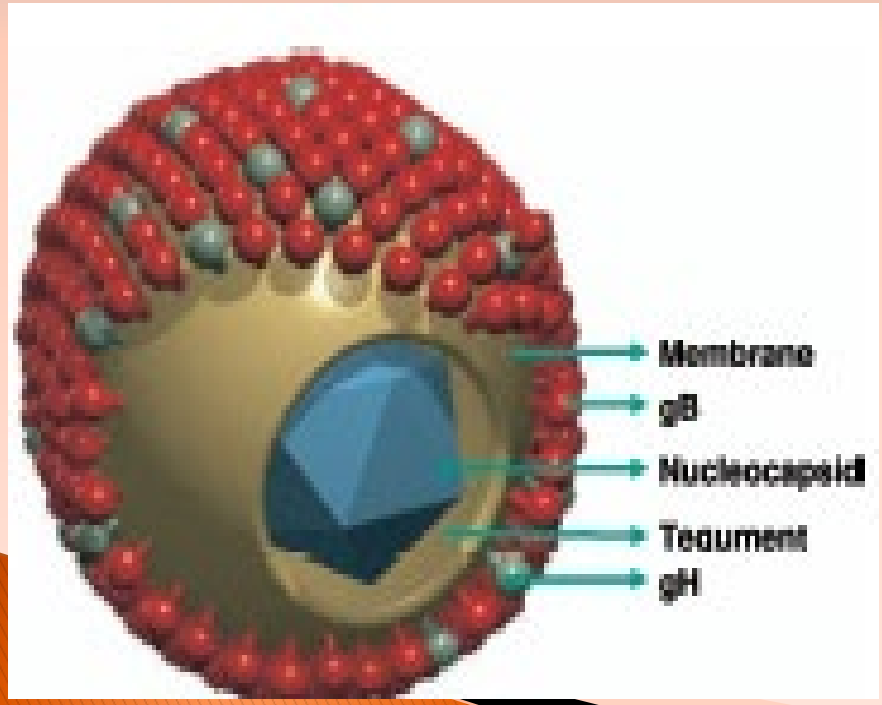
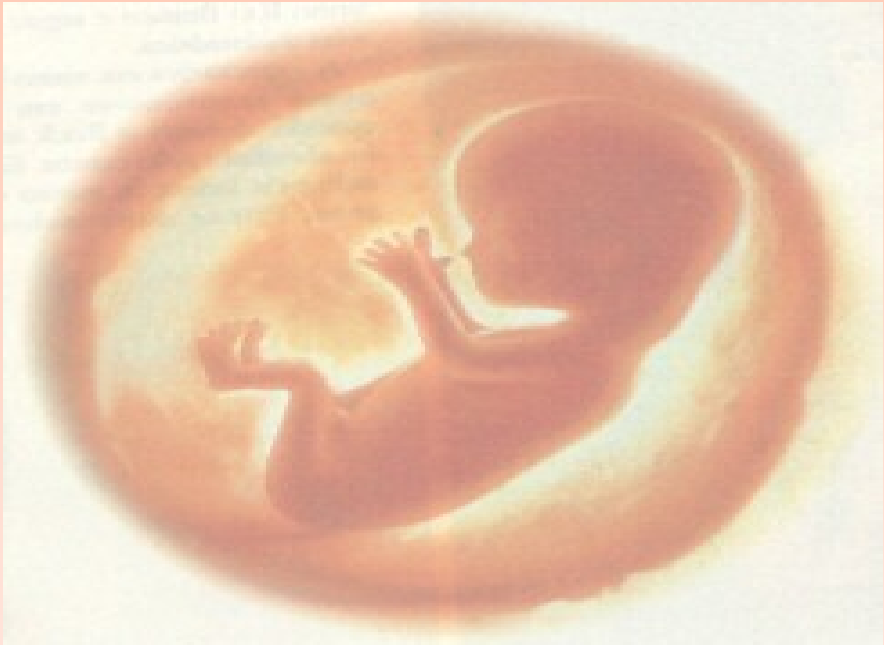
HYPERIMMUNOGLOBULIN and CMV-DNAemia IN PREGNANT WOMEN WITH PRIMARY CYTOMEGALOVIRUS INFECTION

Giovanni Nigro, Rome, Italy
Stuart P Adler, Richmond, VA, USA





NATURAL REASONS FOR IMMUNOTHERAPY IN PREGNANCY (I)

- To avoid fetal rejection (50% allograft) an estrogen-induced immunodepression occurs in pregnancy
- Decreased NK cells and cytotoxic activity, and functions of neutrophils and phagocytes
- Thus in pregnancy infections are common but symptoms are less frequent and severe due to a low immunoreactivity
- The immune response to CMV viremia implies the activation of immune cells (mostly CD8+ T cytotoxic lymphocytes) and production of numerous cytokines

Nigro G. Expert Rev Anti Infect Ther 2017

NATURAL REASONS FOR IMMUNOTHERAPY IN PREGNANCY (II)

- In CMV-seropositive women, maternal IgG antibodies are increasingly transmitted beginning at 6 weeks' gestation and provide increased protection to the fetus against CMV.
- During primary infection the fetus initially lacks CMV IgG and only some weeks after viremia receives low-avidity maternal antibodies and starts his own IgG production.
- Meanwhile maternal stimulated immune cells produce numerous cytokines, which are toxic for fetal cells

Jauniaux E et al Hum Reprod 1995; Pass R et al.J Clin Virol 2006; Bodeus M et al.J Clin Virol 2010;

IMMUNE-MEDIATED CMV PATHOGENICITY IN PREGNANCY

- CMV damages the fetus:
- Directly by intracellular viral replication
- Indirectly by activating an inflammatory process leading to the abortion or to immune-mediated diseases mostly due to the aggression of CMV-infected cells from CD8+ T lymphocytes and to the activity of cytokines (some specifically neurotoxic)
- Regulation of the innate and adaptive immune responses is essential in the interplay between infection and immunopathological process

Cheeran CJ et al. Clin Microbiol Rev 2009

CMV HYPERIMMUNOGLOBULIN (HIG)

- From selected plasma pools of at least 1000 hyperimmune donors identified by screening to have high titer CMV IgG (donors of nonspecific immunoglobulin are not tested)
- 8 steps of filtration, purification and concentration, including pasteurization
- All types of human antibodies

IMMUNOMODULATORY AND ANTIVIRAL ACTIVITIES OF CMV-HIG

- **Antiviral activity:**
  High titer and avidity IgG antibodies, which block CMV antigens including gB and pentamer (gH/gL/UL128/UL130/UL131), **preventing the attachment of neutralized viruses to target cells**

- **Immunomodulatory activity:**
  > Down regulation of interleukin synthesis
  > Blockade of Fc receptors
  > Specific antibodies towards receptors of T-cells (>cytotoxic CD8+ cells) and cytokines, which cannot be linked to fetal cells

Fouts et al. J Virol 2012; Schwab and Nimmerjahn. Nature Rev Immunol 2013

EFFICACY OF ANTI-CMV ANTIBODIES IN ANIMALS: RANDOMIZED STUDIES

- Reduced rate of maternal viremia, fetal deaths and infections, and prevention of placentitis and intrauterine growth restriction by anti-whole virus or anti-gB serum in guinea pigs (Bia et al. JID 1980, Bratcher et al. JID 1995; Chatterjee et al. JID 2001)
- Undetectable virus and lower cerebral inflammation in brains of immune treated newborn mice vs controls (Cekinović et al. J Virol 2008
- HIG passive infusion provided complete protection against fetal loss in pregnant, CD4+ T cell–depleted, RhCMV-seronegative, rhesus monkeys treated with standard HIG or dose-optimized RhCMV-neutralizing HIG prior to the intravenous challenge with RhCMV (Nelson CS et al. JCI Insight 2017)

HIG DECREASES CMV TRANSMISSION IN PREGNANCY

- Nigro G et al. NEJM 2005: transmission decreased (p=0.02) from 40% (19/47) to 16% (6/37) and no symptoms occurred in the infected infants

- Buxmann H et al. JPM 2012: 23% transmission (vs 40% in controls) and no symptoms in infected infants after HIG

- Revello MG et al. NEJM 2014: transmission decreased from 44% (27/62) to 30% (18/61) ($p<0.13$)

- Kagan KO et al. UOG 2018: 7.5% transmission from 40 women with primary CMV infection in the 1st trimester after administration of 200 U/kg of HIG every 2 weeks

Kagan KO et al. (Ultrasound Obstet Gynecol 2018)

• 200 U/kg of HIG every 2 weeks until 20 weeks gestation to 40 women with primary CMV infection < 14 weeks gestation.

• 7.5% transmission rate from 40 women.
• 35% transmission rate in untreated controls (p=0.001).

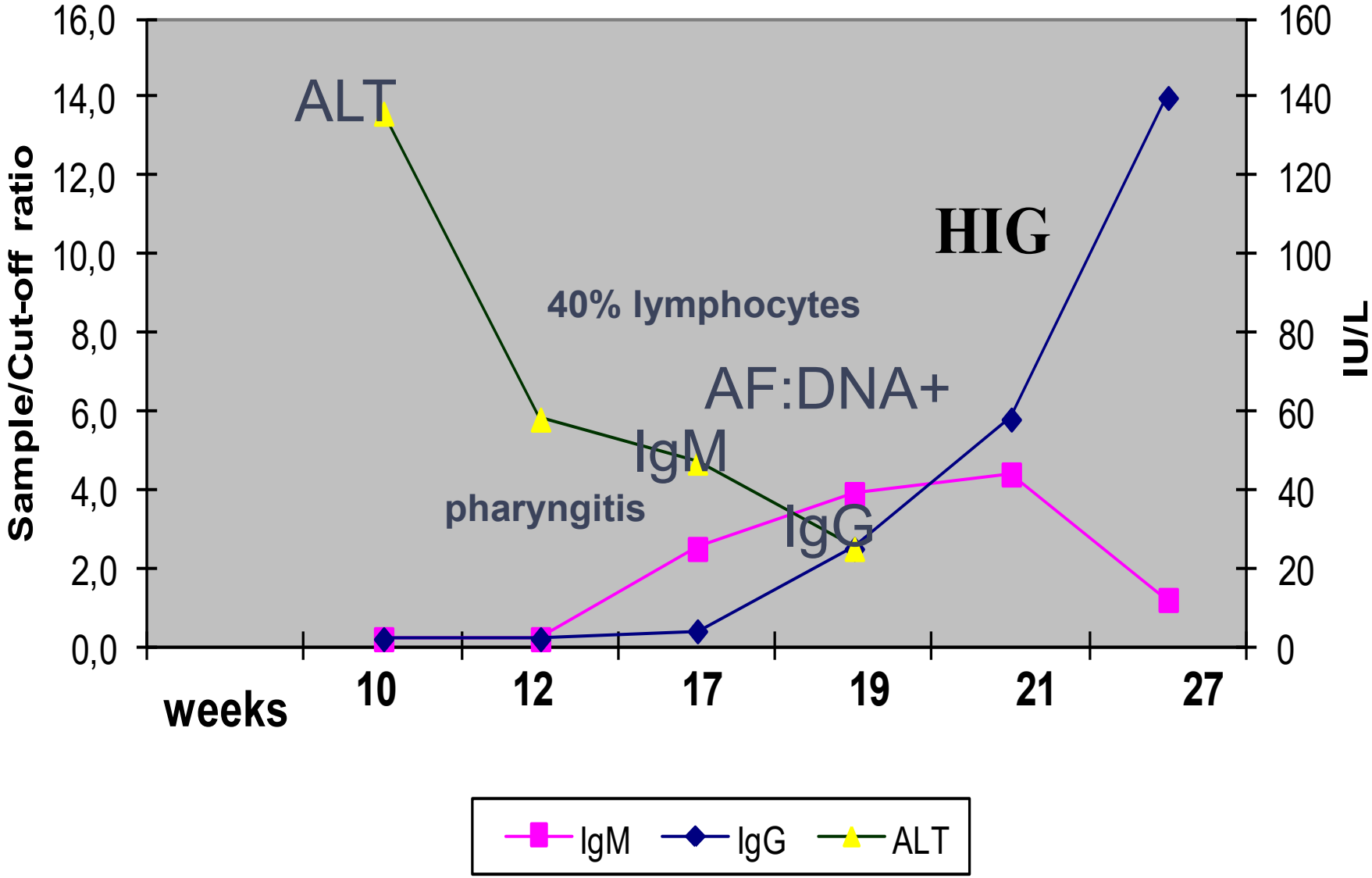
• For HIG treated mothers 1 fetus was infected at amniocentesis, and 2 after stopping HIG at 20 weeks.

• All neonates were asymptomatic

WHEN MOTHER-TO-FETUS CMV TRANSMISSION REALLY OCCURS?

- CMV transmission may occur 4-8 weeks after seroconversion (the mean value between the last negative IgG and the first positive IgG detection
- Seroconversion is concomitant with the detection of only IgM
- Fever or a flu-like syndrome (when present) may be concomitant with CMV viremia
- In fact, viremia precedes CMV IgM by about 2 weeks is also suggested by hypertransaminasemia, even before symptoms first occur

High transaminases (viremia) occurred 2 weeks before pharyngitis, 7 weeks before IgM, 9 weeks bwefore IgG & DNA in AF



HIG AND THE DECREASE OF CONGENITAL DISEASE (CMV+ at 20 WG)

- Nigro G et al. NEJM 2005: decreased CMV disease after fetal infection and disease ($p<0.001$)
- La Torre et al. CID 2006: decrease of CMV-induced placentomegaly by ultrasound ($p<0.001$)
- Nigro G et al. JID 2011: improved outcome in symptomatic children ($p<0.001$)
- Visentin S et al. CID 2012: decreased symptoms in infants after only one HIG infusion ($p<0.01$)
- Japanese CCITSG, J Reprod Immunol 2012: decreased number and severity of CMV disease in 12 children

HIG: SERIOUS ADVERSE EVENTS

- **Nigro G et al. NEJM 2005: NONE**
- **Nigro G et al. J Infect Dis 2011: NONE**
- **Visentin S et al. CID 2012: NONE**
- **Buxmann H et al. JPM 2012: NONE**
- **Japanese Congenital Cytomegalovirus Infection Therapy Study Group, J Reprod Immunol 2012: NONE**
- **Revello MG et al. NEJM 2014:**

HIG group: preterm delivery (5 women), IUGR (2), intrahepatic cholestasis (1), postpartum eclampsia (1)
Saline Solution group: abortion, arthralgia, hypertension (1 each)

- **Blázquez-Gamero D et al. JMFNM 2017: NONE**
- **Kagan KO et al. Ultrasound Obstet Gynecol. 2018: NONE**

Objective of the Study: Association HIG/CMV-DNAemia/outcome

- Study: Large registry database of pregnant women with confirmed primary CMV infection to identify risk factors for fetal infection and neonatal symptoms at birth
- Background: Primary CMV infection in early gestation has the highest rate of fetal and neonatal disease
- Focus: maternal viremia

SUBJECTS

- Women (mostly Italian) who sought consultation for a primary CMV infection during pregnancy between 2010 and 2017
- Each woman agreed to provide clinical data and signed an informed consent.
- Only women whose blood was examined for CMV-DNA (DNAemia) were enrolled

SUBJECTS: VIRAL DIAGNOSIS

Estimated gestational age at maternal infection:

- Seroconversion half way between seronegative and seropositive serum.
- In women with flu-like symptoms or laboratory abnormalities, the beginning of these was defined as maternal infection
- For women with IgM, IgG, and very low avidity at <2 months gestation, CMV infection was estimated as immediately post conceptional

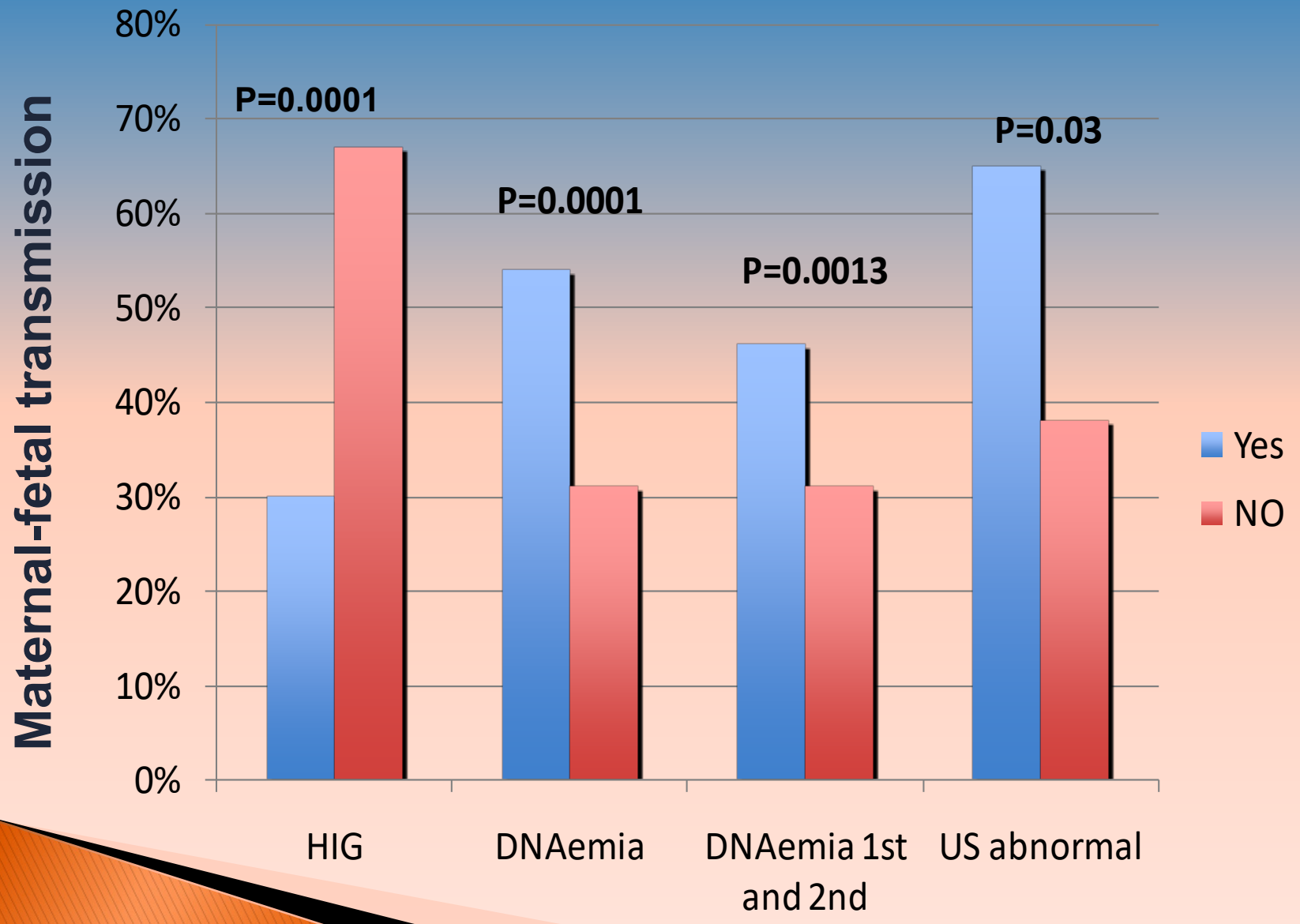
SUBJECTS: PARAMETERS

- **Maternal age at conception**
- **Gestational age at the time of:**
- maternal CMV infection
- first CMV DNA detection in blood
- first HIG infusion
- CMV DNA detection after HIG or 2nd DNAemia in controls
- at delivery
- **Viral load in the amniotic fluid**
- **Number of subsequent HIG infusions**
- **Prenatal manifestations of CMV disease**
- **Birth weight**
- **Clinical and laboratory abnormalities in the infants with congenital infection**

RESULTS

- 304 women (4 sets of twins) were enrolled
- Maternal blood before and after HIG administration was obtained from 85 women, and from 46 non-HIG treated women.
- Termination of pregnancy (after AF+): 6/161 HIG and 17/147 non-treated women
- 281 live births
- 108 infants CMV+ (42 HIG - 66 non)
- 25 symptomatic infants (1 HIG-24 non)

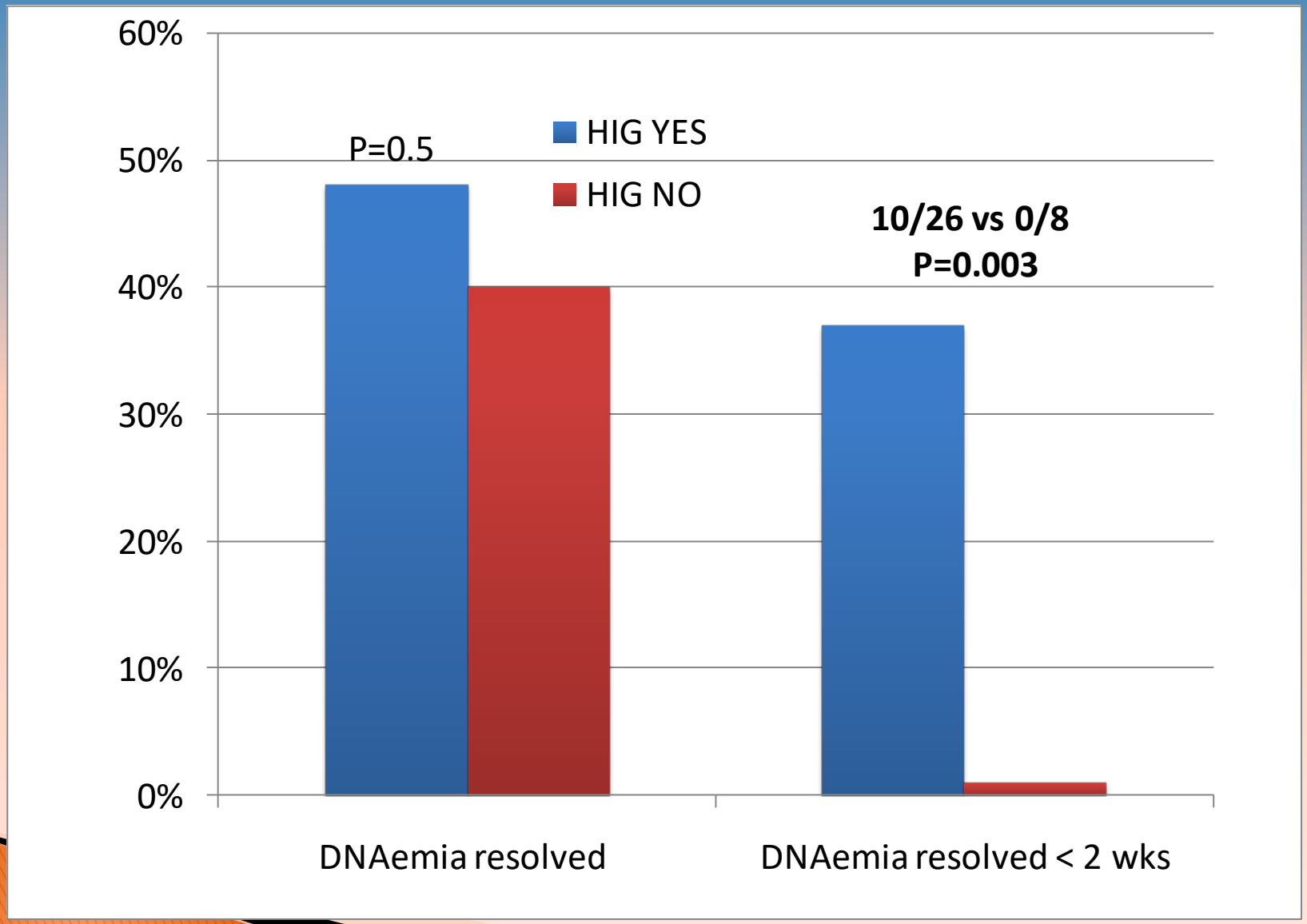
Analysis of possible predictors of congenital infection



HIG and Maternal DNAemia as predictors of congenital CMV infection

Predictor	CMV infected fetuses/ infants	CMV uninfected fetuses/ infants	Univariate P- value	Multivariate P- value
All women (304)	131	173		
No. of mothers: HIG yes HIG no	 48 83	 109 64	P=0.0003	P=0.0003
No. of mothers : DNAemia pos 148 DNAemia neg 156	 81 50	 67 106	P=0.001	P=0.0063

Resolution DNAemia by HIG administration



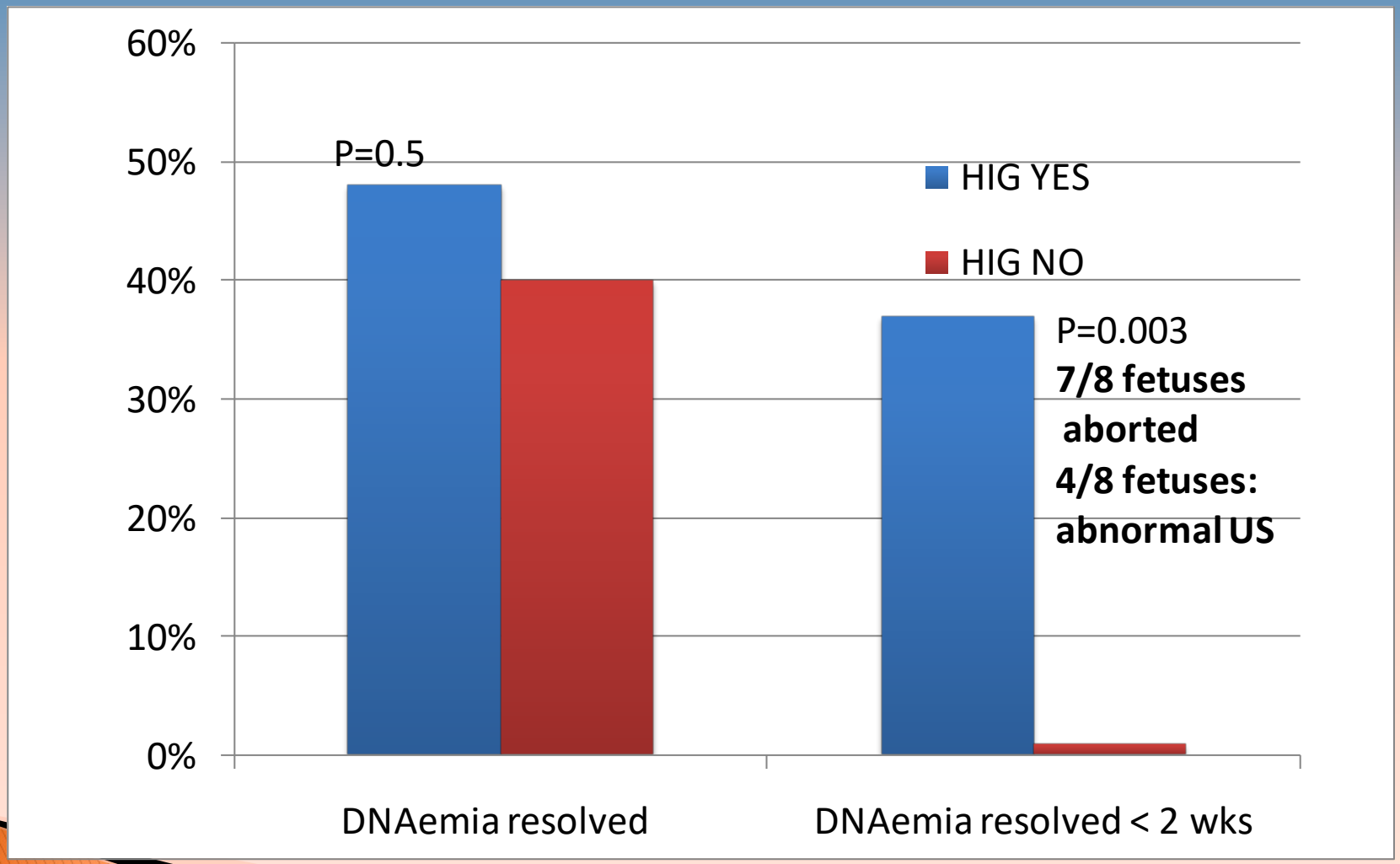
Other predictors of maternal-fetal CMV transmission

Predictor	CMV infected fetuses/infants	CMV uninfected fetuses/infants	Univariate P- value
Birth weight	3094	3299	P=0.0003
Mean WG when mother was infected	14.26	11.73	P=0.04
Mean WG of 1st DNA test	20.1	18.5	P=0.03
Mean WG when 1st HIG was given	22	19	P=0.009

HIG and Maternal DNAemia as predictors of CMV disease

Predictor	CMV symptomatic infants	CMV asymptomatic infants	Univariate P-value
All women (281)	25	257	
No. mothers: HIG yes HIG No	 1 24	 151 106	 P=0.0001
No. of mothers: DNAemia POS DNAemia NEG	 12 13	 122 137	 P=1.0

Early resolution of DNAemia by HIG prevent CMV disease



Factors NOT predictive of congenital CMV infection

Predictor	CMV infected fetuses/infants (131)	CMV uninfected fetuses/infants (176)	Univariate P- value
Maternal age (years)	32	33	NS
Maternal infection <14 WG (179) >14 WG (125)	73 (56%) 58 (44%)	107 (61%) 69 (39%)	p=0.1
Mean doses of HIG for women HIG-treated	3.0	3.4	P=0.22
Mean copy number of CMV DNAemia	3128	2348	P=0.55

MATERNAL-FETAL CMV INFECTION: PREVENTION OR THERAPY?

- To decrease the rates of primary infection in pregnancy, women should be informed about CMV and hygienic measures
- To prevent fetal infection and disease, CMV in pregnancy should be diagnosed as soon as possibile following at least a double screening (8-12 and 14-18 weeks)
- Positive DNAemia at enrollment may have a negative prognostic value
- HIG could decrease CMV transmission and fetal disease (also including cortical malformations and deafness if given early)