Fetal therapies to target inflammation

Dr Sarah Stock

Reader and Consultant Subspecialist Maternal and Fetal Medicine

University of Edinburgh Usher Institute

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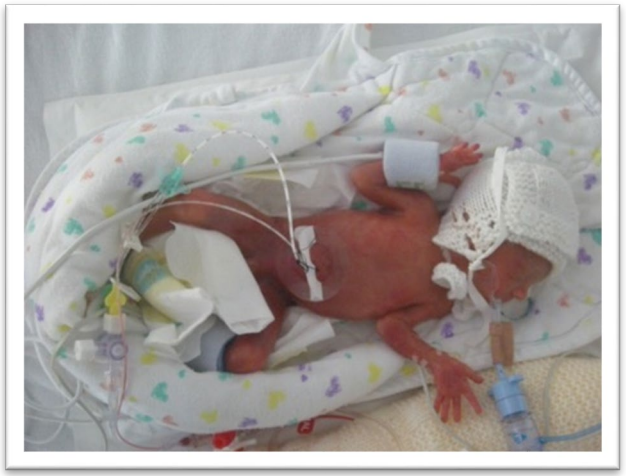
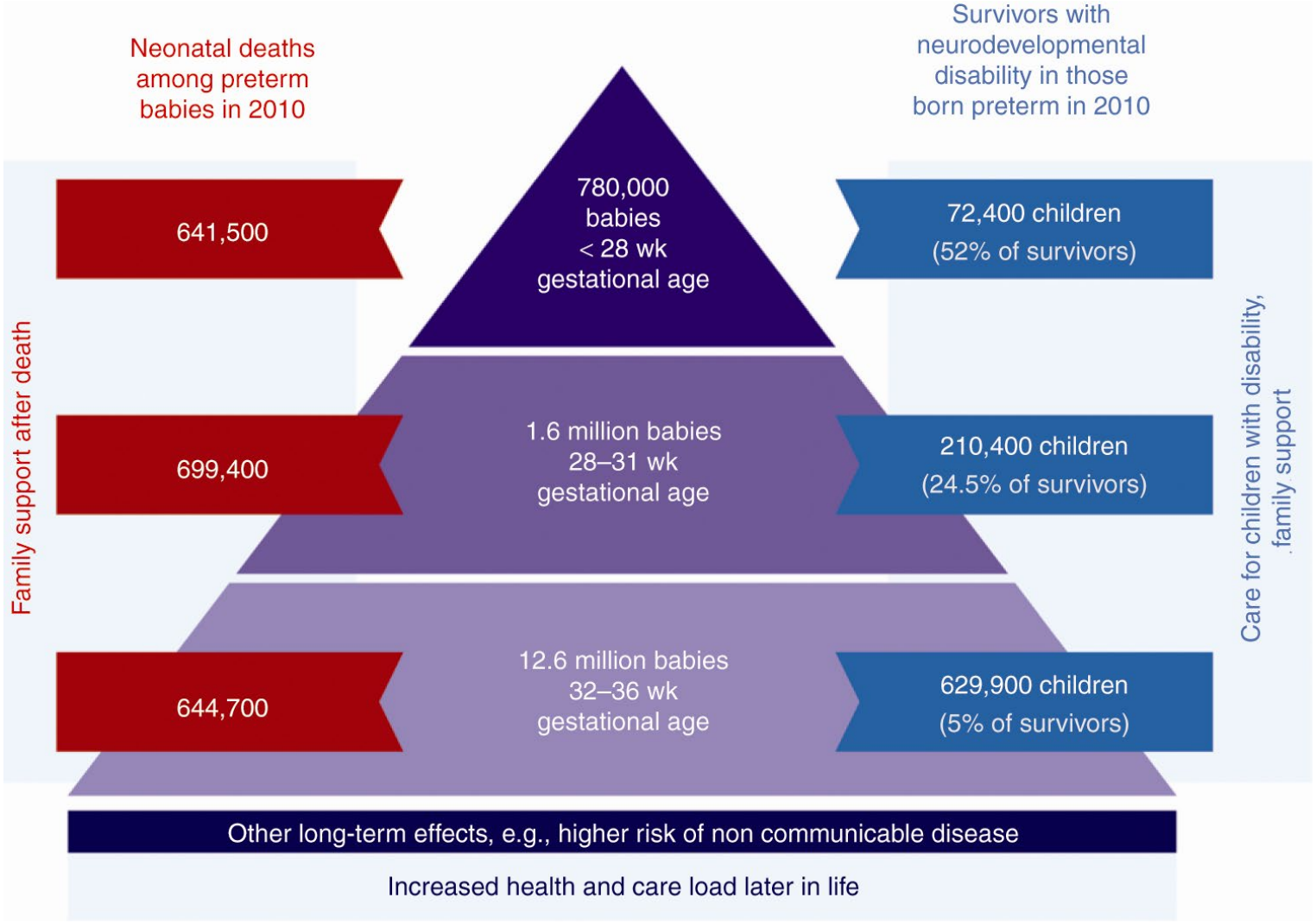
Preterm birth is an inflammatory process

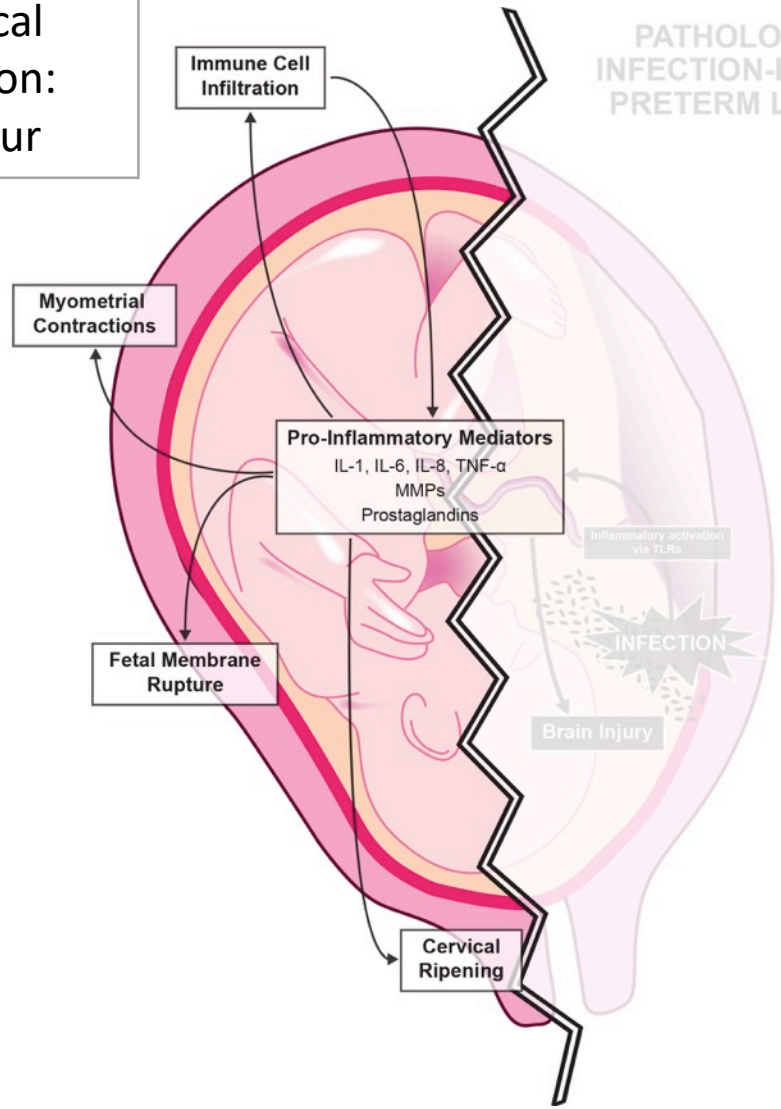


Burden of mortality and impairment for 15 million preterm babies born in 2010



Blencowe H et al 2013 Pediatric Research 74:

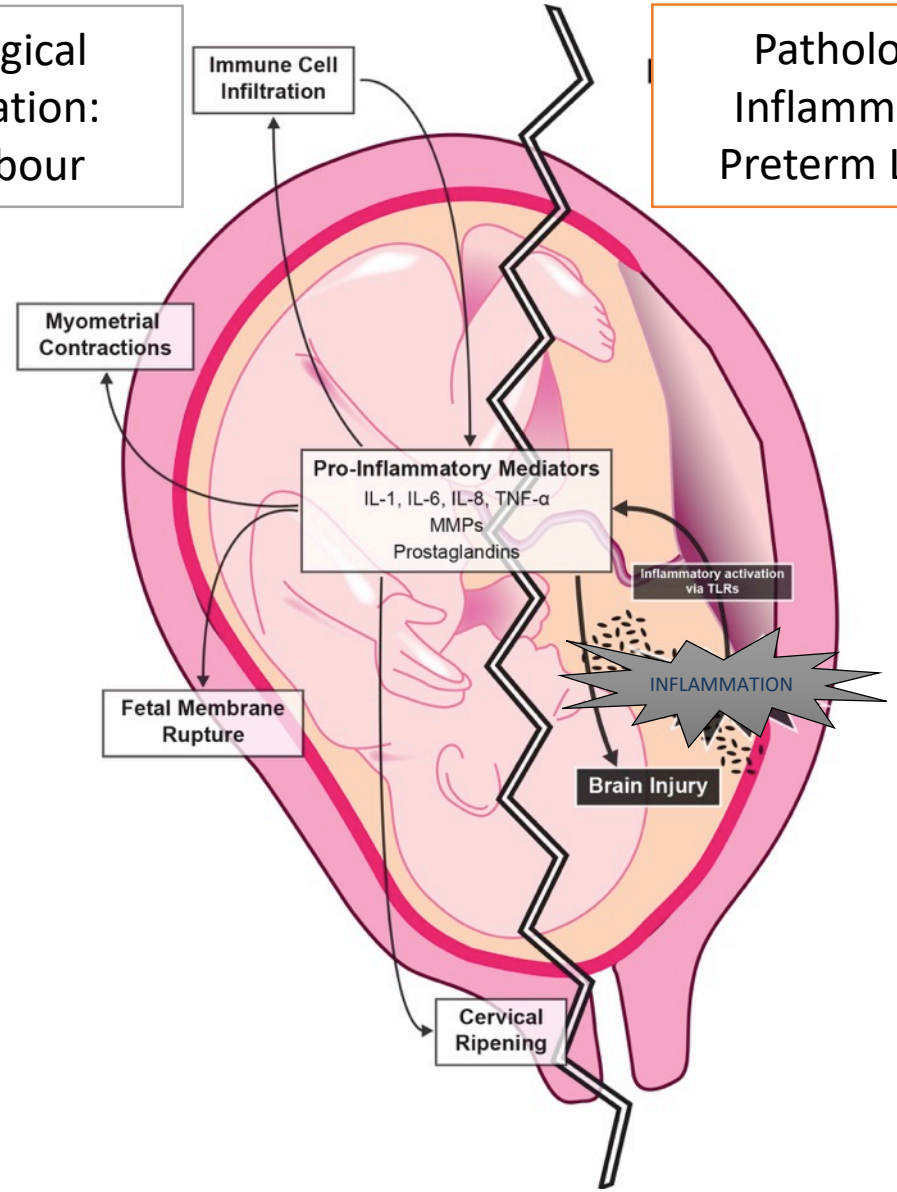
Physiological Inflammation: Term Labour



Rinaldi et al, Expert Rev Clin Immunol, 2011. 7(5), 675-96.

Physiological Inflammation: Term Labour

Pathological Inflammation: Preterm Labour



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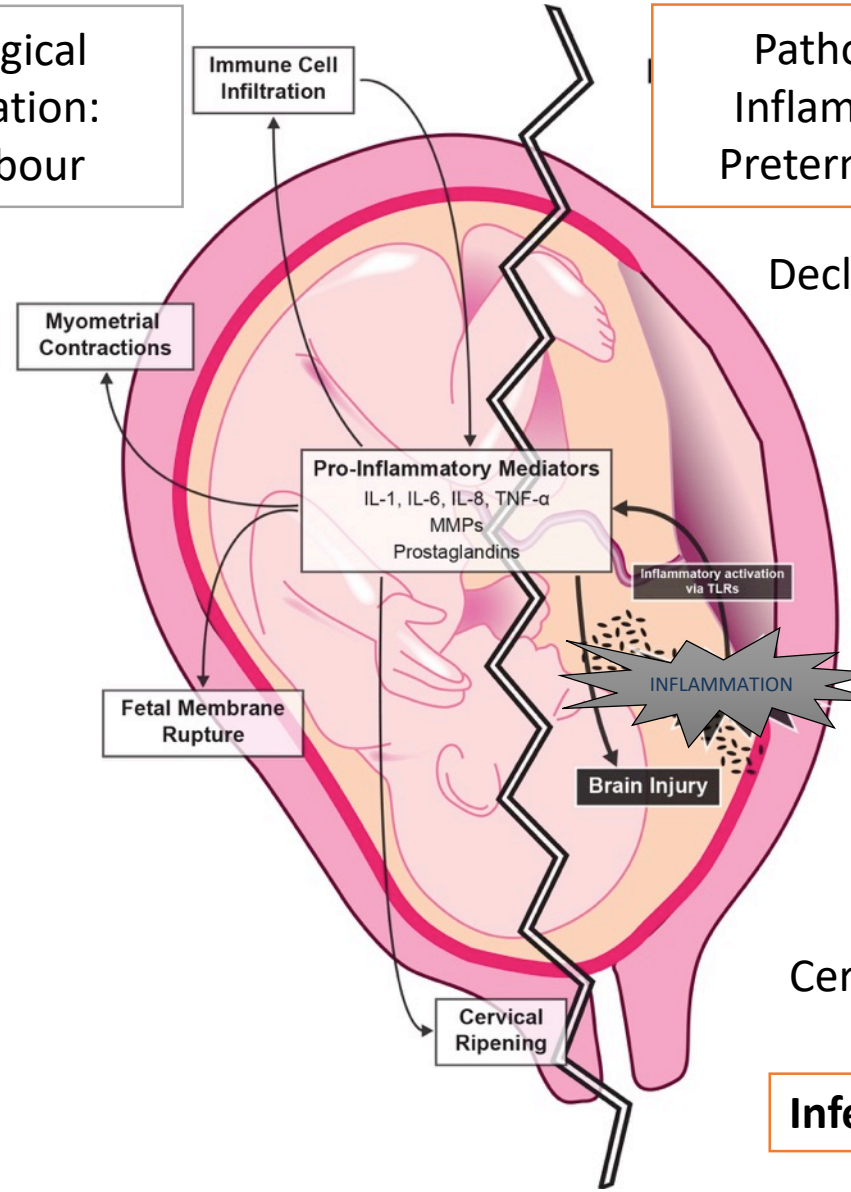
Physiological Inflammation: Term Labour

Pathological Inflammation: Preterm Labour



Decline in progesterone function

Decidual Senescence

Hypoxia/Ischemia

Stress

Abruption/Haemorrhage

Overdistension

Cervical Incompetence

Infection

Rinaldi et al, Expert Rev Clin Immunol, 2011. 7(5), 675-96.

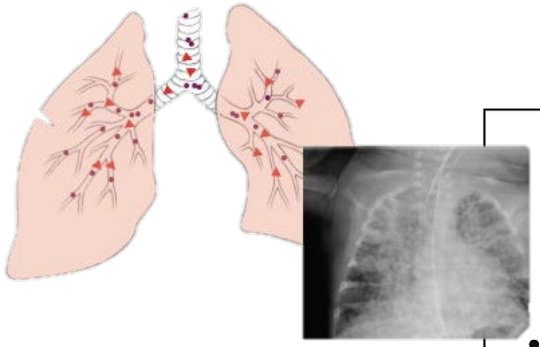
Evidence for the role of intrauterine infection and inflammation

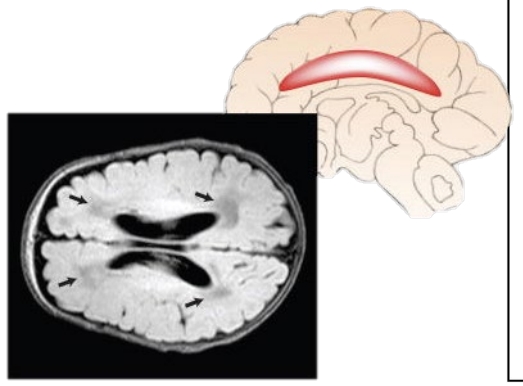
Women who deliver preterm have:

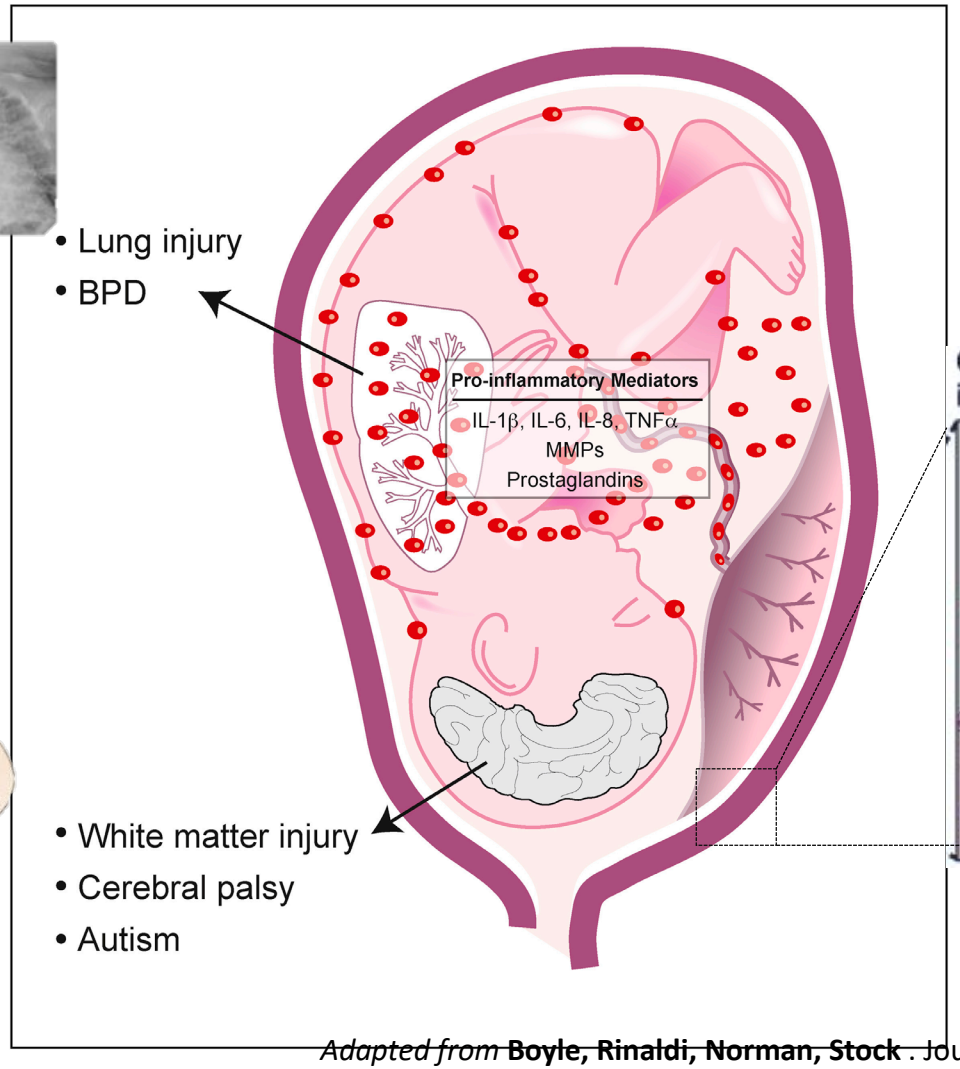
- Higher incidence of chorioamnionitis than those delivering at term
- Greater bacterial load in fetal membranes in preterm labour
- Increased levels of pro-inflammatory mediators in amniotic fluid - e.g. TNF-α, IL-6 and MMP-8

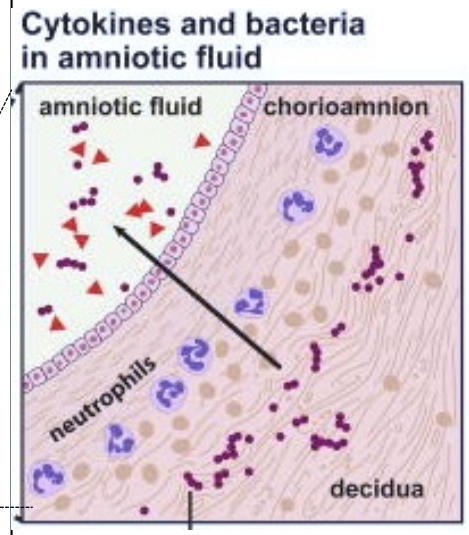
Injection of bacteria or bacterial products increase inflammatory cytokines and effectively induce preterm labour in animal models

Fetal Inflammation and Injury



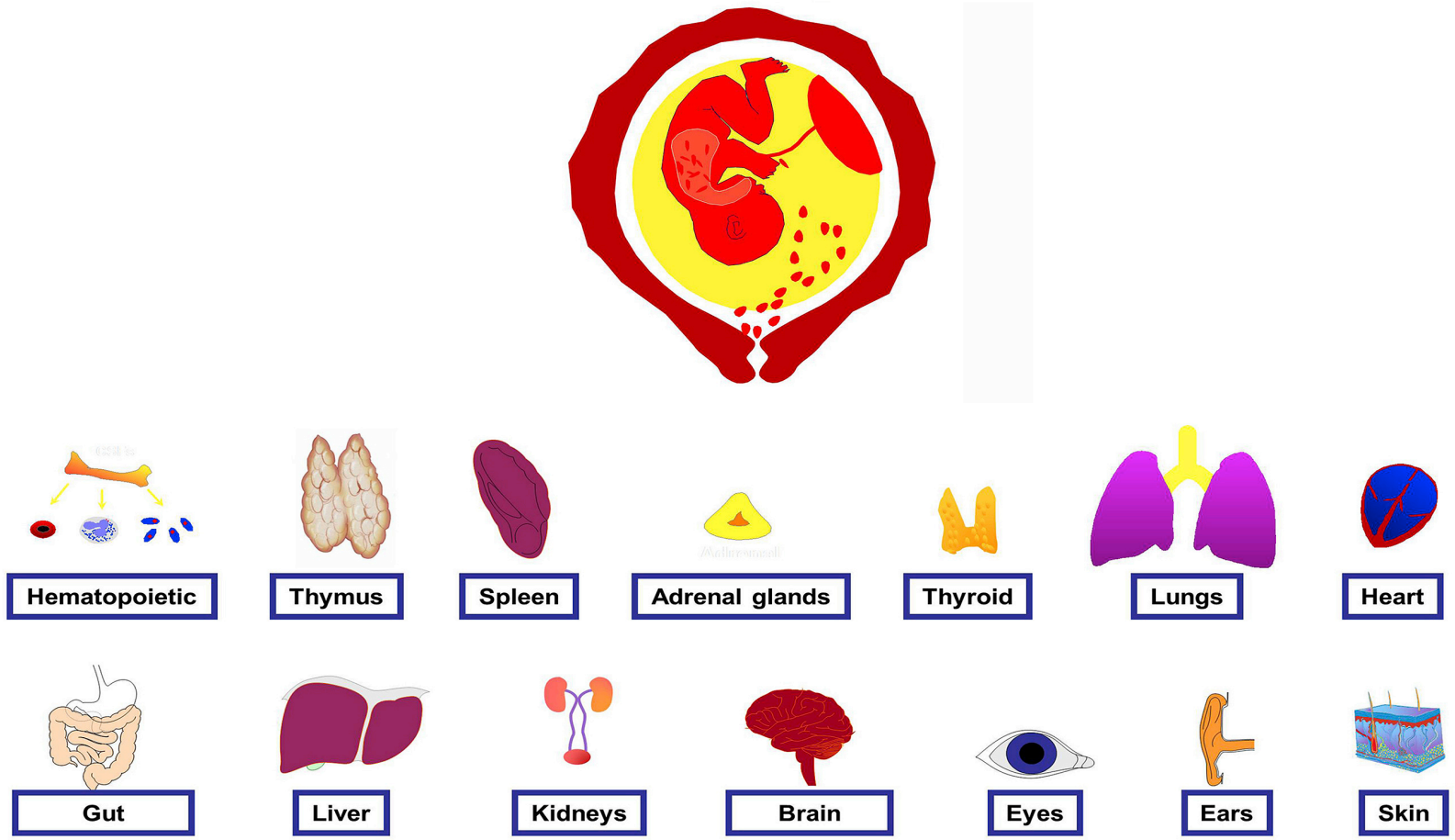






Adapted from **Boyle, Rinaldi, Norman, Stock** . Journal of Reproductive Immunology, 2017

Fetal Inflammatory Response Syndrome (FIRS)



Seminars in Fetal and Neonatal Medicine 2020 25DOI: (10.1016/j.siny.2020.101146)

Fetal Inflammatory Injury Can Occur without Preterm Labour

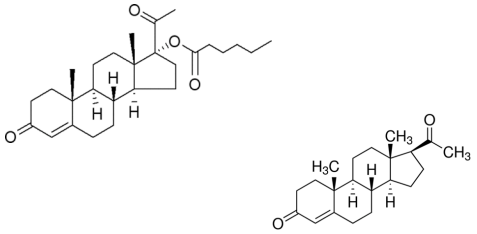
-Chorioamnionitis does not invariably lead to PTB

-Babies can be born with signs of systemic inflammation in the absence of preterm labour

- Changes in brain connectivity can be detected before preterm birth

In animal models, bacteria, and bacterial products which are not sufficient to cause preterm birth still result in fetal injury

Current Strategies to Prevent Preterm Birth and Fetal Injury

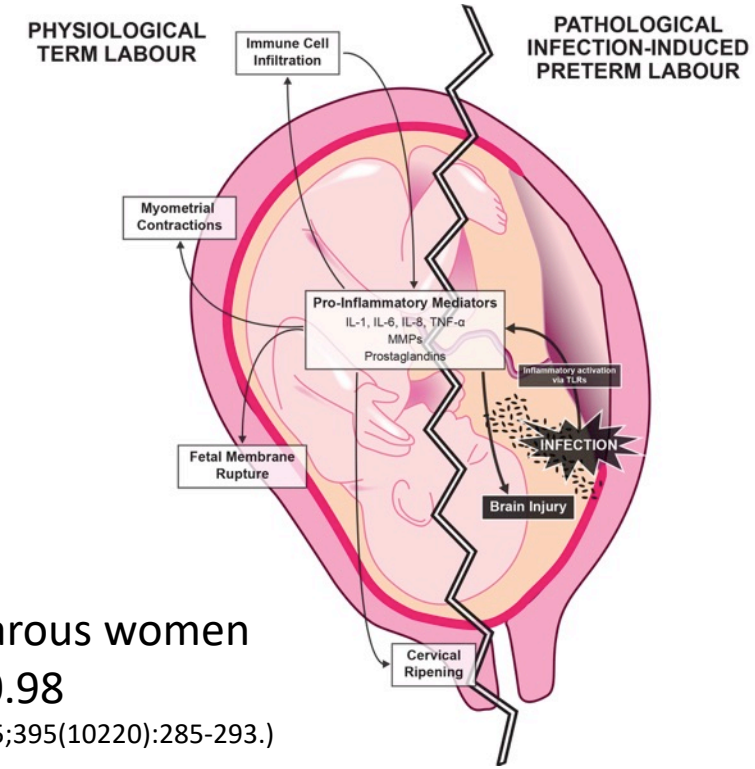


Tocolysis :

-Temporarily decrease myometrial contractions

-Does not improve neonatal outcome

(Haas et al BMJ. 2012 Oct 9;345)



Progestogens:

-Vaginal progesterone and 17-OHPC both reduced birth before 34 weeks' gestation in high-risk singleton pregnancies (Relative risk [RR] 0·78, 95% CI 0·68–0·90)

EPPPIC Group.Lancet. 2021 Mar 27;397(10280):1183-1194.

Aspirin:

- 6-13+6 weeks, Nulliparous women

-PTB RR 0.89, CI 0.81–0.98

(Hoffman MK et al Lancet 2020 Jan 25;395(10220):285-293.)

Antibiotics:

-Do not stop preterm birth

(Kenyon et al Lancet. 2001 Mar 31;357(9261):989-94)

-Increase CP at age 7 years

(Kenyon et al Lancet. 2008 Oct 11;372(9646):1319-27.)

Emerging preterm birth strategies:

- **Phase III**
  - Retosiban (GSK oxytocin receptor antagonist): terminated (no reduction in PTB)
  - Barusiban (Ferring oxytocine receptor antagonist) : No reduction in PTB within 48 h

  - Lipocine (LPCN1107 [Oral 17-OHP]) vs IM 17-OHP– ongoing
  - Oral dydrogesterone (University of Hong Kong) – ongoing

- **Phase II**
  - OBE022 (Ebopiprant) : prostaglandin F2 alpha receptor antagonist

  - Indomethacin: NSAID vs Nifedipine (proposed- Hadassah Medical Organization)

Coler et al. 2021. Journal Clinical Medicine

Preclinical: Targeting Cytokines, Chemokines & Signalling

Substance	Animal	Phenomenon
TNF-α antibody	Mouse	Decreases the rates of fetal death and preterm birth after LPS administration. Suppresses the expression of IL-6, IL-1β, TLR-2, CD14, and COX-1
IL-6R antibody	Mouse	Decreases the rate of LPS-induced PTD
	Human	Inhibits PGE2 production from human primary amniotic epithelial cells
	Rat	Increases the rate of pup mortality[a]
		Increases IL-1 production in the serum[a]
IL-1R antagonist	Mouse	There is no significant difference in the rate of preterm birth
		Decreases fetal cortical brain injury
	Mouse	IL-1 receptor-biased ligand specifically inhibits IL-1R downstream c-jun, and Rho GTPase/Rho-associated signaling delay IL-1β-, TLR2-, and TLR4-induced preterm birth
Cytokine-suppressive anti-inflammatory drugs (CSAIDs)		Review
	Ewe	Suppresses the production of PGE2 in amniotic fluid
		Decreases the IL-6 concentration of maternal plasma
		Inhibits the infiltration of polymorphonuclear cells into fetal lung
	Mouse	Decreases the rate of preterm birth
		Suppresses cytokine and/or chemokine levels of maternal plasma, liver, myometrium, and decidua
		Inhibits neutrophil infiltration into the myometrium
Antibiotics with dexamethasone and indomethacin	Macaque	Prolongs gestation following GBS-induced increases in uterine contractility
		Decreases IL-1β, TNF-α, PGE2, and PGF2α levels of amniotic fluids
		No changes in MMP-9 or -2 expression
COX-2 inhibitor (Celecoxib)	Mouse	Indomethacin and meloxicam but not diclofenac inhibit LPS-induced preterm birth
	Mouse	Reduces the rate of LPS-induced preterm birth
		Reduces the concentrations of PGE2 and PGF2α in uterine tissue
	Rat	Fetal ductal arteriosus is significantly limited[a]
NF-κB inhibitors	Human	In an ex vivo model, NF-κB inhibitor suppresses LPS-induced IL-6 and TNF-α production by maternal and fetal compartments
IKK inhibitors	Human	Inhibits the level of LPS-inducing genes such as IL-6 and TNF-α in primary term choriodecidual cells

Taguchi et al. Reproductive Sciences 2017

Preclinical: Targeting Cytokines, Chemokines & Signalling

- Interleukin-1 Receptor Antagonists:
  - Kineret, canakinumab, and rilonacept – Rx for inflammatory disorders
  - Reduce fetal inflammation (low dose) and preterm labour (intra-amniotic) in animal models
  - Side effects
  - Allosteric regulators

Leitner et al, Am J Reprod Immunol. 2014 May; 71(5): 418–426
Kallapur, S.G. Am. J. Respir. Crit. Care Med. 2009, 179, 955–961
Presicce, P. JCI Insight 2018, 3.

- Broad spectrum chemokine inhibitors (BSCI) Immunoliposome:
  - Block somatostatin receptor type 2 (SSTR2)
  - May directly inhibit uterine contraction
  - Blocks LPS induced PTB in moude model
  - Inhibits GBS induced preterm labour in primate model (but not microbial invasion of the fetus)

Coleman et al. Front. Immunol. 2020, 11, 770
Shynlova, O et al. J. Cell Mol. Med. 2014, 18, 1816–1829

Preclinical: Suppressing Inflammation

Lipid mediators		
ω3/resolvinE3	Mouse	Decreases the rate of LPS-induced preterm birth
		Inhibits IL-6, IL-1β, and TNF-α expression from peritoneal washes
		EPA metabolite resolving E2 also exerts protective effects against LPS-induced preterm birth
Lipoxin A4	Mouse	Does not delay LPS-induced preterm birth
		Decreases the mortality of prematurely delivered pups
		Regulates the local production and activity of prostaglandins
15d-PGJ2	Review	
	Mouse	Delays LPS-induced preterm birth
		Suppresses NF-κB activity, cPLA2 expression, and c-Jun activity in uterine myometrium
	Human	Inhibits NF-κB activity of IL-1β-stimulated amnion epithelial and myometrial cells
Others		
Statin	Mouse	Inhibits complement-activated uterine contraction
	Mouse	Reduces IL-1β and IL-6 expression in the uterus and cervix and serum IL-1β and GM-CSF concentrations
		Reduces IL-1β and IL-6 expression in the uterus, IL-6 and TNF-α in the cervix, and IL-1β, IL-2, IL-12p70, IL-13, TNF-α, GM-CSF, and IFN-γ concentrations in the serum and IL-6 in amniotic fluid
Probiotics, *Lactobacillus rhamnosus* GR-1 supernatant	Mouse	GR-1 reduces LPS-induced preterm birth
		GR-1 SN decreases the LPS-induced IL-1β, IL-6, IL-12p40, TNF-α, CCL4, and CCL5 in maternal plasma; IL-6, IL-12p70, IL-17, IL-13, and TNF-α in myometrium; IL-6, IL-12p70, and IL-17 in placenta; and IL-6, TNF-α, CCL3, and CCL4 in amniotic fluid
Folic acid	Mouse	Reduces LPS-induced preterm delivery and fetal death and IUGR
	Human	Suppresses LPS-induced NF-κB activation of mouse placenta in vivo and in vitro (JEG3)
Melatonin	Mouse	Decreases LPS-induced preterm birth and fetal death
		Reduces the LPS-induced rises in uterine PGE2, PGF2α, and COX-2
N-dimethylacetamide	Mouse	Decreases LPS-induced preterm birth in a dose-dependent manner
		Decreases LPS-induced inflammatory signaling and infiltration of inflammatory cells in placenta
Muscimol ($GABA_A$ agonist)	Mouse	Decreases LPS-induced preterm birth through modulating NO release
N-acetylcysteine (NAC)	Mouse	Decreases LPS-induced preterm birth
		Attenuates LPS-induced IL-6 expression of myometrium
		Attenuates LPS-induced cytokine expression of fetal brain and protects against brain injury

Taguchi et al. Reproductive Sciences 2017

Preclinical: Suppressing Inflammation

- Lipid mediators:
  - 15d-PGJ2: Did delay LPS induced PTB and reduce inflammation in mice

(Pirianov et al (2009) Endocrinology, 150, 699-706 ;

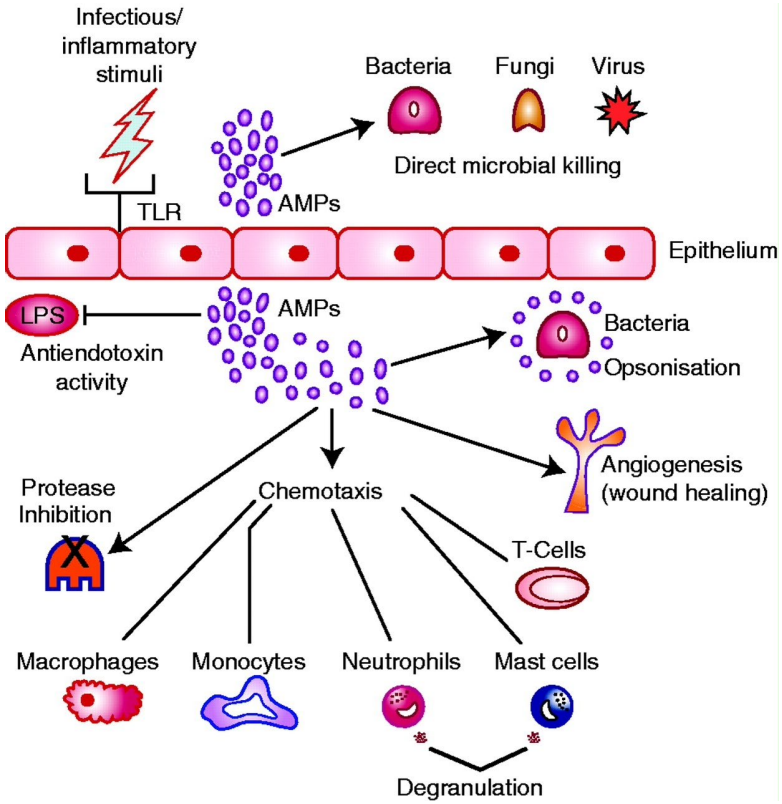
  - 15-*epi*-lipoxin A_4: Did not reduce LPS induced PTB but did reduce inflammation and pup mortality in mice

(Rinaldi et al (2015) Mol Hum Reprod, 21(4):359-68)

- Statins
  - Simvastatin: reduces PTB incidence in mice, and inhibits myometrial contractions, and exhibits key anti-inflammatory effects in ex vivo human tissue (Boyle et al FASEB J. 2019 Feb; 33(2): 2743–2758.)
  - Pravastatin: does not cross the placenta (Pippin)

Preclinical: Other strategies

- Antimicrobial peptides:
  - Cathelicidin-deficient (Camp$^{-/-}$) mice are less susceptible to LPS induced PTB with decrease in IL-6.



Boeckel SRV, Sci Rep. 2019 May 14;9(1):7356

Son GH et al. Int J Mol Sci. 2021 Aug 18;22(16):8905. doi: 10.3390/ijms22168905.

Frew L, Stock SJ. Reproduction. 2011 Jun;141(6):725-35.

Challenges

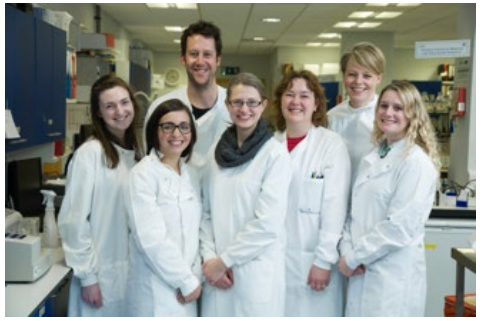
- Balancing pro and anti-inflammatory effects
- May need to treat infection and inflammation
- Mode of delivery of treatments

- Diagnosing preterm labour
- Detection of the fetus with inflammation

- Clinical trials are challenging
  - Feasibility of tocolysis trials
  - Need for long term follow up

- Recognition of risk for preterm birth – prevention

Acknowledgments



Sara Rinaldi
Lorraine Frew
Sara Van Boeckel
Kirsten Wilson
Ashley Boyle
Tina Baker
Heather MacPherson
Jane Norman
Matt Kemp
John Newnham
Donald Davidson
Brad Spiller

Collaborators

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