

Future directions & goals in the management of preterm labour

Session 6: Chairman

Dr Ronald Lamont

**Northwick Park Hospital, Harrow,
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1st International Preterm Labour Congress, Montreux, Switzerland, June 2002

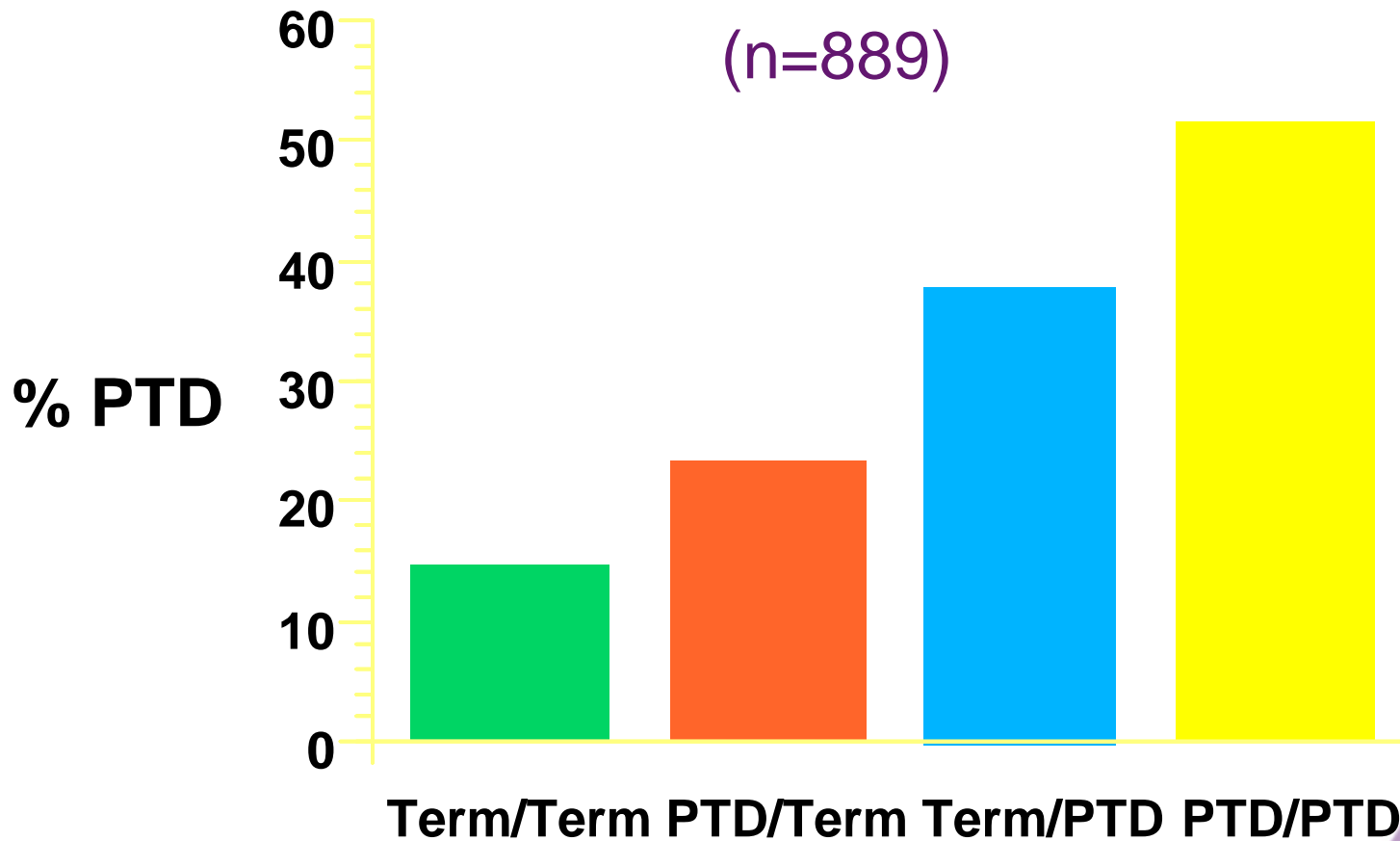


Genetic factors in preterm birth

Professor Kenneth Ward
University of Utah, USA



Prematurity risk based on prior pregnancy outcome



Genetic factors in

- Fetal growth
- Gestational clock, hormonal readiness
- Uterine activity
- Labour cascade
- Membrane strength
- Susceptibility to infection
- Cervical length and elasticity
- Twinning



Utah – ideal population for finding disease genes

- High fertility, early polygamy
- Genealogy database
- Advanced, centralised medical care
- Accurate paternity
- Cooperative, “high-tech” population
- Low rate of smoking, drinking, STD’s drug abuse



Polymorphisms of candidate genes associated with labour

Candidate gene

Reference

Oxytocin receptor

Am J Med Genet 1995

Adrenocorticotrophic hormone

Biol Neonate 1994

Thromboxane A2 receptor

Genomics 1993

Endothelin-1

Nucleic acids 1991

F-actin

Biochemistry 1996

Essential of light chains of myosin

Nat Genet 1996



Reported genetic associations

- MMP-1 promoter
- TNF and cytokines
- CRH
- Toxin susceptibility genes
 - Beware of hidden ethnic bias in case-control association studies



Role of cytokines and other inflammatory mediators

Professor Matthias Winkler
University Hospital, Aachen,
Germany

1st International Preterm Labour Congress, Montreux, Switzerland, June 2002



Interleukin-8 and reproductive tissue

- IL-8 is produced by cervical tissue (Barclay et al 1993)
- IL-1 β induces an increase in the production of IL-8 by lower uterine segment fibroblasts (Winkler et al 1998)
- Local treatment with IL-8 is followed by cervical ripening and dilation in animals (El Maradny et al 1996)



Degranulation of neutrophilic granulocytes →
(IL-8) collagenases

Adhesiveness of capillary endothelium
(e.g., IL-1 β , TNF α)

Chemotaxis for leukocytes, e.g., neutrophilic granulocytes
(IL-8)

Cytokines

Inhibition of tissue protease inhibitors (e.g., IL-1 β)

Stimulation of collagenase production by fibroblasts
(e.g., IL-1 β)

Stimulation of prostaglandin/leukotriene synthesis in uterine
tissues



IL-8 production by human lower uterine segment fibroblasts

	Without progesterone	With progesterone
No stimulation	0.71 ± 0.04	0.77 ± 0.07
LPS	0.81 ± 0.04	$0.68 \pm 0.06^*$
TGF- β_1	2.10 ± 0.15	$1.39 \pm 0.13^*$
PDGF-AB	4.43 ± 0.11	3.93 ± 0.28
IL-1 β	35.6 ± 1.9	$29.0 \pm 2.1^*$
TGF- β_1 + PDGF-AB	9.6 ± 0.8	8.9 ± 0.2
IL-1 β + TGF- β_1	105.0 ± 7.5	114.0 ± 5.5
IL-1 β + PDGF-AB	387.3 ± 25.6	$298.3 \pm 22.1^*$
IL-1 β + TGF- β_1 + PDGF-AB	394.0 ± 41.6	312.5 ± 16.2
* P<0.05		

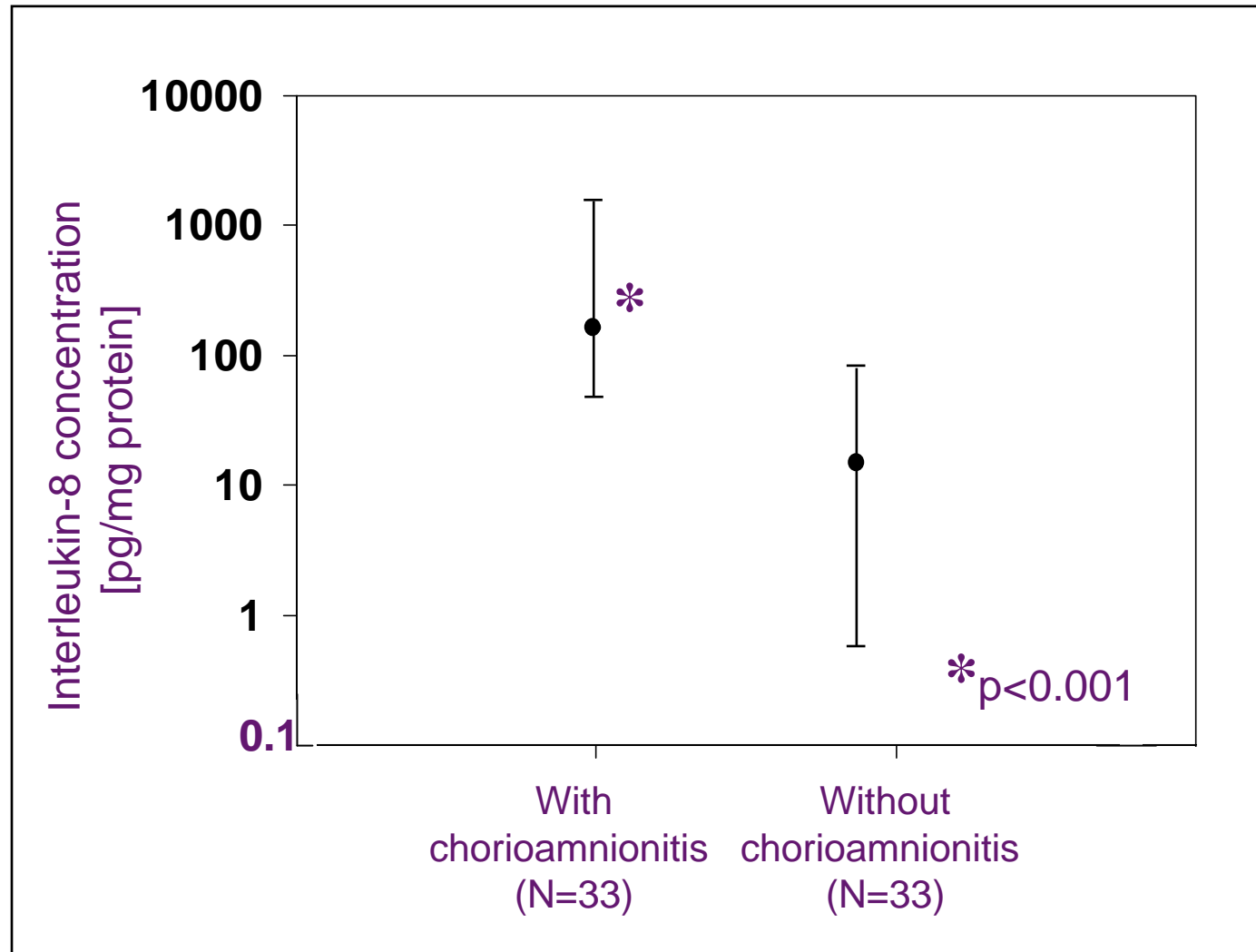


Adhesion molecule concentrations in the lower uterine segment during preterm parturition

	Duration of labour (h)		
ng/mg protein	≤6 (n=7)	>6-12 (N=4)	≥12 (N=9)
ICAM-1	2.9	4.4*	7.2**
ELAM-1	0.11	0.21*	0.23*
VCAM-1	10.1	9.7	7.3
*p<0.05 vs ≥6h ; **p<0.01 vs ≥6h			



Interleukin-8 concentrations in the lower uterine segment in patients with chorioamnionitis



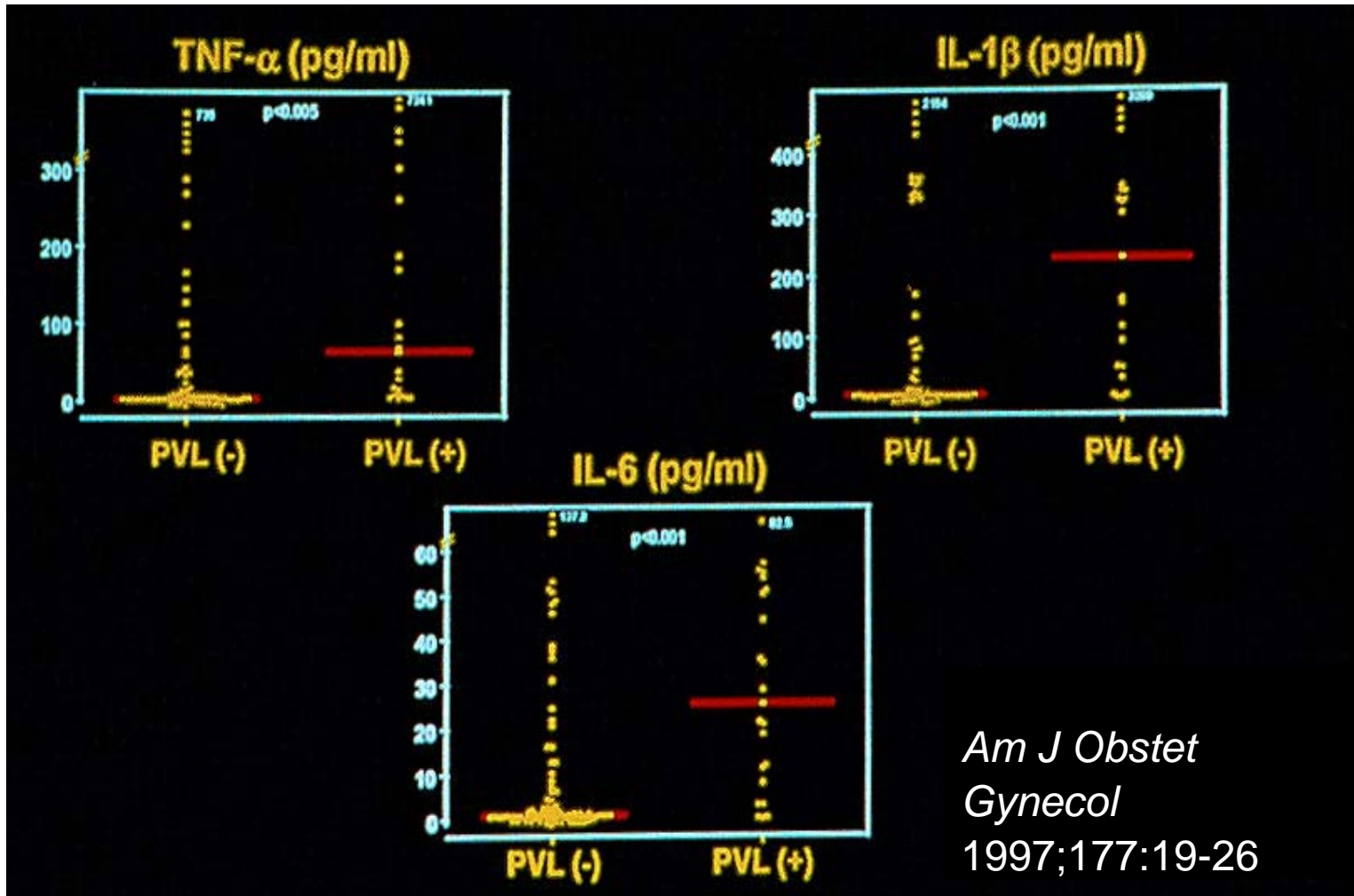
Intrauterine infection and the development of cerebral palsy

Professor Bo Hyun Yoon

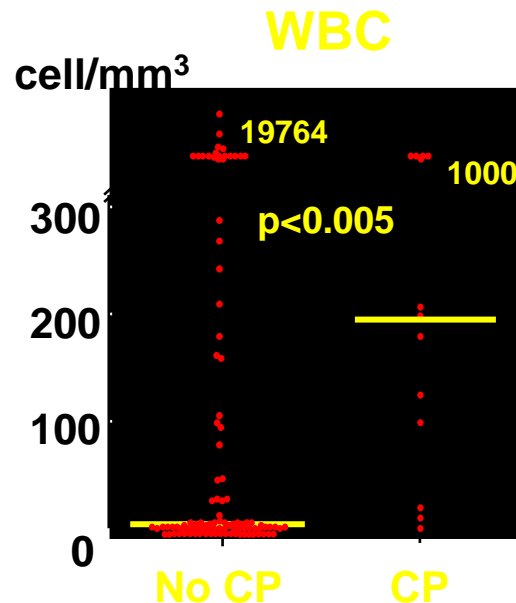
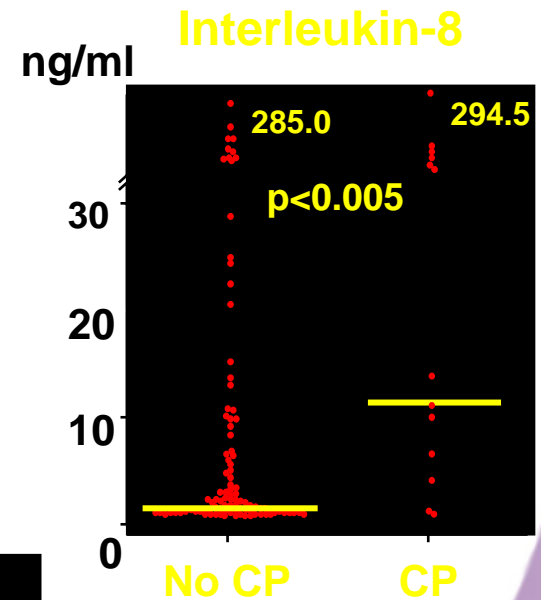
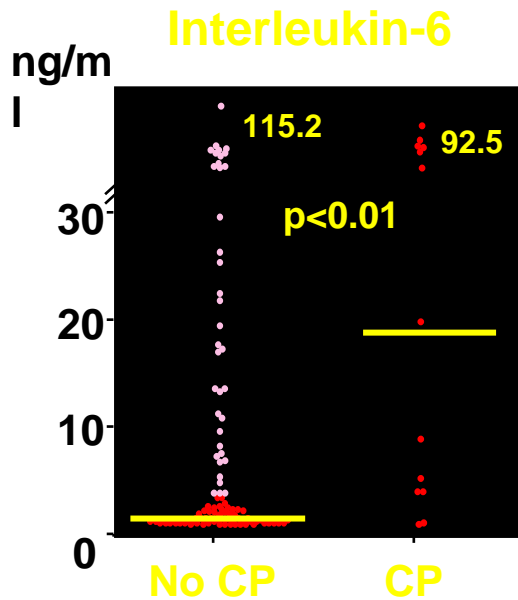
Seoul National University, Korea



Amniotic fluid cytokines according to PVL



Amniotic fluid cytokines & WBC according to CP



*Am J Obstet
Gynecol*

2000;182:675-81



Cerebral palsy (n=14)

**Inflammatory
cluster
(n=11)**

**Non-inflammatory
cluster
(n=3)**

(+) Histologic chorioamnionitis	100% (9/9)
(+) Funisitis	100% (9/9)
Elevated AF cytokines	100% (10/10)
AF WBC count >50 cells/mm ³	100% (10/10)
(+) AF Culture	45% (5/11)
Umbilical arterial pH >7.20	100% (7/7)



Case of cerebral palsy

- PPRM
- AF culture: positive
- AF WBC: >1000 cells/mm³
- AF IL-6: 55.4 ng/ml
- Birth: GA 29.6 wks, 890g
- Funisitis: positive
- Cystic PVL on USG & MRI



- Onset of PTL has protective / survival value
- When intrauterine environment is hostile and threatens the fetus, signals mediating fetal damages (cytokines) also signal the onset of labour



White matter injury in preterm infants

Professor David Edwards,
Hammersmith Hospital, London,
UK

1st International Preterm Labour Congress, Montreux, Switzerland, June 2002



Fetal infection and brain injury

- Definition of brain injury difficult:
 - Ultrasound imaging inaccurate
 - Follow-up studies affected by post-natal life
- Understanding late fetal immunology difficult:
 - Cord blood and amniotic cytokines are helpful, but have multiple actions and are involved in parturition
 - Biology of intrauterine infection poorly understood
- Improved approaches?



How does T cell activation relate to tissue injury?

- Interferon gamma inhibits Th2 and promotes Th1
- Interleukin 4 inhibits Th1 and promotes Th2
- T cells thus polarise to Th1 or Th2
- Inverse relation between number of Th1 and Th2 cells
- Th1 tends to equate to cell mediated immunity and has been associated with injury to host tissues
- Th2 tends to equate to humoral immunity

HYPOTHESIS:

Abnormal MR images soon after birth will be seen in infants who have a T-cell response polarised to Th1



A potential approach to infection and immune associated tissue injury:

- CD4+CD25+ T cells are recently discovered T cells which suppress immune responses
- CD4+CD25+ cells are present in high numbers in the umbilical blood of preterm infants, at least from 23 weeks onward

(Ng, Duggan, Ponchel et al, Blood 2001;98:2736-2744)



Why are CD4+CD25+ cells interesting ?

- CD4+CD25+ cells may be an example of endogenous immune control and modulate the response to infection
- Neonatal thymectomy in mice that prevents CD4+CD25+ cells being produced causes multisystem tissue injury
- CD4+CD25+ cells may prevent self harm during infection



Conclusions and speculations

- Fetal immune activation following exposure to antigen is associated with brain and lung injury
- However, we found:
 - a variable response to bacterial infestation
 - no precise relation between cord blood cytokinaemia and tissue injury
 - that Th1/2 balance does not explain tissue injury
- CD4+CD25+ T cells may regulate potential self-harm during an immune response, and
- We speculate that mechanisms of this sort may explain in part the observed variability

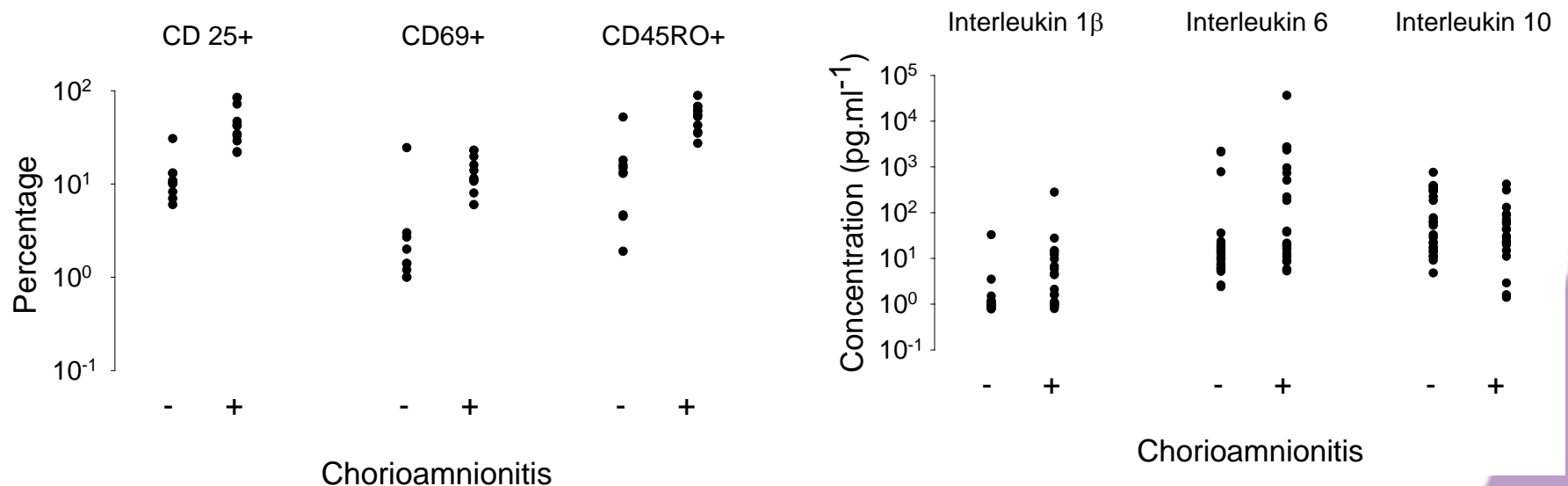


Validation of MRI in preterm infants

- MRI agrees well with neuropathology
- However subtle lesions, such as regions of increased apoptosis, will be missed
- No data on diffuse high signal in white matter
(Jouvet et al AJNR 1999; 20(7): 1343-8)
- Ultrasound predicts white matter changes seen on MRI poorly
(Maalouf et al Pediatrics 2001; 107: 719-27)



Chorioamnionitis is associated with increased pro-inflammatory cytokine concentrations and T-cell activation in fetal blood



(Duggan, Steele et al, unpublished)



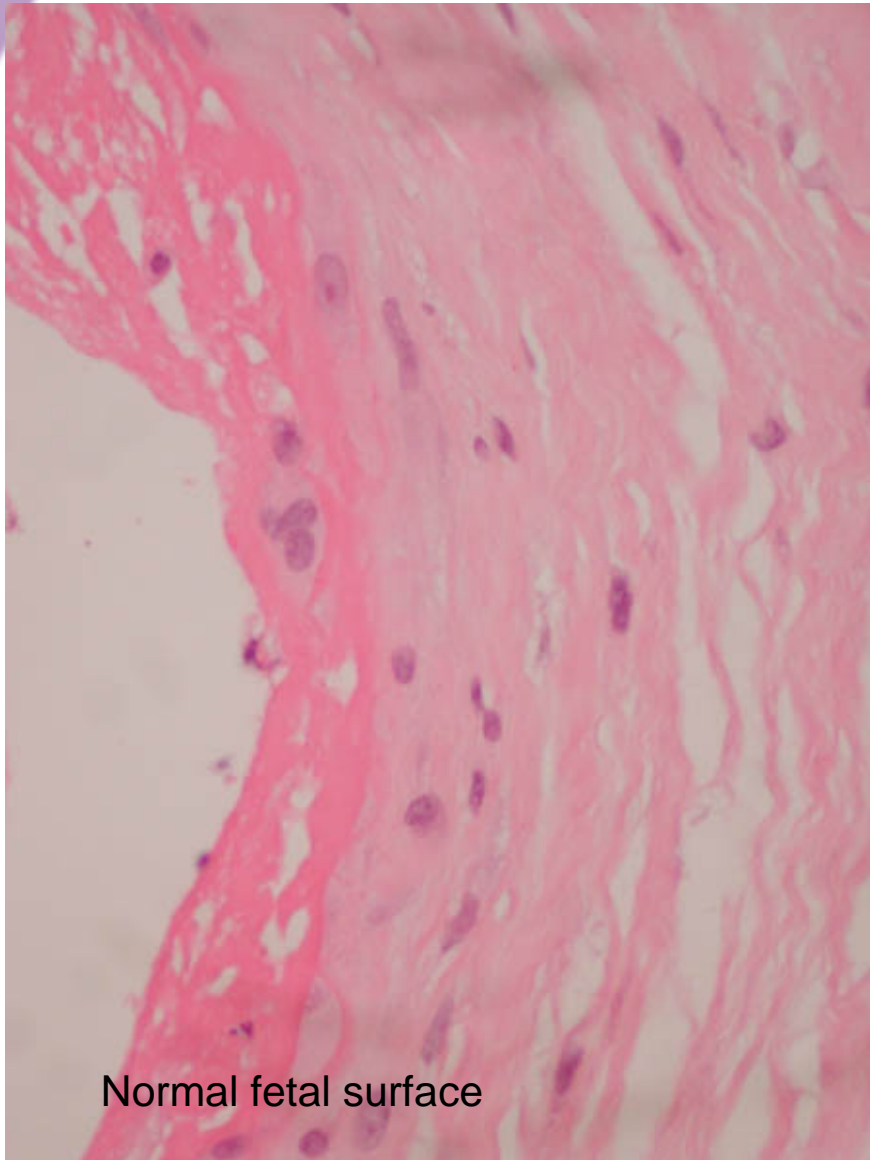
The critical role of perinatal pathology

Dr Iona Jeffrey, St George's
Hospital, London, UK

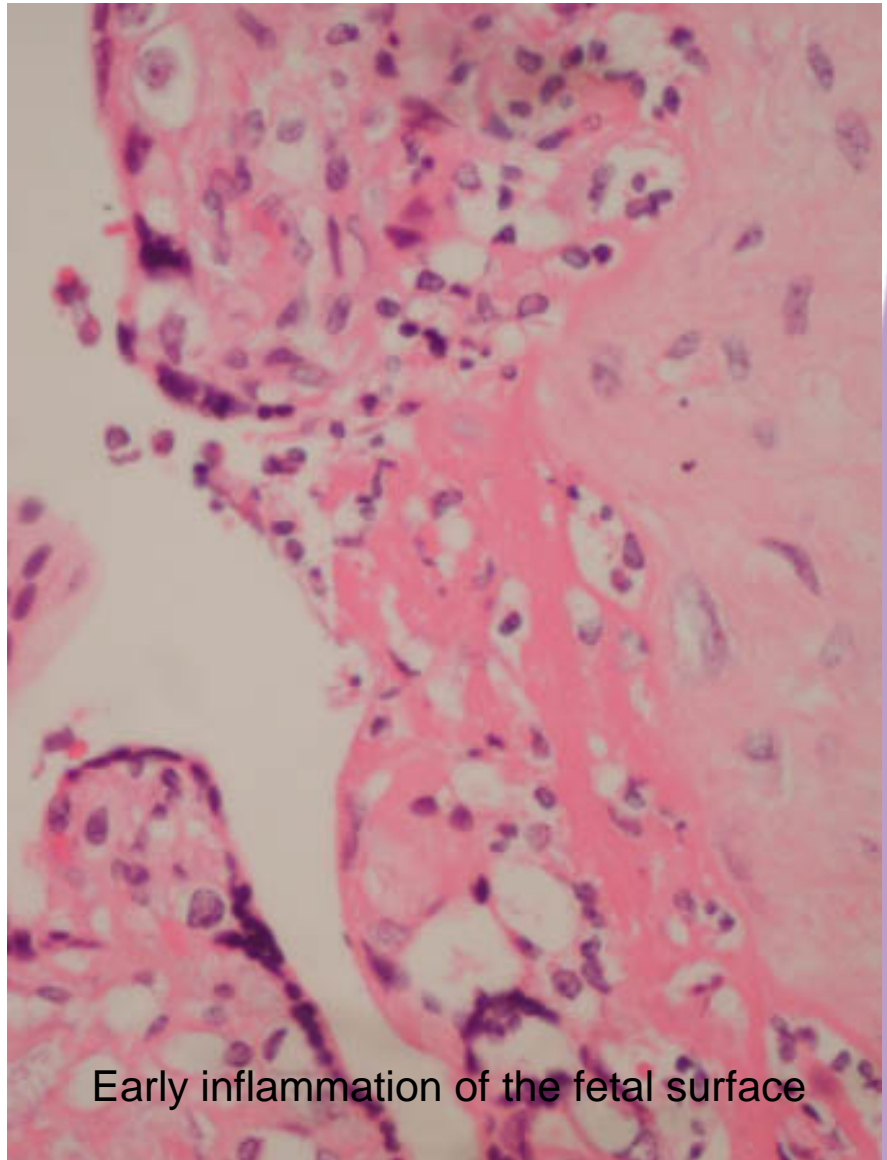
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Acute chorioamnionitis

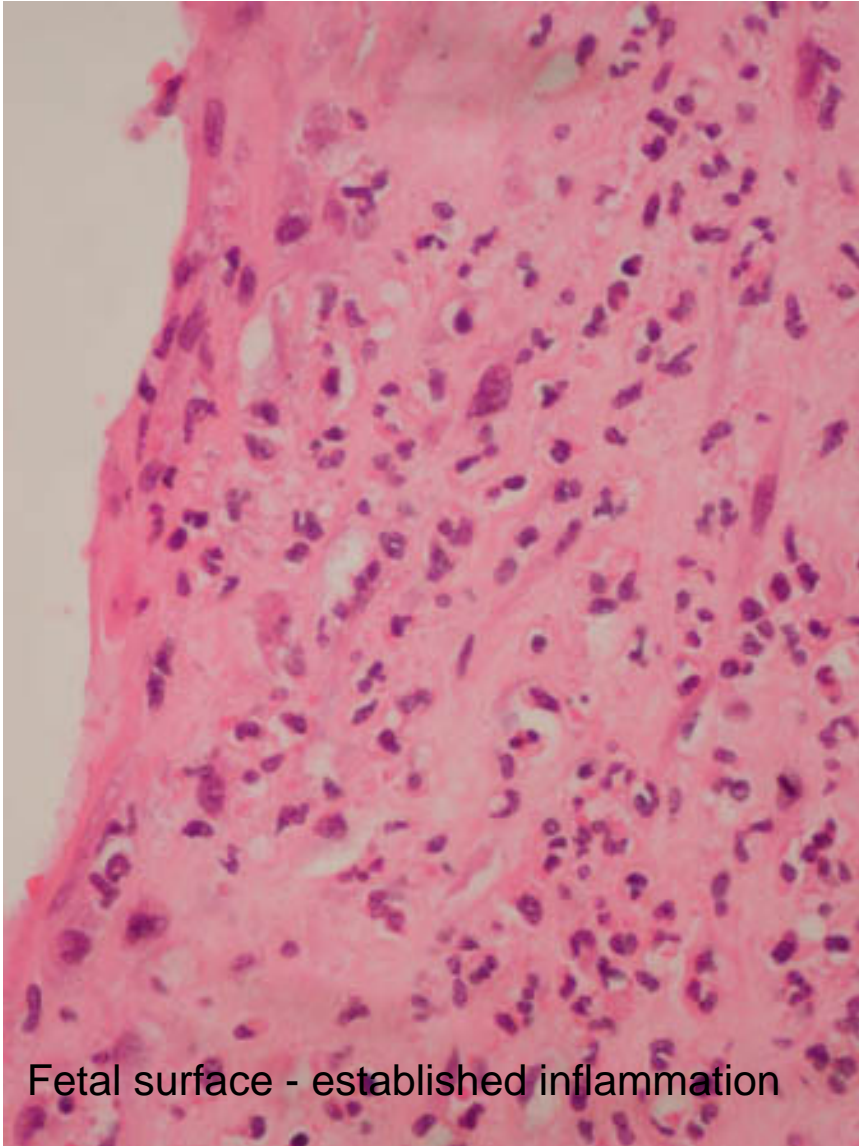


Normal fetal surface

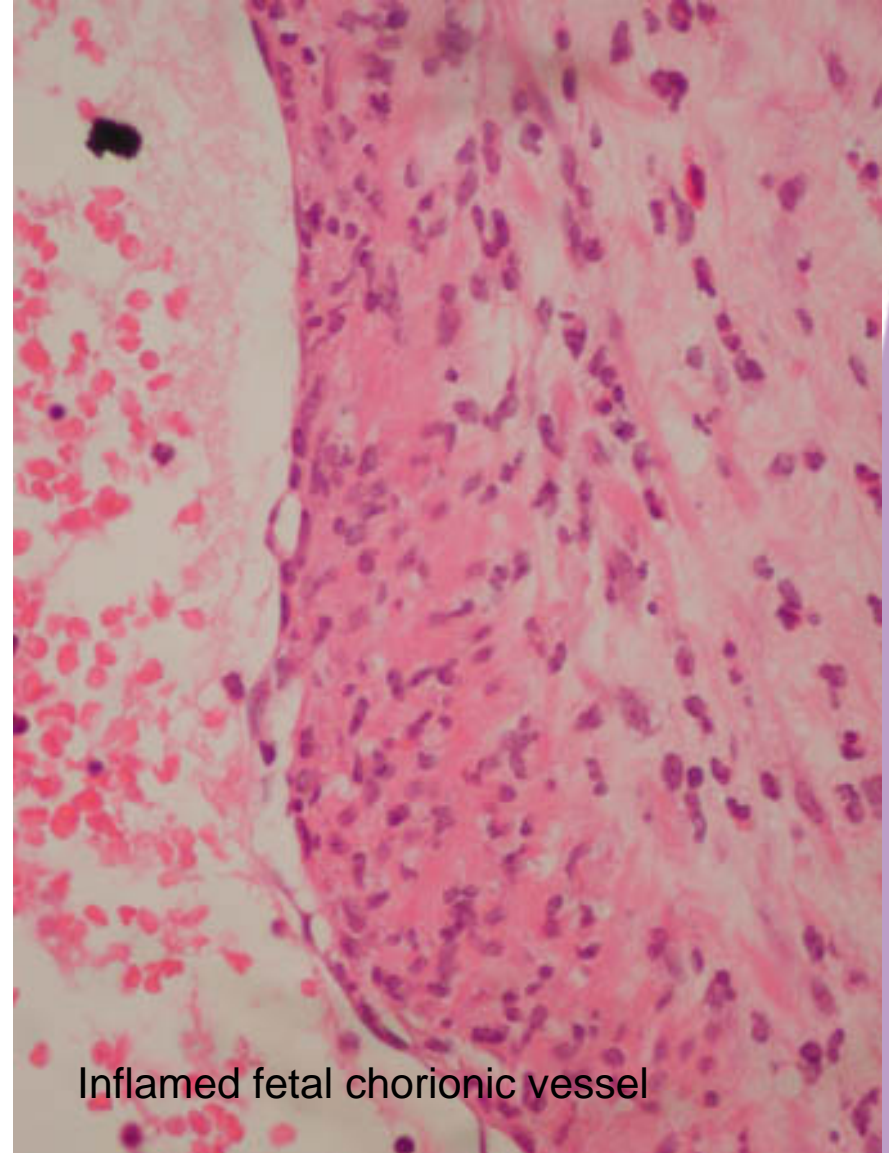


Early inflammation of the fetal surface

Acute chorioamnionitis



Fetal surface - established inflammation



Inflamed fetal chorionic vessel

Preterm labour and preterm birth

Histological acute chorioamnionitis

- Usually caused by infection
 - May not reflect duration
 - May not reflect pathogen
- ?Due to presenting part
- ?Due to placental separation
- ? Due to cord compression



Preterm labour and preterm birth

Abnormal placentation

- Naeye 1989
- Salafia et al 1991
- Arias et al 1993
- Lettieri et al 1994
- Arias et al 1997



Preterm labour and preterm birth

The future of perinatal pathology

- Contribution to epidemiological studies
- Demonstration of complications of PTB
- Research into mechanisms of tissue damage
- Material for genetic studies

BUT

- Future destruction of tissue archives
- Lack of parental consent for research
- Too few perinatal pathologists



Looking to the future

Dr Ronald Lamont
Northwick Park Hospital, Harrow,
UK



Concepts of SPTL and PTB

PROACTIVE

versus

REACTIVE

Reduce risk factors
Improve sociobiological status
Better prediction: OFFN
BV
Cx length

Prevention: Antibiotics
Cx cerclage
Prophylactic tocolytics

Early detection: Patient education
Home monitoring

Tocolytics
Steroids
Intrauterine transfer
Exclude infection



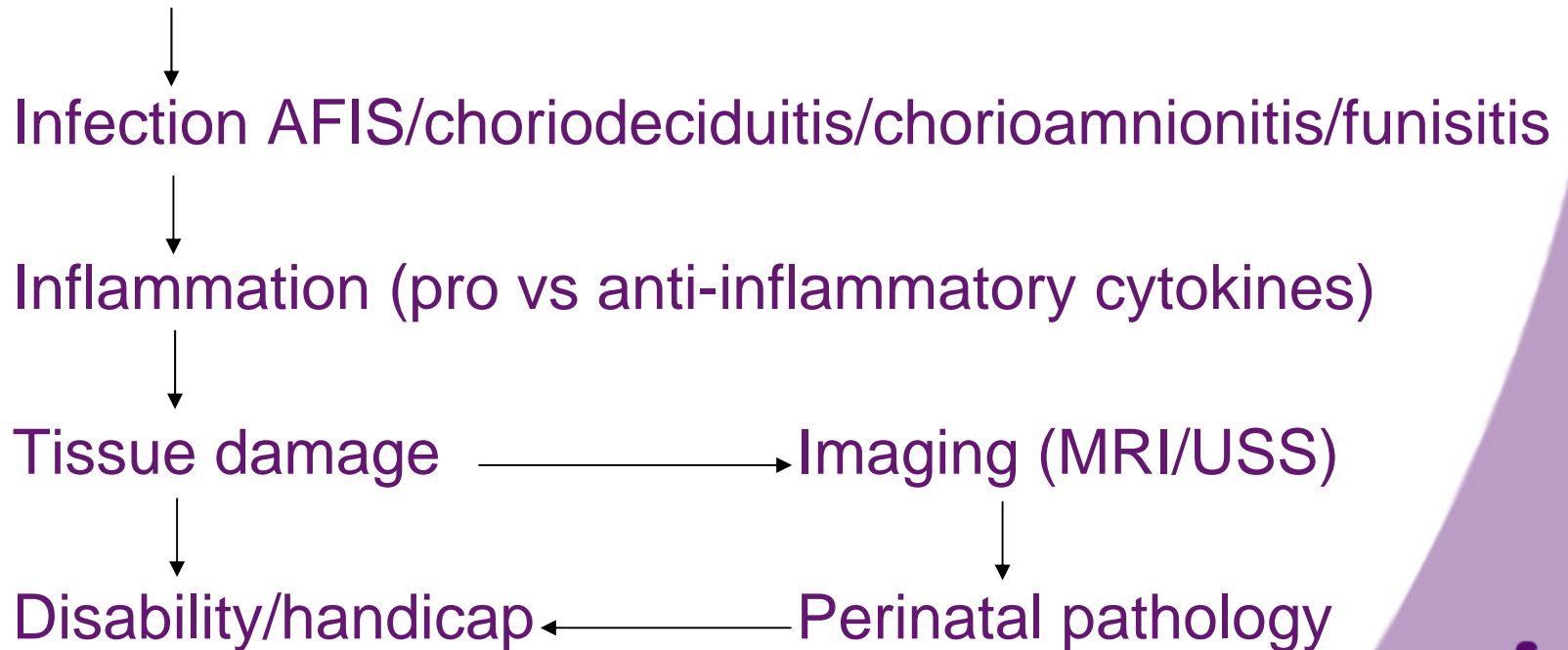
The future: prevention of PTB

- Short Cx on TVUSS – what to do?
- Detection of OFFN – what to do?
- Abnormal genital tract flora – what to do?
 - Screen and treat and rescreen and retreat?
 - Prophylaxis?
 - At what gestation?
 - What antibiotics/dose/duration?
 - Route of administration?
 - What measure of outcome?
 - What risk of PTL?



Immunology of PTB

- Fetal and maternal response to:
Abnormal genital tract flora



The future: genetic factors

Susceptibility

vs

Exposure

Predisposition to
produce pro-inflammatory
cytokines (immunology)

vs

Abnormal colonisation



Controversies in preterm labour

- Aetiology
- Prediction
- Prevention
- Diagnosis
- Intervention
 - Tocolytics
 - Steroids
 - Antibiotics
- Mode of delivery
- In-utero transfer



International consensus

- PTL Council
 - PTL Management Guidelines
 - Not proscriptive
 - Discussion point to achieve consensus and common practice within and across borders
 - Dx; intervention; EBM review of tocolytics
 - Future guidelines
 - In utero transfer; steroids; antibiotic use
- Central database collection
 - Web-based data entry with direct feedback

