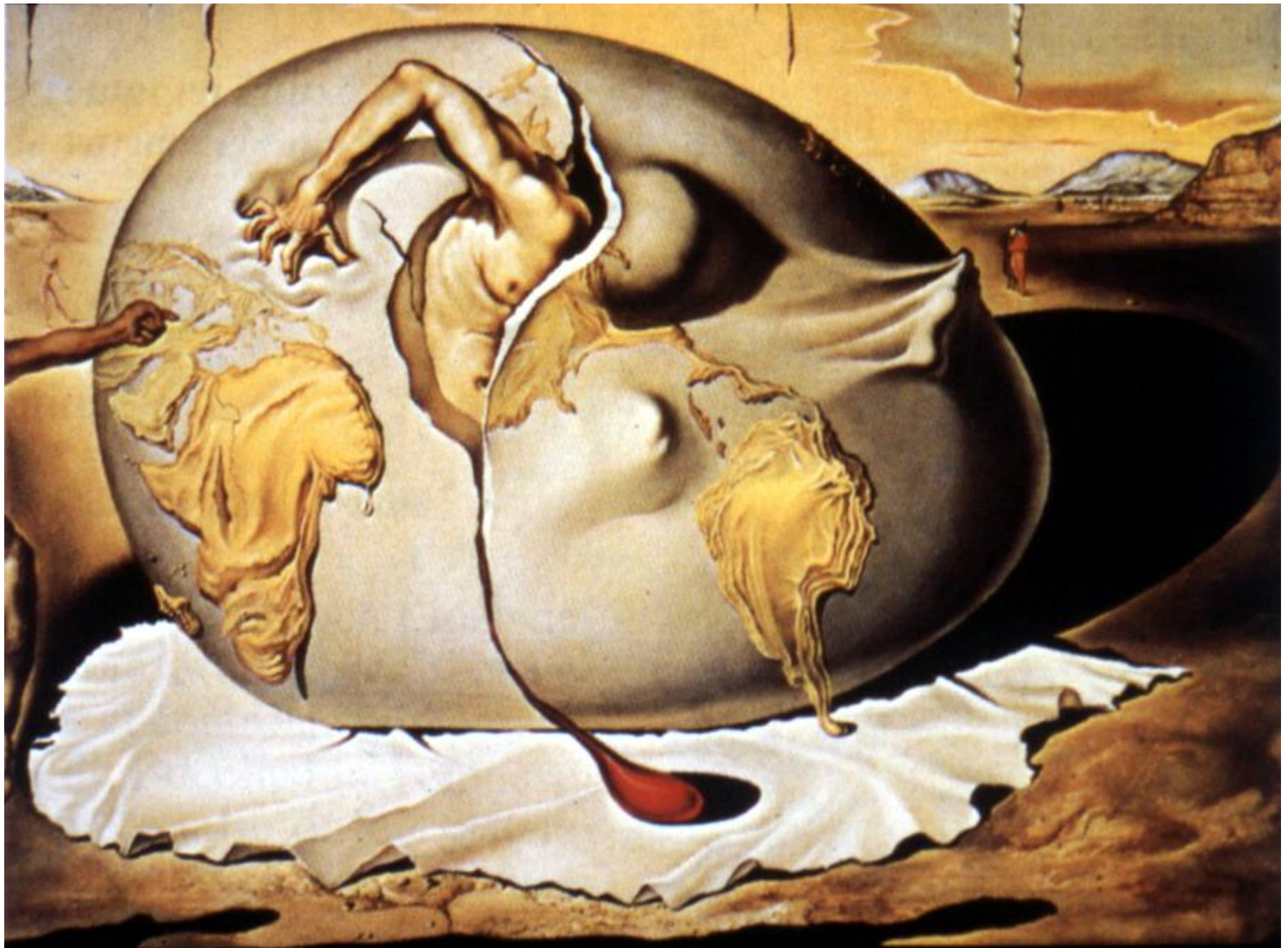


Diagnosis and management of fetal infection. A perinatologist perspective

Yves Ville

The 9th World Congress of
The International Association of Maternal and
Neonatal Health (IAMANEH)

Cairo - November 2, 2006



Neurotropic viruses and cerebral palsy: population based case-control study

Catherine S Gibson, Alastair H MacLennan, Paul N Goldwater, Eric A Haar Kevin Priest, Gustaaf A Dekker and South Australian Cerebral Palsy Research Group

Dried blood spots

N=443 CPs

N=883 Controls

Viral nucleic acid

HSV1-2

CMV

VZV

EBV

Enterovirus

Virus	All types of cerebral palsy (n=227)	Diplegia (n=49)	Hemiplegia (n=81)	Quadriplegia (n=65)
HSV (10)*	0.92 (0.44 to 1.92)	0.85 (0.20 to 3.67)	1.04 (0.35 to 3.03)	0.31 (0.04 to 2.33)
CMV (66)	1.30 (0.92 to 1.83)	1.03 (0.52 to 2.02)	1.04 (0.61 to 1.78)	1.62 (0.94 to 2.80)
Herpes group B (23)†	1.69 (0.98 to 2.92)	2.45 (1.02 to 5.89)‡	2.38 (1.15 to 4.92)‡	0.00 (0.00 to 0.89)‡
Herpes group A (73)§	1.25 (0.90 to 1.74)	0.95 (0.49 to 1.84)	1.11 (0.67 to 1.85)	1.45 (0.84 to 2.48)
Any herpes virus (88)¶	1.52 (1.09 to 2.13)‡	1.41 (0.74 to 2.67)	1.38 (0.83 to 2.30)	1.25 (0.71 to 2.20)
Enterovirus (10)	1.63 (0.74 to 3.62)	1.55 (0.35 to 6.90)	1.83 (0.60 to 5.58)	1.12 (0.25 to 4.97)
Any virus (96)**	1.64 (1.17 to 2.28)‡	1.58 (0.83 to 2.98)	1.43 (0.86 to 2.37)	1.29 (0.74 to 2.24)

Epidemiology

SERONEGATIVE PREGNANT WOMEN **43.5** [IC95%:42.1 – 44.9] to **51.5** [48 – 54.5] %

SEROCONVERSION **1%** [IC95%:0.6 – 1.4]

VERTICAL TRANSMISSION RATE **47.4 %** [IC95%:24.5 – 71.1]

PREVALENCE AT BIRTH **0.5 %** [IC95%:0.2 – 0.8]

500 / 100,000 liveborn NN in France

PERINATAL MORTALITY **0** [IC95%:0 – 8.2] to **4.7** [0.98 – 13.1] %

SEQUELAE

SYMPTOMATIC

25 [IC95%:3.2 – 65.1] to **43.7** [31.4 – 56.7] %

ASYMPTOMATIC

8.6 [IC95%:0 – 17.8] %

CMV Congenital Infection

PRIMARY INFECTION

5-10% Severe

- IUGR
- Microcephaly
- Ventriculomegaly
- Seizures
- Spasticity

NND

30%

5-10% Moderate

- Hepatomegaly
- Splenomegaly
- Hepatitis
- Thrombocytopenia

Sequelae

30%

90% Asymptomatic

- No clinical sign

5-15%

60%

Intellectual Assessment of Children Born with Asymptomatic Congenital CMV Infection.

204 children, aged 5-200 Mo.

8% Hearing loss (1/2 bilateral, 2 excluded)

Compared with

177 Uninfected control siblings aged 6-203 Mo

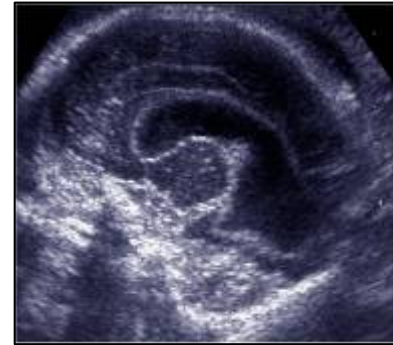
Test (Age range)	Infected cases			Controls		
	n	x	sd	n	x	sd
Stanford Binet FSIQ (30-42Mo)	34	83.62	15.97	23	84.74	19.9*
WPPSI FSIQ (60-72Mo)	28	85.43	17.68	46	91.98	18.74
WPPSI FSIQ (84-156Mo)	47	94.23	15.35	70	93.56	13.56
Developmental Profile FSIQ (16-156Mo)	159	117.26	22.45	130	115.41	20.81

***, below normal in both groups. NS from Normal and between groups otherwise**

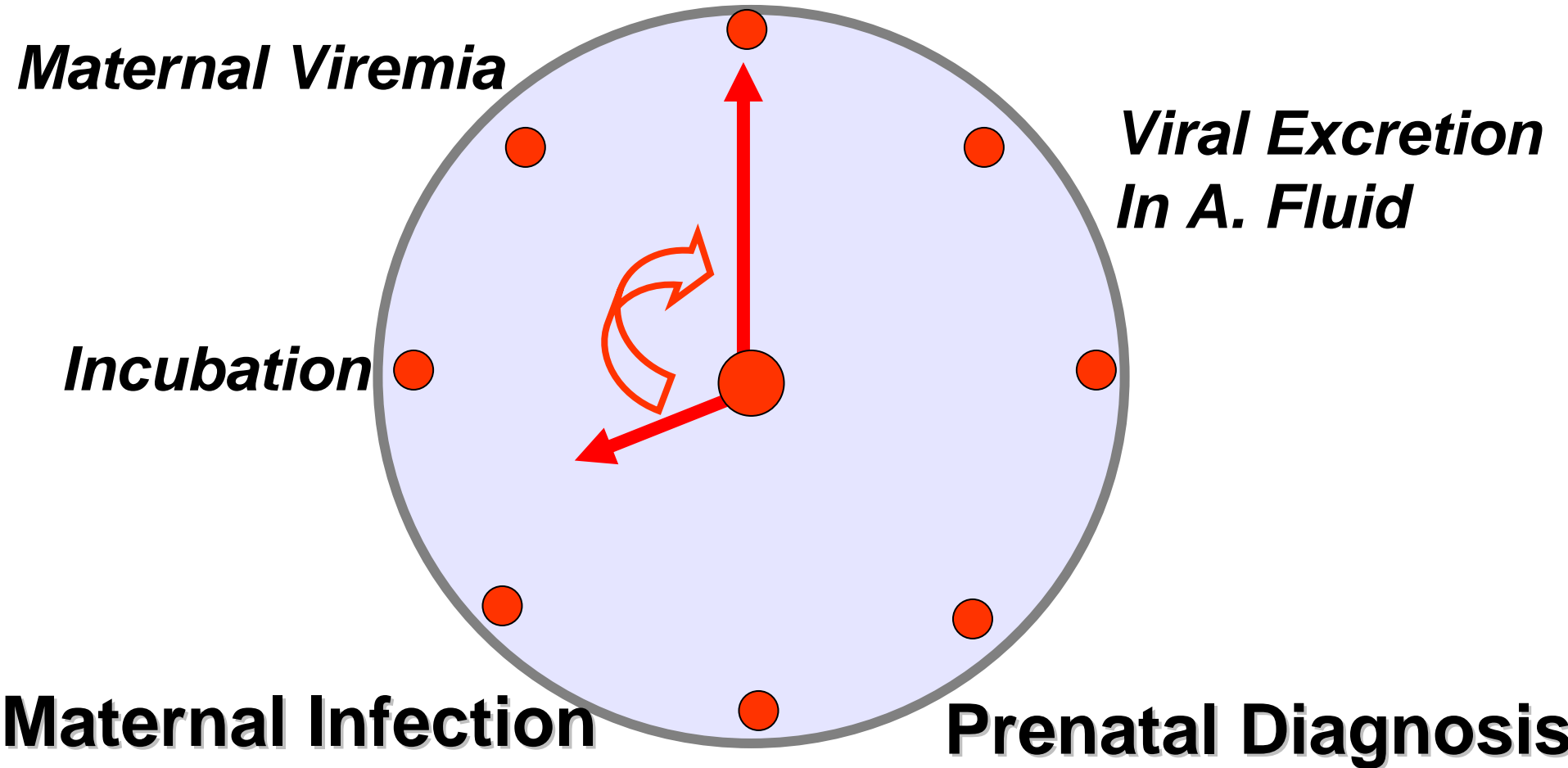
Fetal CMV Infection

Diagnostic value of Ultrasound

Guerra	2000	30	20 %
Liesnard	2000	55	25 %
Enders	2001	17	12 %
Hohlfeld	2001	26	19 %

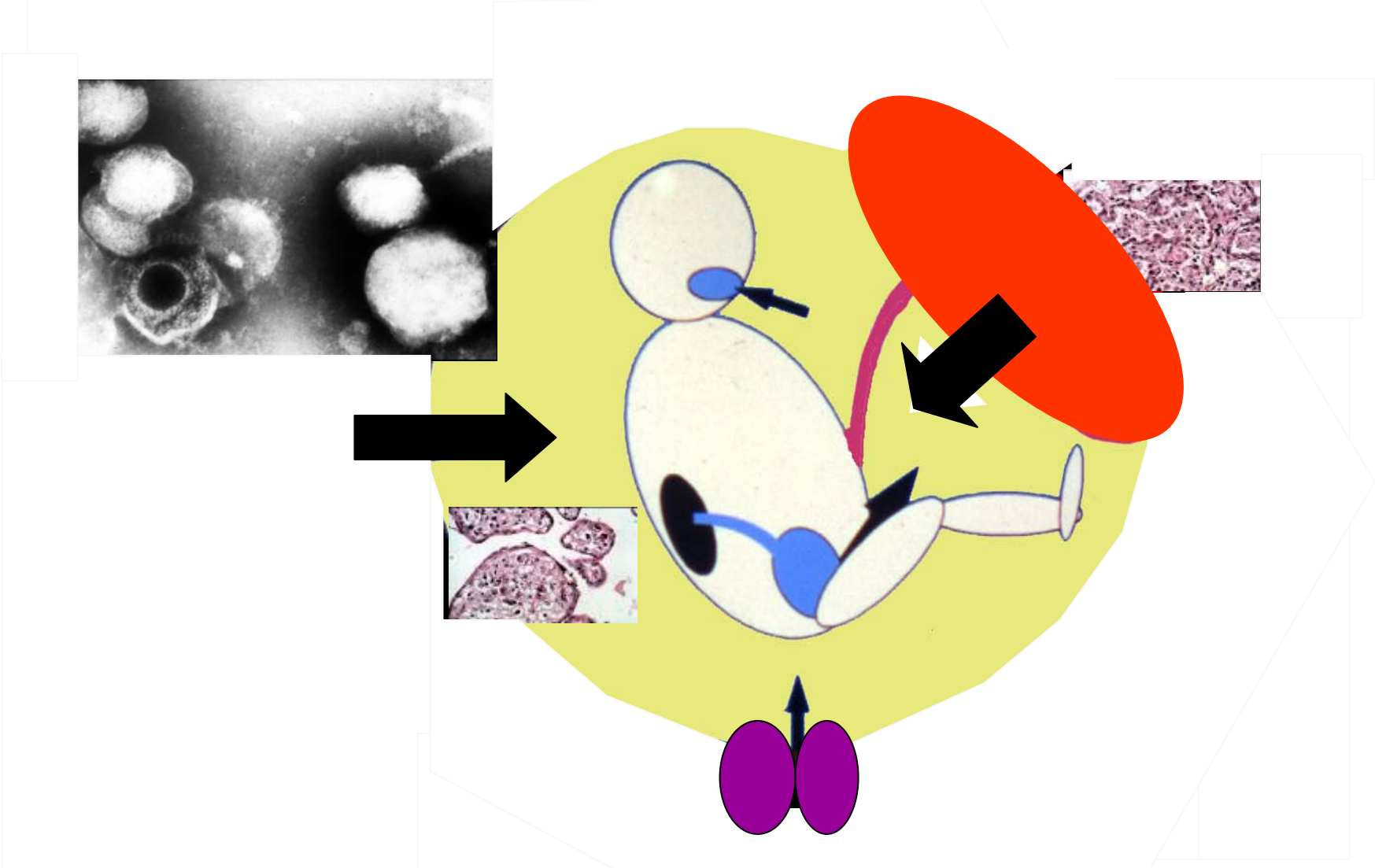


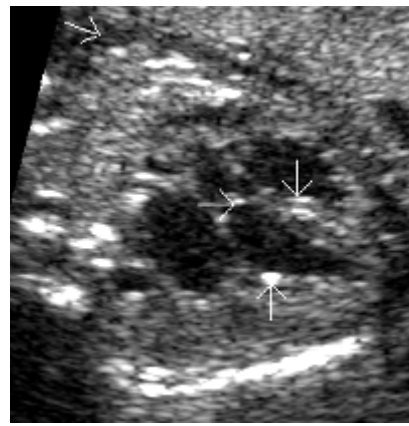
Fetal Infection



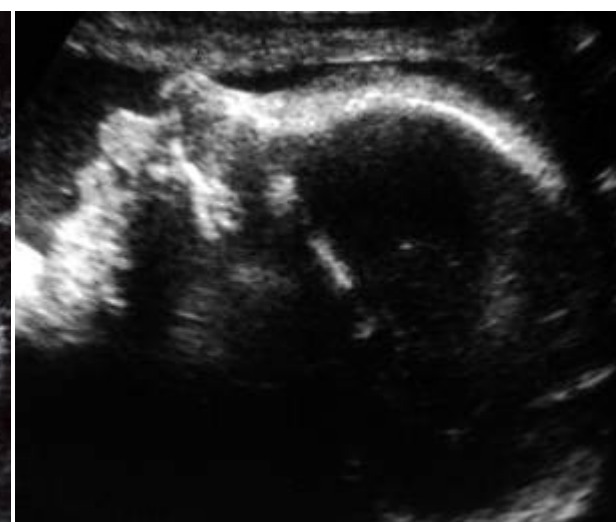
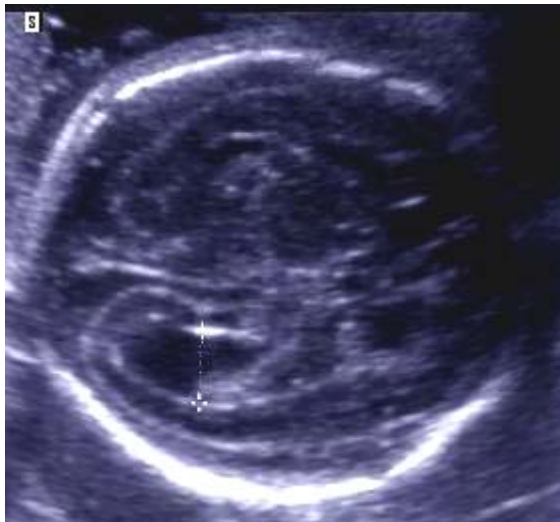
Fetal Affection ?

6 WEEKS from seroconversion 22 WEEKS OF GESTATION

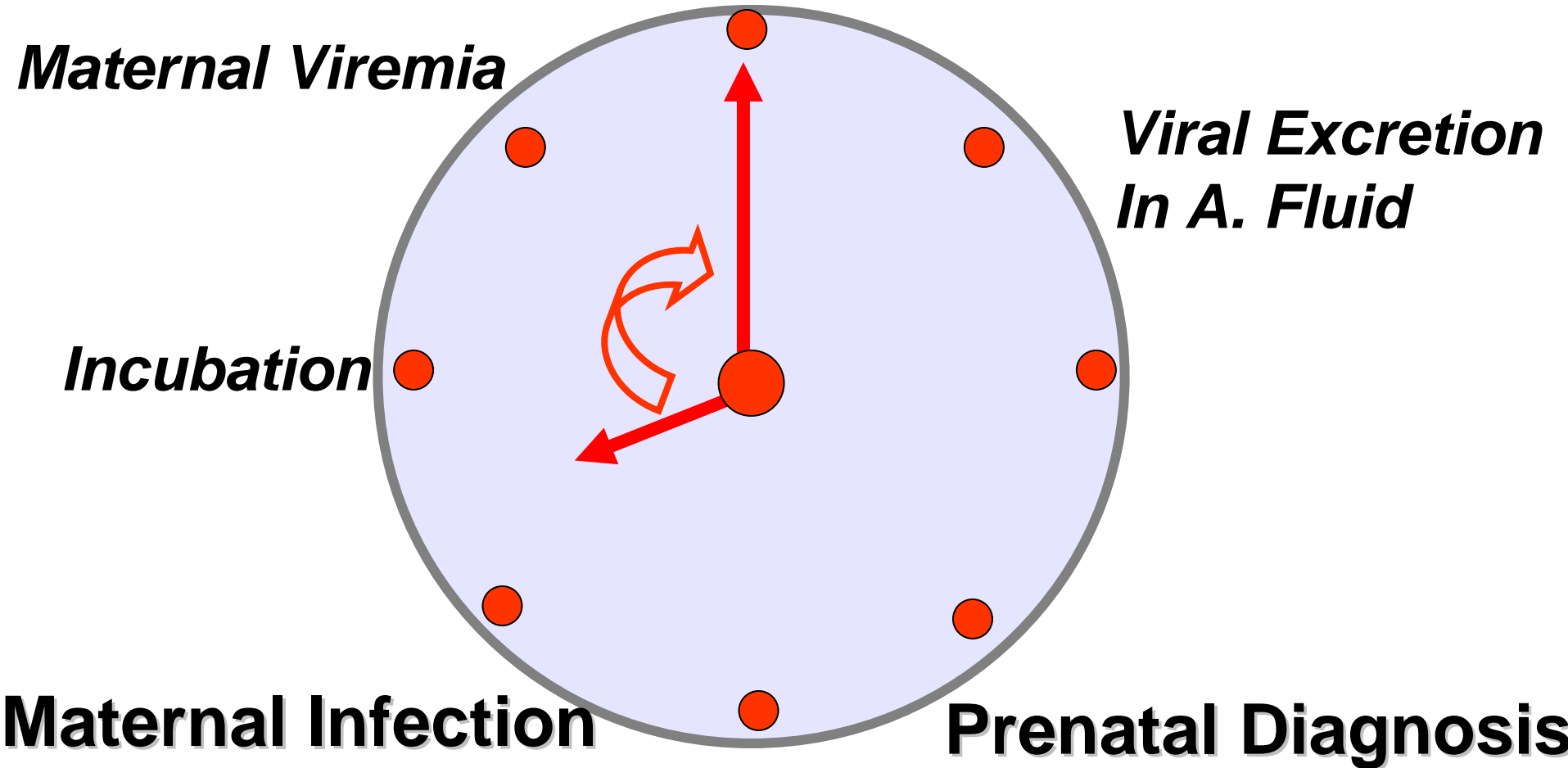




Fetal CMV Infection is a progressive disease

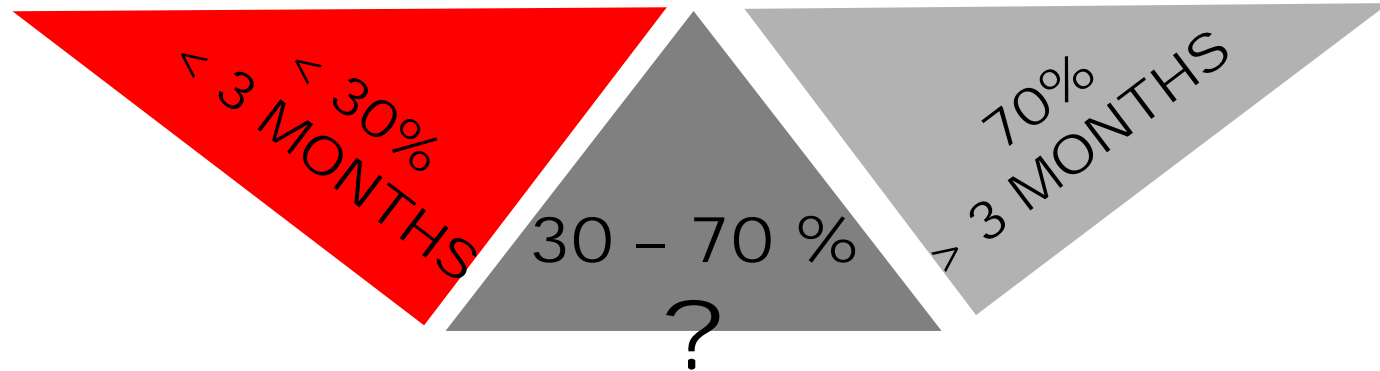
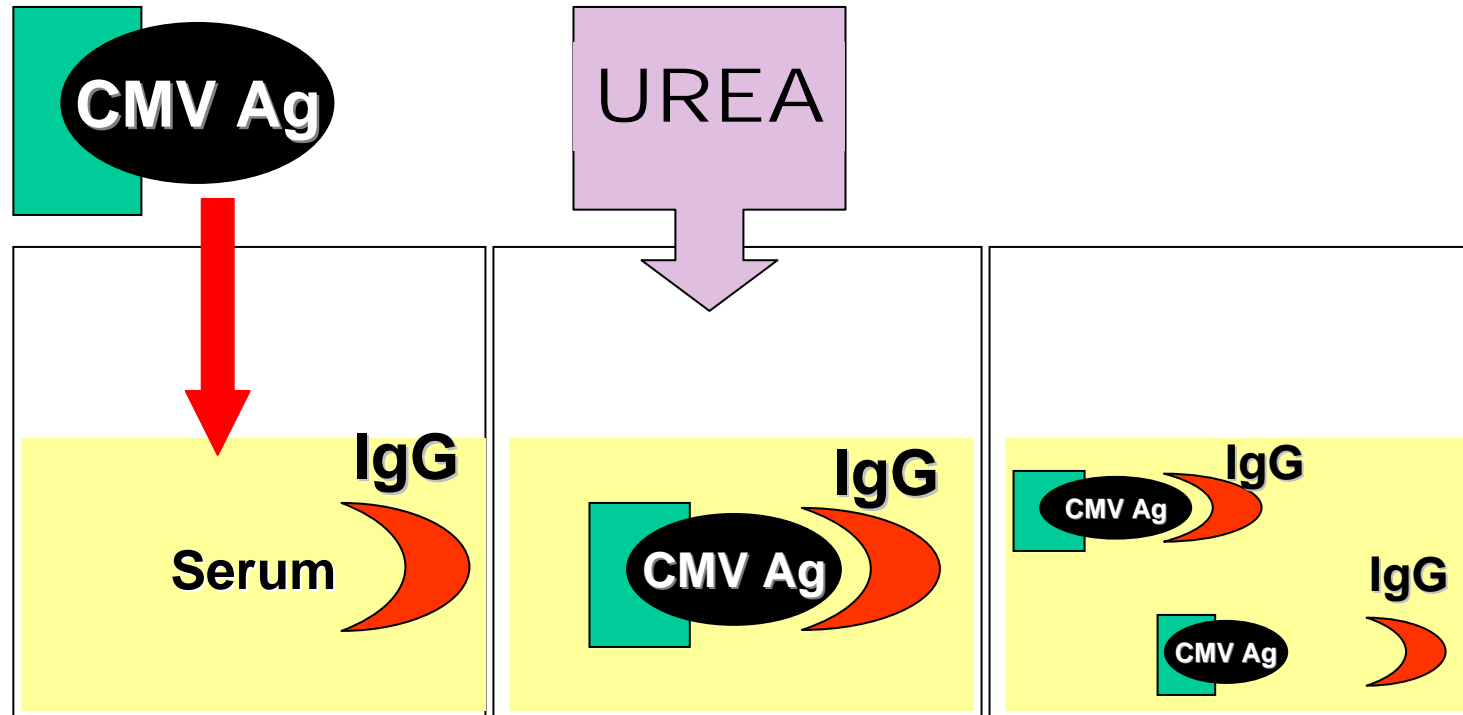


Fetal Infection



Fetal Affection ?

Anti-CMV IgG Avidity



DIAGNOSIS OF FETAL CMV INFECTION IN AMNIOTIC FLUID

Bodeus 1999

	Amniotic Fluid (N=35)	
	PCR (+)	PCR (-)
Culture (+)	25	1. <i>b</i>
Culture (-)	1 . <i>a</i>	8
Total	26	9

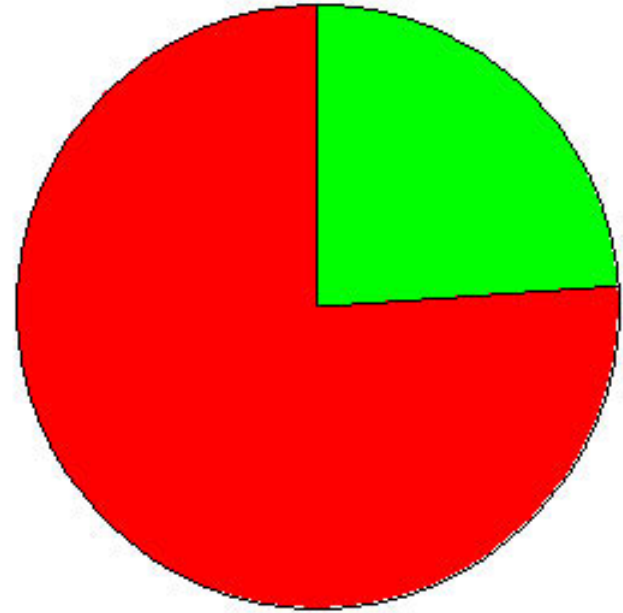
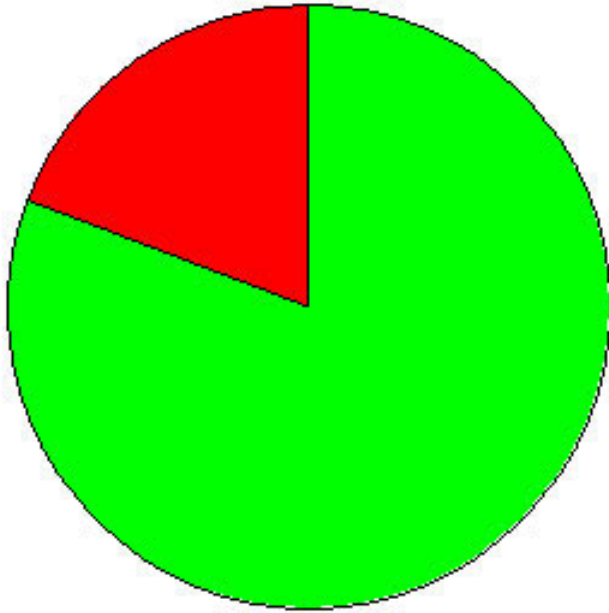
a. Repeated equivocal result in PCR

b. Inhibition of the PCR reaction

**Timing &
Natural History**

	AF Culture (+/infected NN)	
	<5w from SC	<u>>6w from SC</u>
<u>GA >23w</u>	11/21(52)	21/22(96)
GA < 22w	5/14 (36)	10/13(77)

**Any US abnormality
5/26 (19%) vs 35/46 (76%):**



$p < 10^{-4}$

***Good outcome
(no anomaly)***

***Bad outcome
(any anomaly)***

Significance of IUGR ?

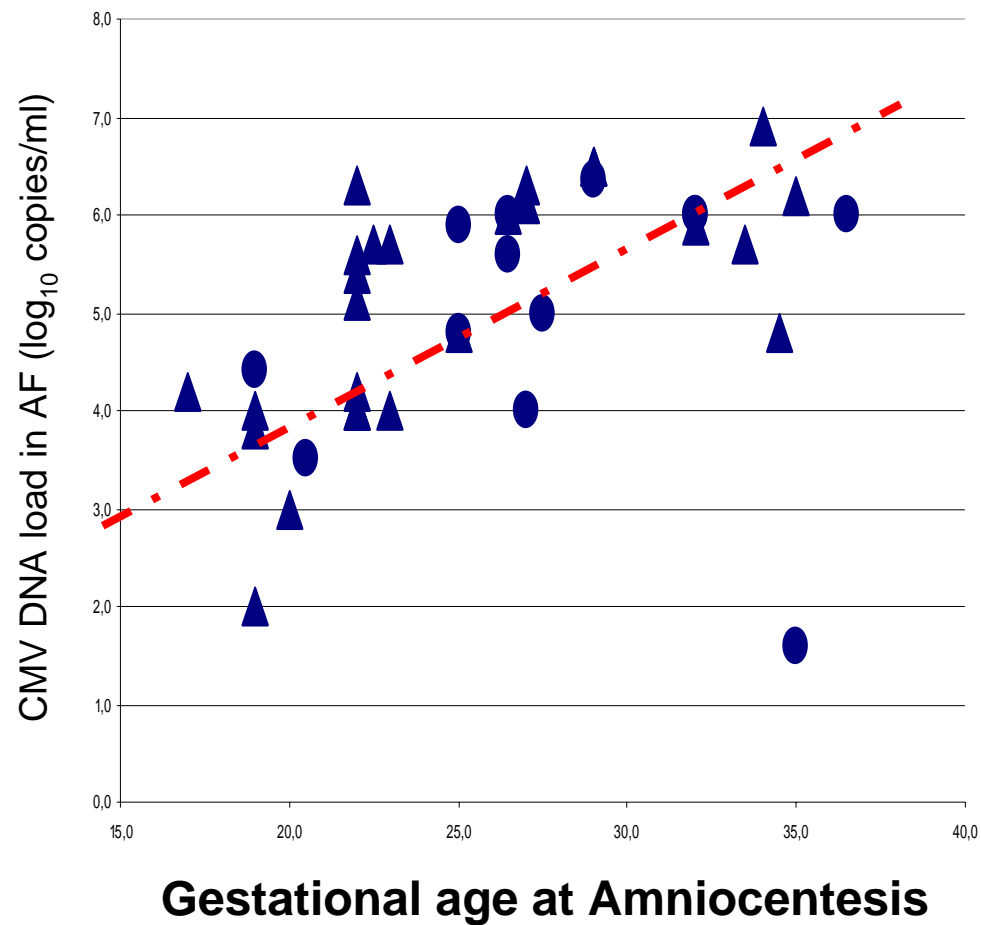
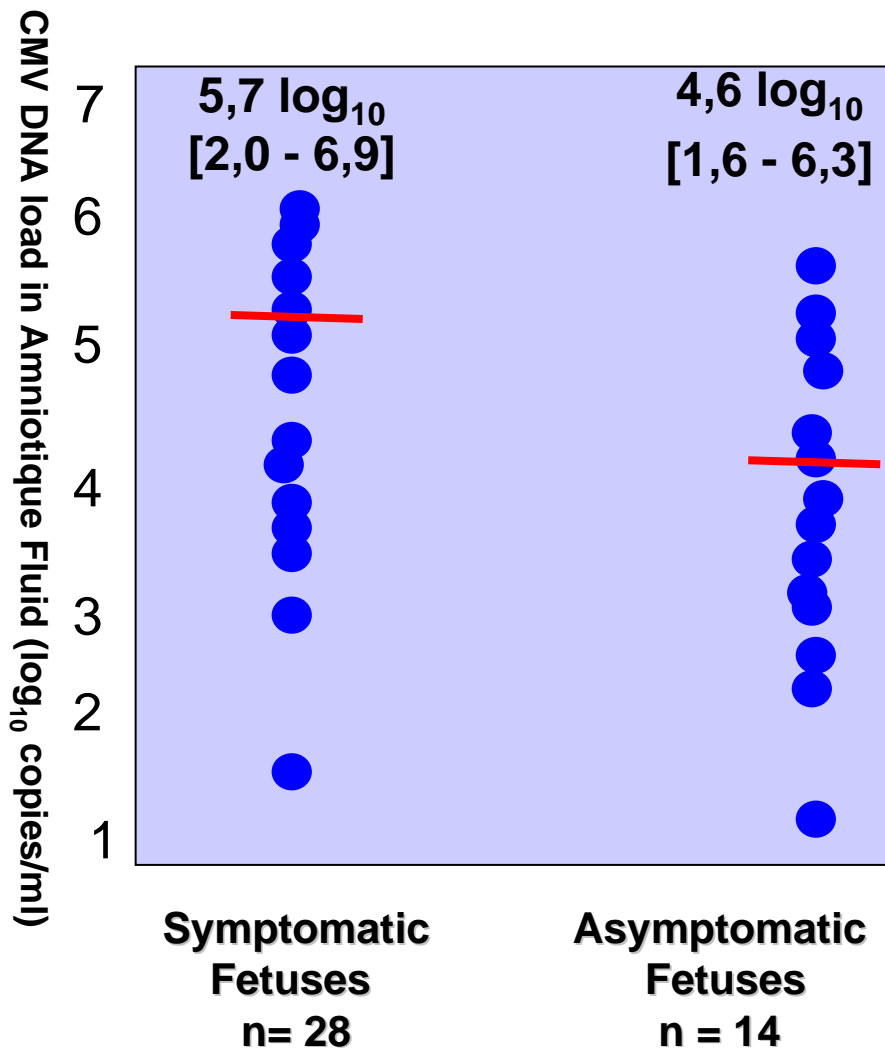
MRI, FBS, Platelets, Liver function test ?

N = 131 Neonates

NORMAL Neurological examination CT scan	ABNORMAL Neurological examination Or CT scan
42 / 114 (37%)	8 / 17 (51%)

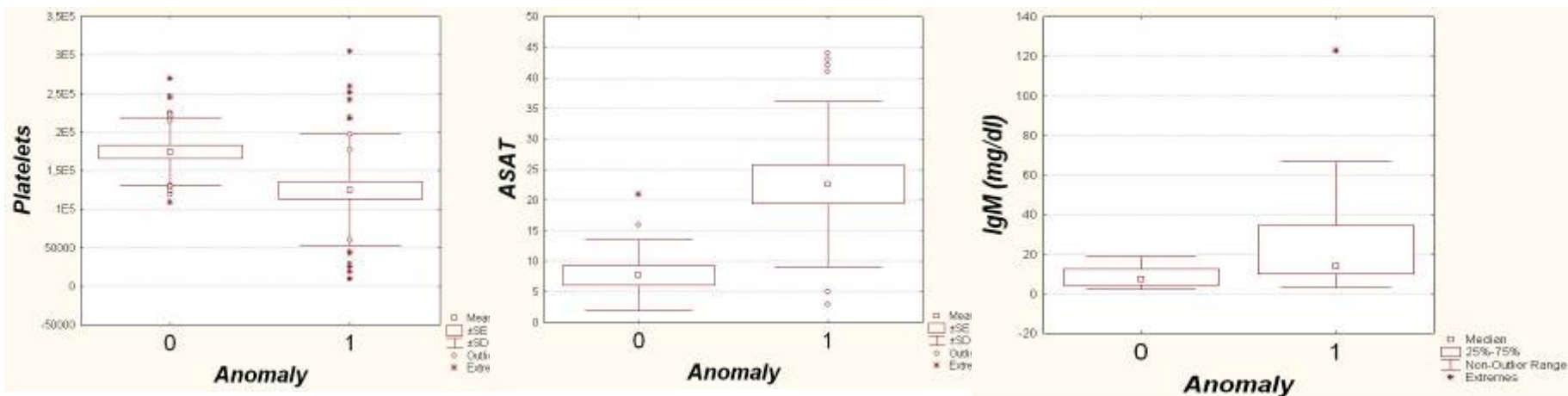
(Boppana et al 1997, Pass et al 1980, Noyola et al 2001)

VIRAL LOAD in AMNIOTIC FLUID



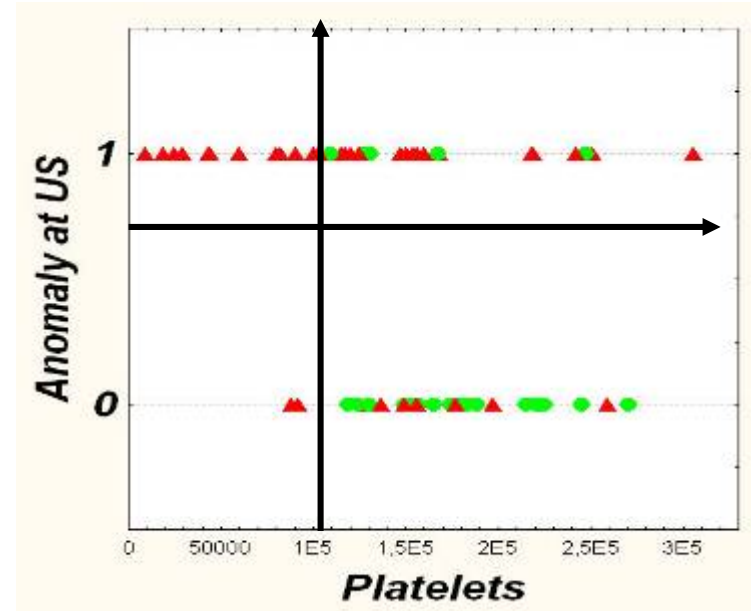
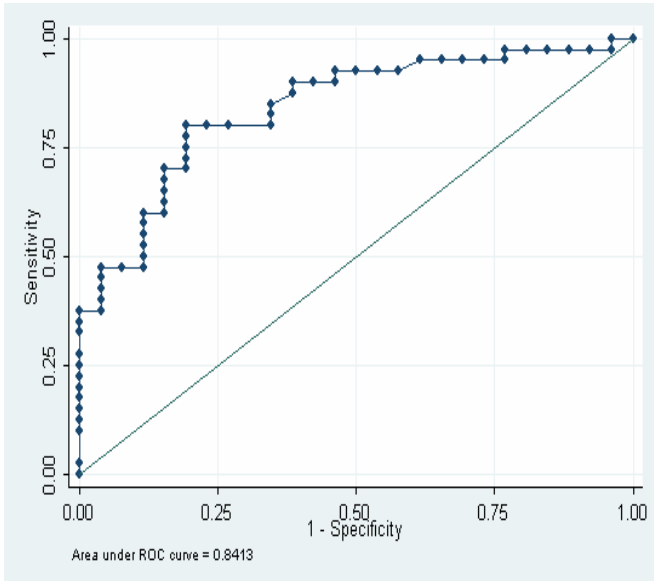
Simple logistic regression model for the prediction of anomaly:

Variable	OR	95% CI	p
Anomaly at US (if present)	13.4	[4.0;44.2]	$<10^{-4}$
Thrombocytopenia (per 10000/mm ³ decrease)	1.10	[1.04;1.25]	0.006
ASAT (per 1 unit increase)	1.18	[1.04;1.34]	0.01
IgM (per 1 mg/dl increase)	1.12	[1.02;1.24]	0.02



Multiple logistic regression model for the prediction of anomaly:

Variable	Adjusted OR	95% CI	p
Anomaly at US (if present)	9.7	[2.7;34.6]	$<10^{-4}$
Thrombocytopenia (per10000/mm ³ decrease)	1.1	[1.01;1.20]	0.05

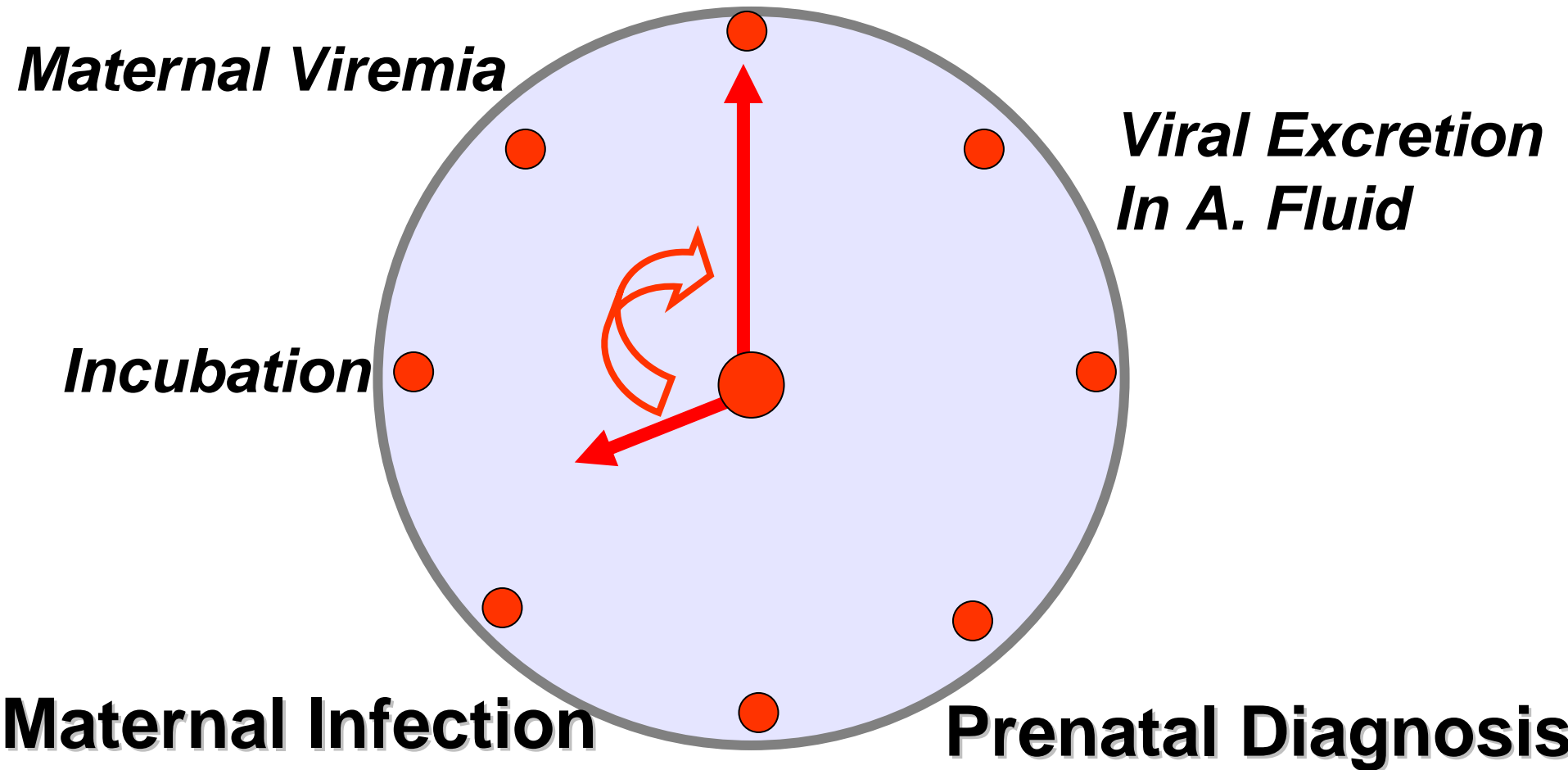


Some examples....:

- Based on this model, the probability of an abnormal outcome would be:

Findings:	Probability:
Normal US 225 000 platelets	0.22
Normal US 150 000 platelets	0.36
Normal US 100 000 platelets	0.47
US anomaly 50 000 platelets	0.84
US anomaly 100 000 platelets	0.90

Fetal Infection



Fetal Affection ?

PCR Positive in the AF

Infected Fetus

ULTRASOUND
Referral Centre
2/ Month

MRI

FETAL BLOOD SAMPLE
At Diagnosis and 32 w
Abnormal US

Affected Fetus

Non Affected Fetus

SEVERE

MODERATE

ASYMPTOMATIC

Termination

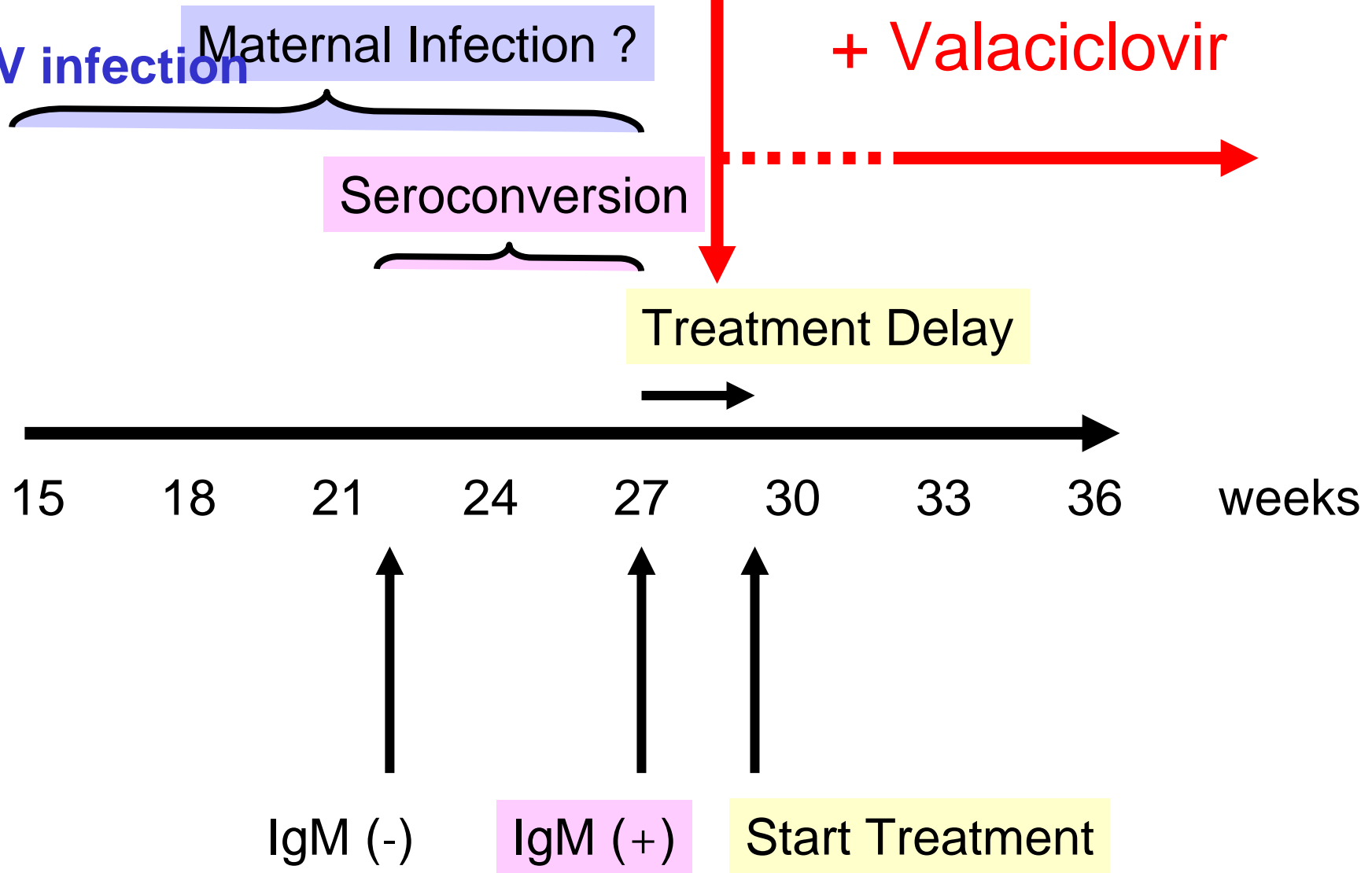
Treatment ?

Follow-up

Update

in

CMV infection



Update in

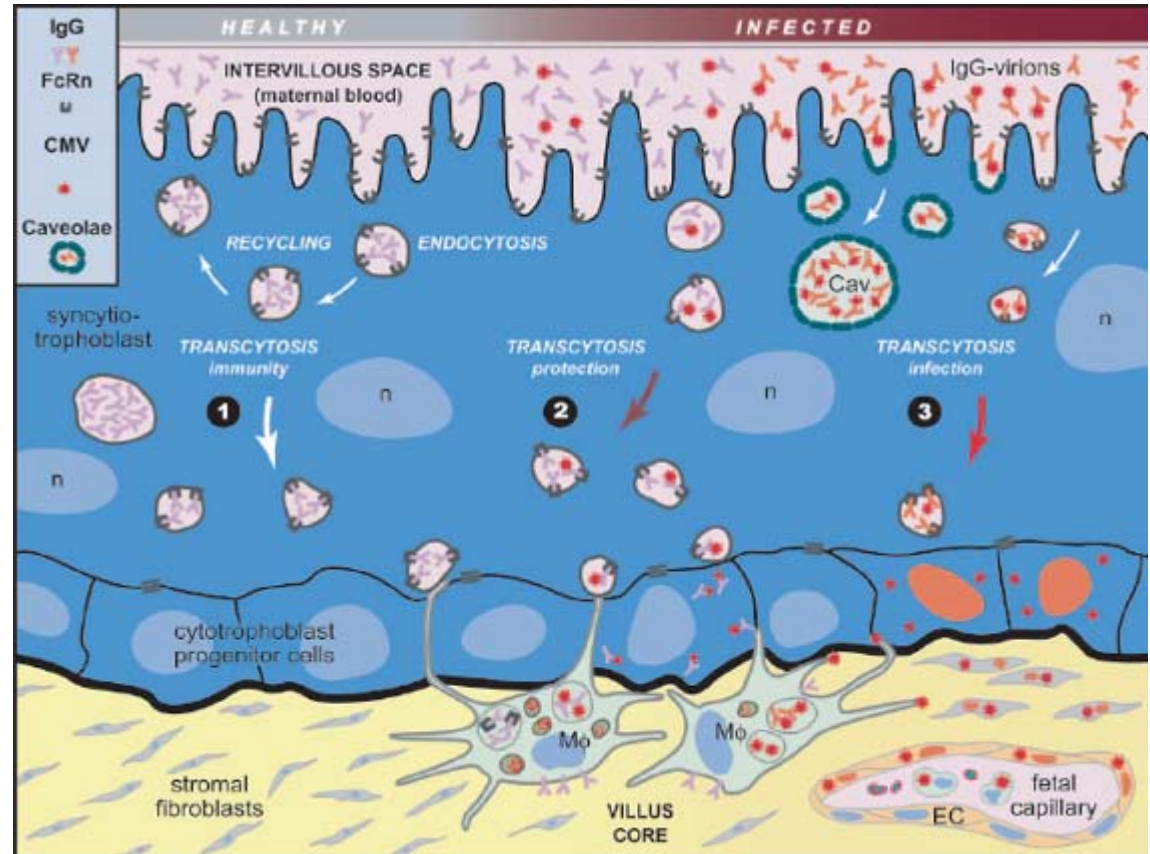
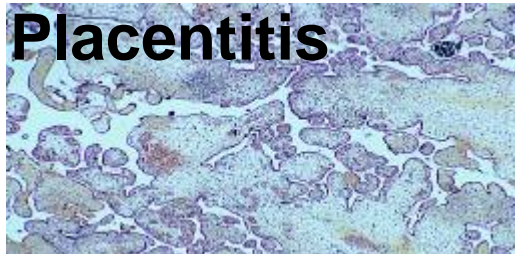
CMV infection

Immunological basis for therapy

CMV is co-opting the Ig-G antibody receptor for transcytosis (FcRn-mediated transcytosis)



Placentitis



Blocked ONLY by Highly neutreulizing antibodies

Passive Immunization during Pregnancy for Congenital Cytomegalovirus Infection

Giovanni Nigro, M.D., Stuart P. Adler, M.D., Renato La Torre, M.D., and Al M. Best, Ph.D., for the Congenital Cytomegalovirus Collaborating Group*

Update in CMV infection

79 Underwent amniocentesis before or at enrollment and >6 wk after maternal seroconversion

**CMV hyperimmune globulin
200 U / kg maternal weight
Monthly**

Predictor	Symptomatic Group (N=8)	Asymptomatic Group (N=37)	Univariate P Value [†]	Multivariate P Value [‡]
No. of infants whose mothers received HIG	1	30	<0.001	<0.001
No. of fetuses with ultrasonographic evidence of disease before HIG therapy	8	14	0.002	<0.001



**Ventriculomegaly (2)
IUGR (8)
Microcephaly (1)
PVL (2)**

31 Elected to receive hyperimmune globulin (200 U/kg)

14 Elected not to receive hyperimmune globulin

14 Elected to receive hyperimmune globulin

Anti – CMV Drugs

Inhibitors of CMV DNA Polymerase/Phosphatase (Purine Analogs)

GANCICLOVIR

- Specific / CMV
- Powerful
- Toxic (Hematology)

Prodrug: Valganciclovir

ACICLOVIR

- All HVZV
- Less viral-static effect
- No toxicity

Prodrug: **VALACICLOVIR**

Treatment of infected fetuses with Valaciclovir 8g per day orally to the mother

N = 19

Primary-infection

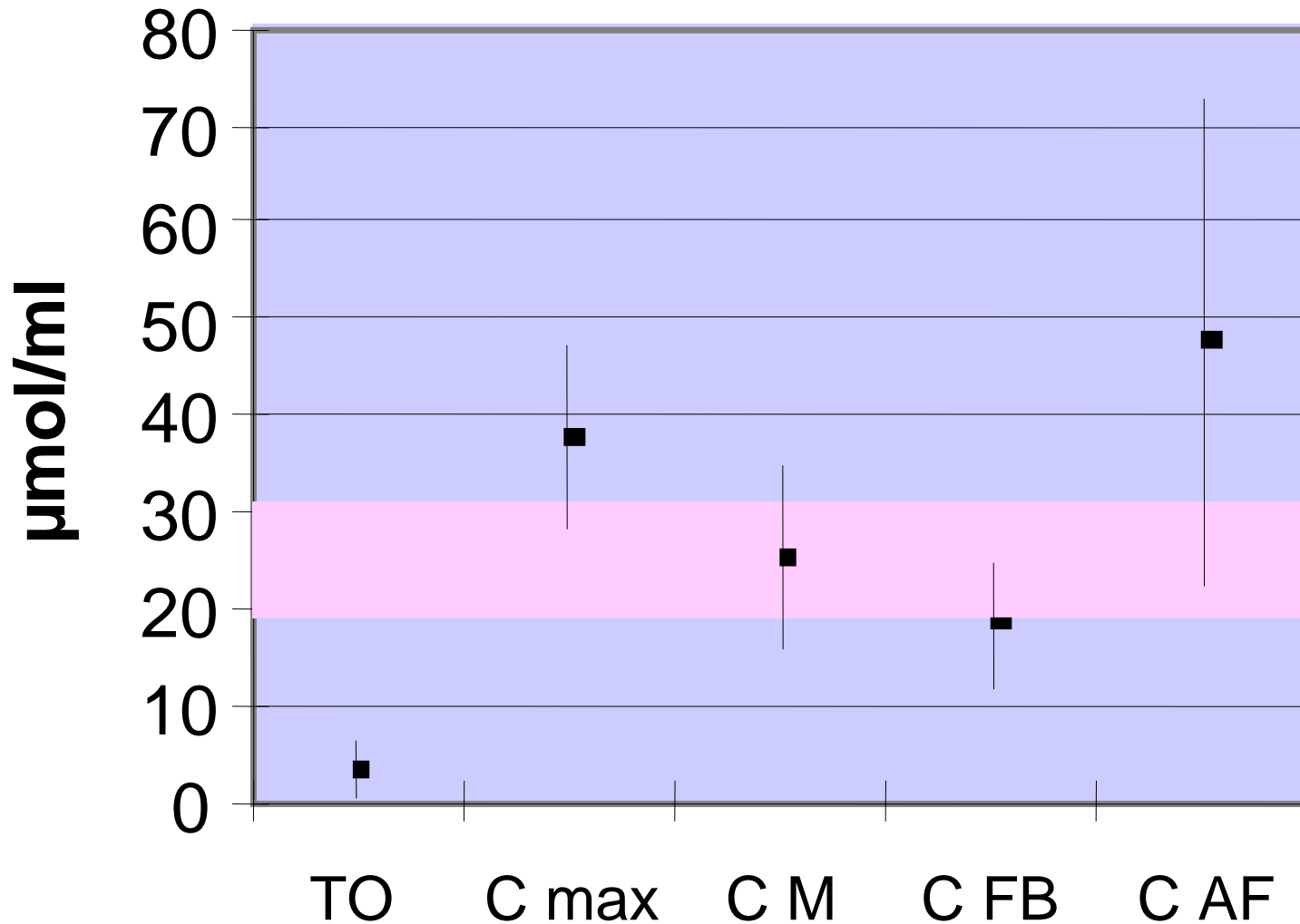
Positive Amnio

8 to 20 weeks after seroconversion

- **Thrombocytopenia (9)**
- **Hepatitis (6)**
- **Ascitis / hepatomegaly (2)**
- **Hyperrechogenic bowel (10)**
- **Ventriculomegaly @ 12 mm (1)**
- **Head Circumference on the 5th centile (1)**

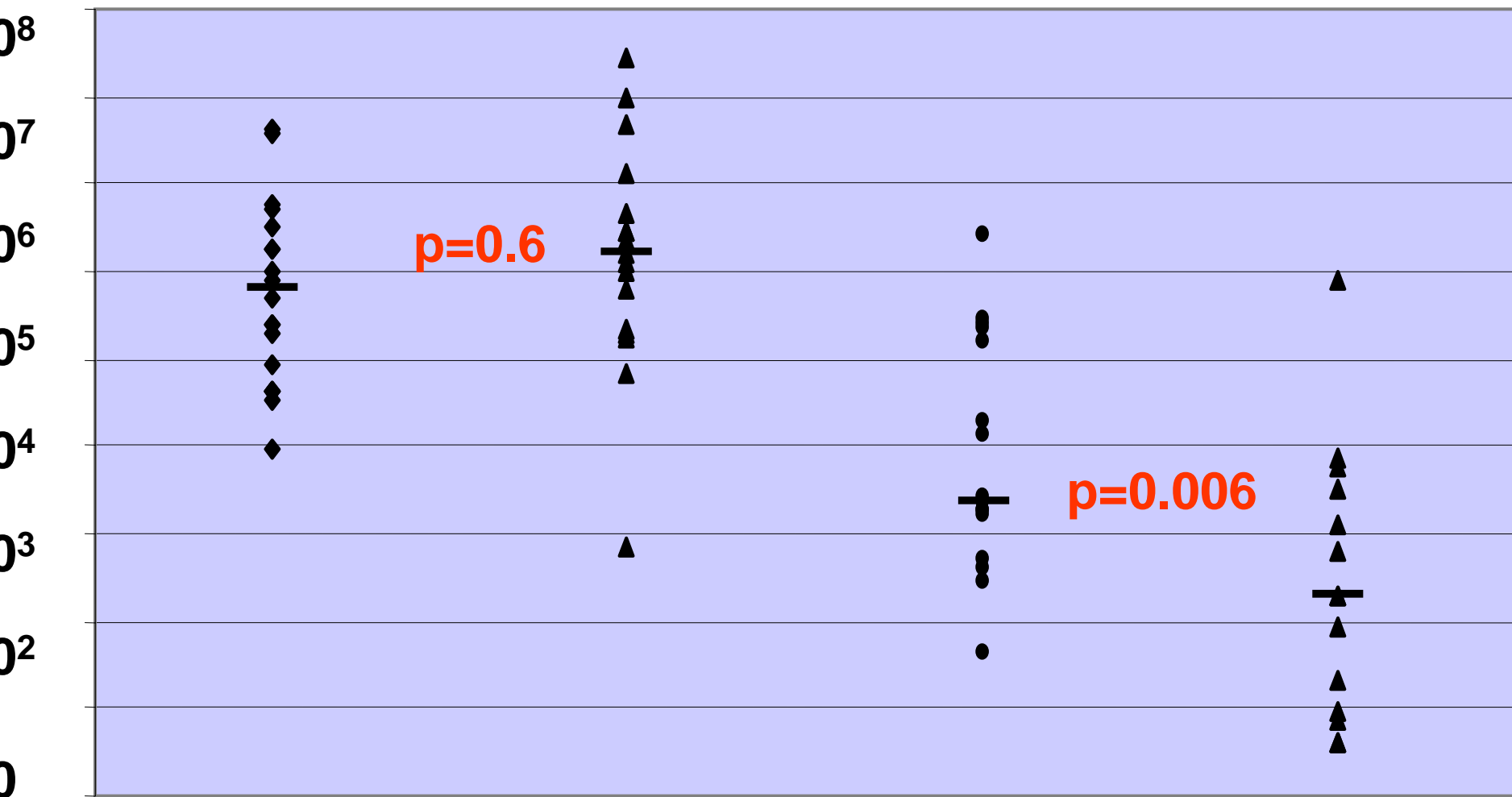
PHARMACOKINETICS OF VACV

Following oral administration 8 g/day



IN FETAL BLOOD

L



Before

During

Before

During

Amniotic Fluid

Fetal Blood

OUTCOME (n=19)

10 asymptomatic infants @ 4 Mo to 3 years.

2 hearing loss @ 3 Mo and 2 years.

6 TOP for progressive US abnormalities.

1 Iatrogenic Fetal Death

125 Patients in each arm
40% reduction in vertical Transmission

MATERNAL SEROCONVERSION

RANDOMIZATION

Valaciclovir 8g / day

Vs.

Placebo

Hyperimmune CMV IgG

6 weeks

AMNIOCENTESIS

INFECTED

NON-INFECTED

RANDOMIZATION

Valaciclovir 8g / day

Vs.

Placebo

Hyperimmune CMV IgG