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Syphilis et grossesse : enjeux et prise en charge

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Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Caroline Charlier-Woerther

Titre : Syphilis et grossesse

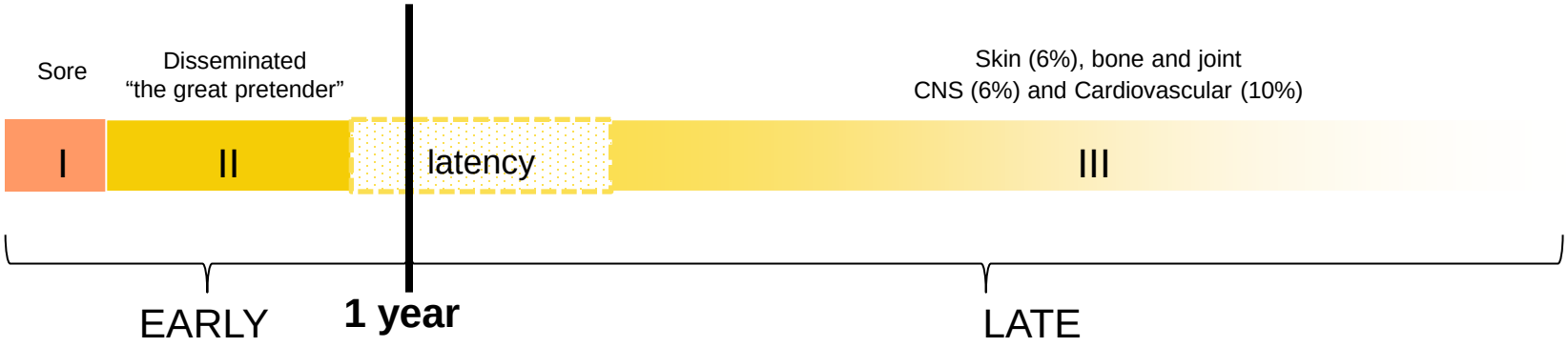
- Consultant ou membre d'un conseil scientifique — ☐ OUI ☑ NON
- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents — ☐ OUI ☑ NON
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations

  Eumedica train ECCMID 2016 / Pfizer ECCMID 2014 — ☑ OUI ☐ NON
- Investigateur principal d'une recherche ou d'une étude clinique

  2 protocoles avec financement public
  "MONALISAGENBIO" ANR 2015 / "MONALISA BABY"CRC 2014 — ☑ OUI ☐ NON

Syphilis

- Treponema pallidum : spirochete
- Human reservoir, not cultivable
- 3 phases

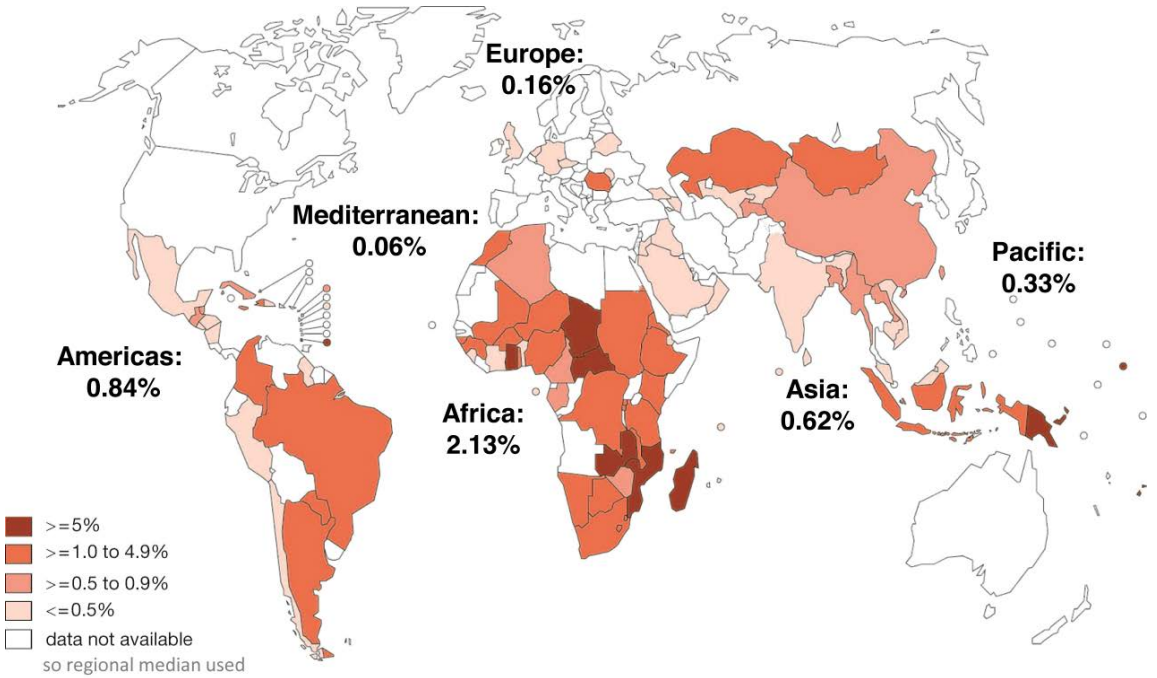


- Sexual transmission
  - Contact abraded infected lesion and mucosa or altered skin → 30%
- Vertical transmission

Syphilis and pregnancy epidemiology

- 1,860,000 pregnant women infected
- 1/3 of pregnant women not tested worldwide
- Only 30% women tested and treated in Africa

Global Estimates of Syphilis in Pregnancy



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Newman PlosMed 2013

Syphilis and pregnancy epidemiology

- Worldwide
  - 1.3% of mortality < 5 yrs attributed to syphilis
  - number of infants w/ congenital syphilis > w/ congenital HIV
- France
  - 0.06% of pregnancies have positive serological testing
  - 10 cases of congenital syphilis between 2012/2015 (1/3 DOM/TOM)

Saloojee Bull WHO 2004
CNR Data

The burden of syphilis in pregnancy

- Congenital syphilis

Child born from an untreated / bad treated mother

Child with clinical/ biological signs of congenital syphilis

- Consequences
  - Fetal loss 40%
  - Premature delivery 20%
  - Congenital infection
    - Early < 2 yrs (1/3)
    - Late < 2 yrs (2/3)

] Neonatal mortality 20%
Long term impairment 20%

Newman PlosMed 2013
CDC 2013

Maternal transmission is linked to 3 parameters

- Term of pregnancy at infection
  - From 16 WG (exceptionally from 11WG) → Placenta crossing

  Vertical transm. increases with gestational age /decreases in severity
  - At delivery → Contact infected maternal genital secretions

- Stage of infection

Stage	Rate of transmission
Primary/ Secondary (early)	60-100%
Early latent	40%
Late latent	8-10%

Charlier 2014

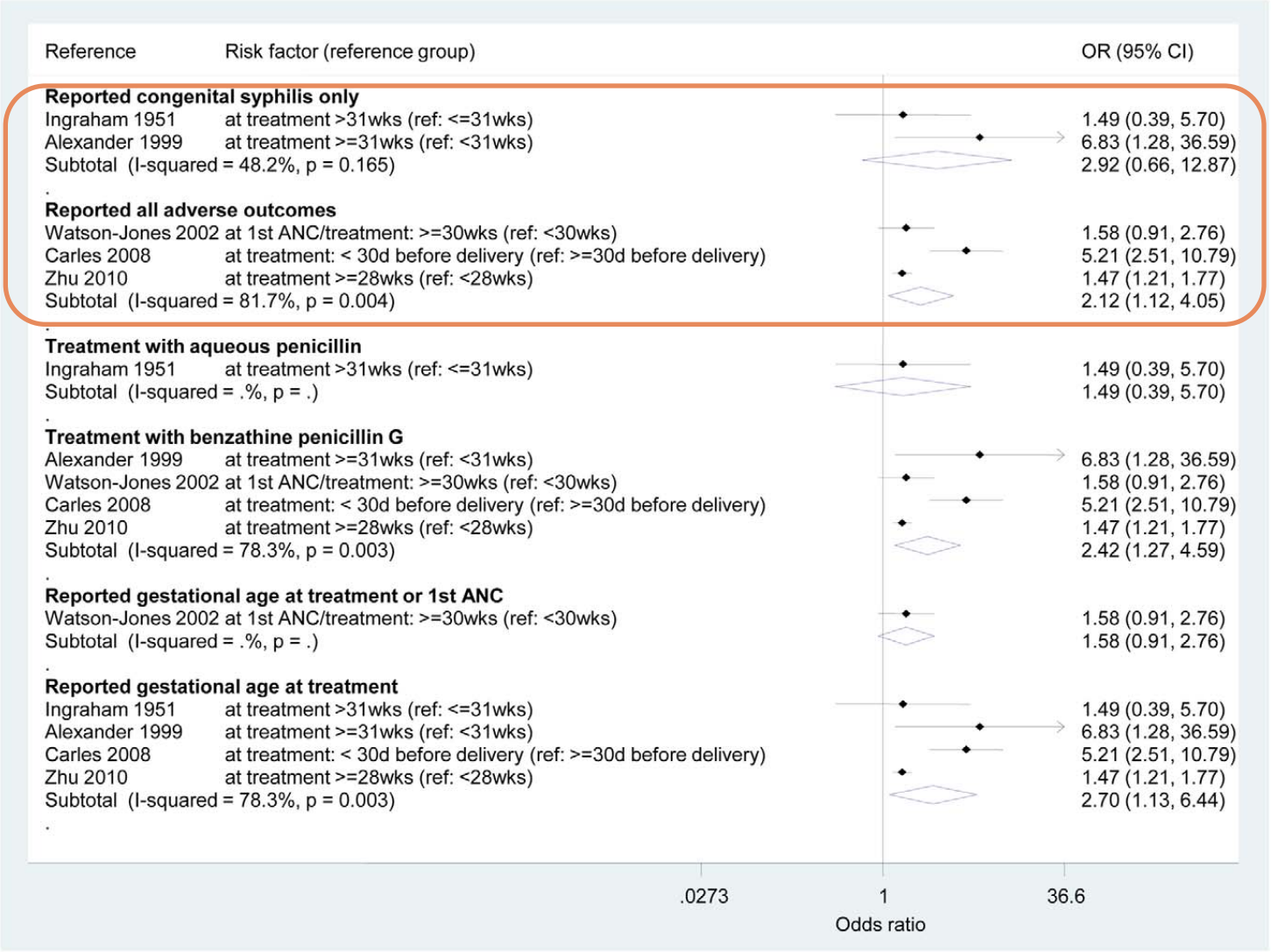
Maternal transmission is linked to 3 parameters

- Term of pregnancy at infection
- Stage of infection
- Maternal treatment
  - Adequate penicillin based treatment administered before the third trimester and at least > 30d before delivery is the most important parameter

Tableau 2 Facteurs de risque d'atteinte fœtale.
Table 2 Risk factor of fetal effects.

	Absence d'atteinte fœtale (56 cas)	Atteinte fœtale (29 cas)	*p*
< 3 consultations	17 (30,3 %)	16 (55,5 %)	0,025
Absence de traitement	2 (3,6 %)	13 (44,8 %)	0,01
≥ 2 injections Extencilline®	43 (76,8 %)	9 (31 %)	0,001
Délai traitement—accouchement inférieur à un mois	10 (17,8 %)	22 (75,9 %)	0,001
Taux moyen VDRL chez la mère	35	46	NS

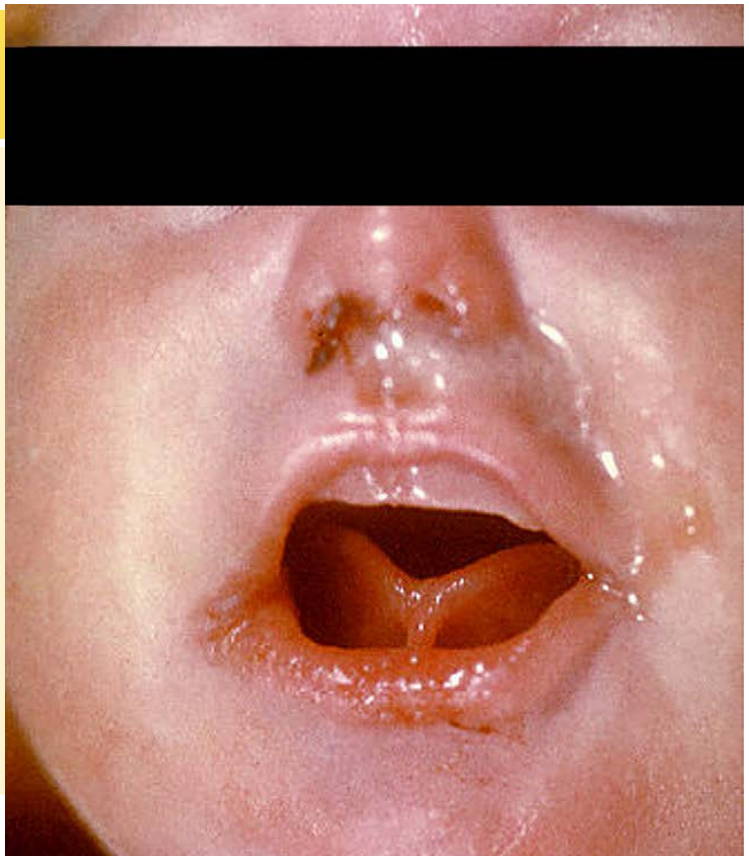
Carles JGOBR 2008



Hawkes Plos Med 2013

Congenital syphilis

Antenatal ultrasound signs	Early Syphilis
Fetal loss Growth restriction Hydrops fetalis Ascites Hepatomegaly Hydrocephaly Brain calcifications	Osteochondritis 61% Hepatomegaly 61-100% Splenomegaly 49% Petechial lesions 41% Other (contagious) skin lesions 35% Meningitis 25% Adenomegaly 32% Jaundice 30% Anemia 30% **Nasal discharge** 22% Nephrotic syndrome 20%



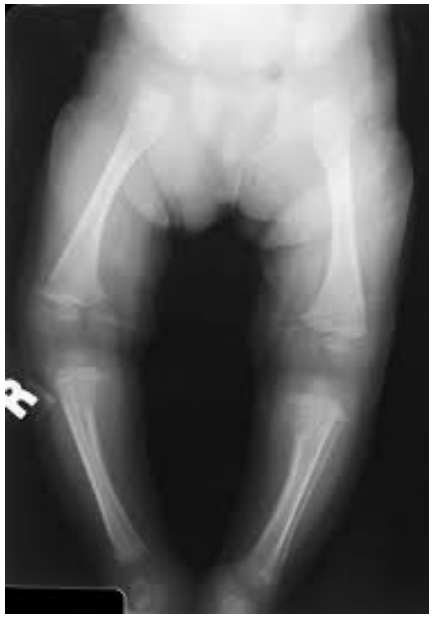
Walker Semin fet Obstet Dis 2008
Charlier LPM 2014

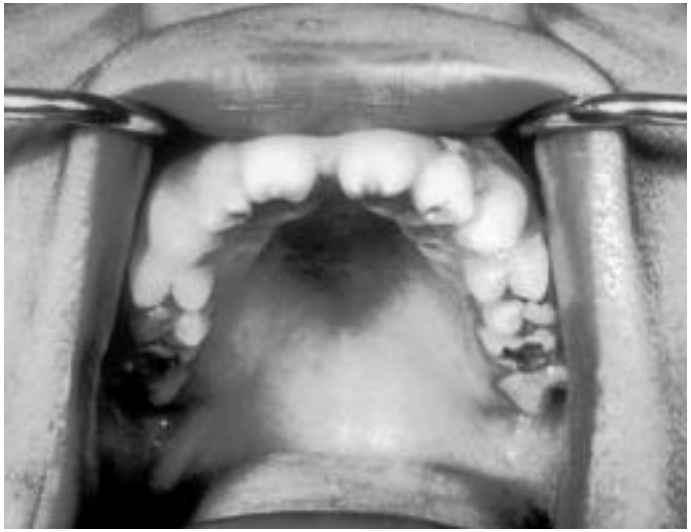
Congenital syphilis

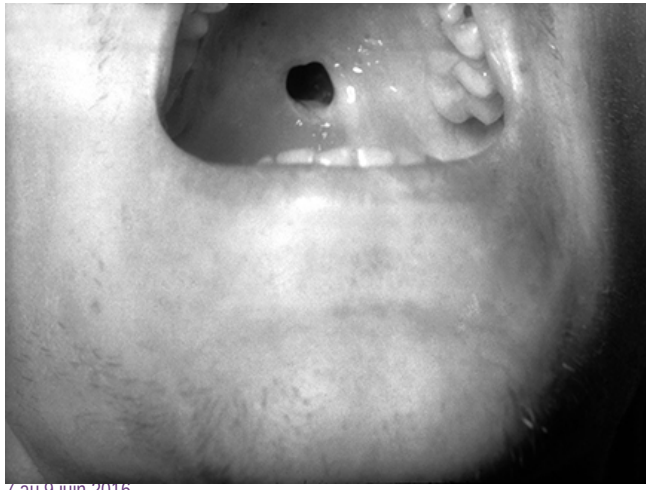
Antenatal ultrasound signs	Early Syphilis	Late Syphilis
Fetal loss Growth restriction Hydrops fetalis Ascites Hepatomegaly Hydrocephaly Brain calcifications	Osteochondritis 61% Hepatomegaly 61-100% Splenomegaly 49% Petechial lesions 41% Other (contagious) skin lesions 35% Meningitis 25% Adenomegaly 32% Jaundice 30% Anemia 30% Nasal discharge 22% Nephrotic syndrome 20%	Frontal bossing 30-87% Saddle nose Keratite 25-50% Ear loss Hutchison teeth 55% Bone lesions 30-46% Raghades 76%

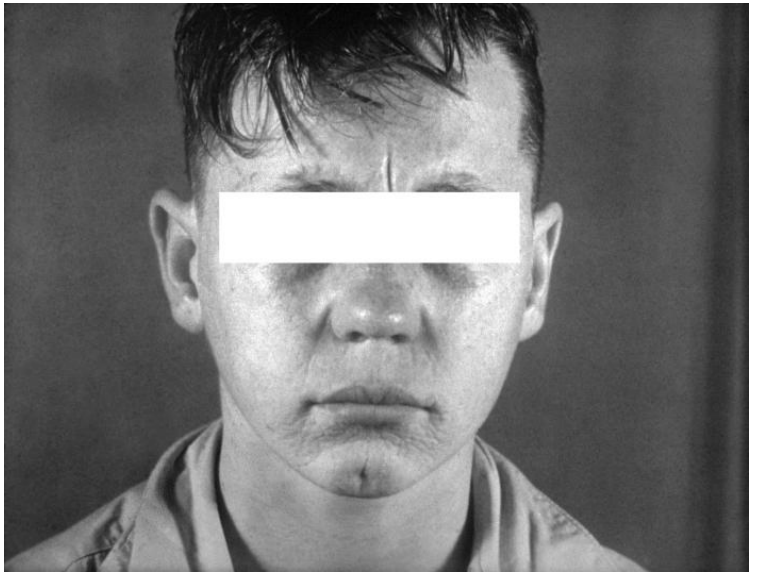
Walker Semin fet Obstet Dis 2008
Charlier LPM 2014

Congenital syphilis





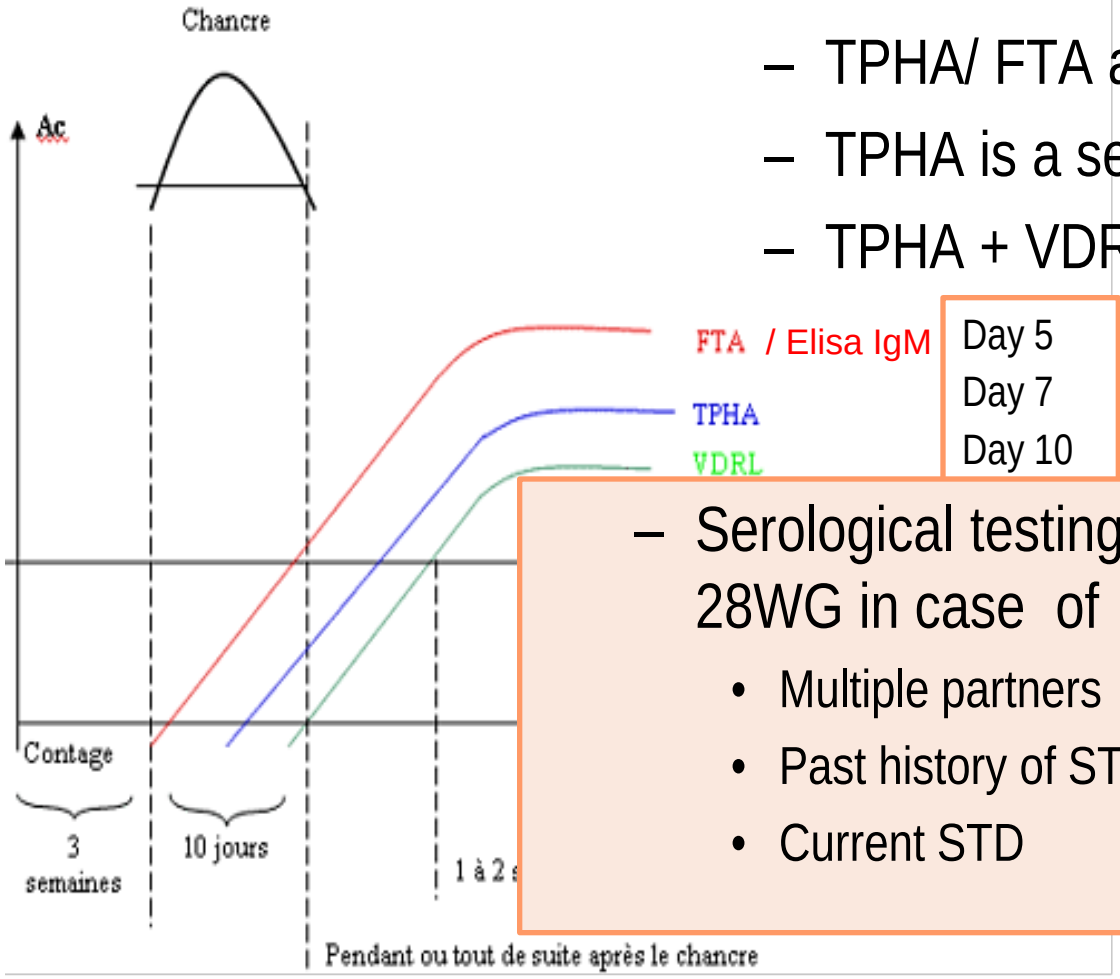




CDC

Maternal diagnosis

- VDRL is not specific of *Treponema*
- TPHA/ FTA are not specific of *pallidum sp.*
- TPHA is a serological scar
- TPHA + VDRL- → IgM , FTA, repeat



Day 5
Day 7
Day 10

- Serological testing should be repeated at 28WG in case of
  - Multiple partners
  - Past history of STD
  - Current STD

Maternal treatment : 7 points

- Treat ideally before 16 WG, at least before T3
- Penicillin in all cases
- Prevention of Jarisch- Herxheimer
- Evaluation for other STD
- Evaluate partners
- Evaluate the newborn
- Check for VDRL decrease at M3, M6 and M12

+ at delivery++

Maternal treatment

- Early infection : < 1yr

→Penicillin 2.4 M units/ week 2 weeks : 2 doses

→Xylocain allowed in pregnancy

- Later infection : > 1yr

→ Penicillin 2.4 M units/ week 3 weeks

Maternal treatment : penicillin allergy

- Desensibilization

DÉSENSIBILISATION ORALE À LA PÉNICILLINE

(d'après Stark et Sullivan J. Allergy and Clin. Immunol. 1987)

Consentement éclairé signé par le patient

SURVEILLANCE MÉDICALE RÉGULIÈRE ++++

N° dose	Unités administrées	Voie d'administration	Espacement entre les doses	Dose et concentration
1	100 ui			1 ml (100 u/ml)
2	200 ui			2 ml
3	400 ui			4 ml
4	800 ui			8 ml
5	1 600 ui			1,6 ml (1 000 u/ml)
6	3 200 ui	ORALE	15 minutes	3,2 ml
7	6 400 ui			6,4 ml
8	12 800 ui			12,8 ml
9	25 000 ui			2,5 ml (10 000 u/ml)
10	50 000 ui			5 ml
11	100 000 ui			1 ml (100 000 u/ml)
12	200 000 ui			2 ml
13	400 000 ui			4 ml
14	200 000 ui			
15	400 000 ui	SC	15 minutes	
16	800 000 ui			
17	1 000 000 ui	IM	15 minutes	
18	Dose thérapeutique	IV	Chronologie habituelle sans jamais espacer plus de 8 heures les doses délivrées	

Voie veineuse impérative - Chariot de réanimation à proximité adrénaline, corticoïde injectable, antihistaminique disponibles

Faire préparer par la pharmacie de l'hôpital les dilutions de pénicilline de 100 000 ui/ml à 100 ui/ml à partir de la phénoxyméthylpénicilline (Oracilline suspension 1 000 000 ui/10 ml).

Passer à la péni G (flacons à 1 000 000 ui) pour les injections.

Maternal treatment : Jarisch-Herxheimer

- Release of treponemic LPS after the 1st penicilin dose
- Flu-like → hypotension
- Starts 1-2 hrs, peaks at 8th hrs and resolve < 48 hrs after penicillin administration
- 30 to 50% of maternal cases
- → Uterine contractions/ premature delivery?

Paracetamol 1g 2hrs before injection,
To be repeated for 48 hrs : 1g x 3 /d
In case of persisting fever : prednisone (0.5mg/kg/d)

Neonatal evaluation : 3 situations

- → Clinical evaluation + VDRL serum mother / child
- Classification CDC proven/ highly probable/ probable/ possible/ less likely and unlikely

- Situations requiring maximal evaluation and antibiotic treatment
- Situations with minimal risk
- Situation without risk of congenital syphilis : no further evaluation, no neonatal treatment

Adapted from CDC

and from Necker / CNR procedure

Maximal evaluation and treatment

WHO?

- PCR positive on any infant sample

(CSF/ nasal discharge, skin, blood, placenta…)

- VDRL NN/mat > 4
- IgM NN positive
- VDRL NN positive and
  - Clinical signs in NN OR
  - Maternal treatment not performed or not adequate (not penicillin, to late (< 4 wks before delivery), no serological response)

Maximal evaluation and treatment

WHAT?

- CBC
- Liver tests
- CSF examination (PCR, VDRL, IgM)
- Long bones radiographs
- (Brain imaging, ophtalmologist evaluation)

- Penicillin IV 150,000 U/kg/d (25,000 U/Kg x 6/d)
- For 10 -14d (14 d in neurosyphilis)

Minimal risk

WHO?

- VDRL NN positive and
  - VDRL NN/mother < 4
  - No clinical signs in NN
  - Maternal treatment performed and adequate (penicillin, >4 wks before delivery, good serological response)

WHAT?

- No further evaluation
- Penicillin IM 50,000 U /kg single dose
- Serological monitoring

No risk

WHO?

- VDRL NN negative and
  - No clinical signs in NN
  - Maternal treatment performed and adequate (penicillin, < 16 WG, good serological response)

WHAT?

- No further evaluation
- No treatment
- No serological monitoring

Congenital syphilis

- Subsequent evaluation by the pediatrician
  - Clinical / 3 months for 2 years
  - Serological testing at M3 M6 M12
  - VDRL negative at M6, TPHA negative at M12

- Management of Treponema exposure at delivery
  - All staff in contact with the infant < 24 hrs of treatment
  - Skin / mucosal contact with infections lesions (nasal discharge, skin or mucosal infected lesions)
  - Penicillin 2.4M U 1 dose
  - Clinical evaluation W2 + Serology M1,M3,M6 and M12

Syphilis and breastfeeding

- No transmission through the milk
- Transmission possible in case of lesion on the nipple
- Penicillin is not contra-indicated during lactation

References

- Procédure syphilis Necker / CNR syphilis 2015
- Sexually Transmitted Diseases Treatment Guidelines. Recommandations du CDC
- 2008 European Guideline on the management of Syphilis.
- Charlier, Benhaddou, Dupin . La Presse Médicale 2015.