Cas clinique grossesse

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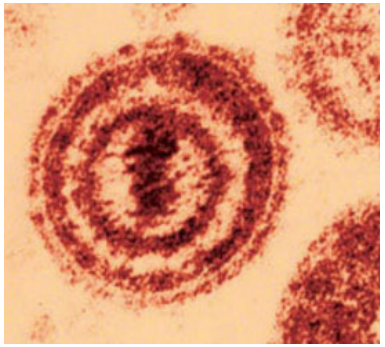
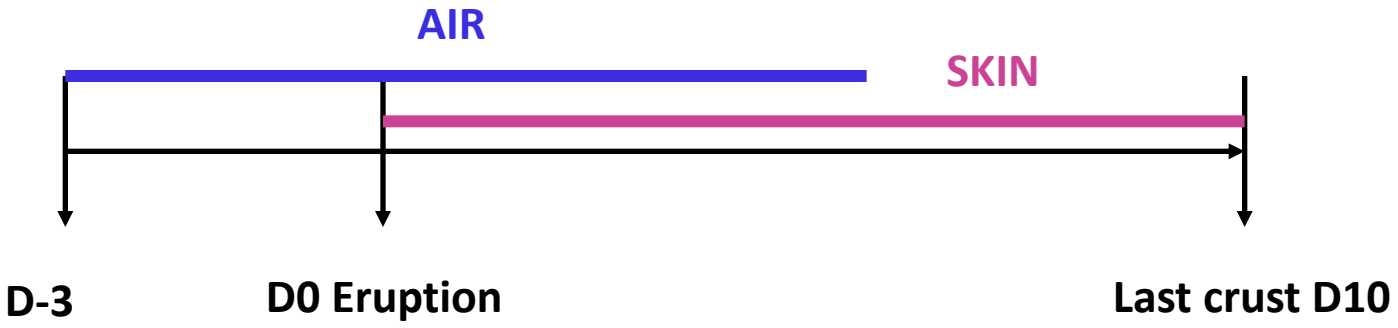
Varicella zoster virus and pregnancy

DNA virus epidermo- and neuro-tropism

AIR > skin transmission

800,000 cases / yr in France only





Varicella zoster virus and pregnancy

- Highly contagious: attack rate 60-90%

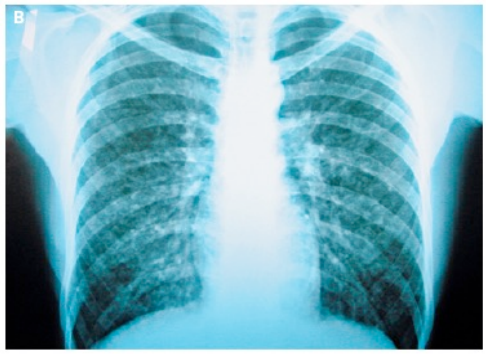
- Uncommon in European pregnancies
  - Séroprevalence Europe > 90% (80% in Asia /Africa)
  - >90% of women not recording varicella are indeed protected

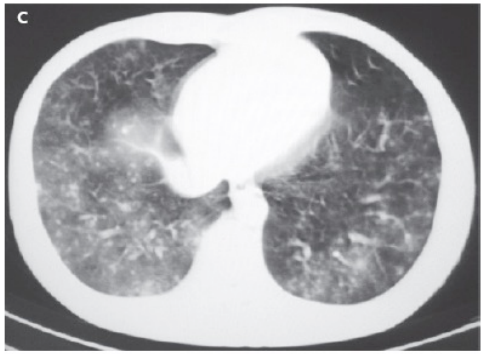
- **Varicella contact**
  - Frequent call
  - Occurrence in a really non immune woman : 1/1000

Saadatian-Elahi 2007, Knwoles 2004, Daley 2008, Sauerbrei 2007

Varicella is more severe in adults

Adults = 10% of varicella cases but 26% of hospitalizations and **69% of related deaths**

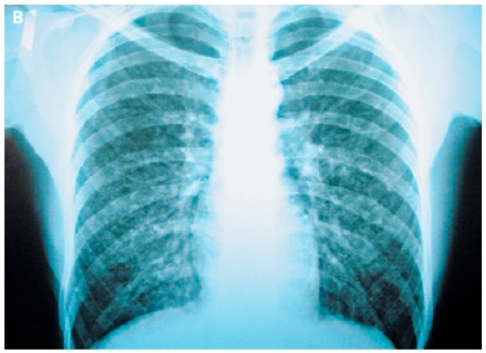


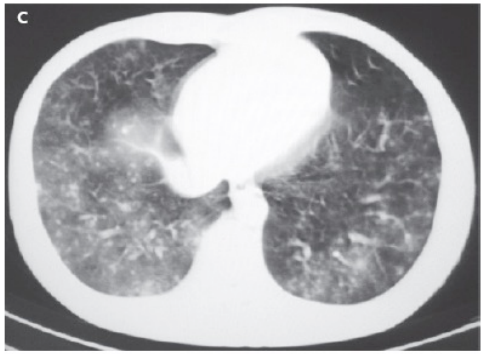


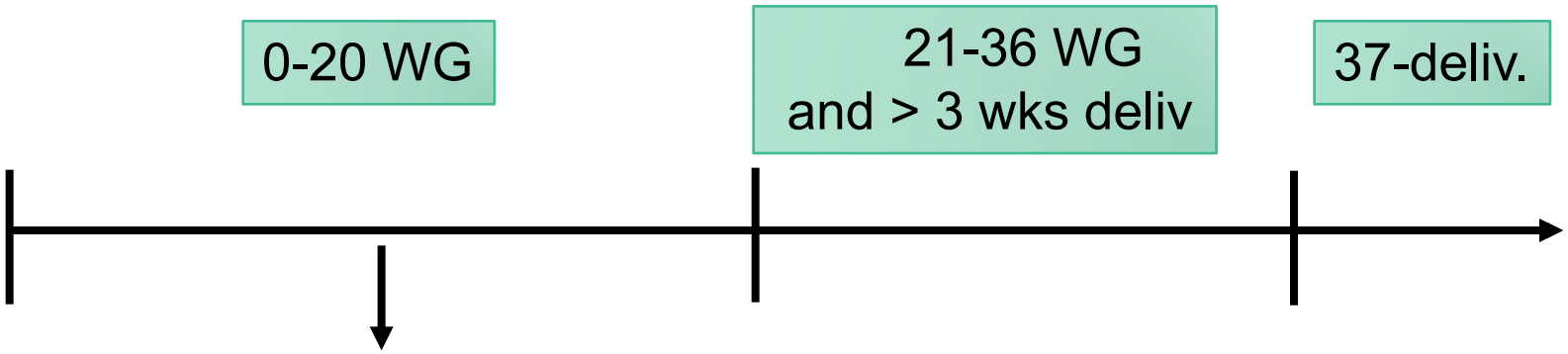
Varicella is even more severe in pregnant women

Viral pneumonia

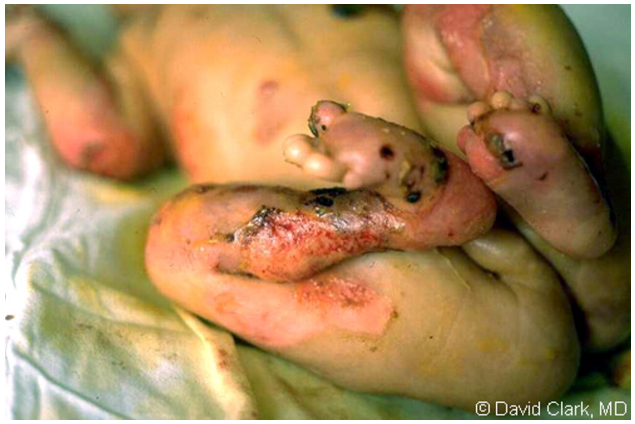
- Mostly 3rd term
- Mostly tobacco smoking OR 5 [1.6-16.7]
  and > 100 skin lesions OR 15 [1.9-130]
- More severe in pregnancy







Congenital varicella
Risk 1-2%

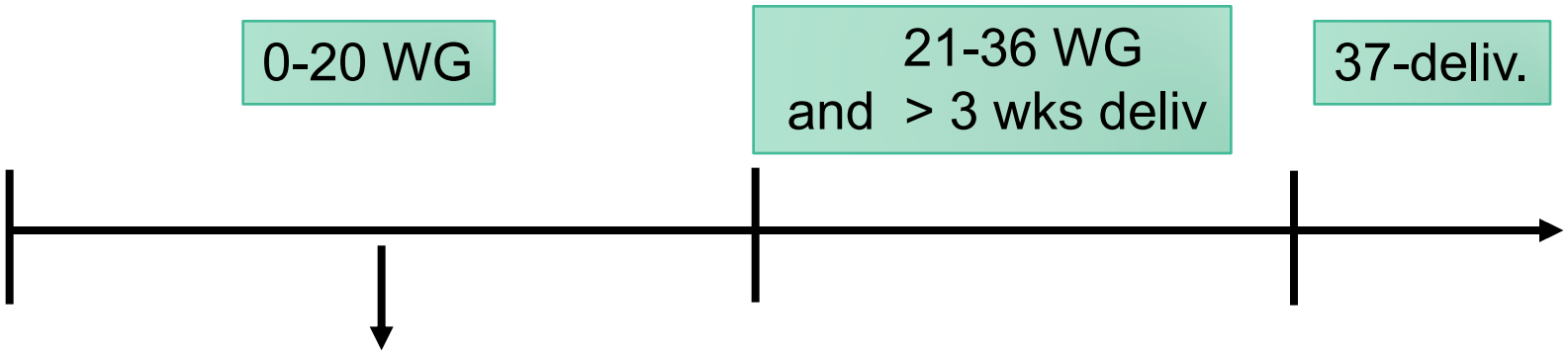


Fetal infection = 25% of maternal infection
Fetal malformation = 12% of infected fetuses

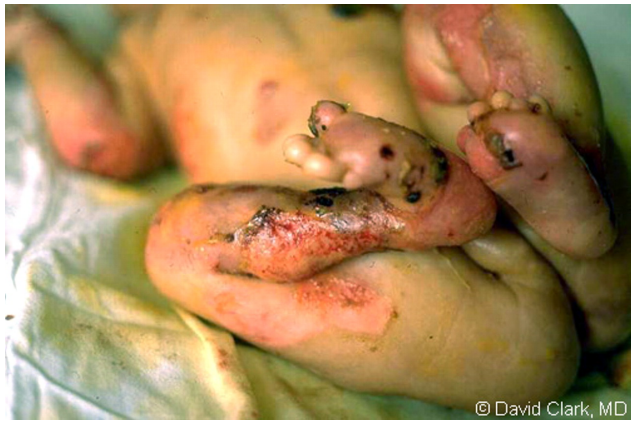
Pastuszak 1994, Tan 2006,
http://aapredbook.aappublications.org/content/1/SEC131/SEC289/G3503.expansion.html

Embryofoetopathy

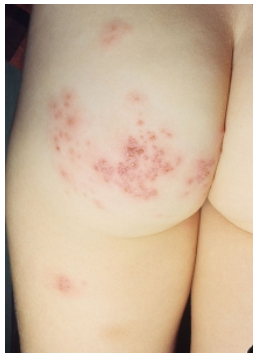
Skin lesions	100%
CNS : microcephaly, autonomous nervous system	70%
Eye: microphtalmia, optical nerve atrophy, cataract chorioretinitis	70%
Muscles: limb hypoplasia	70%
Growth retardation	30%



Congenital varicella
Risk 1-2%



Shingles <1 yr
Risk 1-2%*



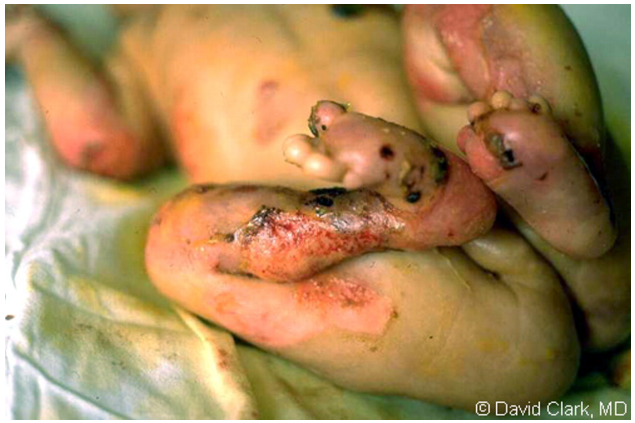
Pastuszak 1994, Tan 2006,
http://aapredbook.aappublications.org/content/1/SEC131/SEC289/G3503.expansion.html

0-20 WG

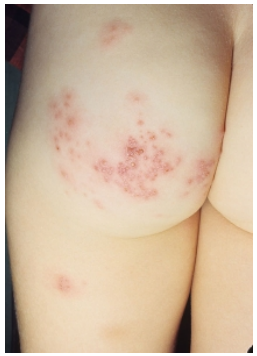
21-36 WG
and > 3 wks deliv

37-deliv.

Congenital varicella
Risk 1-2%



Shingles <1 yr
Risk 1-2%*



Neonatal varicella

< 10 d
Skin rash + visceral lesions
30% mortality without IGIV
D-21-D-7 : 25% :v. néonatale
D-5- D+2 : risque maximal

Pastuszak 1994, Tan 2006,
http://aapredbook.aappublications.org/content/1/SEC131/SEC289/G3503.expansion.html

Management of varicella exposure 3 questions, 1 test

1. Is the contact at risk ?

- Intrafamilial contact
- > 5 min face to face
- > 15 min - 1 hr in the same room (local guidelines)
- With a contagious patient (48-72hrs before rash-last crust)

Management of varicella exposure 3 questions, 1 test

1. Is the contact at risk ?

2. Is the patient immune?

- = Definite history of chickenpox or herpes zoster
- Serology can be performed if does not delay Ig adm

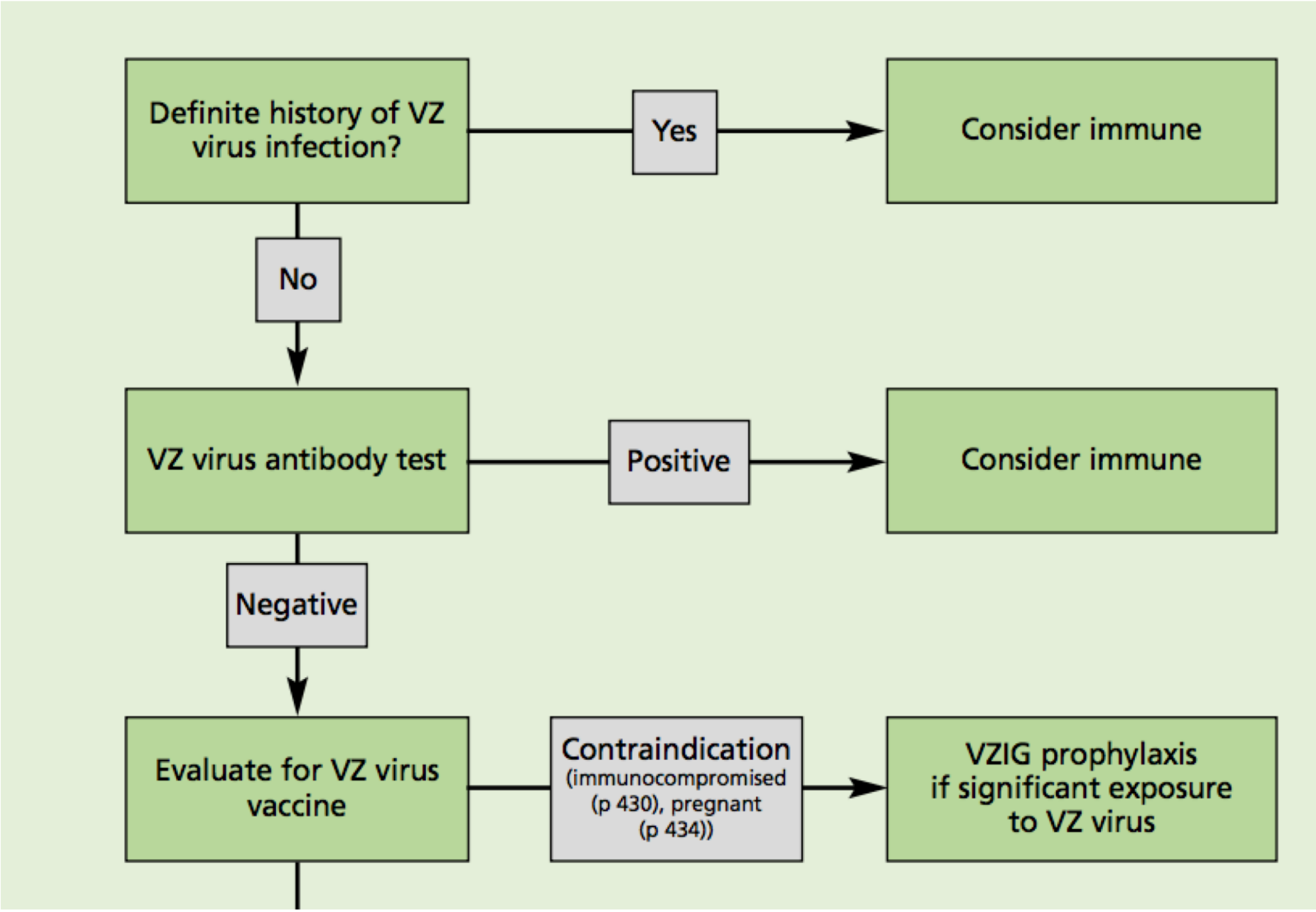
Management of varicella exposure 3 questions, 1 test

1. Is the contact at risk ?

2. Is the patient immune?

3. How long ago is the contact ?

- < > 96hrs?
- < > 10 days? US


Definite history of VZ virus infection?
Yes
Consider immune
No
VZ virus antibody test
Positive
Consider immune
Negative
Evaluate for VZ virus vaccine
Contraindication (immunocompromised (p 430), pregnant (p 434))
VZIG prophylaxis if significant exposure to VZ virus

Anti-VZV Immunoglobulins

Reduction of varicella cases

Reduction of varicella severity

Avoidance of congenital varicella

IV or IM according to local guidelines
The earlier the better

- **UK guidelines 2015**
  - **212 pregnant patients / Ig within 10 days after exposure**
    → 50% varicella (no severe infection),
    5% infraclinical varicella, 45% no infection

- **Cohen CMAJ 2011 : métaanalysis**
  - **0 congenital infection among 142 pregnant patients treated with**
  - **Versus 14/498 (3%) among untreated pregnant patients**

Zaia 1983, Enders 1994 Cohen CMAJ 2011

VARICELLE PENDANT LA GROSSESSE : RECOMMANDATIONS DE PRISE EN CHARGE NECKER-ENFANTS MALADES

COMAI 18 Septembre 2009

Services de Gynécologie Obstétrique, Néonatologie, Maladies Infectieuses et tropicales, Pharmacie, Microbiologie et Pharmacologie SVP

PRISE EN CHARGE D'UN CONTAGE VARICELLEUX

Prophylaxie post exposition

- Est-ce un contact à risque ?
- La patiente est-elle protégée vis à vis de la varicelle ?
- Quelle est l'ancienneté du contage?

- Contact à risque
- Patiente non protégée
- Contage ≤ 4 jours

Pas d'isolement de la femme enceinte seronégative vis à vis de ses enfants avec varicelle

CIII

- Vaccin vivant administré dans les 72H efficace mais CI
- Immunoglobulines spécifiques en ATU 1 ml (25 UI) /kg IV (0,1 – 1ml/kg/h).
- En accord avec les obstétriciens
- Information sur le risque d'échec et la CAT en cas de fièvre/ éruption

PRISE EN CHARGE D'UN CONTAGE VARICELLEUX

Prophylaxie post exposition

- Est-ce un contact à risque ?
- La patiente est-elle protégée vis à vis de la varicelle ?
- Quelle est l'ancienneté du contage?

- Contact à risque
- Patiente non protégée
- Contage > 10 jours

- Pour certains : Antiviraux : valaciclovir 1g x 3/J pendant 15jours hors AMM
- En accord avec les obstétriciens
- Information sur le risque d'échec et la CAT en cas de fièvre/ éruption

CIV

VACCINATION EN POST PARTUM EN L'ABSENCE DE VARICELLE

Management of varicella

1. Documentation

2. Air and contact isolation

3. Oral valaciclovir 3 g/d 7 days (IV ACV if severe varicella)

4. Fetal evaluation if < 20 WG

5. Anti_VZV Ig to the infant
if maternal rash starts within D-5 → D+2 around delivery

Management of varicella

- Mum and baby remain together (air+ contact isolation)
- Breastfeeding allowed
- Close monitoring of the neonate

Management of shingles

- No fetal risk
- Contact isolation for the mother
- Maternal treatment in ophtamic shingles

References

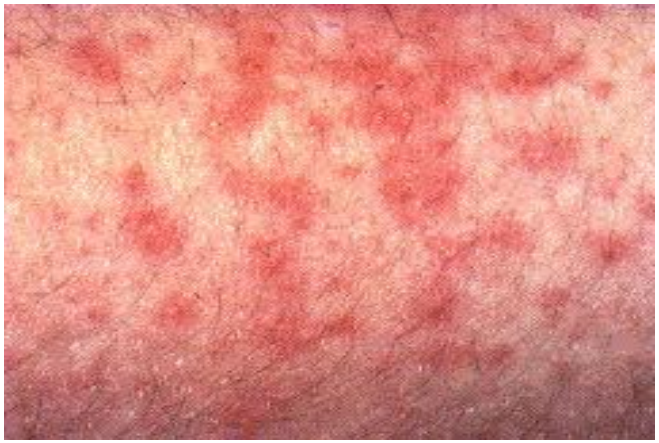
https://www.cdc.gov/chickenpox/hcp/clinical-overview.html

https://ecdc.europa.eu/en/varicella/facts

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/456562/Green_Book_Chapter_34_v3_0.pdf

B19 et grossesse

- Contagiosité de J-7 à J0 (avant éruption)
- Taux d'attaque = 10-50% (50% contact familial)
- 50% des femmes en âge de procréer non-immunes
- Séroconversion grossesse: 1-3%



Clinique maternelle
Asymptomatique 40%
Sd grippal
Rash en dentelle /joues claquées
Articulations : 80% des adultes

Gratacos JID 1995, Enders Prenat Diag 2004, Bonvicini JCM 2011

B19 et grossesse

TME : 0% avant 8SA puis 35% | T2: 57% avant 20SA 23% ap 20SA | T3 67%

T1 | T2 | T3 Peripart.

13% fausses couches

33-50% infection fœtale
→ 9% perte fœtale (si 13SA< inf. mat. < 20SA)
→ Anasarque fœtale
- 15% si infection mat < 22SA
- Jamais si infection mat > 28SA
- Par atteinte erythroblaste et myocarde

Asymptomatique

Peripartum
Rash
Thrombopénie
Myocardite grave rare

Pas de malformation associée
Perte fœtale < 0.1% si inf maternelle > 20SA
Pas d'anasarque si inf maternelle > 28 SA
Possible séquelles neurologiques à long terme*

Nyman Obstet Gynecol 2002
Enders Prenat Diagn 2004
Bonvicini JCM 2011
Miller 1998
*De Jong AJOG 2012
*Dembinski BJOG 2002

B19 et grossesse

- **Infection fœtale 1-3 sem après l'infection maternelle**

- **Conséquences fœtales**
  - **Perte fœtale**
  - **Hydrops**
    - Non immunologique lié à l'anémie sévère qui se développe en moyenne 2-6 sem après infection mat. (max 12 semaines)
    - **Signes échographiques**
    - **Le traitement est l'exsanguino-transfusion fœtale**
    - **La mortalité spontanée de l'anasarque est de 30 à 50%**
    - **Les immunoglobulines ne sont pas indiquées**
    - **Pas d'antiviral**

Nyman Obstet Gynecol 2002
Enders Prenat Diagn 2004
Bonvicini JCM 2011
Miller 1998

B19 et grossesse

- **Suivi maternel**

1. Sérologie maternelle immédiatement en post contage

- IgG+ → protégée
- IgG+, IgM+ → infection aigue : évaluation obstétricale
- IgG-, IgM- et < 20SA → pas de protection vis à vis de l'infection : refaire sérologie S3

2. Sérologie maternelle 2-3 semaines + tard

- IgM sortent avant le rash, vers J10 après le contage, persistent 2 -4 mois,
- IgG sortent 1 semaine après le rash
- Apport de la PCR B19 sanguine : sensibilité 96%

3. Suivi échographique / sem pendant 12 semaines si inf. maternelle confirmée

Nyman Obstet Gynecol 2002
Enders Prenat Diagn 2004
Bonvicini JCM 2011
Miller 1998

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 9 WG*) → 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%

Harter AJOG 1976
Fiumara Clin Obstet Gynecol1975

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

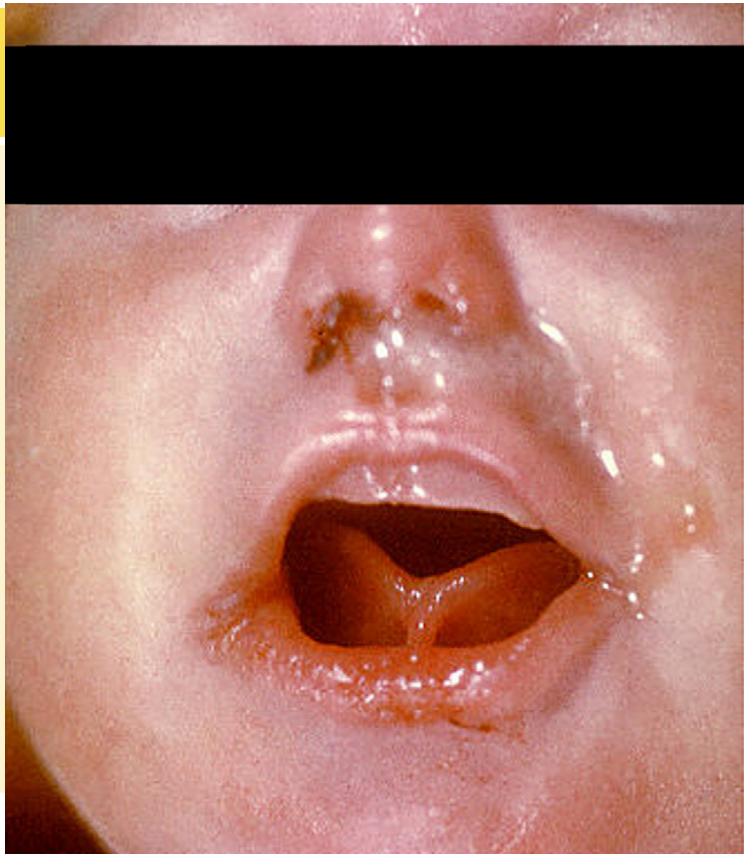
Tableau 2 Facteurs de risque d'atteinte fœtale.
Table 2 Risk factor of fetal effects.

	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

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%



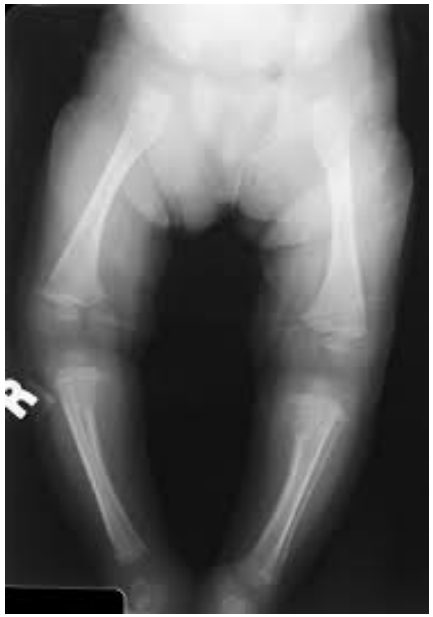
Walker Semin fet Obstet Dis 2008
Charlier LPM 2014

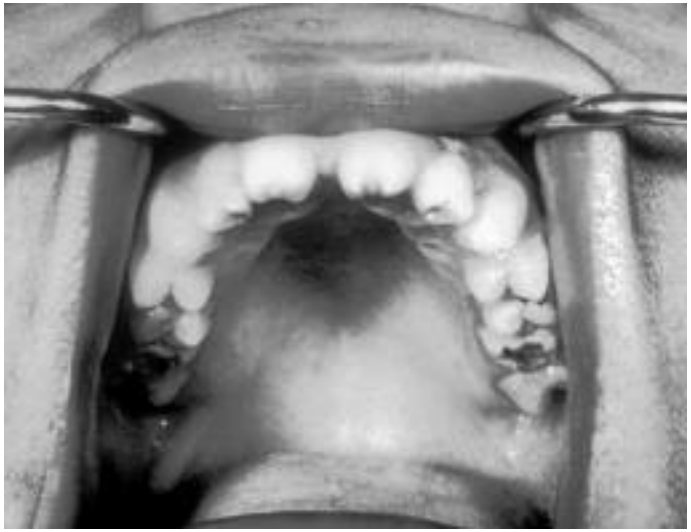
Congenital syphilis

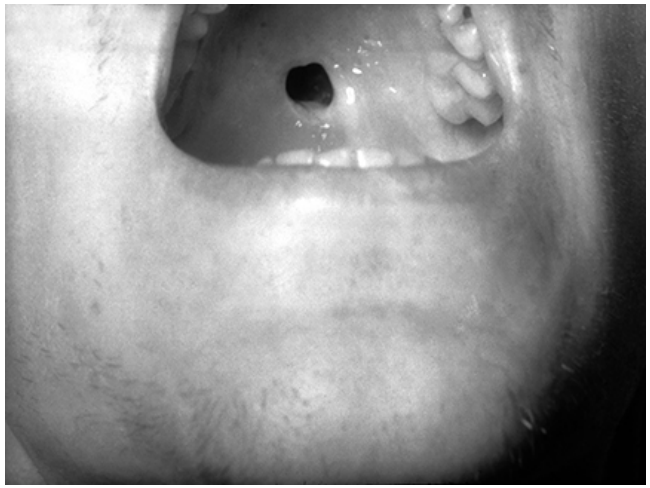
Antenatal ultrasound signs	Early Syphilis	Late Syphilis
Fetal loss Growth restriction Hydrops fetalis Ascites Hepatomegaly Hydrocephaly Brain calcifications	Osteochondritis 61% Hepatomegaly 61-100% Splenomegaly 49% Petechial lesions 41% Other (contagious) skin lesions 35% Meningitis 25% Adenomegaly 32% 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%**

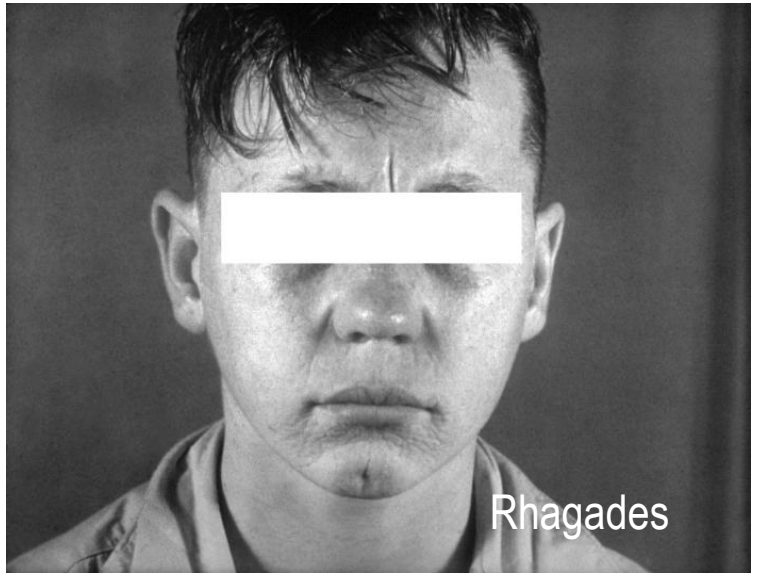
Walker Semin fet Obstet Dis 2008
Charlier LPM 2014

Congenital syphilis



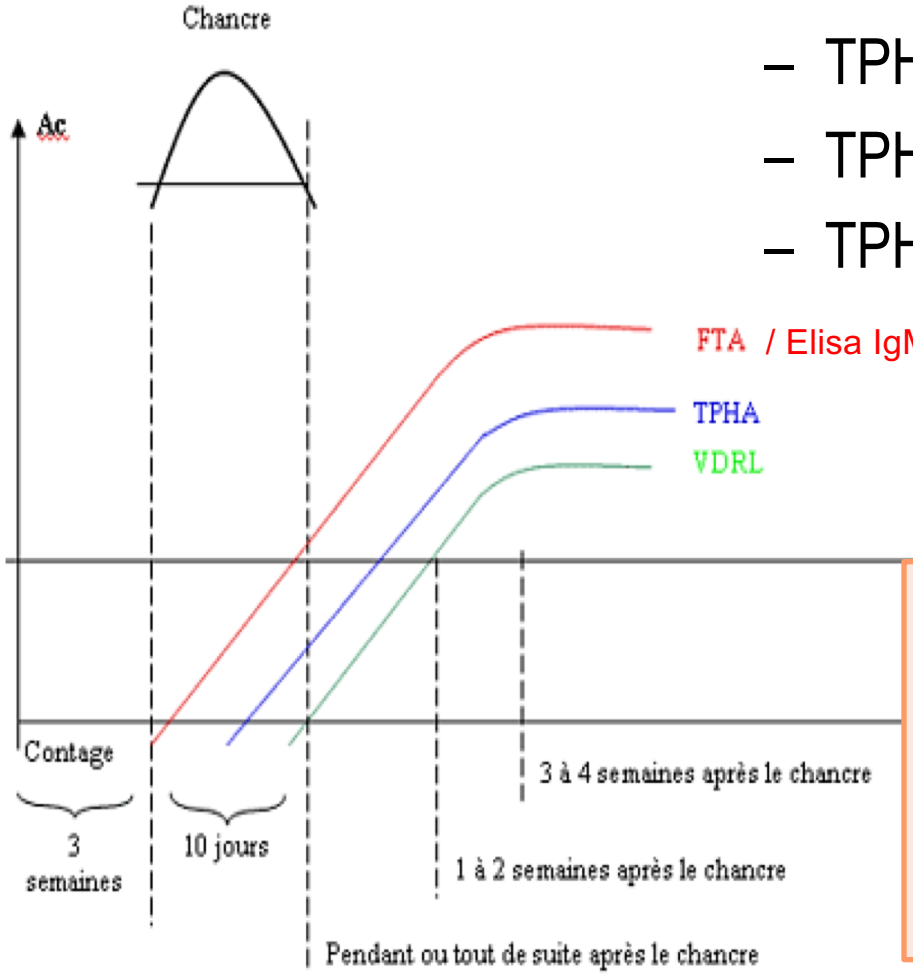






CDC

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 diagnosis

- **VDRL + TPHA –**

→False positivity

→Double check and check for ACC

- **Positive treponemic test (Elisa/ TPHA…)**

→Start treatment immediately in all cases, except the proof of complete adequate previous treatment is available

→ And double check (Elisa, IgM, FTA…) and perform VDRL

Treponemic tests cannot distinguish between venerial and non venerial infections

Maternal treatment : 7 points

- Treat ideally before 16 WG, at least before T3
- Penicillin in all cases
- Prevention of Jarisch- Herxheimer
- Evaluation for other STI
- 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

→NO MISSED DOSE

Pregnant women who miss any dose of therapy must repeat the full course of therapy.

https://www.cdc.gov/std/tg2015/tg-2015-print.pdf

Maternal treatment : penicillin allergy

- **Tolerance induction**

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.

CNR

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

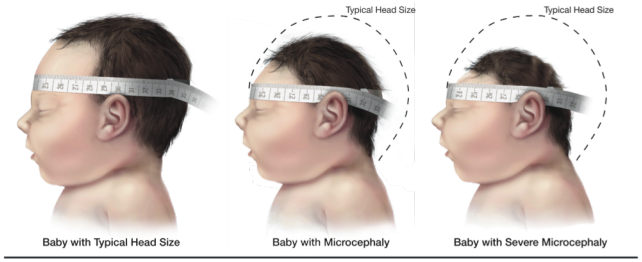
- No transmission through the milk
- Transmission possible in case of lesion on the nipple
- Penicillin is not contra-indicated during lactation

Zika et grossesse

- **Premier flavivirus tératogène**
  - Placenta : infecte trophoB extravilleux, cytotrophoB
  - Foetus : **neurotrope**, infecte progéniteurs neuronaux

Miner Cell 2016
Gladwyn-Ng Nat Neurosciences 2017

Syndrome Zika congénital



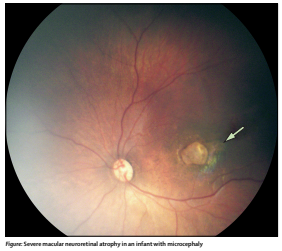
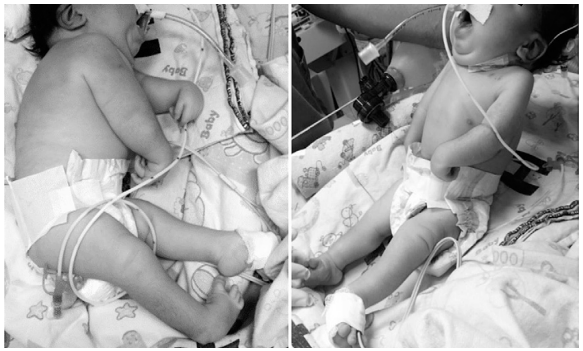


Figure: Severe macular neuroretinal atrophy in an infant with microcephaly



- **Microcéphalie**

  sévère < -3DS, modérée <- 2DS

- **Autres anomalies cérébrales**

  calcifications, dilatation ventriculaire, malformations corticales

- **Oeil** (macula)
- **Arthrogrypose**
- **Pied bot**

Moore. Characterizing the pattern of anomalies in Congenital Zika Syndrome for pediatric clinicians. JAMA Pediatr 2017;171(3):288-295

The New England Journal of Medicine

Pregnancy Outcomes after Zika

KEY POINTS FROM

Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas

by B. Hoen et al.

MARCH 15, 2018

The New England Journal of Medicine

Pregnancy Outcomes after Zika

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MARCH 15, 2018

Prospective Cohort Study

N=546

French Territories in the Americas

- Eye abnormalities
- Chromosomal defects
- Microcephaly
- Intracranial calcifications
- Lissencephaly
- Neural-tube defects
- Skeletal abnormalities
- Ventriculomegaly

Prospective Cohort Study

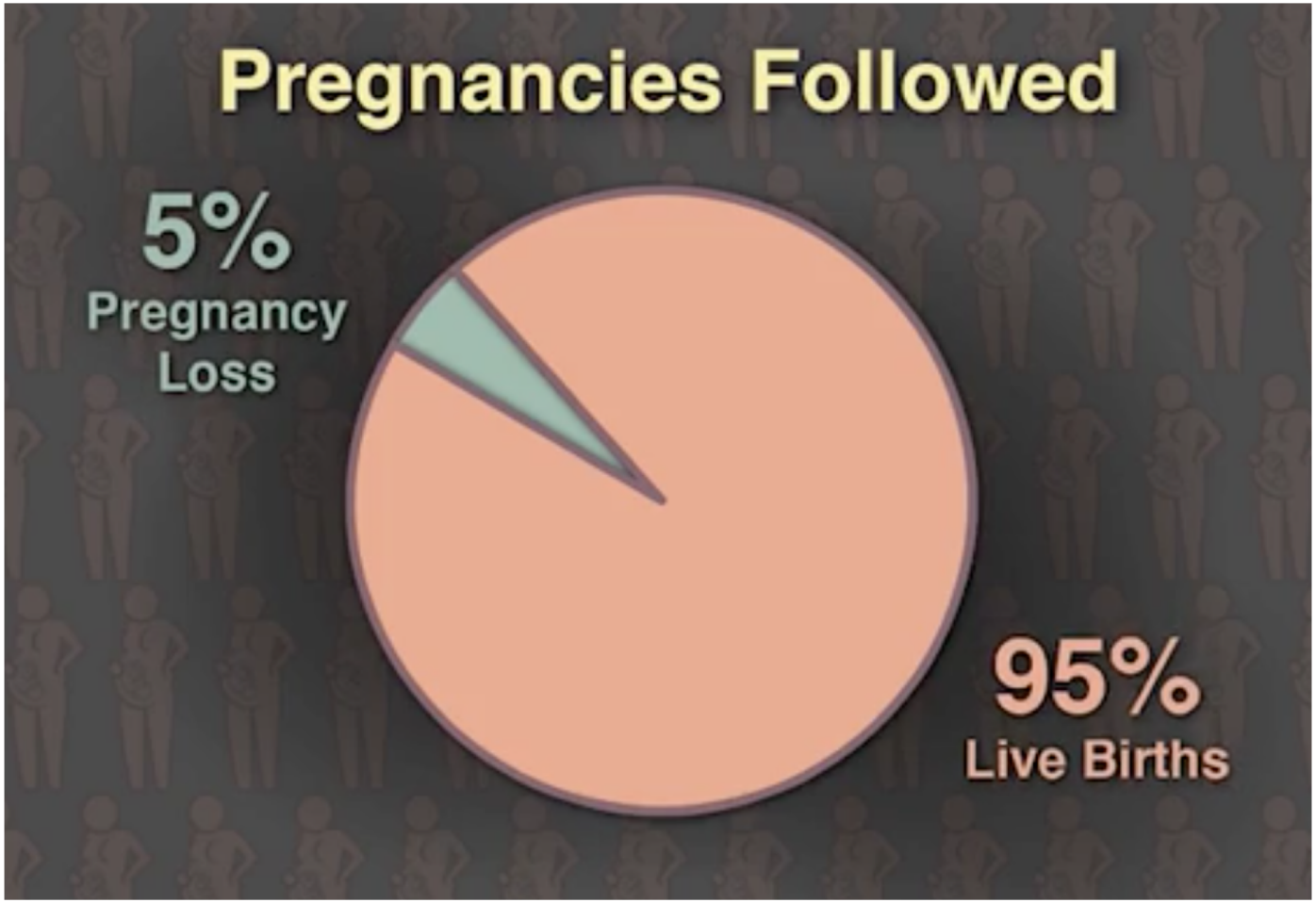
N=546

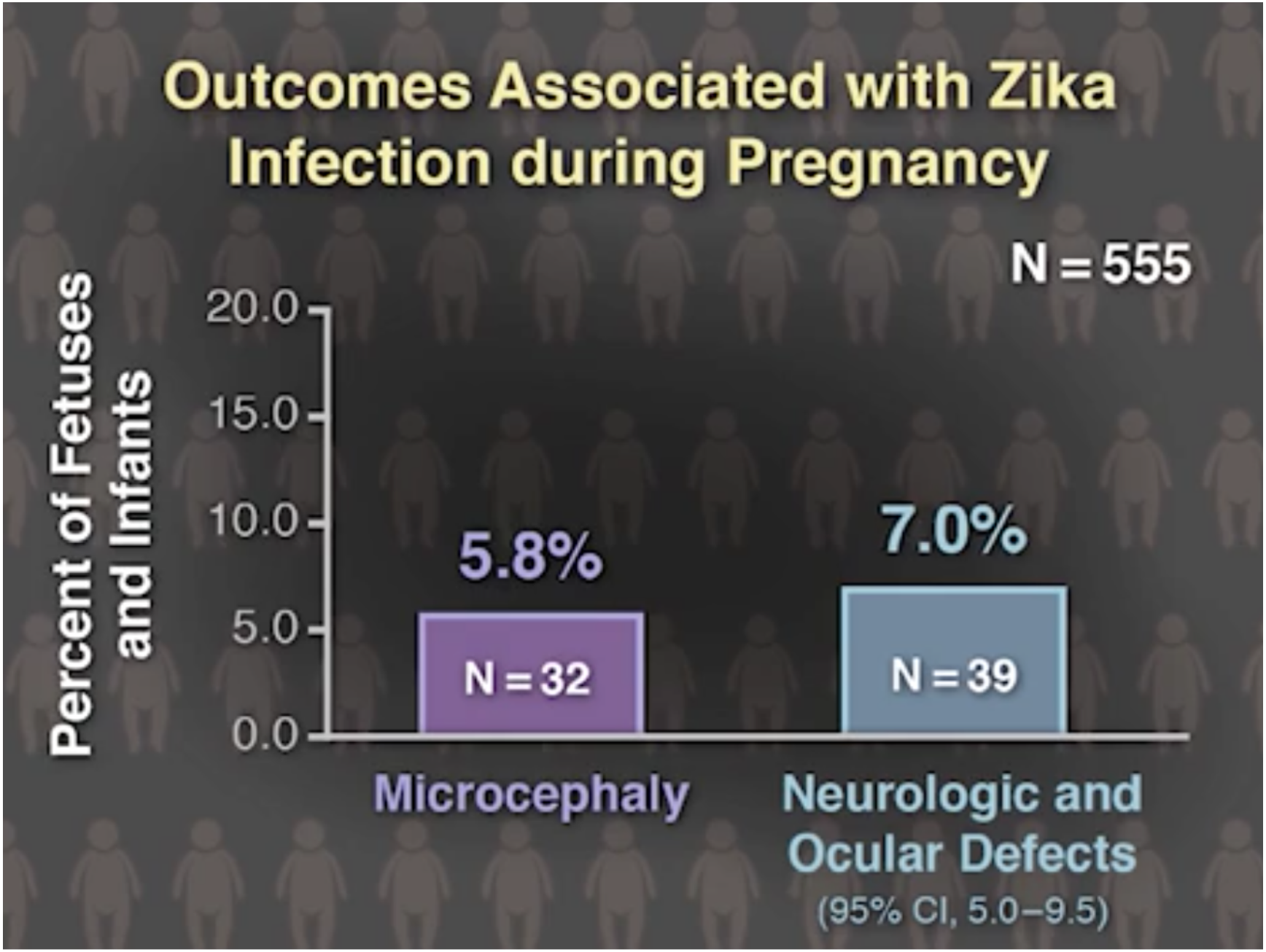
Symptoms of Acute ZIKV Infection:

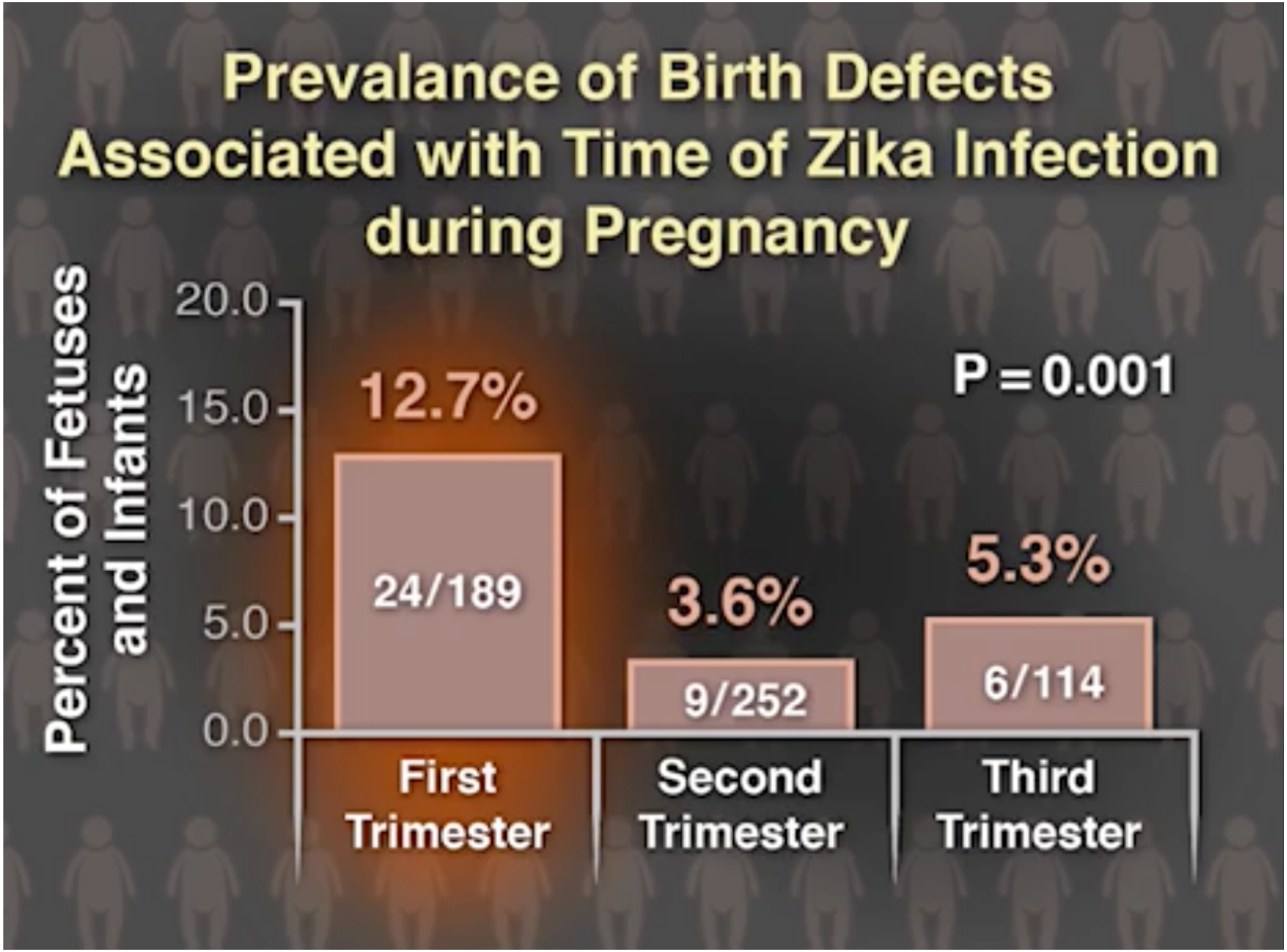
- ✓ Pruritic rash
- ✓ Fever
- ✓ Conjunctival hyperemia
- ✓ Arthralgia
- ✓ Myalgia

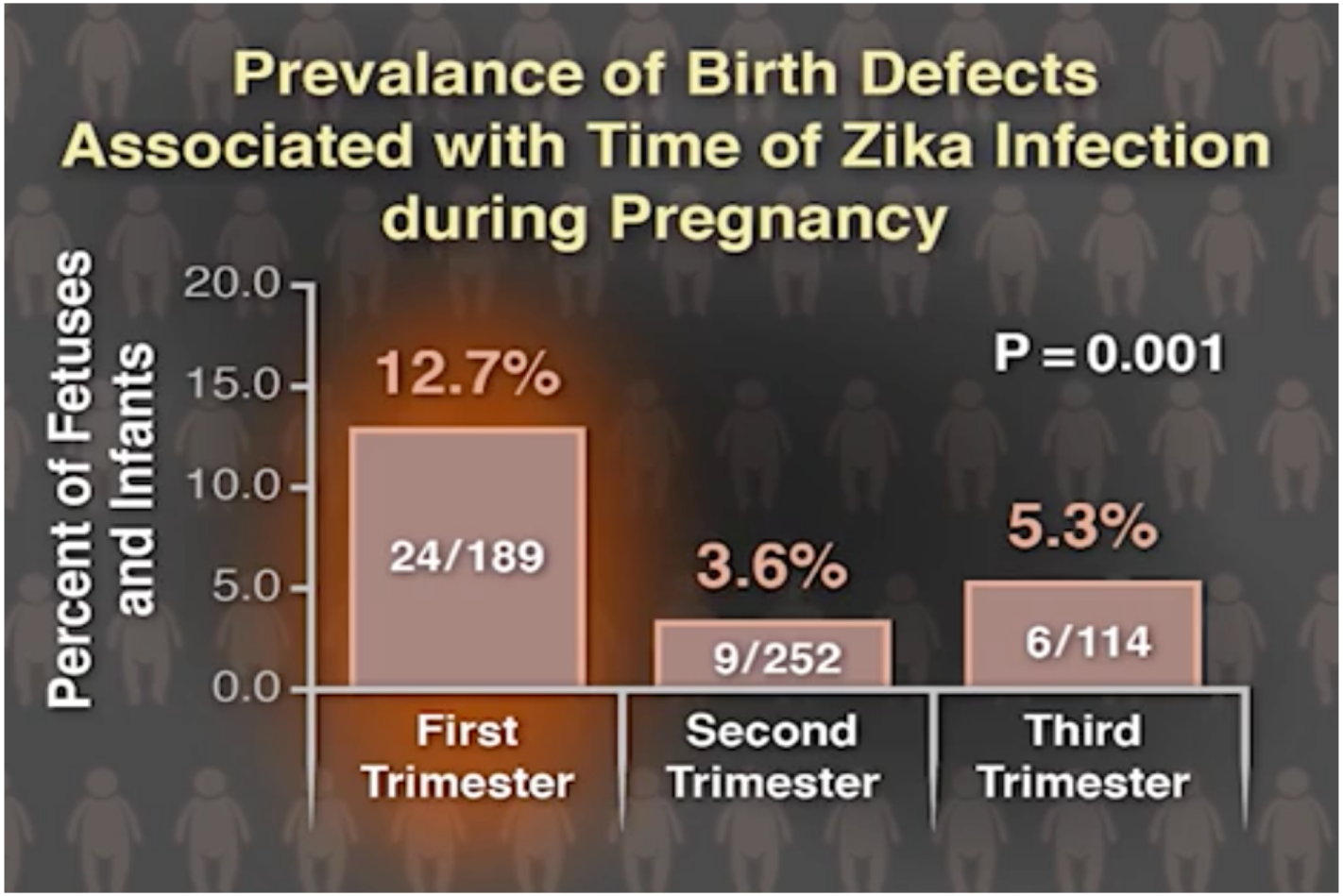
Positive ZIKV RT-PCR Test:

March 2016–April 2017


Pregnancies Followed
5%
Pregnancy
Loss
95%
Live Births


Outcomes Associated with Zika Infection during Pregnancy
N = 555
Percent of Fetuses and Infants
20.0
15.0
10.0
5.0
0.0
5.8%
N = 32
7.0%
N = 39
Microcephaly
Neurologic and Ocular Defects
(95% CI, 5.0–9.5)


Prevalance of Birth Defects Associated with Time of Zika Infection during Pregnancy
Percent of Fetuses and Infants
20.0
15.0
10.0
5.0
0.0
12.7%
24/189
3.6%
9/252
5.3%
6/114
P = 0.001
First Trimester
Second Trimester
Third Trimester



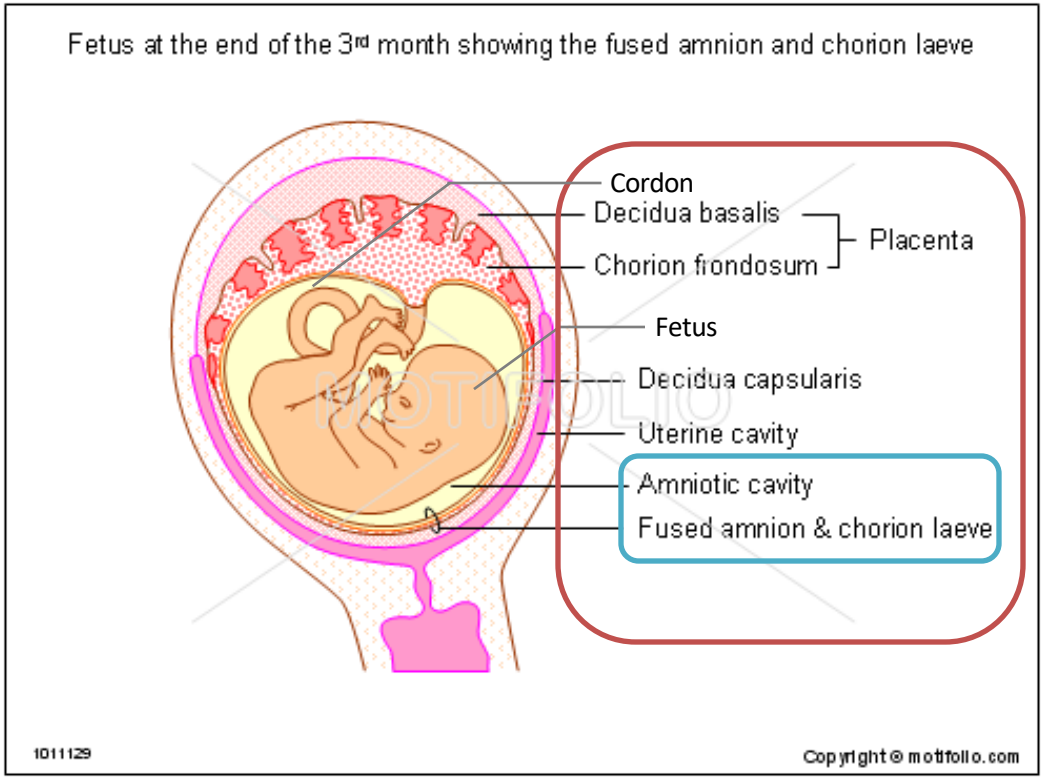
	T1	T2	T3
Birth defects	12.7%	3.6%	5.3%
Congenital Zika syndrome	6.9%	1.2%	0.9%
Severe microcephaly	3.7%	0.8%	0%

Hoen NEJM 2018

Hoen NEJM 2018

Infection intra-utérine

- **Remplace le terme de chorioamniotite**



Infection intra-utérine

Chorioamniotite

Infection intra-uterine définition

- **Remplace le terme de chorioamniotite**
- **Diagnostic clinique**

Confirmé si température ≥ 38°C, sans autre cause associée à ≥ 2 signes :

- tachycardie fœtale > 160 bpm ≥ 10 min
- douleurs utérines ou travail spontan,
- liquide amniotique purulent à l'orifice cervical

III Intrauterine inflammation or infection

Fièvre supérieure à 39°C 1 fois ou > 38°C 2 fois + ≥ 1 critères suivants :

- tachycardie fœtale > 160 bpm > 10 minutes,
- hyperleucocytose > 15 000/mm^3 hors corticothérapie maternelle,
- liquide purulent prélevé au niveau du col,
- arguments biochimiques ou microbiologiques dans le LA (examen direct positif, culture microbiologique positive, glycosamnie basse, hypercellularité du liquide).

Higgins Obstet Gynecol 2016

Infection intra-uterine epidémiologie

- **Données épidémiologiques**
  - 1-4% des grossesses
  - 25% des patientes avec RPM, soit d'emblée, soit secondairement
  - Facteurs de risque :
    - Durée rupture des membranes,
    - ATCD IIU,
    - IST ou vaginose

Infection intra-utérine

- CRP < 5 mg /L exclut le dg
- Ponction de liquid amniotique n'est plus recommandée

- Agents en cause : flore vaginale/ fécale
  - Streptocoque B - autres
  - *E. coli*
  - Anaérobies
  - Candida < 1%

  → Plurimicrobien dans au moins 2/3 des cas

Infection intra-utérine
Traitement

- **Déclencher la naissance**: voie basse ou césarienne

- **Antibiothérapie maternelle : Bétalactamine/aminoside**

  Cefotaxime 1g x 3/j

  Gentamicine 5-7mg/kg/j

  Métronidazole 500mg x 3/j optionnel si césarienne

- **Durée antibiothérapie**
  - 1 dose post accouchement
  - + long si bactériémie
  - + long si persistence de la fièvre ou obésité