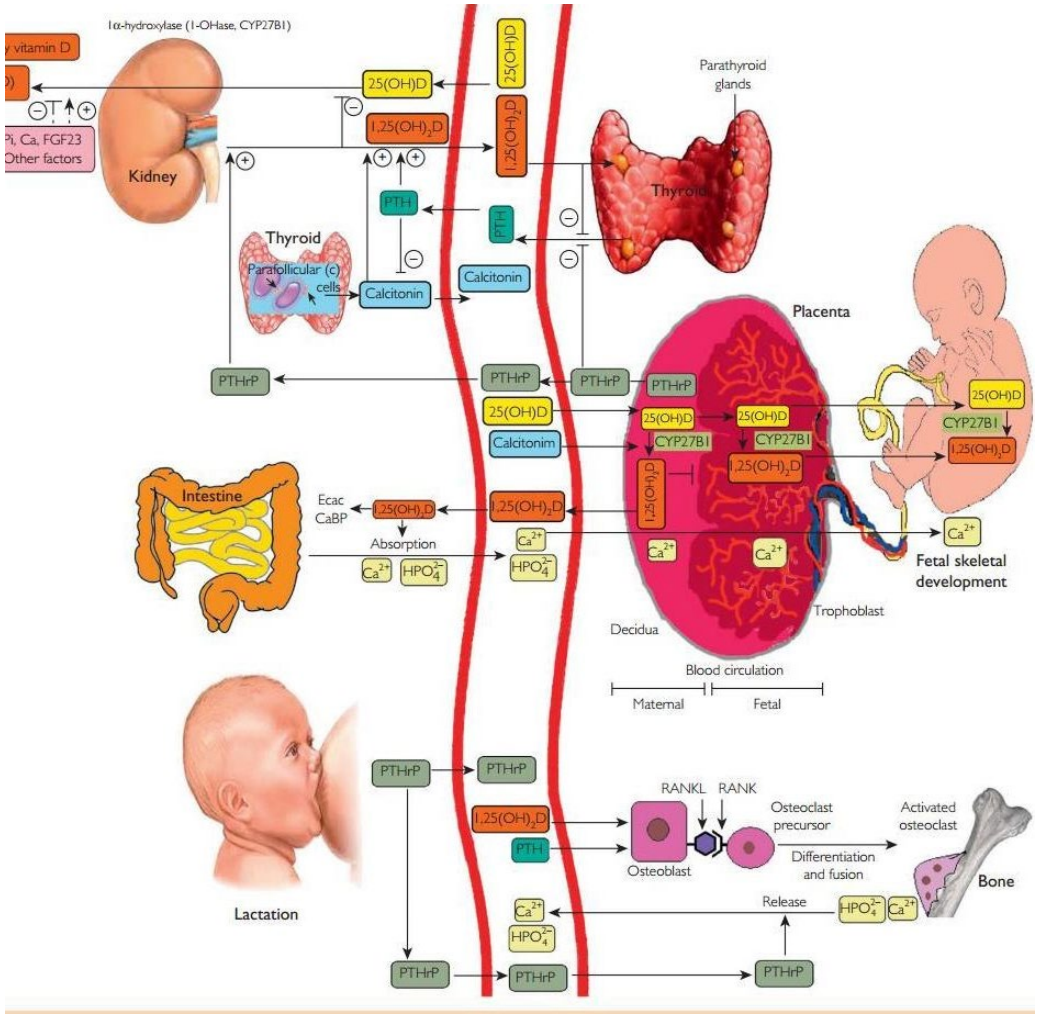
Transplacental transfer

- Antibodies rely on active transport
  - Via Fc receptors on trophoblasts (start to develop T2 (wk 14)
  - Active transport begins in T2 and rapid increases over T3
- Conception
  - Limited exposure to maternal abs
- Organogenesis
  - Limited exposure to maternal abs



Transplacental transfer

- Biologics for psoriasis are monoclonal abs
  - (Except etanercept - receptor-Ab fusion protein and certolizumab - pegylated monoclonal antibody lacking an Fc moiety)
- Animal studies
  - Behave like maternal abs



Antibody exposure to the foetus

- The monoclonal biologics do not all cross the placenta equally
- Immunoglobulin (Ig)G1 (adalimumab, infliximab, secukinumab, ustekinumab, guselkumab, tildrakizumab, risankizumab) and IgG4 (ixekizumab) monoclonal antibodies are likely to cross the placenta to a similar extent, with preferential transport of IgG1 over IgG4
- Infliximab and adalimumab levels were higher in infants at birth than in the maternal circulation (median 160 and 153% of maternal levels), and were detectable for up to 6 months after birth

Antibodies and the foetus

- Certolizumab, a pegylated monoclonal antibody lacking an Fc moiety, crosses the placenta by passive transfer, with median levels of 4% of mothers' blood levels

- Etanercept, a receptor-antibody fusion protein, which includes the Fc domain of human IgG1, is present at much lower levels in neonatal cord blood (2.5–3.3% of maternal levels), and rapidly declines in the weeks after birth, even with breast-feeding

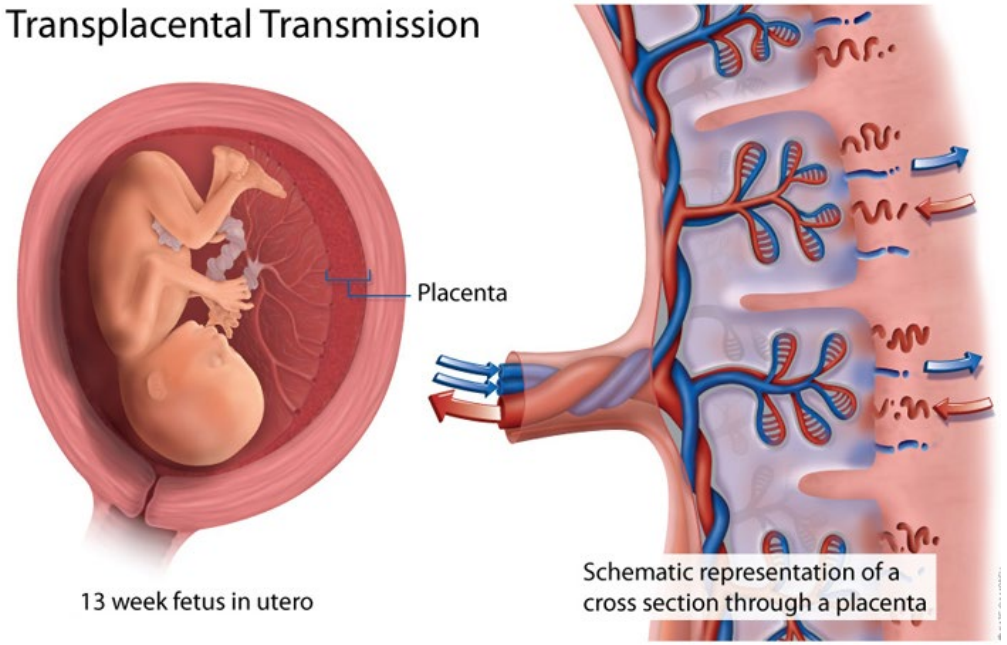
Any evidence of harm?

Risks of biologics

- There are three main risk considerations in using biologics during pregnancy:
  - Teratogenicity and malformations (early pregnancy)
  - Foetal and neonatal immunosuppression and immune development (last trimester to 6 months of age)
  - Increased maternal immunosuppression (particularly later pregnancy)

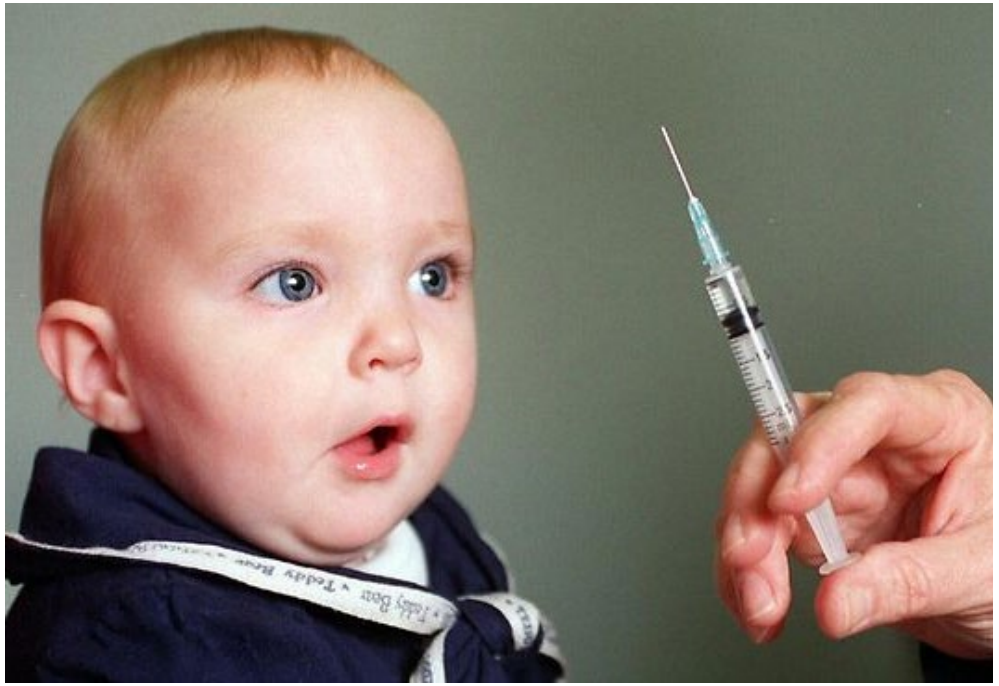
Transplacental transfer

- Rituximab
  - Lymphopaenia at birth



Risks of *in utero* exposure

- Immune development in exposed fetus/neonate
  - Limited information
- Routine childhood vaccinations (e.g. DPT)
  - Safe and effective
    (but limited evidence)
- Live vaccines
  - Guidelines - wait 6/12
  - (Polio and rotavirus)
- Seek Immunology
  input if more urgent vaccinations required
  for travel



Immunosuppression in the neonate

- Caution needs to be taken with live vaccines (MMR, polio and rotavirus), following 3rd trimester foetal exposure to anti-TNF biologics

- The current recommendation is to delay live vaccines until the infant is 6–12 months of age. Alternatively, some experts recommend stopping the biologics after the 2nd trimester to reduce this risk

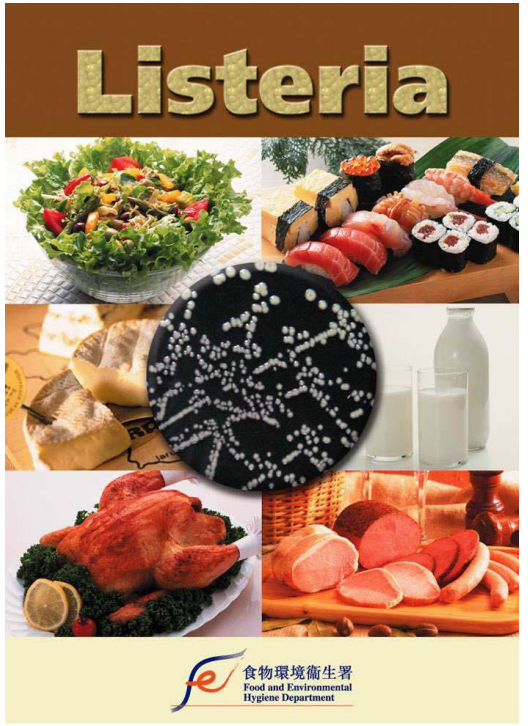
- Data for anti-IL-12 and IL- 23 are not yet available, so the precautionary approach would be to follow similar restrictions

Maternal immunosuppression

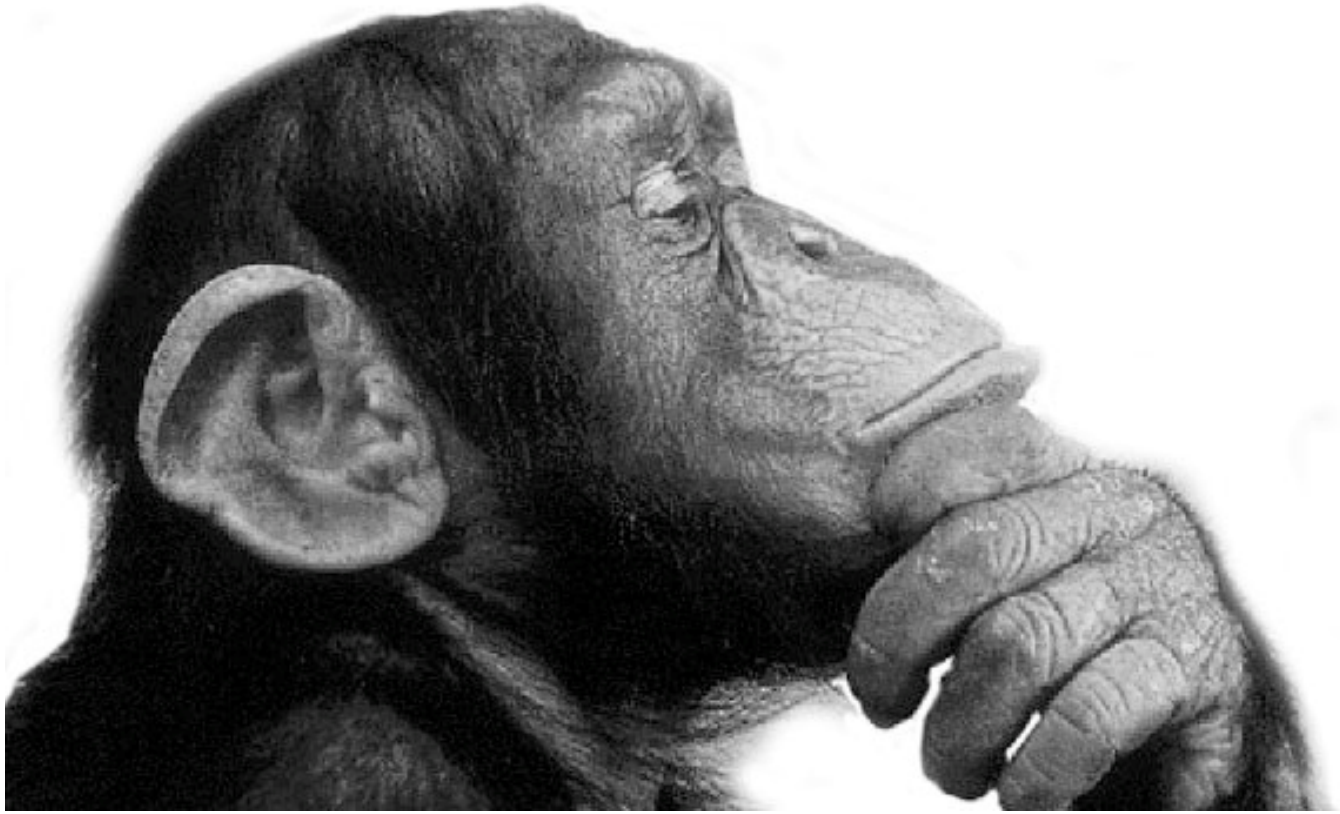
- Pregnancy is a state of relative immunosuppression and therefore there is a theoretical risk of serious and opportunistic maternal infections, particularly in the 3rd trimester

Risks to the pregnant patient

- Of special concern is the increased risk of *intracellular infections, such as Listeria monocytogenes*
- Guidance on safe food consumption during pregnancy should be reinforced (https://www.mpi.govt.nz/document- vault/3675).65



Let’s look at the safety of individual classes of biologics in the context of pregnancy….



FROM THE ACADEMY

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics

- TNF-a inhibitors are safe in pregnancy and during lactation
- TNF-a inhibitors are safe in men attempting conception with their partners Because of drug delivery to the fetus, neonates and infants should be considered immunosuppressed for at least 1-3 months (depending on the TNF inhibitor) postpartum in mothers who have been on TNF-inhibitors
- There is a greater theoretical risk with use during the third trimester of pregnancy owing to transplacental transfer of TNF-a inhibitors
- **Exception:** certolizumab pegol has shown minimal to no placental transfer

Menter A et al. *J Am Acad Dematol.* 2019.

Evidence

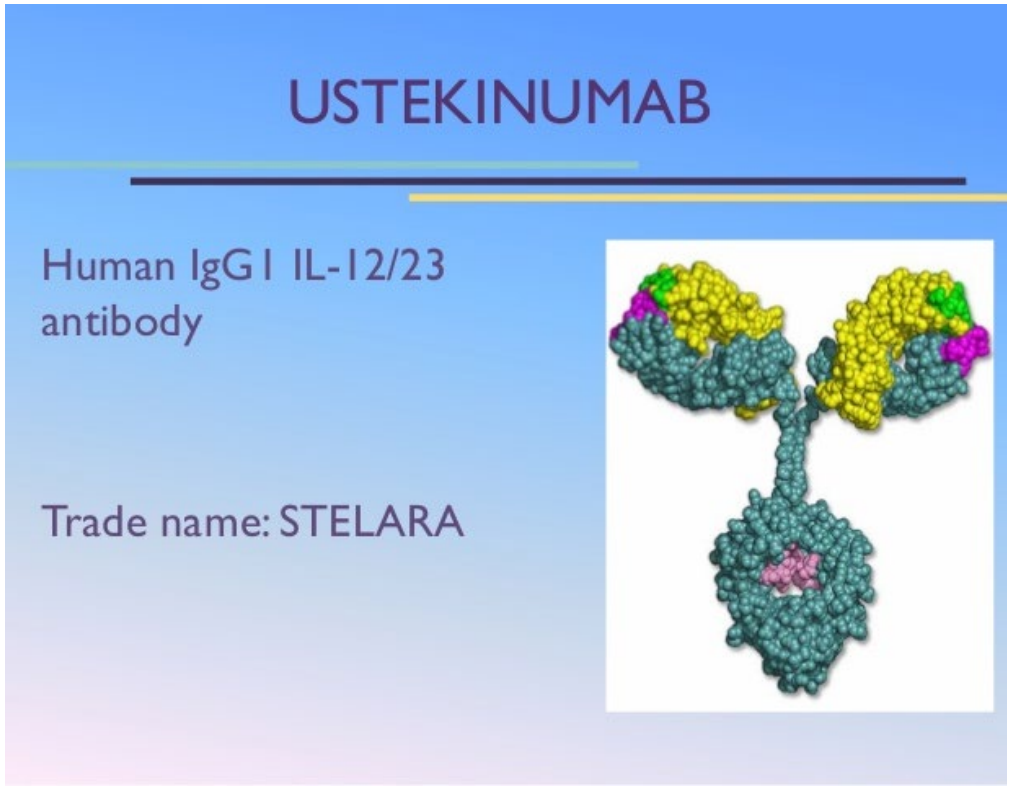
Anti-TNF summary

- Global pregnancy outcome
  - No difference in compared to disease controls
- Unfavourable pregnancy outcome
  - No difference in compared to disease controls
- Unfavourable neonatal outcome
  - May be increase in neonatal infections
  - May effect immunisation to 6/12 of age

Ustekinumab

ADEC B1

- Ustekinumab IgG1 monoclonal antibody binding to the p40 subunit of IL-12 and IL-23
  - Monkey studies
    - No evidence of maternal toxicity, embryotoxicity or teratogenicity
  - Female fertility
    - No studies, except in mice (no adverse effect)
  - Male fertility/mating
    - No effect in monkeys



Maternal Pregnancy Outcomes during Ustekinumab Studies (PHOENIX +ACCEPT)

- 981 female patients (473 CBA)
- 29 pregnancies (26 outcomes):
  - 14 live births (54%) /64.6%
  - 5 spontaneous abortions (19%) /17%
  - 7 elective abortions (27%) /18.4%
  - 3 cases with unknown outcomes

NPF/AAD 2019 Verdict on IL-12/23

- Pregnancy and lactation
  - The safety of IL-12/IL-23 inhibitors during pregnancy and lactation is uncertain
  - Il-12/IL-23 inhibitors are acceptable for men attempting conception with their partner

- Breast-feeding
  - No human data
  - As ustekinumab has a molecular weight of 149 000 kDa, the amount in milk is likely to be very low and absorption is unlikely because of its destruction in the infant's gastrointestinal tract

Secukinumab in pregnancy

Outcomes in psoriasis, psoriatic arthritis and ankylosing spondylitis from the global safety database

- Secukinumab is a human IgG1 monoclonal antibody that binds IL-17A.
- The Novartis global safety database covers any adverse events reported in all secukinumab indications and includes 11 140 clinical trial patients and 96 054 patient-years of post-marketing data.
- 292 pregnancies reported
  - 141 (48.3%) came from clinical trials
  - 79 (27.1%) were spontaneous reports
  - 72 (24.7%) were from post-marketing surveillance
  - 238 cases of maternal and 54 of paternal exposure (Table 1). The secukinumab dose was 300 mg in 125 patients (42.8%), 150 mg in 19 (6.5%) and unknown in 148 (50.7%).

Secukinumab global safety database

- Rates of spontaneous abortions overall (30 of 292, 10.3%) were in line with observed rates for the general population with the mean maternal age of 30.6 years (15–20%)
- Rates of spontaneous abortion for patients with known outcomes were 30 of 153 (19.6%), again in accordance with established rates
- Most spontaneous abortions occurred within 10 weeks of pregnancy and there were no stillbirths (> 20 weeks' gestation).

- The majority of patients (where known) discontinued secukinumab in the first trimester of pregnancy (155, 65.1%)
- 18 maternal cases who did not discontinue treatment, three of whom continued treatment throughout pregnancy or discontinued in the third trimester
- Within these 18 cases there were four elective terminations, three spontaneous abortions, one pregnancy ongoing, one healthy neonate and nine cases lost to follow-up or unknown

- Three congenital abnormalities were reported (three of 292, 1% overall; three of 153, 20% in patients with known outcomes), in line with the general population rate, and there was no pattern of abnormality

- Secukinumab was not suspected to be linked to any of these cases by the treating physician.

Conclusions on Cosentyx in pregnancy study

- Adds to what is known
- Limitations – small numbers and incomplete follow up
- Most ceased secukinumab in the first trimester

Breastfeeding

- Not known if secukinumab is excreted into breastmilk

Ixekizumab

- Ixekizumab is a humanized IgG4 monoclonal antibody that neutralizes IL-17A
- There are limited data on the use of ixekizumab in pregnant women
- In developmental toxicity studies, ixekizumab was shown to cross the placenta and was present in the blood of offspring up to 6 months of age
- Animal studies do not, as yet, indicate direct or indirect harmful effects with respect to pregnancy, embryonic or foetal development, parturition or post-natal development
- As there are no human data, ixekizumab is currently contraindicated during pregnancy

Summary of pregnancy and lactation

IL-17 Inhibitors (NPF/AAD)

- There are no studies on human pregnancy
- Animal studies with ***secukinumab*** have shown no harm to the developing foetus
- Animal studies with ***ixekizumab*** at higher doses than recommended have shown no harm to the developing fetus, but higher neonatal deaths were observed
- Animal studies with ***brodalumab*** at higher doses than recommended have shown no harm to the developing fetus
- All IL-17 inhibitors are likely acceptable for men attempting conception with their partner
- The presence of IL-17 inhibitors in excreted human milk has not been studied

What about Il-23 inhibitors?

- Tildrakiuzmab, Guselkumab and Risankizumab

Guselkumab

- Guselkumab is a fully human IgG1 lambda monoclonal antibody that blocks the p19 subunit of IL-23.
- There are no available data on TREMFYA use in pregnant women to inform a drug associated risk of adverse developmental outcomes
- In the phase II and phase III clinical trials pregnant patients were excluded
- Human IgG antibodies are known to cross the placental barrier; therefore, TREMFYA may be transmitted from the mother to the developing foetus

Guselkumab

- CLINICAL DATA Controlled Trials
- Pregnancy was an exclusion criterion in TREMFYA phase II and III
- VOYAGE 1 (48 wk) **– 2 pregnancies** in study subjects (one GUS and one ADA) and 4 partner pregnancies
  - No abnormal pregnancy outcomes were reported. Of the two maternal pregnancies, 1 outcome was normal and the other was unknown. Of the four partner pregnancies, 3 outcomes were normal and 1 was unknown.
- In the VOYAGE 2 study (48 wk)**, 2 pregnancies** were reported on
  - The pregnancies were ongoing at time of the study report.
  - Three partner pregnancies were reported in VOYAGE 2 (1 each for a partner of a subject randomised to guselkumab, for the partner of a subject randomised to placebo but crossed over to guselkumab prior to the pregnancy, and one partner of a subject randomised to adalimumab who was withdrawn from therapy.)
  - One resulted in normal delivery, one was ongoing at the time of the report, and one was unknown.

Tildrakizumab

- Tildrakizumab is a humanized IgG1, monoclonal antibody designed to selectively block IL- 23 by binding to the p19 subunit.

- ACD Poster:
  - Among 528 female patients who received tildrakizumab through phases 1 to 3, 14 pregnancies were reported Pregnancies occurred in patients for whom contraception failed (n = 6) and patients who did not use contraception (n = 8)
  - Reported pregnancies included 2 in the phase 1 trials (P05661: n = 1; P05839: n = 1) and 12 in the phase 2/3 trials (P05495: n = 2; reSURFACE 1: n = 5; reSURFACE 2: n = 5)
  - Tildrakizumab treatment was discontinued in all cases after confirmation of pregnancy

Tildrakizumab

- The duration of exposure to tildrakizumab in patients who became pregnant was variable
- Outcomes were reported for all 14 pregnancies that occurred during the clinical development program of tildrakizumab
- Pregnancy outcomes included 6 cases of foetal loss (2 spontaneous abortions [14.3%] and 4 elective abortions [28.6%]) and 7 full-term and 1 premature live births with no identifiable congenital anomalies (57.1%)

Tildrakizumab

- All of the pregnancies that continued to full term resulted in healthy babies with no congenital anomalies
- The rate of spontaneous abortion (14.3%) was similar to that seen in the general population (12%–15%)5
- Additional data from a larger number of outcomes following tildrakizumab exposure are required to fully evaluate the safety and tolerability of tildrakizumab in pregnancy

Risankizumab

- **Fertility**
  - No effects on male cynomolgus monkey
  - Not directly assessed in female monkeys
  - No human data
- **Pregnancy Category B1**
  - Limited data are insufficient to inform any drug-associated risks
- Should be used in pregnancy only if benefits outweigh risks
- Enhanced pre- and post-natal developmental toxicity study in cynomolgus monkeys
  - No observed effects on growth/development/no malformations
- Unknown if excreted into breast milk

Summary of IL-23 inhibitors

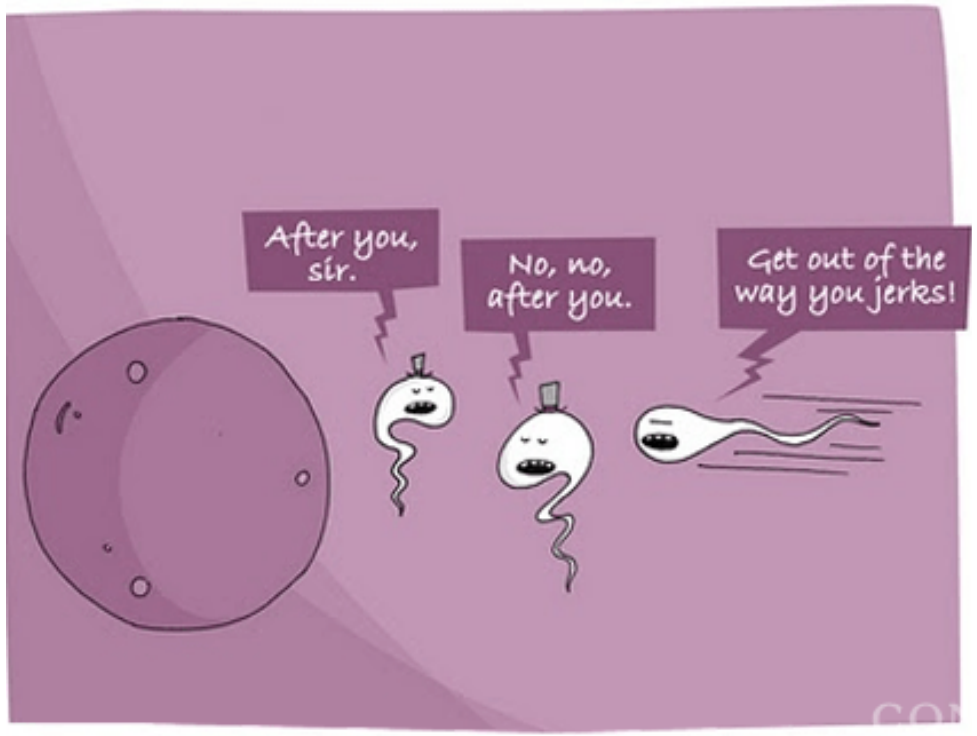
- Pregnancy and lactation
- Safety during pregnancy for IL-23 inhibitors is unknown
- The presence of IL-23 inhibitors in secreted human milk has not been studied; however, antibodies are effectively secreted during lactation and caution is recommended.

Biologics and breastfeeding

- Not known what quantity of milk each child consumes
- Not known how much proteolytic digestion occurs
- Not known the degree of absorption of any drug

Biologic therapies in fathers - Fertility

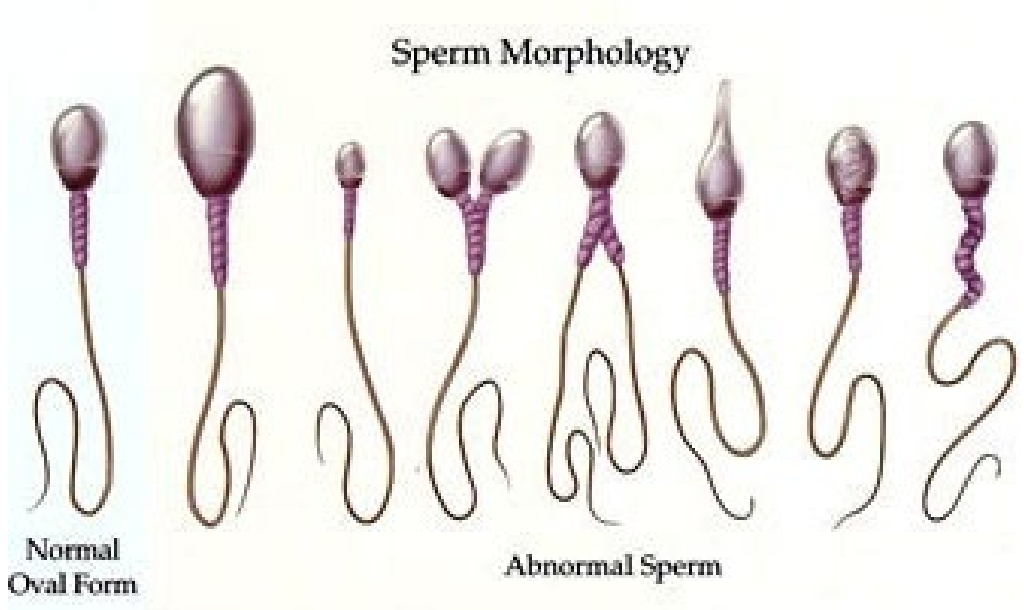
- Limited published experience in men
- Sperm quality – 25 men (ADA, ETN, IFX)
  - No differences vs healthy controls
  - Sperm count and motility may even be improved



How the gentlemen died out.

Paternal anti-TNF exposure

- No evidence
  - Spontaneous abortions
  - Adverse events such as premature delivery
  - Cong. abnormalities
- 25 pregnancies (20 fathers)
  - 23 healthy babies
  - 1 miscarriage
  - 1 therapeutic T1 termination for hydrocephalus (Dad on MTX)



Paternal pregnancy outcomes during Ustekinumab Studies

PHOENIX 1+2

- 40 partner pregnancies
  - 31 live births
    (1 polydactyly)
  - 3 spontaneous abortions
  - 1 elective abortion
  - 3 continuing pregnancies
  - 2 unknown

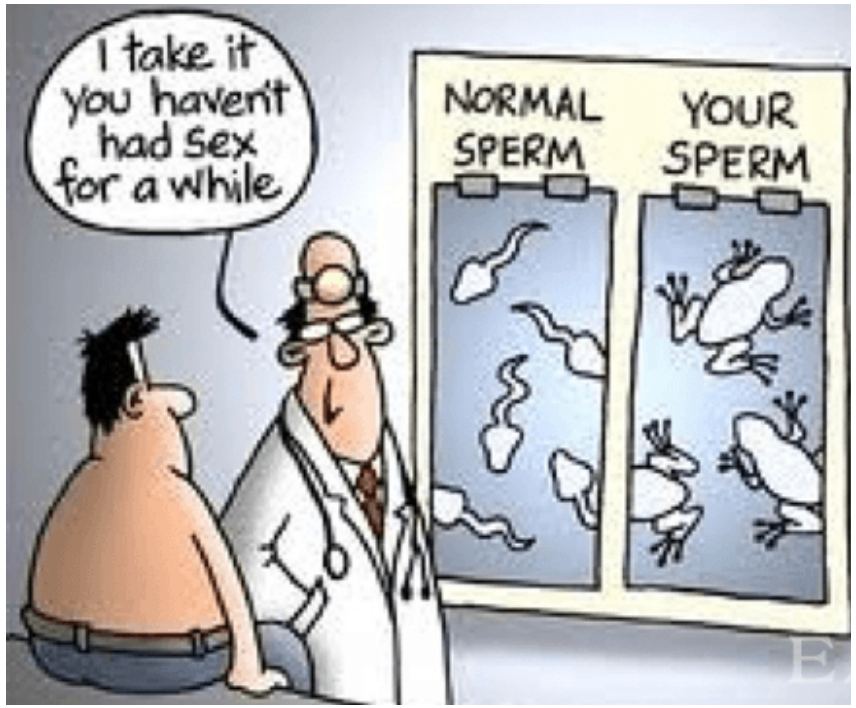
Conclusions
Pregnancy

- No difference - infliximab/adalimumab/etanercept
- Safe peri-conceptually
- Safe in early pregnancy
- Recommended to suspend < week 23 to avoid transplacental transfer
- Delay immunisation in neonate to 6/12 at least
- Not enough evidence for other biologics

Conclusions

Breastfeeding

- Few case reports
  - No negative impacts noted
- Not enough evidence for other biologics
- JAAD 2014 – “The biologic medications are likely compatible for use while breast-feeding”
- BAD 2014 – ”breast-feeding should be contraindicated in any woman on a biologic until further evidence is available”



Key messages

- All babies are precious, and data now mandates that we should approach this topic early in our female psoriasis patients of child-bearing age

CONTACT

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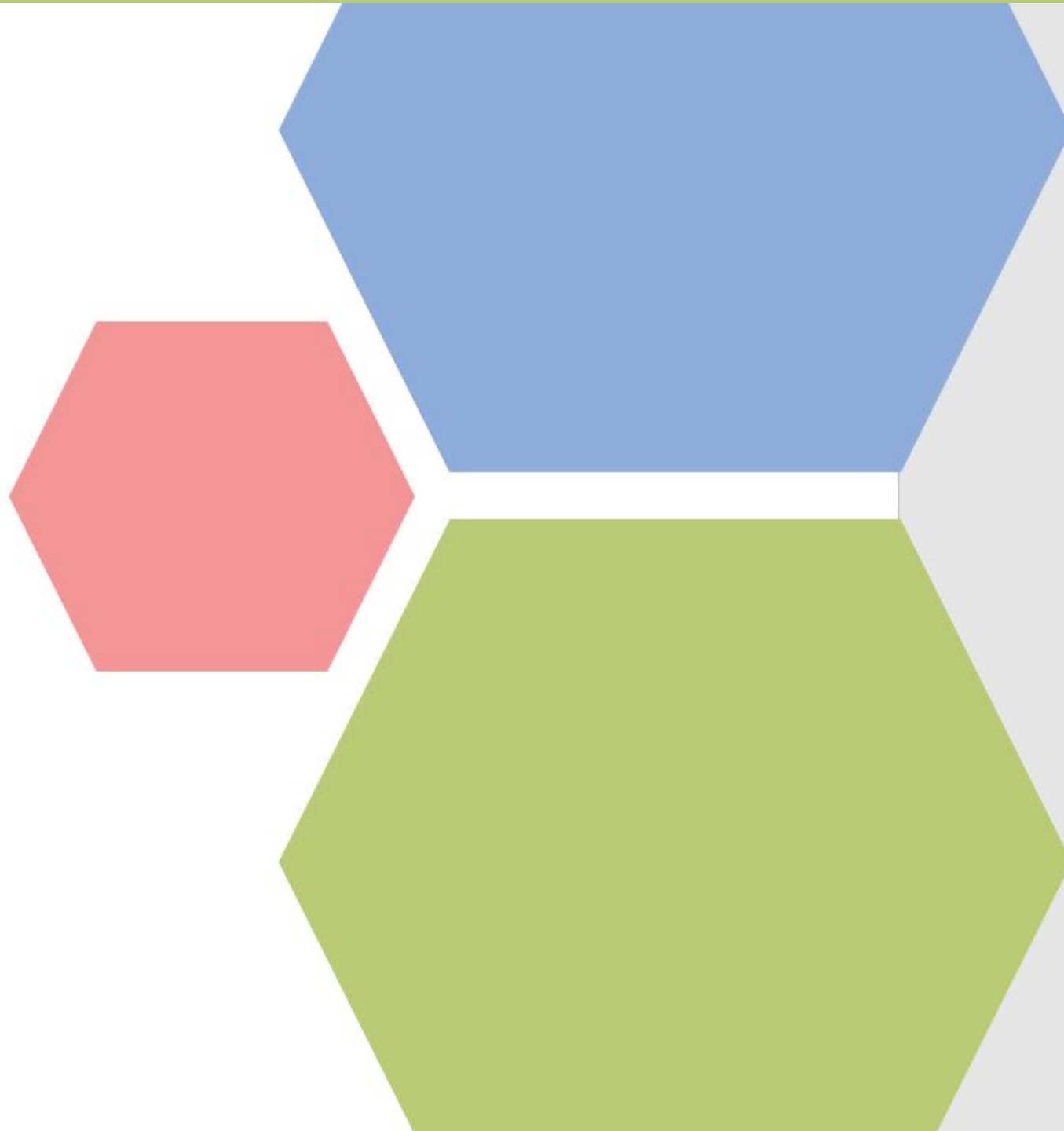

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