Prévention de l'infection congénitale à CMV: La clef est dans la précocité de l'intervention par le dépistage et traitement des infections primaires du 1er trimestre

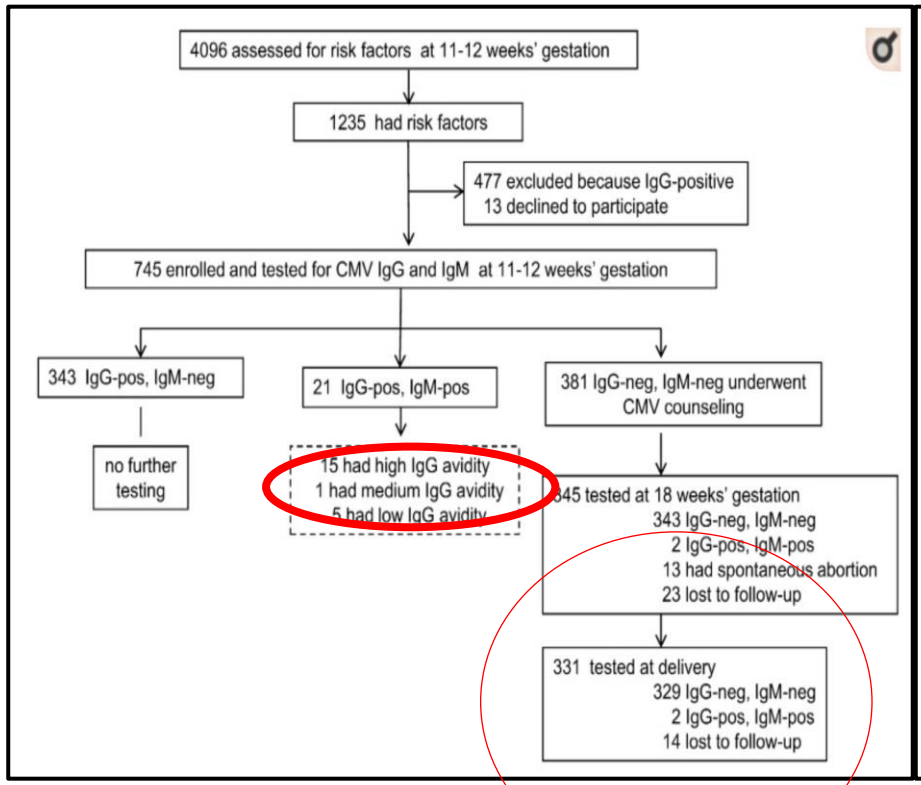
Natsuyuki Nakanishi, Compact object, 1962, MOMA

Recommandations en décembre 2018: Pas de dépistage prénatal ni néonatal

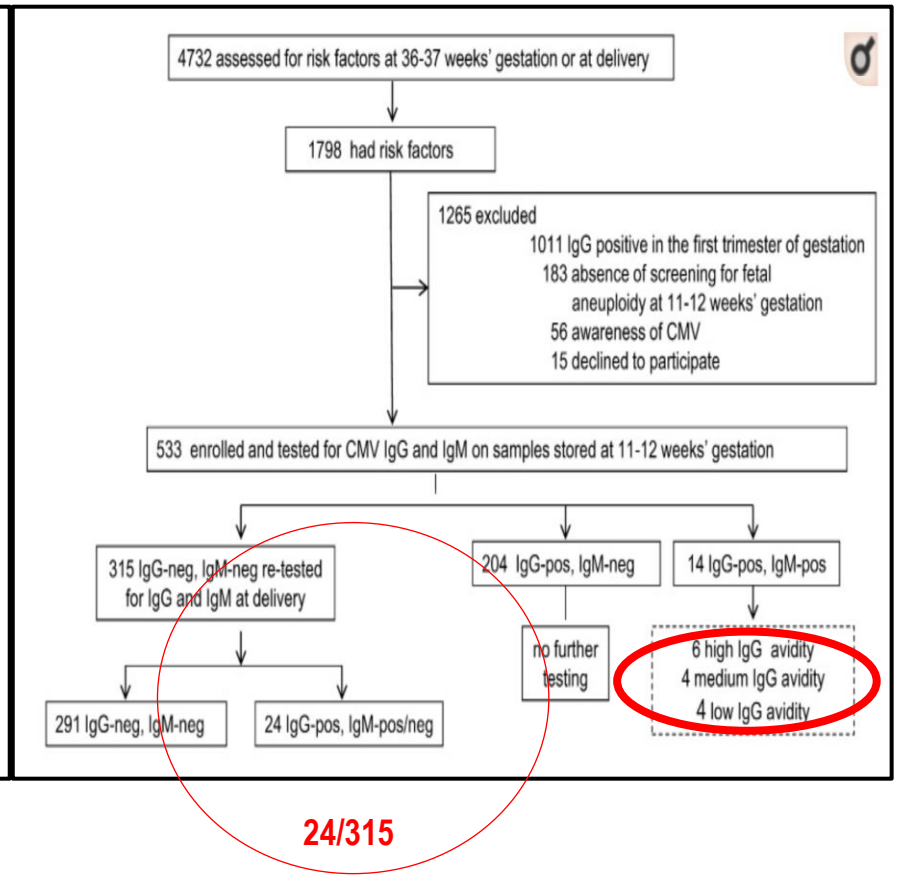
Conseils de prévention pendant toute la grossesse dés le premier trimestre

- **Inutiles après 14 semaines**
- **Trop tardif au premier trimestre**
- **Conseils pré-conceptionels ++**

Intervention: conseils



Contrôles



EBioMedicine. 2015

Prévention de la transmission chez les femmes infectées

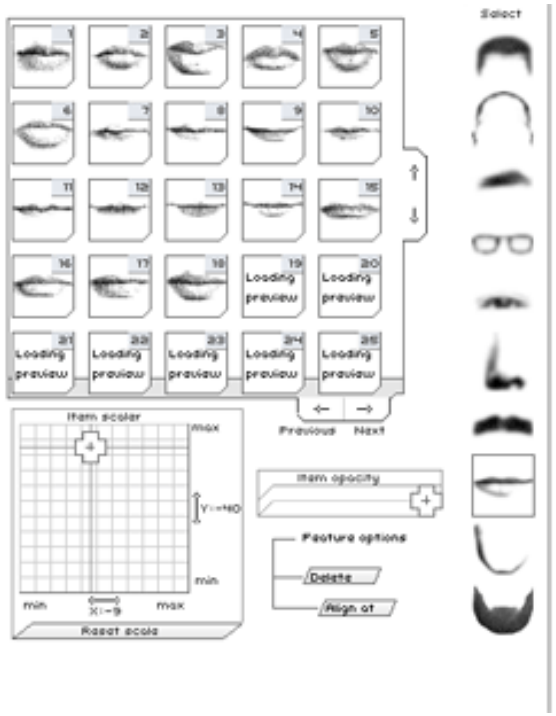
Identifier l'infection maternelle :

- Faisable pour les infections primaires par une sérologie en début de grossesse
- Impossible pour les infections non primaires

1 Leruez-Ville et al, CID, 2017, 2 Pu

Portrait robot des femmes enceintes risquant une primo-infection CMV

Cibles du dépistage prénatal



- Moins de 35 ans
- Niveau socio-économique élevé
- Travaillant
- Séronégative à la grossesse précédente
- 1er enfant en crèche
- Intervalle entre les grossesses de moins de 2 ans

Algorithme de dépistage sérologique pendant la grossesse

IgG et IgM en début de grossesse

IgG + et IgM –
exclut primo-infection du premier trimestre

IgG+ et IgM+ ou IgM zone grise

Tester l'avidité des IgG

- **Avidité élevée = exclut primo-infection pendant la grossesse**
- **Avidité intermédiaire n'exclut pas une primo-infection du premier trimestre ou de la période périconceptionnelle**
- **Avidité basse= Affirme une primo-infection pendant le premier trimestre de la grossesse**

IgG- et IgM-
exclut primo-infection du premier trimestre

IgG- et IgM+

PCR CMV sanguine
ET/OU
Refaire sérologie 10 jours plus tard

Dépistage sérologique pendant la grossess à Necker (2011-2016)

11, 728 femmes

6353 (54%)
IgG+/IgM-

381 (3,2%)
IgG+ /IgM+

22 (0,2%)
IgG-/IgM+

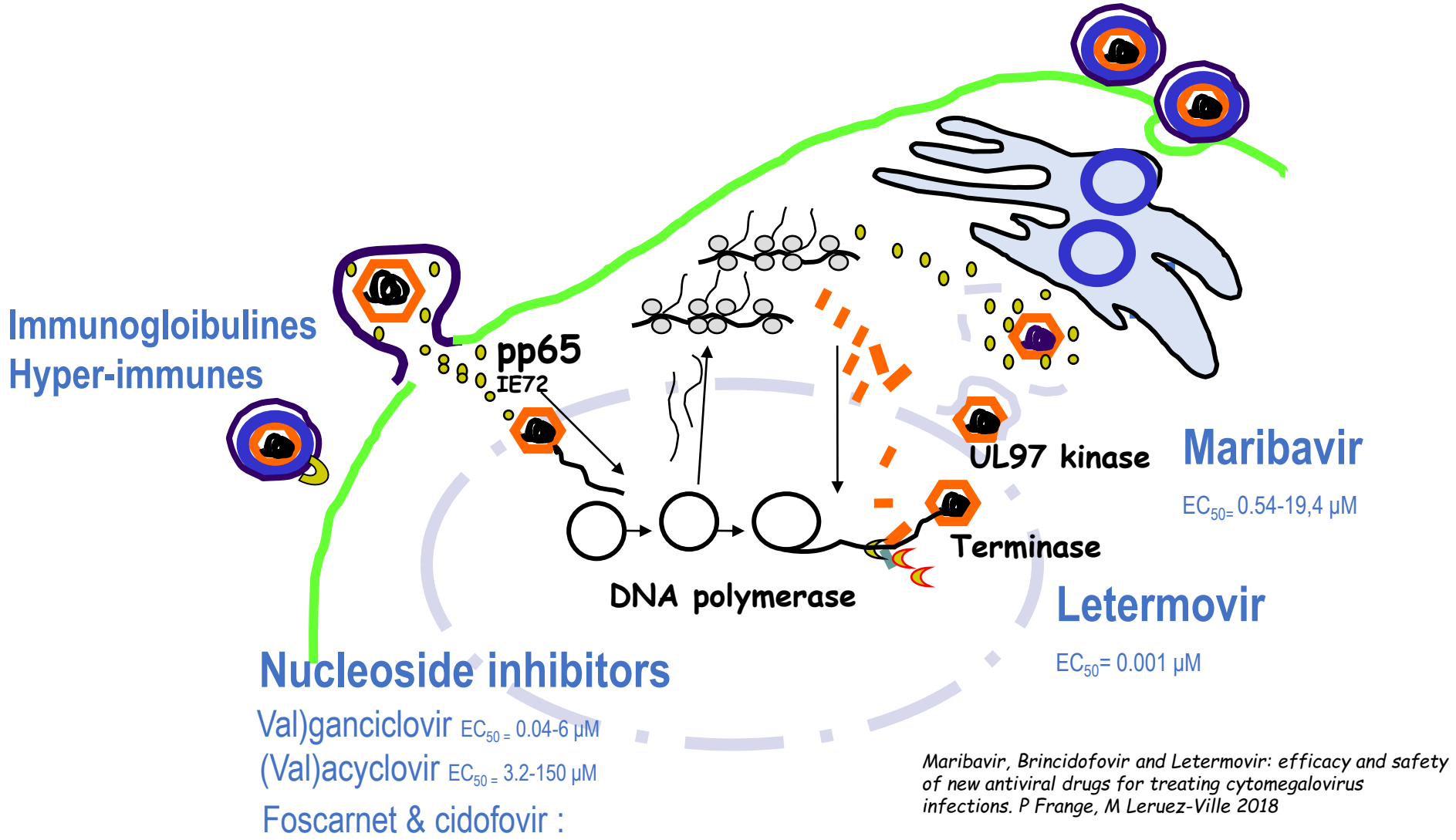
4972 (42%)
IgG-/IgM-

73% (279/381)
avidité des IgG élevée
Primo-infection exclue

27% (101/381)
avidité des IgG basse ou intermédiaire
PI prouvée ou suspectée du 1er trimestre
0,9% population totale

27% (27/101)
infections fœtales
0,23% de la population totale

Les anti-CMV



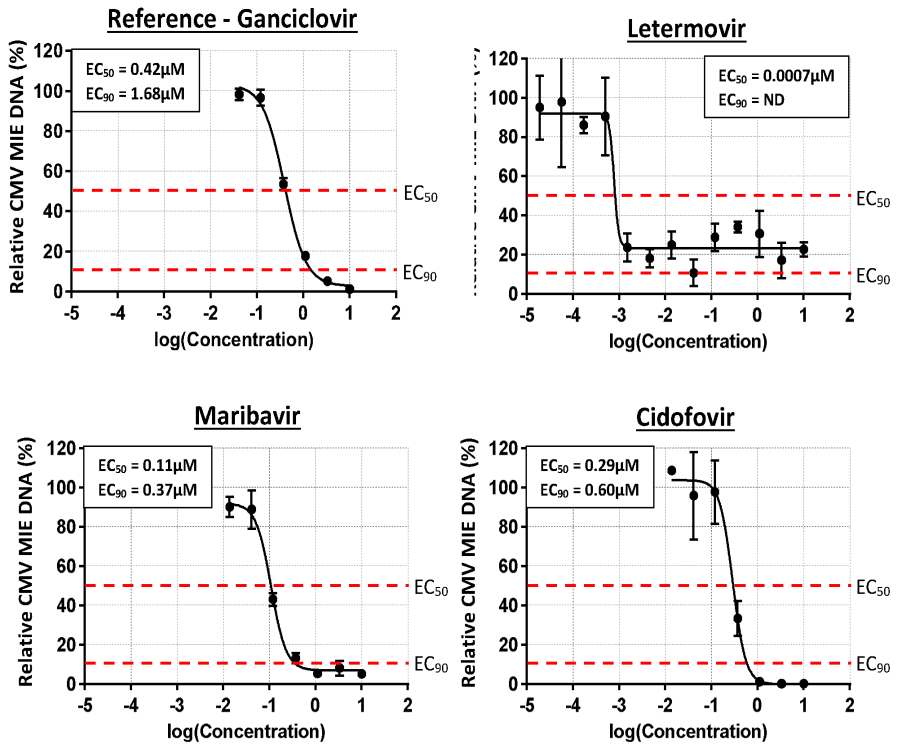
Maribavir, Brincidofovir and Letermovir: efficacy and safety of new antiviral drugs for treating cytomegalovirus infections. P Frange, M Leruez-Ville 2018

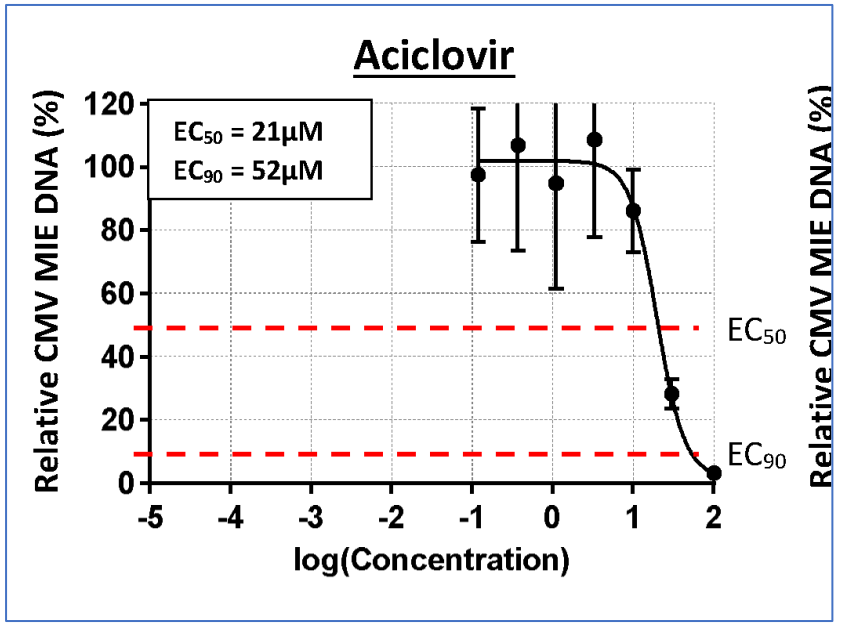
EC_{50} =half maximum effective concentration calculated in CMV (AD169) infected human fibroblasts, Chemaly R et al, Antiviral Res, 2019

Efficacité des anti-CMV sur les cellules trophoblastiques

EC_{50} webasses pour GCV, LTM and MBV

Mais hautes pour (21µM) ACV

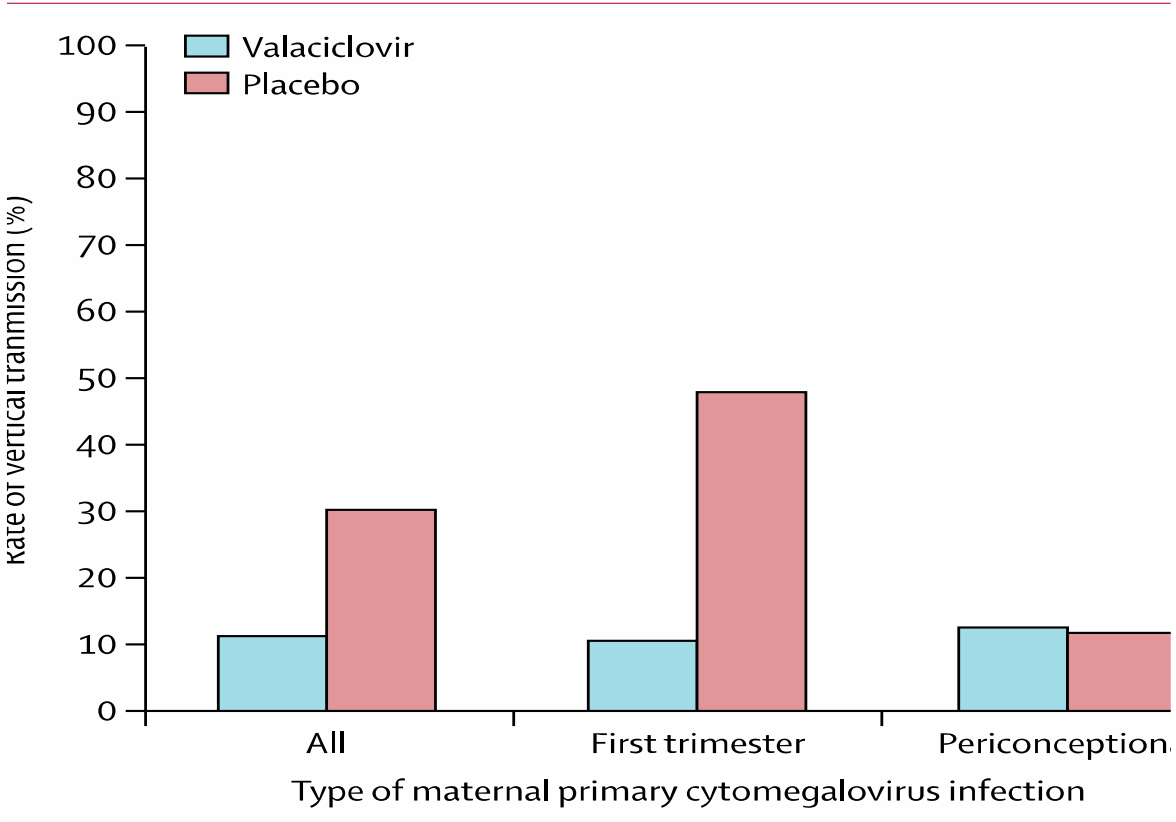




Hamilton ST, AAC, 2020

Invasive Diagnosis the earlier the better

- Rationale : *Effective secondary prevention with VACV @ MPI*



ure 2: Rate of vertical transmission among study participants

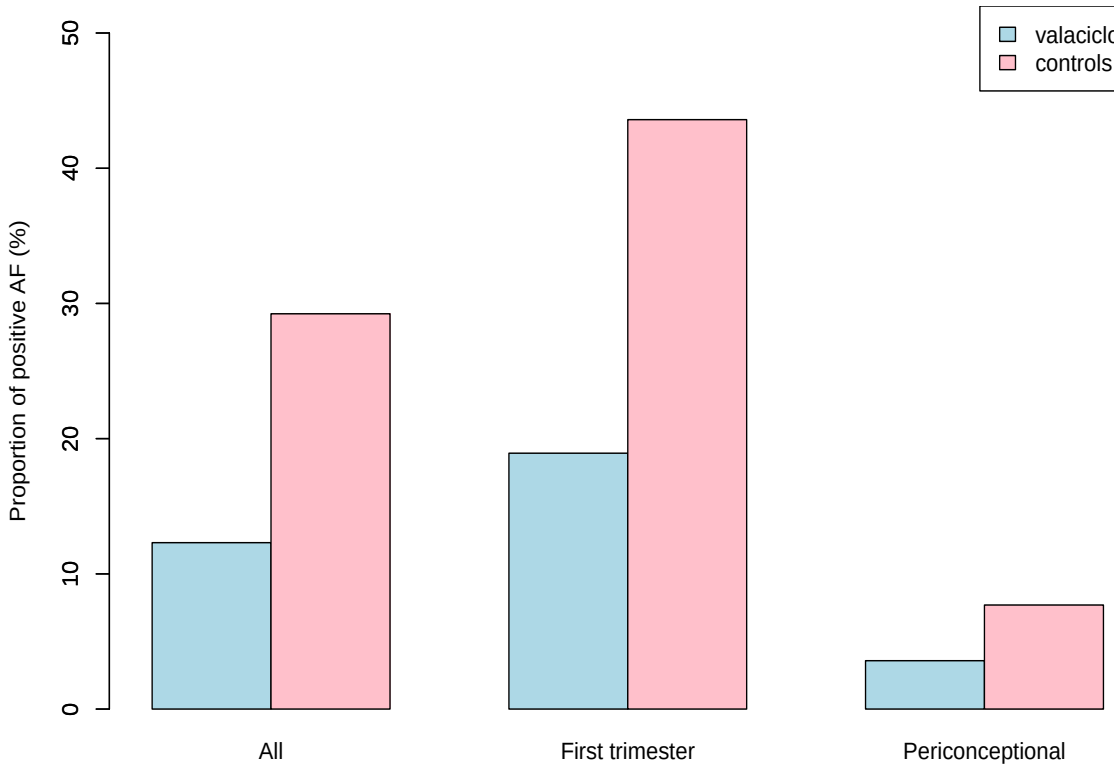
90 women with PI in the 1st trimester or the periconceptionnal period
45: treated with 8g/j until amniocentesis
45: treated with placebo until amniocentesis

Significant decrease of transmission from 29% without treatment to 11% with treatment

Shahar-Nissan, Lancet, 2020

Invasive Diagnosis the earlier the better

- Rationale : *Effective secondary prevention with VACV @ MPI*



Variable	Odds Ratio	95% confidence interval	P value
Treatment by VCV	0.318	[0.12-0.841]	0.021
Periconceptional infection	0.122	[0.0338-0.439]	0.001
Gestational age at amniocentesis, weeks	0.994	[0.699-1.41]	0.972

Faure Bardon UOG 2021

VACV safe ?

8 tablets x 2 / D *vs* 4 tablets x 4/ D ?

Variable	*Secondary prevention (n = 81)*		*Tertiary prevention (n = 141)*	
	Four doses of 2 g (n = 42)	*Two doses of 4 g (n = 39)*	*Four doses of 2 g (n = 130)*	*Two doses of 4 g (n = 11)*
GA at treatment initiation (weeks)	12.3	12.3	23	20
Duration of valacyclovir treatment (days)	49	33	112	97
Periconceptional infection	14 (33)	17 (44)	—	—
Vertical transmission	7 (16)	2/33† (6)	—	—
Acyclovir level (mg/L)* in:				
Maternal plasma	4.49	8.85	—	—
Amniotic fluid	6.02	7.06	—	—
Acute renal failure	0 (0)	1 (3)	0 (0)	1 (9)
Duration of valacyclovir treatment (days)	—	4	—	18
Clinical symptoms	—	Anuria, lumbar pain	—	Anuria, lumbar pain
Maximum serum creatinine level (µmol/L)	—	120	—	300

Renal toxicity developed in 2/50 (4%) women who were on 8 tablets x 2/ D
vs 0/172 4 tablets x 4 /D (*P = 0.009*)

Ville Y, Leruez-Ville M. Ultrasound Obstet Gynecol. 2021

Invasive Diagnosis the earlier the better

- Rationale : *Risk of cCMV limited to **2Mo<Conception<3Mo***

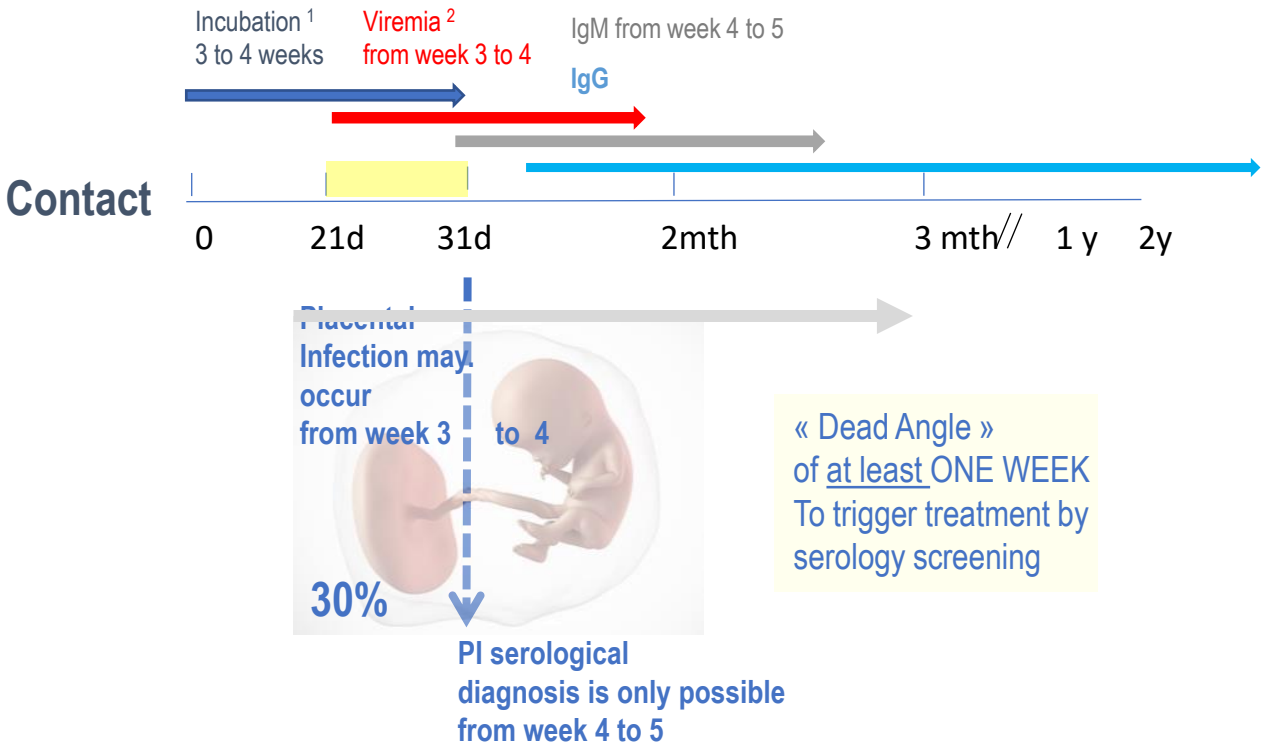


TABLE 5
Risk of CMV congenital infection (transmission) and SNHL or neurodevelopmental impairment, according to gestational age at maternal primary infection

	Transmission rate	SNHL or neurodevelopmental impairment if fetus is infected	SNHL or neurodevelopmental impairment if transmission is unknown
First trimester	36.8% (95% CI, 31.9–41.6)	22.8% (95% CI, 15.4–30.2)	8.4%
Second trimester	40.3% (95% CI, 35.5–45.1)	0.1% (95% CI, 0–0.8)	0%
Third trimester	66.2% (95% CI, 58.2–74.1)	0% (95% CI, 0–2.1)	0%

CMV, cytomegalovirus; *SNHL*, sensorineural hearing loss.

Chatzakis. Timing of primary maternal cytomegalovirus infection and rates of vertical transmission and fetal consequences. Am J Obstet Gynecol 2020.

Chatzakis et al AJOG 2020

Séquelles à long terme des nouveau-nés infectés après Primo-Infection maternelle du premier trimestre

Que change le dépistage maternel et le diagnostic prénatal ?

Histoire « naturelle »

434 Nouveau-nés dépistés (1980-1993)
35 Nouveau-nés infectés après PI maternelle T1
N=35, 1 perdu de vue

32% (11/34)séquelles neurologiques
17% (4/24)déficit intellectuel

9% (3/34) épilepsie
6% (2/34) IMC **
3% (1/34) choriorétinite
23% (8/34) déficit auditif **

(Pass et al, JCV, 2006)

p<0,001 ⟷

p=0,004 ⟷

Dépistage sérologique au premier trimestre Amniocentèse après 17 semaines

N=103
20 IMG (19%), 1 mort foetale, 82 nouveaux nés , 5/82 (6%) perdus de vues

2,6% (2/77)séquelles neurologiques
0/77 déficit intellectuel

0/77 épilepsie
2,6% (2/77) IMC*
0/77 choriorétinite
20% (16/77) déficit auditif ***

(Faure-Bardon et al, CID, 2018)

Invasive Diagnosis the earlier the better

- Limit irrationale decisions : **1/74** *TOP @ 15 weeks'*
- Respect women' utility-based decision

Conditional / Tentative pregnancy:
Model of antenatal screening for aneuploidies

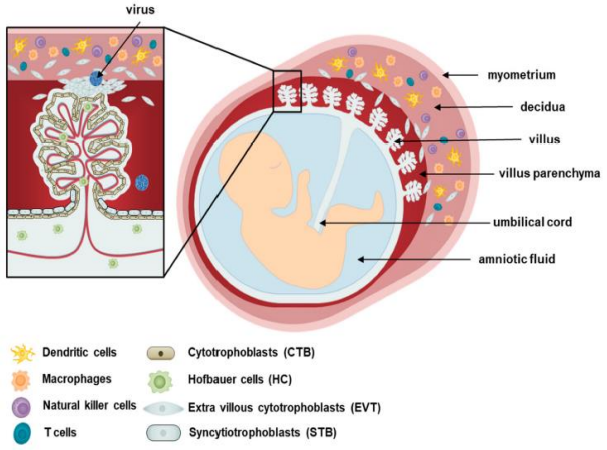
Early characterization of risk:
Prevention
- Primary
- Secondary
- Tertiary

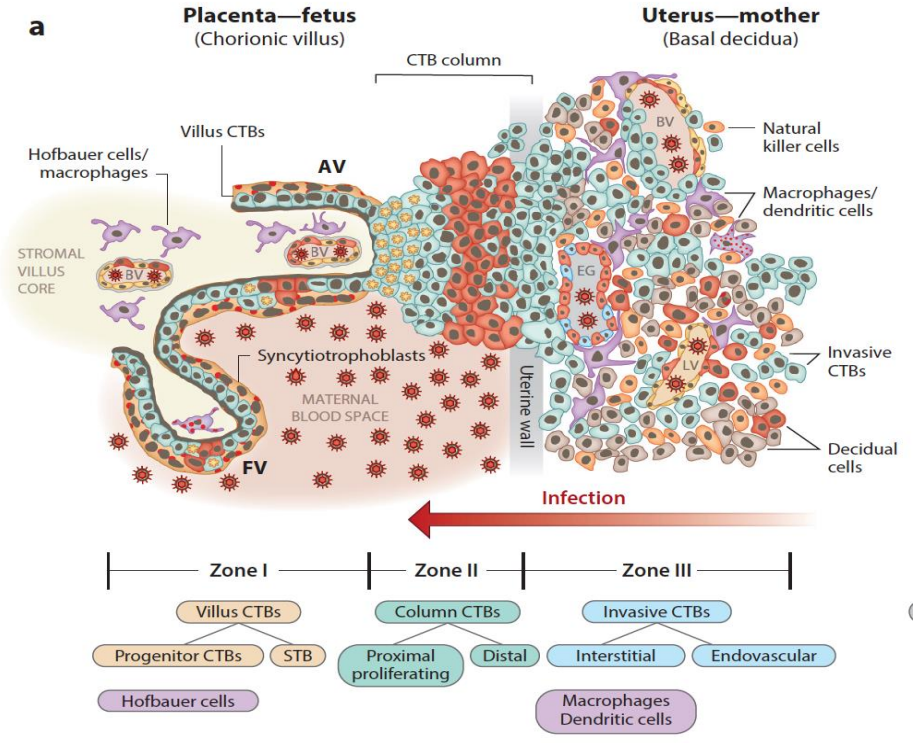
Peretti-Watel 2001, Beck 2001

Invasive Diagnosis the earlier the better

- Rationale : *Risk of cCMV limited to **2Mo<Conception<3Mo***

Early invasion of Cytotrophoblast





Tetsumi KUDO 1963, Composition

Annu. Rev. Virol. 2018. 5:273–99

Invasive Diagnosis the earlier the better
VACV @ MPI & CVS @ 13 weeks'

- 74 women with primary infection :
  - PCR CMV in CVS at 13 (11-16) weeks
  - PCR CMV in AF at 17 (16-23) weeks

- 44 PCR CMV in saliva at birth in 44
  - 6 lost for follow-up
  - 1 TOP for maternal distress
  - 24 normal ultrasound + normal MRI @ 32 weeks'

Invasive Diagnosis the earlier the better

- Early Reassurance

N=74	POSITIVE CVS	NEGATIVE CVS
POSITIVE AF	4	5
NEGATIVE AF	1	64

DNA load Maternal	DNA load in CVS Log copies/µg DNA	DNA load in AF log copies/ml	Sequelae
	0	4.4	NONE
	0	4.9	TOP (maternal distress)
	0	5.6	NONE
	0	6.9	NONE
	0	6.8	Normal MRI 32 W

5/69 delayed CMV passage

44 PCR Neonatal saliva

43 negative , one positive

1/44 delayed CMV passage

8.7%

Invasive Diagnosis the earlier the better

- Early Diagnosis

VACV	DNA load Maternal	DNA load in CVS Log copies/µg DNA	DNA load in AF log copies/ml	Sequelae
N	2.7	5.8	6.0	Uni HL, vestib sy
Y	0	5.3	6.5	NONE
Y	0	2.4	4.2	NONE
Y	3	3.9	5.9	NONE

VACV	DNA load Maternal	DNA load in CVS Log copies/µg DNA	DNA load in AF log copies/ml	DNA load in AF log copies/ml	Sequelae
13-39	3.8	3.2	0	0	None M0

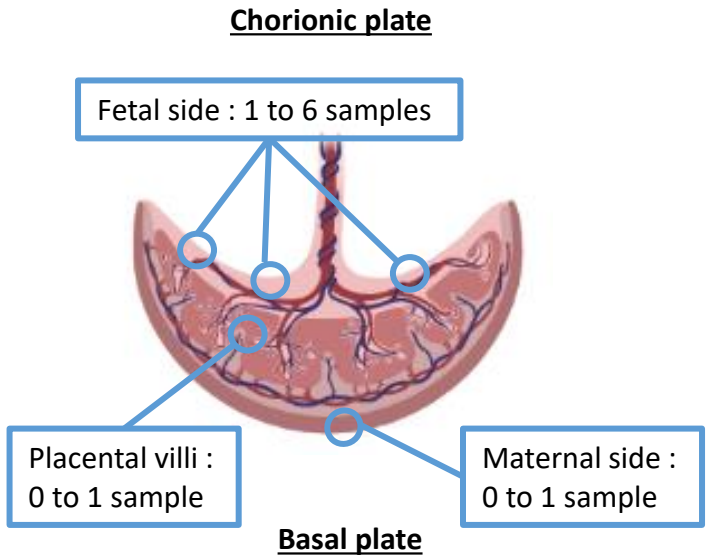
N=74	POSITIVE CVS	NEGATIVE CVS
POSITIVE AF	4	5
NEGATIVE AF	1	64

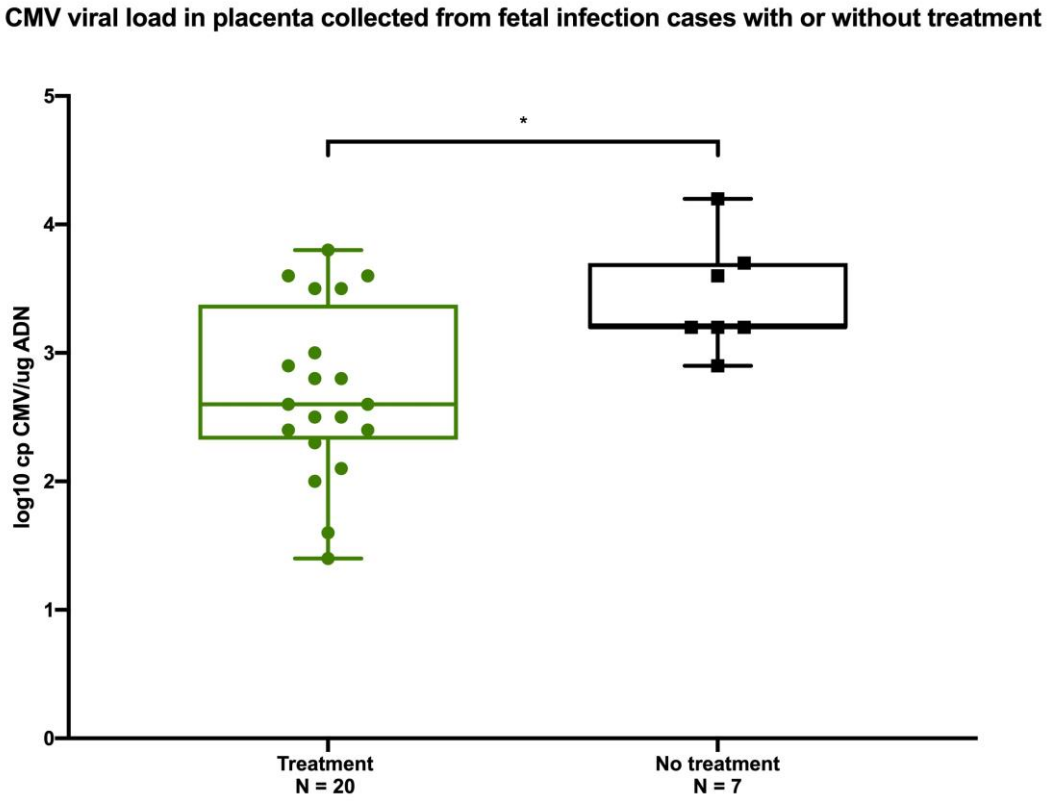
Maternal CMV PCR in whole blood at the time of CVS

- 15 cases without maternal viremia results
- 39 cases with negative CMV PCR in whole blood:
  - 37 CMV PCR negative in CVS
  - 2 (5%)CMV PCR positive in CVS
  - 33 CMV PCR negative in amniotic fluid
  - 5 (13%) CMV PCR positive in amniotic fluid
  - 1 amniotic fluid not tested (TOP for genetic abnormalities)
- 22 cases with positive CMV PCR in whole blood
  - 19 CMV PCR negative in CVS
  - 3 (14%)CMV PCR positive in CVS
  - 18 CMV PCR negative in amniotic fluid
  - 4 (18%) CMV PCR positive in amniotic fluid

CMV DNA in placentae from first trimester primary infection with or without fetal infection and with or without valaciclovir

- 100% of CMV PCR were positive in placenta from transmitter mothers
- 100% of CMV PCR were negative in placenta from non transmitter mothers





35 from women with primary infection in the 1st trimester:

- *26 with fetal infection*
- *9 without fetal infection*

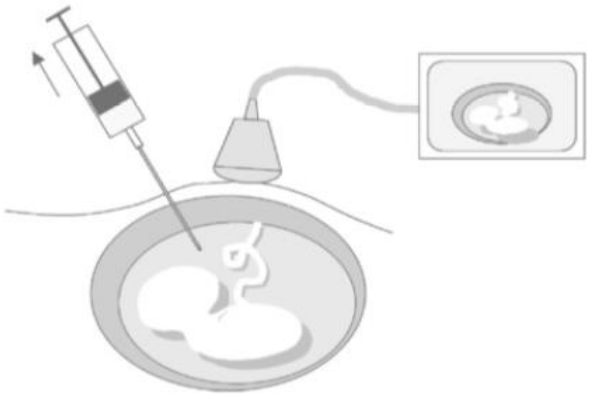
→ Infection of the placenta is the sine qua non condition for fetal infection after maternal primary infection in the first trimester

→ CMV placental infection is not focal but spread over the whole tissue

→ CMV PCR in a focal trophoblast biopsy should have a very high negative predictive value for early fetal infection

→ Valaciclovir treatment given from the 1st trimester significantly decreases CMV viral load in infected placenta

Amplification du génome viral par PCR
Dans le liquide amniotique



- Se et Sp de 100% sur le risque de symptômes
- Risque de fausse couche < 1/1000

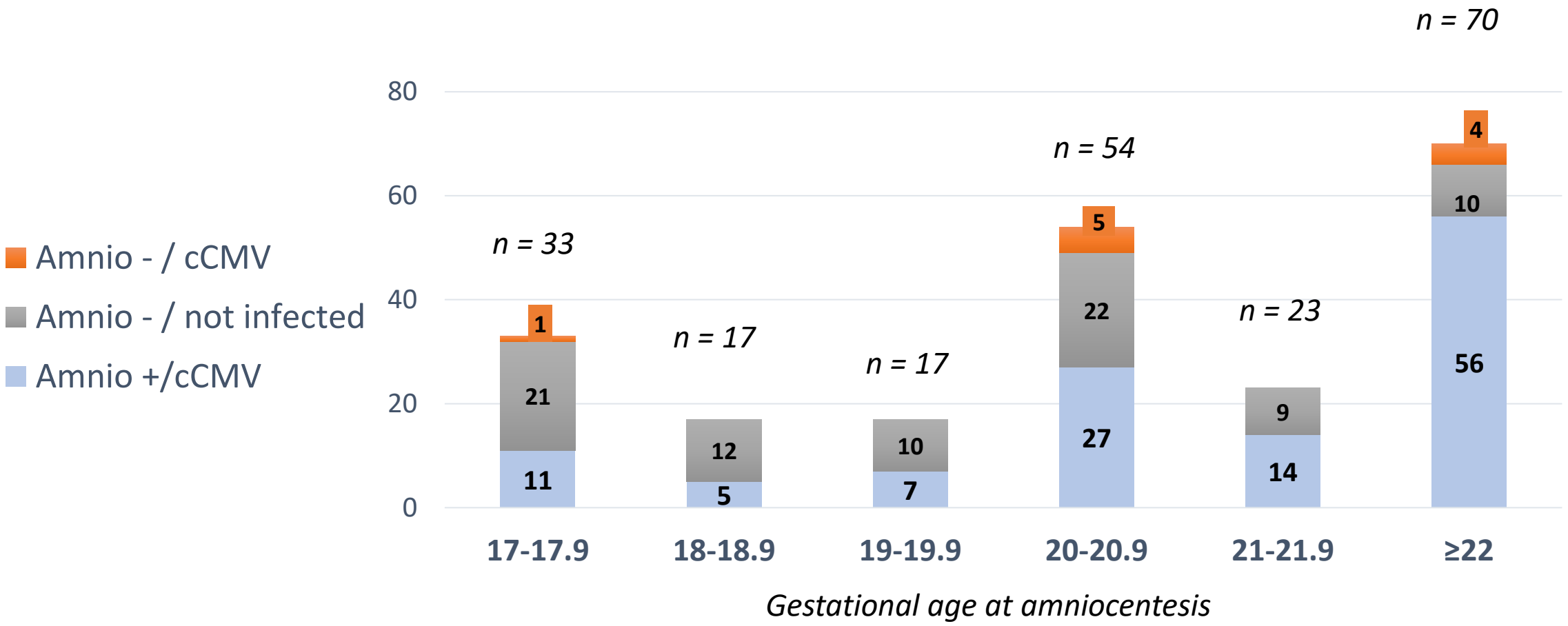
- Au moins 8 semaines après l'infection maternelle [1]
- A partir de 17 semaines d'aménorrhée [1]

- 8-10% PCR (-) & Urine (+) à la naissance [3]

Aucun enfant symptomatique à 2 ans

1 Enders M, et al. Prenat Diagn. 2017 Apr;37(4):389-398 2017
2 Guerra B, et al.Am J Obstet Gynecol. 2008 Apr;198(4):380.e1–7
3 Bilavsky E,et al . Clin Infect Dis. 2016 Apr 24;

Amniocentesis in Pregnancies with MPI < 14 WG (n= 314)



All « false negative » were asymptomatic at birth and at a mean age of 12 months of life

A guide to stepwise approach to identify and treat congenital infections
Fetal symptoms / Ultrasound features: PROGNOSIS

- **CYTOMEGALOVIRUS**

Value of prenatal ultrasound : Routine V. Focused

Prediction of sequelae at 2 years in 160 infected infants

	Se	Sp	VPP	VPN
Routine screening (22 & 32 weeks) : Diagnosis at birth				
N=160, All sequelae n=29	**48%**	73%	28%	**86%**
N=160, Severe sequelae n=15	**60%**	72%	18%	**94%**
Focused ultrasound : Prenatal diagnosis				
N=70, All sequelae n=12	92%	41%	24%	96%
N=70, Severe sequelae n=5	100%	38%	11%	100%

Leruez et al UOG 2020

A guide to stepwise approach to identify and treat congenital infections
Fetal symptoms / Ultrasound features: PROGNOSIS

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Leruez et al UOG 2020

Invasive Diagnosis the earlier the better

- Early prognosis

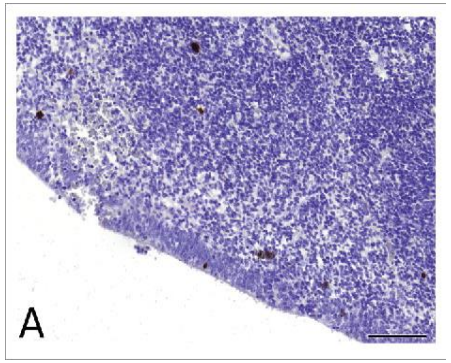
Fetuses infected after maternal primary infection in the 1st trimester

- **Symptomatic at birth:** **34%**
- **Sequelae at 30 months:** **35%** mild to severe, **23%** moderate to severe
- Sequential combination of 2nd trimester assessment + MRI:
  - ✓ Symptoms at birth (**PPV= 53% NPV= 82%)**
  - ✓ Mod/severe sequelae at 30 months (**PPV= 32% NPV= 100%)**
- **Benefits of MRI**
  - ✓ Brain features seen in 26% of those with normal ultrasound
  - ✓ In 36% of those with sequelae: normal US in the 3rd trimester / abnormal MRI
- **Both 2nd trimester assessment and MRI normal:** residual risk of **mild hearing loss in 17%**

Lee WEN, 1997, Journey of a yellow man

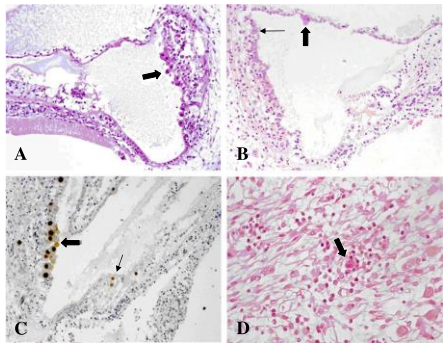
Invasive Diagnosis the earlier the better

- Efficient tertiary prevention: 2-Hit Hypothesis



Infected fetal brains with PPARγ expression

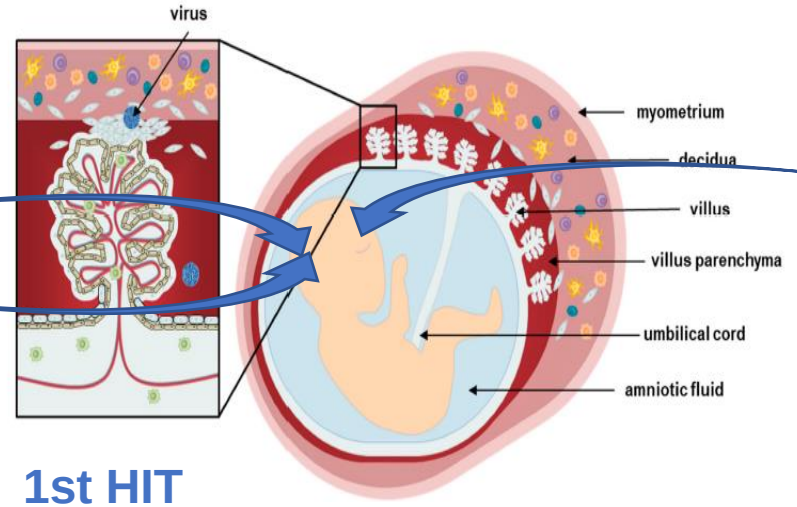
Rolland et al, Plos Pathogen, 2016



Gabrielli L, Acta Neuropathol Commun 2013

Neural stem cells are predominantly affected @ 10-12w

CMV+ & CD8+ cells in the stria vascularis of the cochlea @ 10-12 w



1st HIT

Embryonic injury

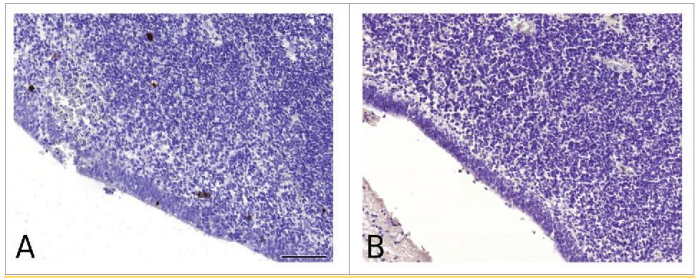
2nd HIT

Fetal Viremia-related Inflammatory lesions

Invasive Diagnosis the earlier the better

- Efficient tertiary prevention: 2-Hit Hypothesis

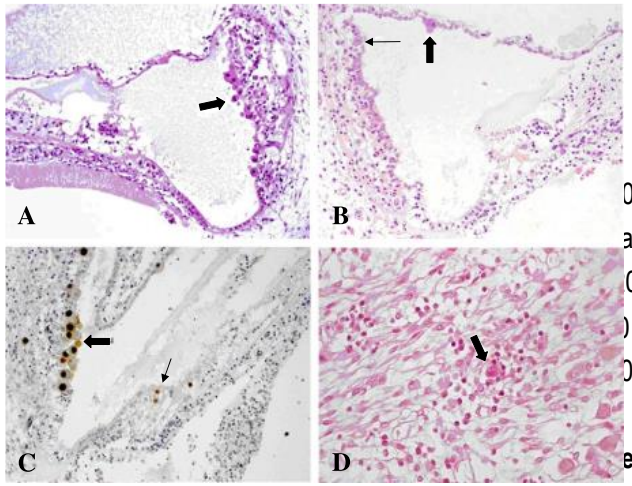
Neural stem cells are predominantly affected



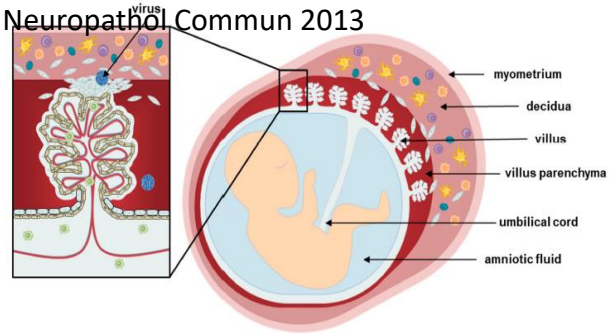
A=Infected fetal brains with PPARγ expression
B= Uninfected fetal braisn: no PPARγ expression

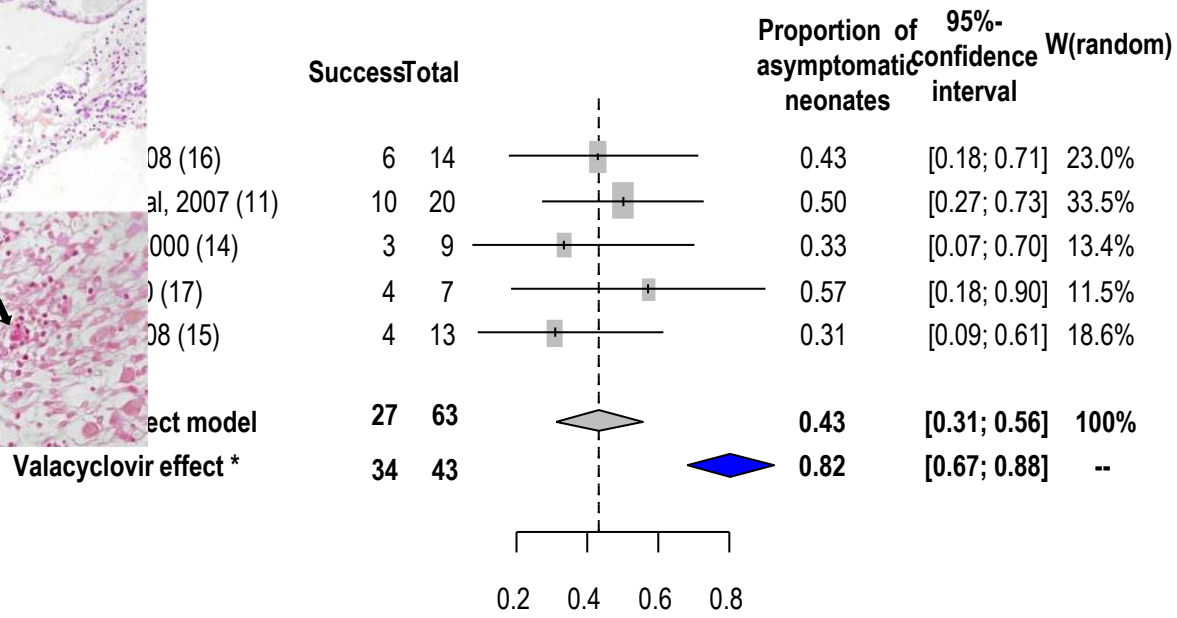
Rolland et al, Plos Pathogen, 2016

CMV+ &CD8+ cells **in the stria vascularis of the cochlea**



Gabrielli L, Acta Neuropathol Commun 2013



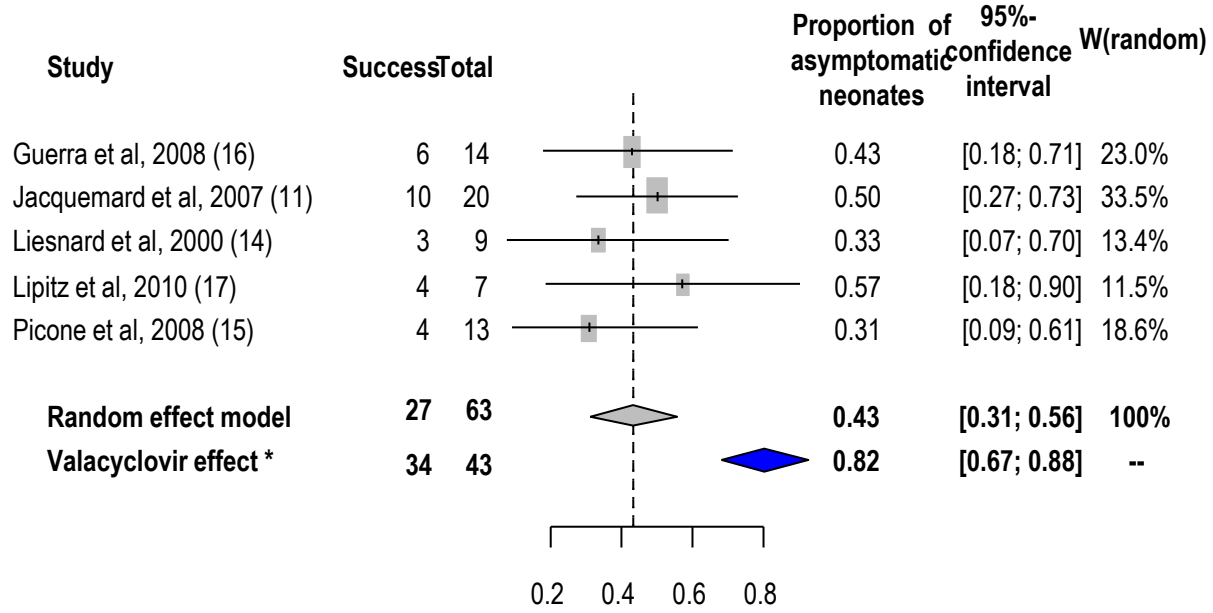


Comparison to a historical group
Valacyclovir increased the proportion of asymptomatic neonates, from 43% without treatment to 82% with treatment

Leruez AJOG 2016

Invasive Diagnosis the earlier the better

- Efficient tertiary prevention



Comparison to a historical group
Valacyclovir increased the proportion of asymptomatic neonates, from 43% without treatment to 82% with treatment

Leruez AJOG 2016

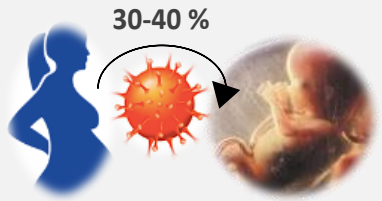
	Val-GCV	Val-ACV	LMV
Genotoxicity in vitro	Yes [1]	no	no
Teratogenicity in animal models	Yes at high dosage [2] (testicular abnormalities at 4 to 5 times higher /peak concentration observed in humans)	Yes at high dosage[2] (Birth abnormalities in ≈ 10% of rats treated in the embryonic period with a high dosage 4 times higher /peak concentration observed in human treated with 8g/day	no
Safety data in human pregnancy	Not available	Reassuring safety data in human pregnancy at all stages[3,4]	Not available
Tolerance	Frequent neutropenia	Good	Good

1=Wutzler P et al, Antiviral Res, 2001 ;2=Nihi F et al, Toxicol SCI, 2014;
3= Stone K et al, A Clin Mol Teratol; 2004; 4= Pasternak B, JAMA, 2010

Final conclusion

Screening for
CMV MPI @ T1
IgG IgM ± IgG avidity

Diagnosis of MPI @ T1

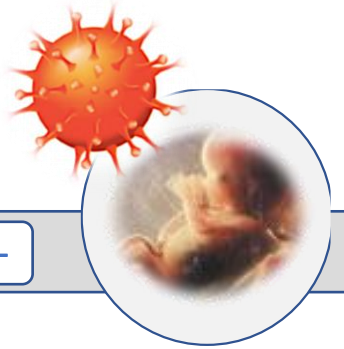


Diagnosis of fetal infection
Amniocentesis > 17 weeks'
MPI-Amniocentesis : 8 weeks

PCR -

Stop Valacyclovir

PCR +

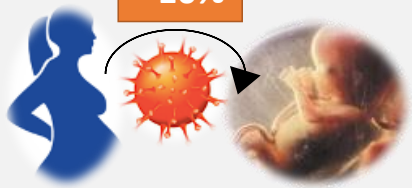


FÉDÉRATION FRANÇAISE CPDPN
Centres Pluridisciplinaires de Diagnostic Prénatal

Discuss an early diagnosis:
CMV PCR on trophoblast
obtained by CVS @ 14 weeks

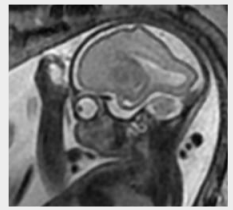
Start ASAP Valacyclovir 8g / d

≈ 10%



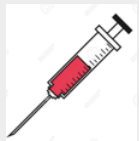
Refine prognosis

Every fortnight



@ 32 weeks'

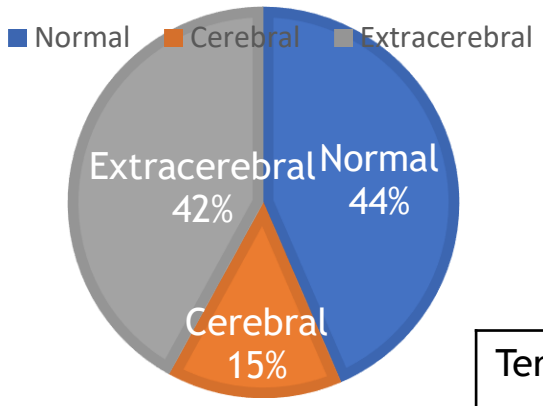
±



Fetal viremia +
Fetal platelet count
@ 20-22 weeks'

Continue antiviral treatment

IMPACT OF MRI IN LATE OUTCOME PREDICTION



US FINDINGS ON 2ND TRIMESTER EXAM

	Normal (N=27)	Extracerebral (N=26)	Cerebral (N=9)
Termination	4%	4%	44%
Symptoms @ birth	26%	48%	40%
Mild sequelae	12%	15%	-
Mod/severe sequelae	18%	30%	-

	Prediction of TOP or symptoms @ birth		Prediction of moderate / severe sequelae	
	PPV	NPV	PPV	NPV
2nd Trimester US + 3rd trimester MRI	53%	82%	32%	100%

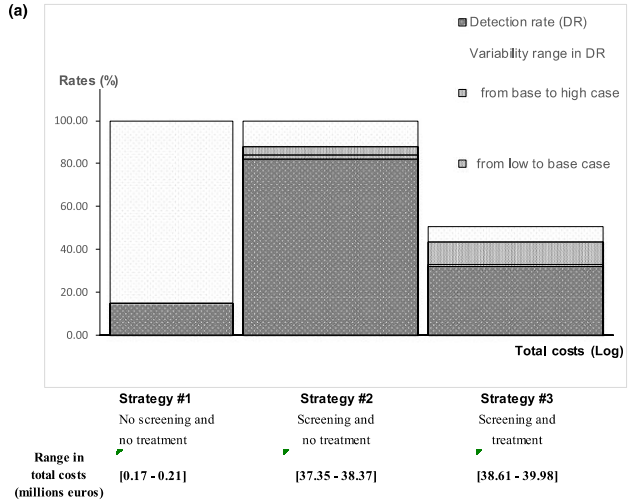
Both 2nd trimester assessment and MRI normal: residual risk of mild hearing loss in 17%

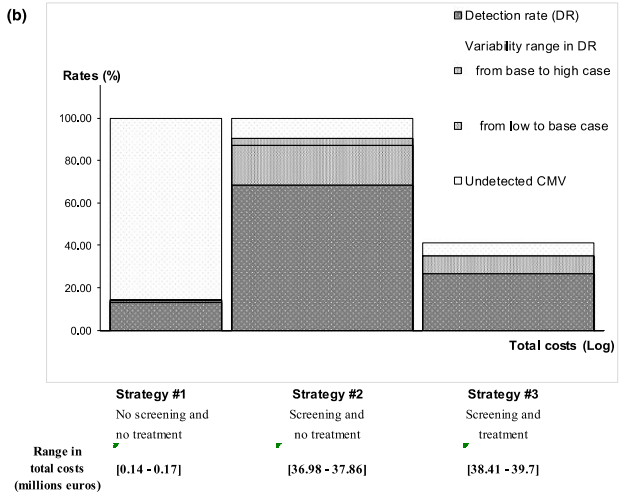
Faure Bardon BJOG 2020

Cost-effectiveness study from the perspective of the French national health insurance system of screening + secondary prevention in 1,000,000 pregnant women

38M€ to increase detection rates from 15% to 94%.
Secondary prevention results in 58% decrease of severely infected newborns for a 3.5% additional total costs

CMV serological screening followed by valaciclovir prevention may prevent 58% to 71% of severe cCMV cases for 38 € per pregnancy.





https://doi.org/10.1111/1471-0528.16966

Conditions non remplies pour offrir un dépistage de masse de l'infection à CMV pendant la grossesse (HCSP 2016-2020)

- ✓~~Dépister au 3ème trimestre serait une source d'anxiété et de dilemmes~~
- ✓**~~Nécessité d'un traitement pour la prévention secondaire de l'infection~~**
- ✓L'évaluation pronostique est réservée à quelques centres experts
- ✓~~L'efficacité des thérapeutiques antivirales ne sont pas démontrées par des essais randomisés~~
- ✓Le dépistage augmenterait les IMG non justifiées sans diminuer le risque de séquelles
- ✓Il n'existe pas de tests permettant le diagnostic de l'infection n on primaire
- ✓La connaissance de l'infection par le public est insuffisante
- ✓La connaissance de l'infection par les professionnels est insuffisante
- ✓~~Les études épidémiologiques sont de petite taille et monocentrique~~
- ✓~~Les règles d'hygiène individuelle semblent plus prometteuses~~

L'Infection congénitale à cytomégalovirus (CMV)

Haut Conseil de la Santé Publique	Académie Nationale de Médecine
Recommandations en décembre 2018: Pas de dépistage prénatal	**Recommandations en décembre 2019: Dépistage prénatal à 11-14 SA**
40 à 50 séquelles graves/an (registre du handicap à 7ans) 50% des cas non primaire sans diagnostic possible	Histoire naturelle: entre 200 et 350 enfants/an avec séquelles graves Oui mais on peut diagnostiquer les 50% restant
Même risque pour les femmes séropositives	Oui mais les femmes séronégatives ont un sur-risque très important (x4)
Echographie de routine repère les fœtus avec séquelles graves	Faux: l'échographie ne repère que 20 à 25% des cas sévères
Insuffisance de facteurs pronostiques fiables	Faux: échographie ciblée + IRM : VPN de 100% séquelles graves , risque résiduel de 10% d'hypoacousie
Le dépistage sérologique rate des primo-infections maternelles Il a des faux positifs	Dépend de la sensibilité du test IgM et de la date de la sérologie Non, sérologie = IgM + IgG + Avidité
Augmentation indue des IVG et IMG	NON / cadre légal de l'IMG qui sont ciblées sur les lésions sévères