

# Mechanisms of placental transfer for small molecules and biologics

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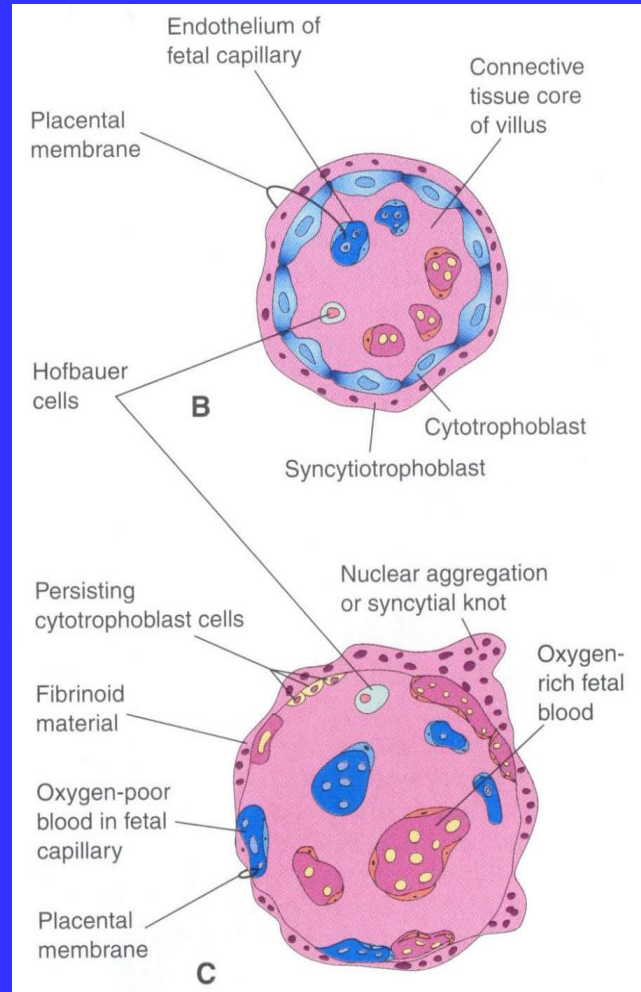
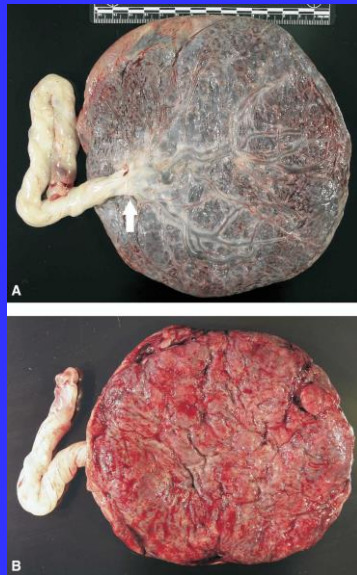
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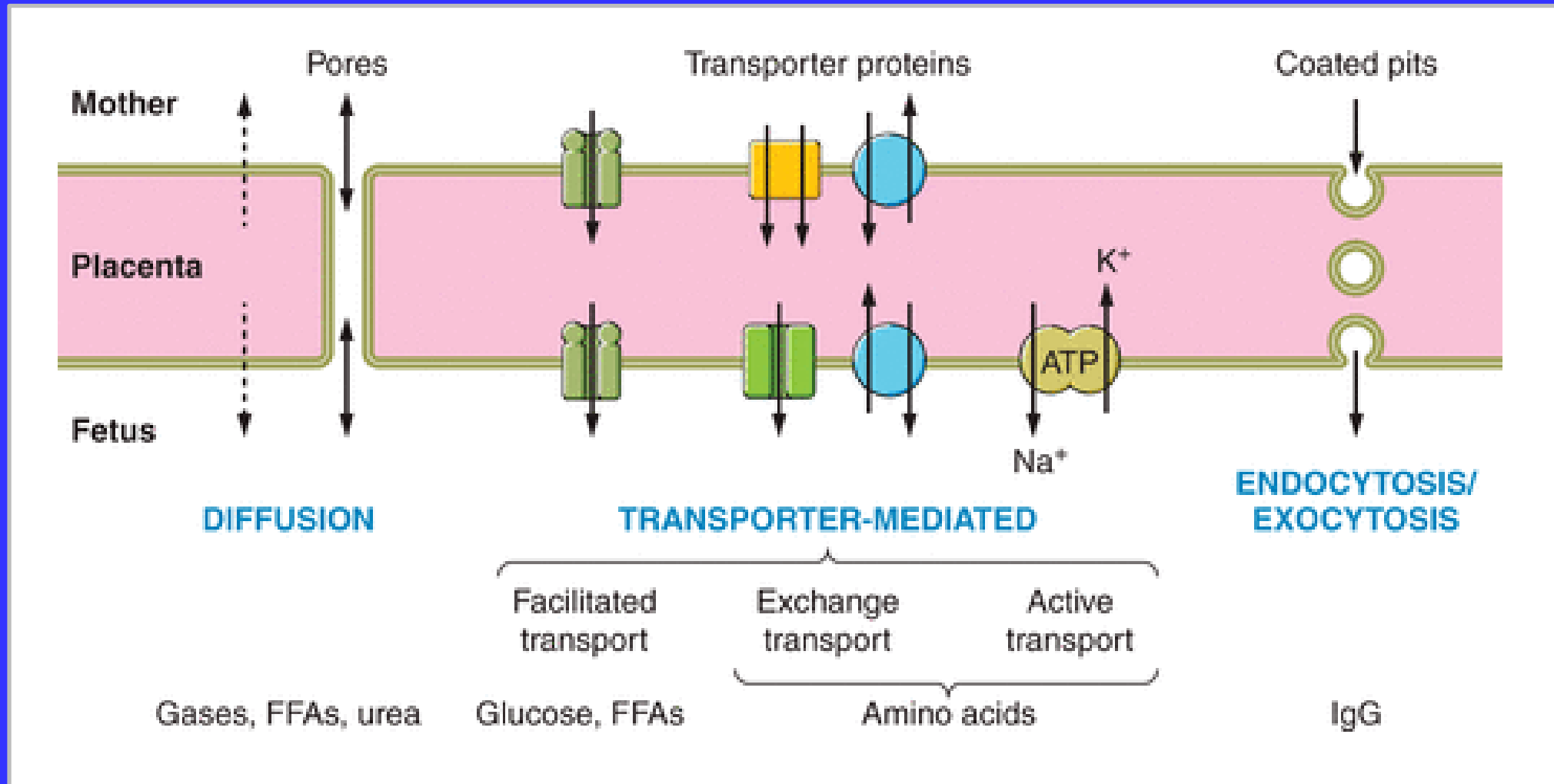
**I have no conflicts of interest**

# The placenta – not just a conduit



	6 weeks	Term
<b>Fetal/Placental Weight Ratio</b>	<b>0.18</b>	<b>7.23</b>
<b>Villous volume occupied by vessels (%)</b>	<b>2.7</b>	<b>28.4</b>
<b>Trophoblast Surface area (m<sup>2</sup>)</b>	<b>0.08</b>	<b>12.5</b>
<b>Mean Trophoblast Thickness (μm)</b>	<b>18.9</b>	<b>4.1</b>
<b>Maternofetal Diffusion Distance (μm)</b>	<b>55.9</b>	<b>4.8</b>

# Placental Transport Mechanisms



# Drug transporters in human placenta

## Roles

- Control uptake and transport of drugs
- Protect critical tissues/cells from xenobiotics

## Originally classified by function, now by sequence homology of genes

- Solute carrier (SLC) transporters
  - Mainly involved in uptake of substances (eg amino acids, SLC3, 7)
- ATP-binding cassette (ABC) transporters
  - Involved in efflux of substances

Expression changes across gestation and with drug-drug interactions, obstetric condition and single-nucleotide polymorphisms.

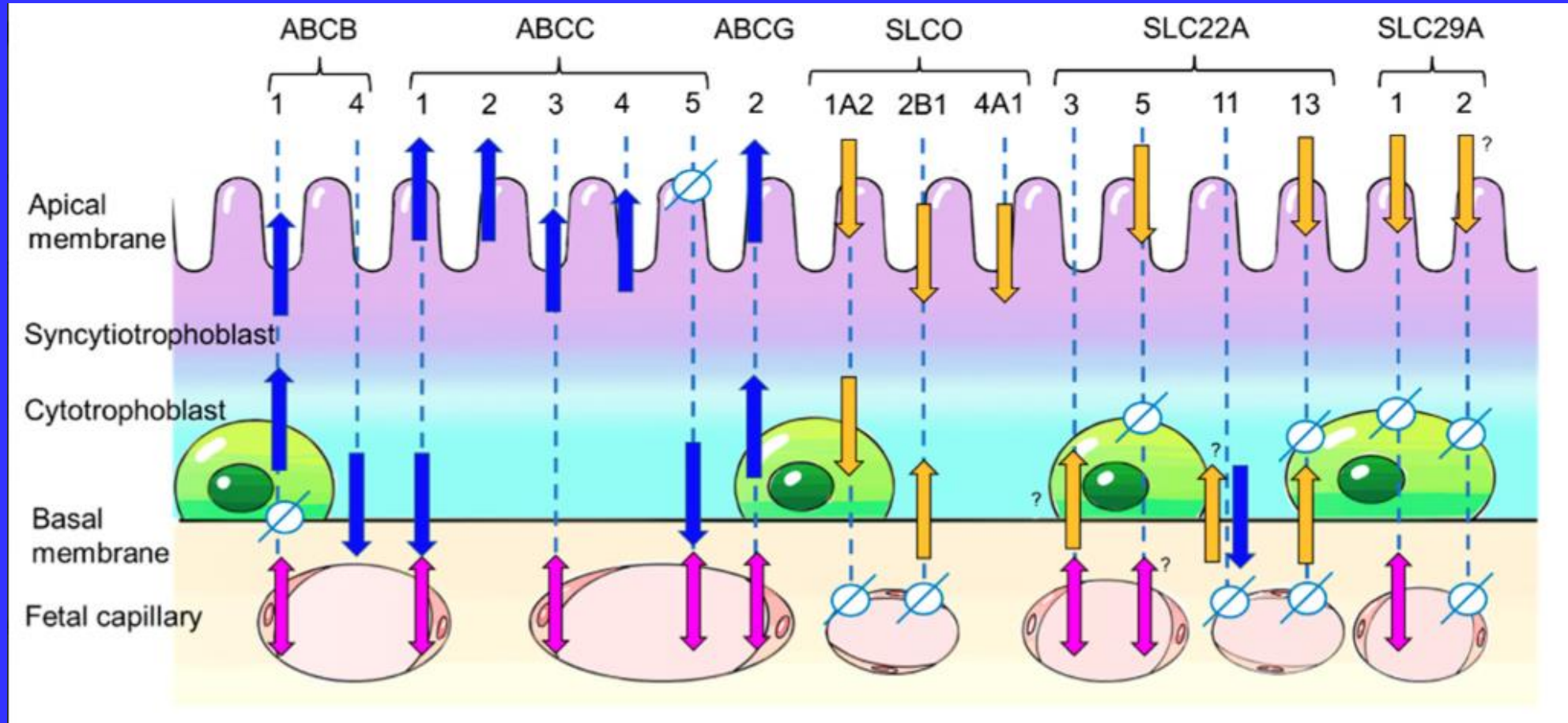
## SLC transporters

- Secondary active and passive transport
- More than 400 transporters in over 60 families
- SLCO (Organic anion transporting polypeptide: OATP) family
- SLC22A (Organic cation transporter: OCT, organic cation transporter novel type (OCTN) and organic anion transporter: OAT)
- SLC29A (Equilibrative nucleotide transporter: ENT) family
- SLC47A (Multidrug and toxin extrusion: MATE) family

## ABC transporters

- Highly conserved
- Use ATP hydrolysis for energy
- Originally identified as multidrug resistance factor (P-glycoprotein: P-gp)
- P-gp encoded by ABCB1 expressed in syncytiotrophoblast apical membrane transports cationic hydrophobic compounds
- 7 subgroups (ABCB, C and G are drug transporters)
- 2 nucleotide binding (NBD) and 2 transmembrane domains (TMD)

# Localization of drug transporters in placenta



# Factors influencing placental transport

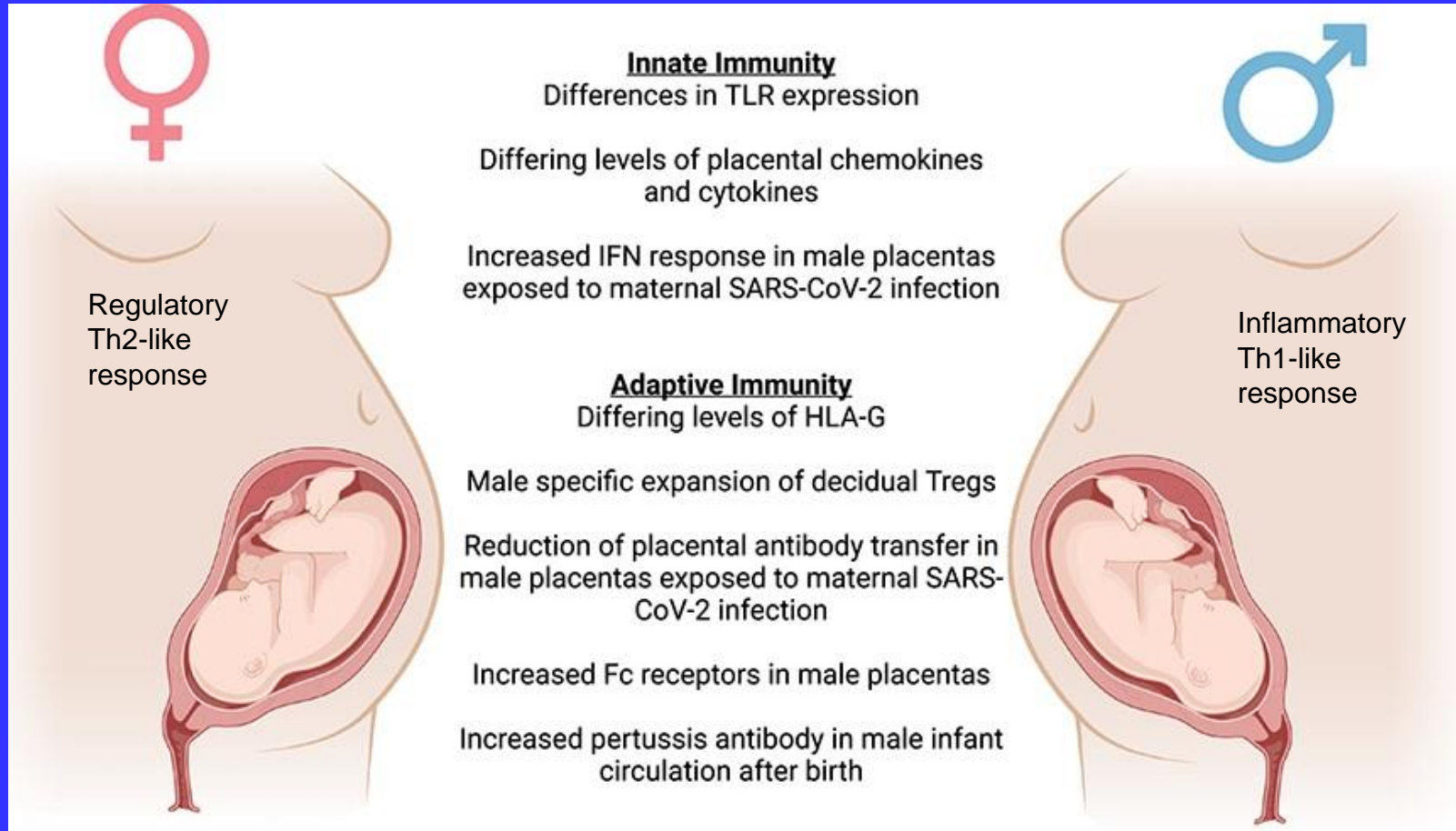
- Molecular weight, charge
- Free vs bound
- Maternal and fetal plasma protein binding affinity and amount
- Lipid solubility, pH gradients
- Diffusion capacity
- Maternal and fetal blood flow
- Expression and localization of placental transporters
- Placental binding and metabolism
- Gestational age
- Placental energy generation (obesity, diabetes)
- Fetal sex



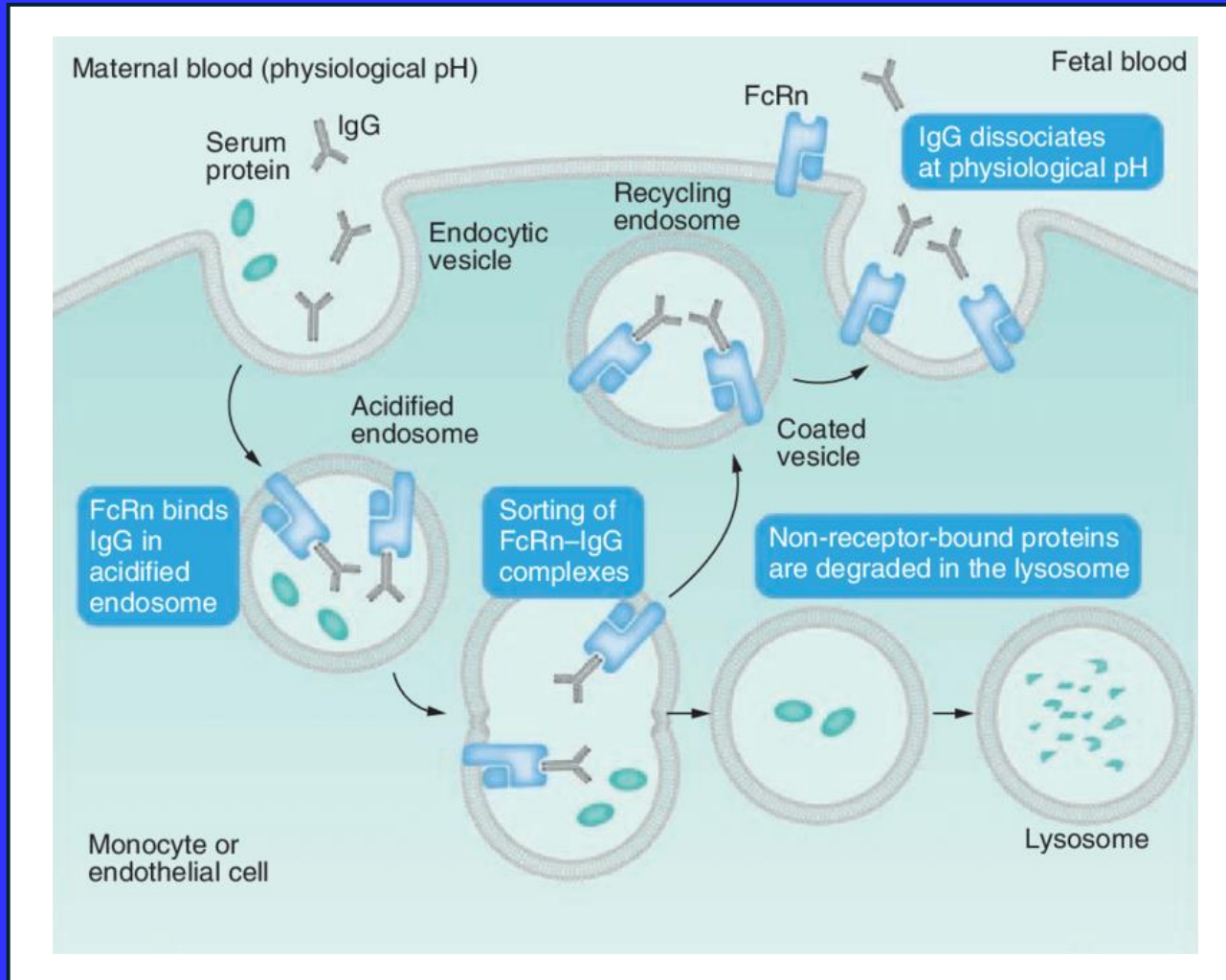
# Evidence for Sexual Dimorphism in Placental Function

- Differences in gene expression, 1<sup>st</sup> trimester and term
  - *immune genes expressed at higher level in female placenta (JAK1, IL2RB, Clusterin, LTBP, CXCL1, IL1RL1, TNFR)*
- Sexual dimorphism in placenta gene expression linked to failure of X-linked inactivation (Gong et al JCI, 2018)
- Inflammatory, hypoxia, apoptosis and autophagy responses
- Antioxidant defenses, expression of antioxidant enzymes
- Fatty acid transporters and fatty acid oxidation
- Response to maternal adiposity and inflammatory status
- microRNA expression in normal pregnancy
- Aromatase expression with preeclampsia
- **Linked to differences in outcome male vs female fetus**

# Sex-specific differences in immune response in pregnancy



# Active transport of IgG in placenta



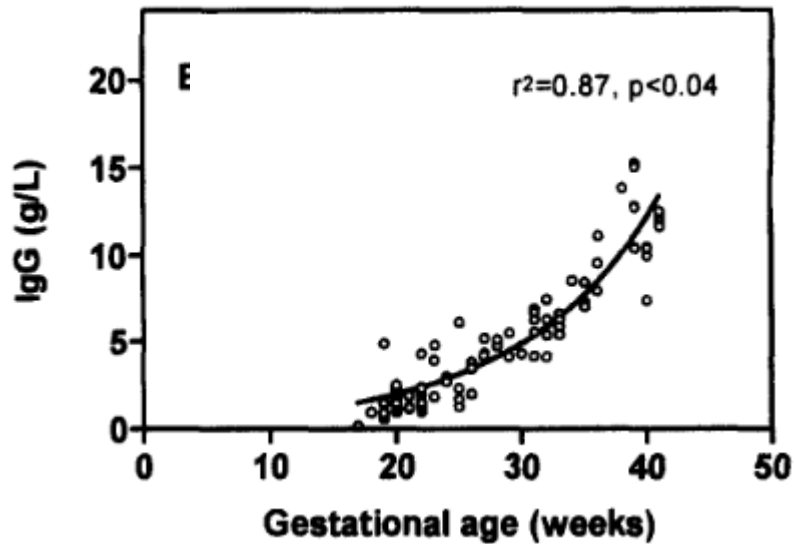
Of 5 antibody classes only IgG is transferred across the placenta via neonatal Fc receptor (FcRn)

FcRn shows pH dependence of IgG binding, high affinity at pH6.0 but 100x lower affinity at pH7.4

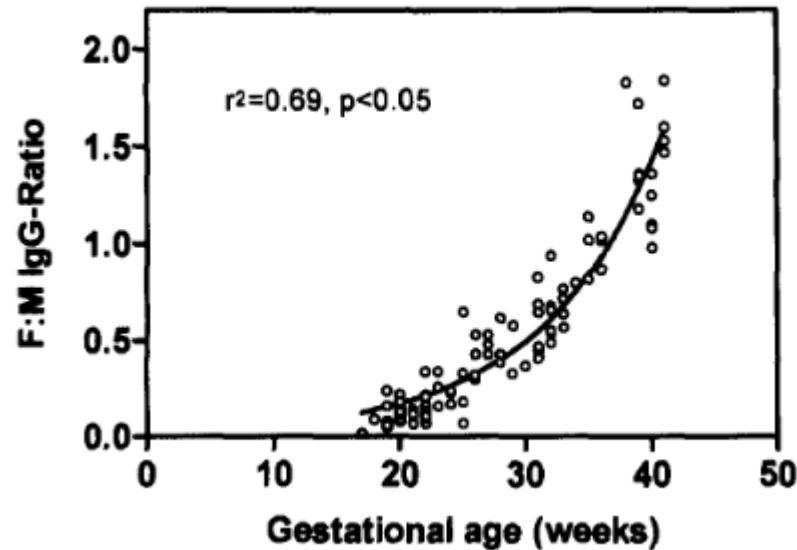
Thus FcRn is unable to bind IgG at the apical side of STB facing maternal blood

# Placental transfer of IgG across gestation

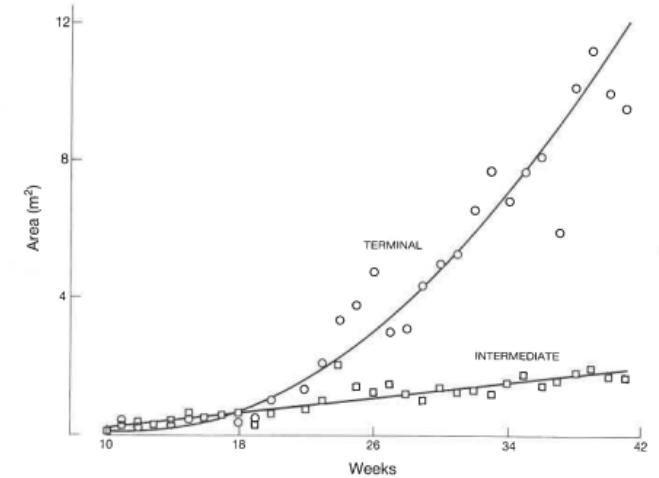
Umbilical vein IgG



Fetal/maternal ratio



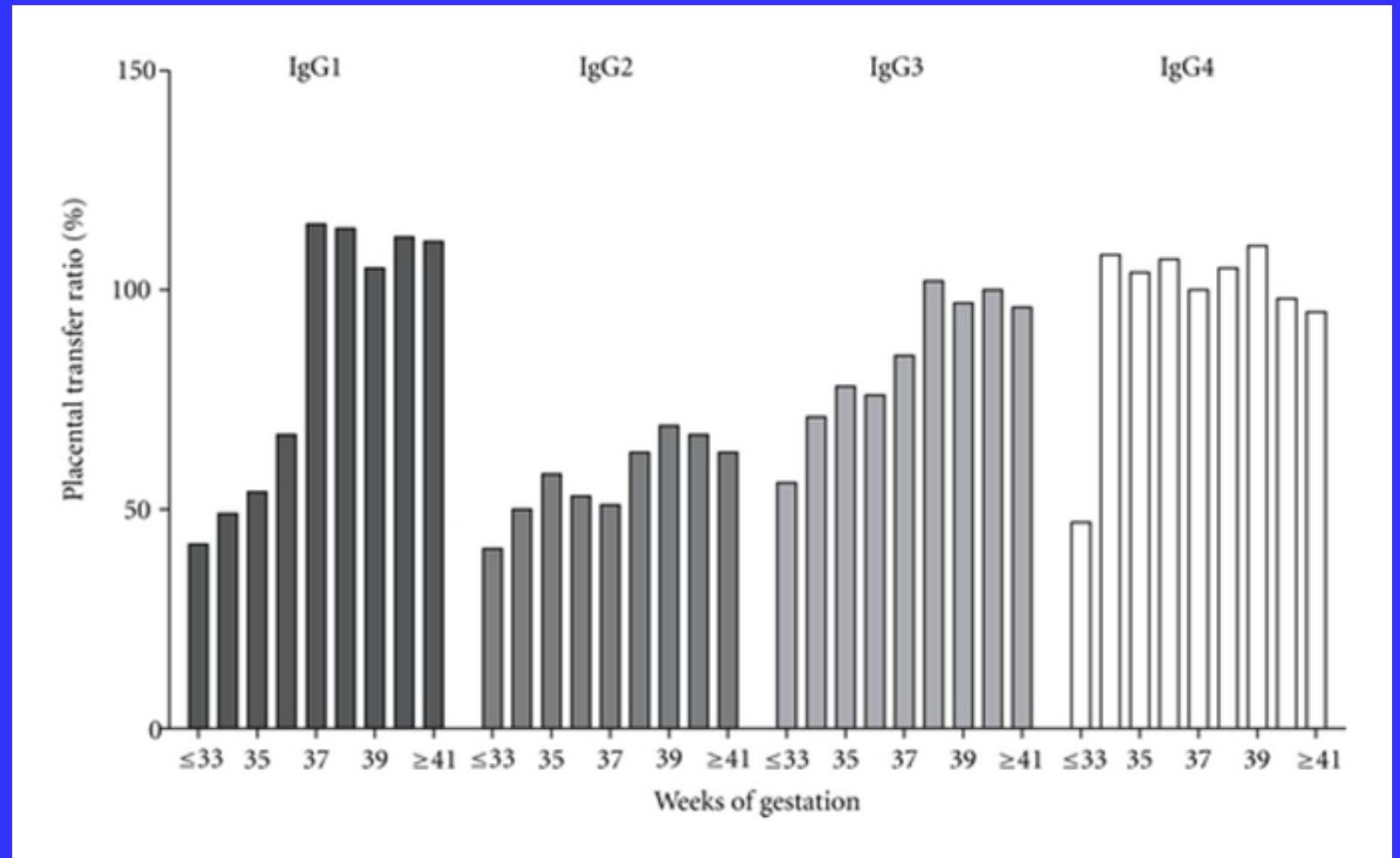
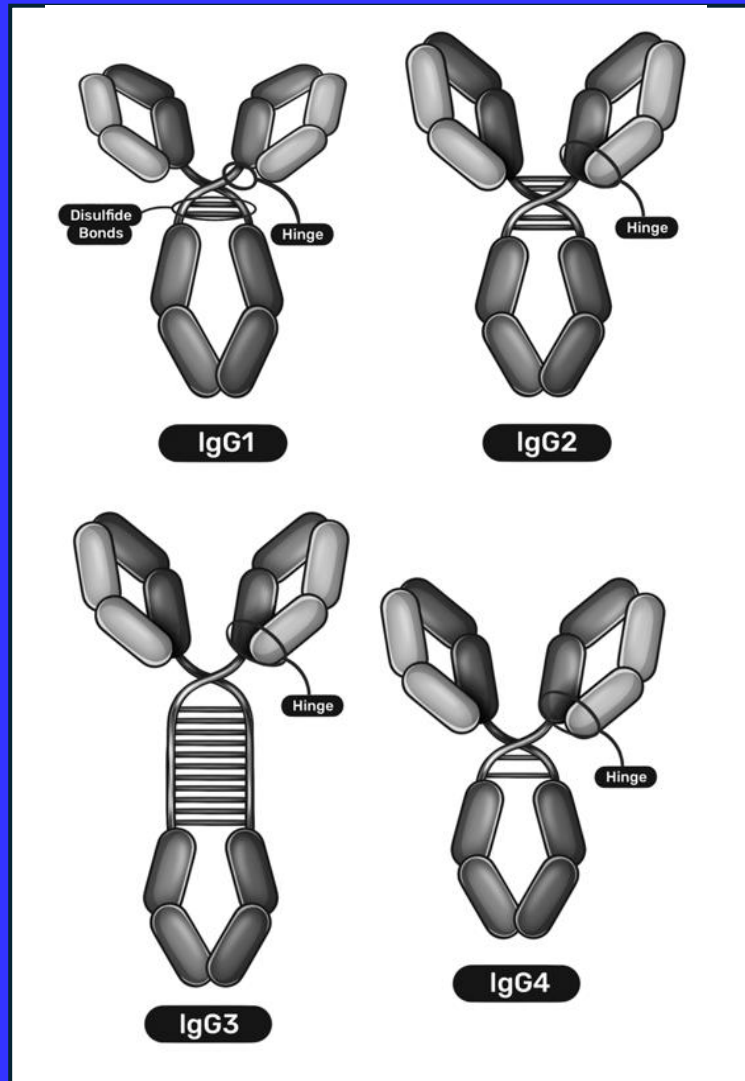
Placental surface area



Malek A 1996

Majority of IgG acquired by fetus in last 4 wks of gestation and exceeds maternal level by 20-30% at term  
Lower levels (esp IgG1 and IgG2) seen in preterm infants  
Low birth weight associated with impaired placental transfer of IgG1 and IgG2 subclasses  
Maternal age, weight, parity and type of delivery do not affect placental transfer

# Placental transfer of IgG subclasses in late gestation



IgG1 > IgG4 > IgG3 > IgG2

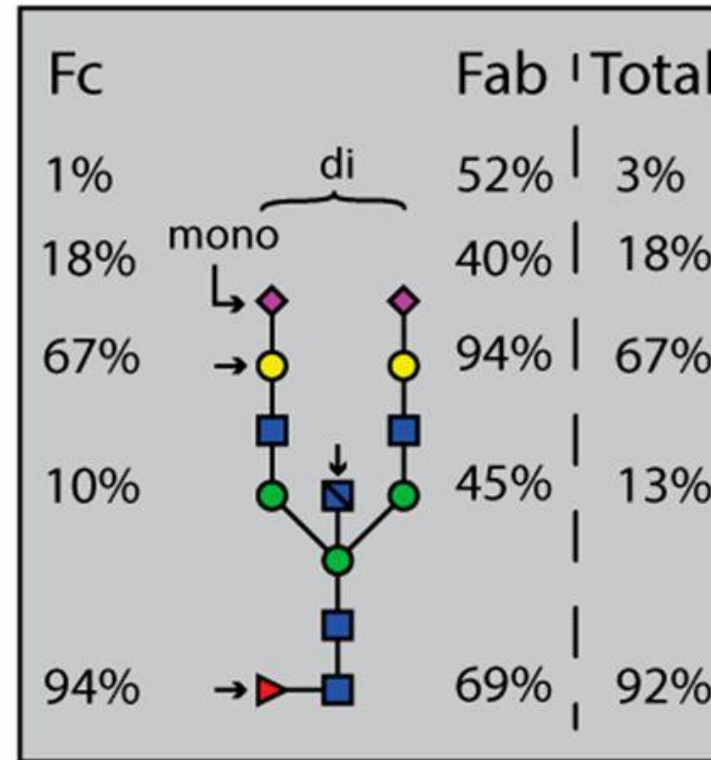
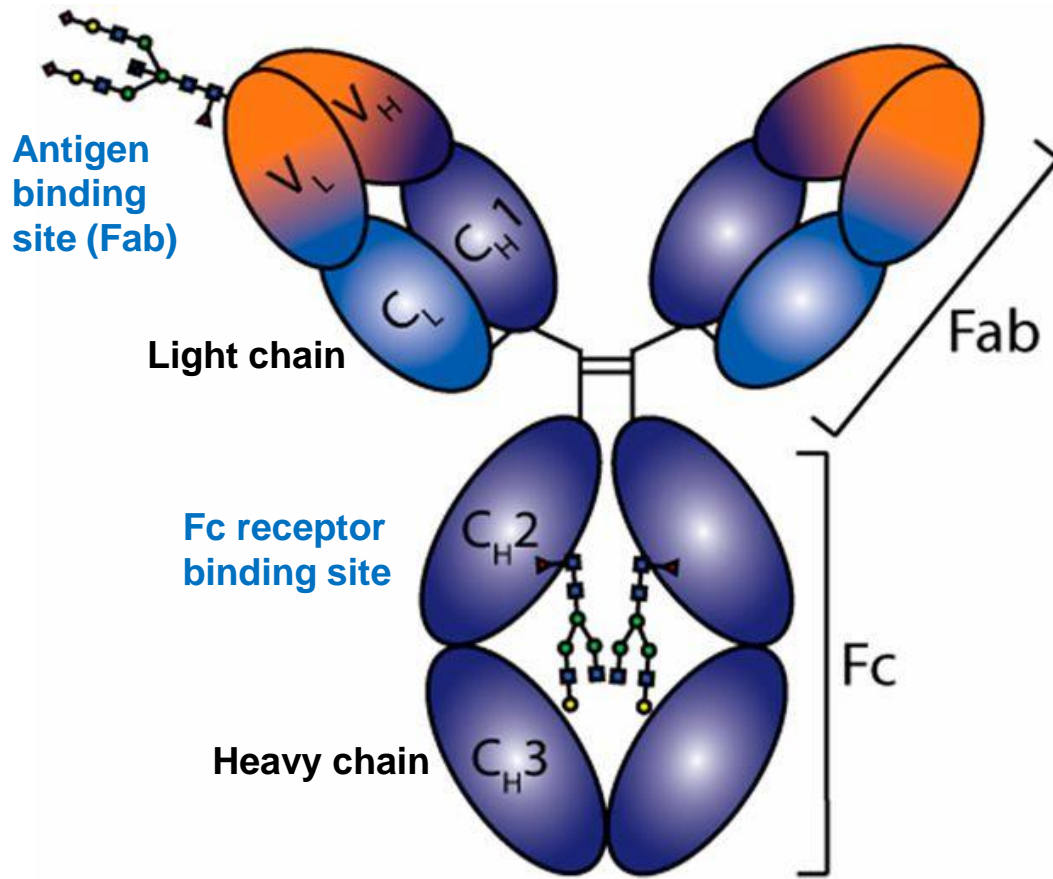
Palmeira P et al 2012

# Factors limiting efficacy of placental transfer after maternal immunization

- Time between immunization during pregnancy and delivery
- Gestational age of fetus at birth
- Total maternal IgG level
- Maternal vaccine-specific IgG and IgG subclass concentrations
- Maternal pathologies such as hypergammaglobulinemia, HIV infection, placental injury with malaria, intrauterine growth restriction (IUGR)?

# Glycosylation of IgGs

Van de Bovenkamp, F et al 2016



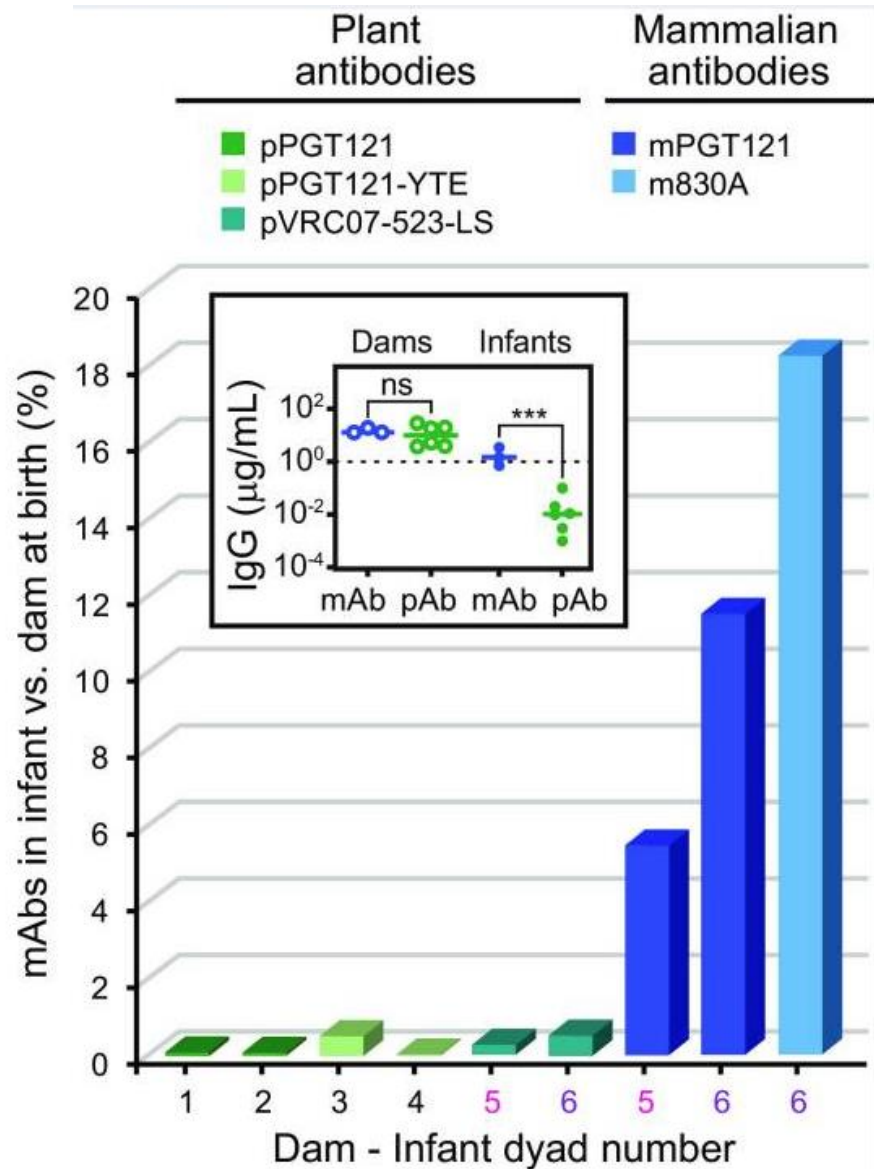
- ◆ Sialic acid
- Galactose
- Bisecting GlcNAc
- Mannose
- GlcNAc
- ▶ Fucose

Conserved N-linked glycan at Asn 297 in 2nd IgG domain of heavy chain in Fc region affects structure and function  
 Galactosylated antibodies are transferred preferentially due to enhanced binding to FcRn  
 Maternal infection may alter glycosylation e.g. Fc-glycan profiles of SARS-Cov-2 infected individuals

# Transfer of Anti-TNF $\alpha$ antibodies

- Infliximab and adalimumab are IgG1 antibodies and have preferential transfer starting at end of 2<sup>nd</sup> trimester – neonatal levels may exceed maternal levels and persist for up to 12 months
- Etanercept – fusion protein with modified Fc portion that binds to TNF $\alpha$  has low capacity for transfer, minimal levels in fetus at birth
- Certolizumab (Fab conjugated to polyethylene glycol, PEG), an anti-TNF therapy missing the Fc portion, does not cross placenta and can be used throughout pregnancy





# Transfer efficiency of plant and mammalian antibodies in primate placenta

# Summary

- Placenta is not simply a conduit, its function changes across gestation and with fetal sex and medical condition
- Placenta has evolved a range of transporters to handle molecules of a range of sizes to nourish but also protect the fetus
- Many factors influence placental transport
- Transfer of small molecules is effected by drug transporters
- IgG is transported via neonatal Fc receptor (FcRn)
- Glycosylation of IgG antibodies affects binding to FcRn and transport across the placenta



Thank you