Pregnancy and Lyme Disease

Analysis of literature and guidelines

Dr. Ir. D.E. Uitdenbogerd PhD

Stichting Tekenbeetziekten

Why this particular analysis?

Every year questions about lyme disease in pregnancy and over the years several experiences about congenital lyme disease!

To find out what the literature says and why the risk is underestimated in regular medicine

- Checked many ‘long lists of literature’ posted by patient groups for additional sources
- Pubmed search on congenital lyme / pregnancy and lyme
- Read all the articles and put reviews aside

Part 1: Investigating the risk

Focus on:

- Population studies (large groups of patients are followed prospectively or investigated retrospectively)

- Case studies (some pregnancies and outcomes are described in detail)

- Which studies are used in the Dutch guideline (2013)?

- What do other countries' guidelines say on this topic?

CBO 2013 Dutch Lyme guideline

- Profylaxe criteria tick bite similar to non-pregnant women
- “Chance on vertical transmission is small”
- “Only seldom spirochetes are found”
- Treatment LD similar to non-pregnant women
- Treatment further reduces the risk of transfer
- Determine IgM in neonates
- Relation abnormalities in babies and LD in pregnancy not clear

Based on:

Population studies (retrospective: Gerber 1994, Strobino 1999, prospective: Maraspin 1996, Lakos 2010)

Case studies: autopsy of miscarriage, still born or babies that died after birth (Schlesinger 1985, Gardner 2000, Shirts 1983, MacDonald 1987, Weber 1988)

Population studies in the Dutch guideline

Retrospective population studies (not lyme pregnancies!):

Gerber 1994: investigation among (pediatric) neurologists, whether they ever had seen children with congenital lyme (none)

-> loop: congenital lyme does not 'exist' for neurologists

Strobino 1999: survey among mothers of 796 children with heart deficiencies: 112 had tick bite or lyme disease during pregnancy, 54% had positive test and where officially diagnosed and treated.

Control group: 704 children with heart murmur, rithm problems and non-cardiac chest pain; 39% had positive test. Difference not significant.

-> control group not really a control group, and %% in both groups very high!

-> undiagnosed and untreated lyme not included in analysis but could be present

Prospective population studies:

Maraspin 1996: 58 EM cases during pregnancy, most (53) treated with 14 days IV Ceftriaxone (!)

-> no clear relation with adverse outcomes in babies

-> treatment and conclusion not applicable to Dutch situation

Continued: Lakos 2010

Lakos 2010: followed 95 lyme-pregnancies (Hungary, period of 22 years), included were EM, ACA and facial palsy cases:

- Untreated 30% (3/10) spontaneous abortions compared to treated 5% (4/85)
- Adverse outcomes 60% (6/10) compared to treated 16% (14/85)
- No relation with duration infection, serological test result of mother, memory of tick bite
- Complications heterogen, no 'congenital syndrom'
- Newly born babies only showed IG of mother

Additional poster of Lakos 2010: 124 cases;

- *"Adverse outcomes were seen in 7/87 (8%), 9/25 (36%), 8/12 (67%) of the parentally (IV Ceftriaxone, IV Penicillin), orally treated (Amoxicillin) and untreated women, respectively".*
- *"There was a higher risk of pregnancy loss if the infection was shortly before or after the conception, while other complications were more frequent when the infection happened later during pregnancy".*
- *"Pregnancy loss was significantly more frequent amongst untreated patients than among the parenterally treated women in our study population".*
- *"Our present data definitively support the superiority of high dose IV penicillin or parenterally administered Ceftriaxone over the oral antibiotic treatment".*

-> Chance on adverse outcome 21x (untreated) resp. 6x (orally treated) compared to IV treated Lyme pregnancies

Prospective studies NOT used in the Dutch guideline

Markowitz 1986: followed 19 lyme pregnancies:

- 5 adverse outcomes with syndactyly, cortical blindness, death of fetus, premature birth, rash in new born.

Nadal et al 1989: tested 1416 mothers and 1434 children at birth: serology positive in 12 mothers:

- 7 babies had adverse outcomes with 1 ventricular septal defect, 2 hyper bilirubinemy, 1 musculair hypotony, 1 under weight, 1 macrocephaly, 1 supraventriculair extrasystolen.

Strobino 1993: followed 2000 pregnancies, at intake, birth and 6 months after birth: serology and questionnaire about Lyme risk factors and abnormalities in the baby.

- Risk subgroups: tick bite within 3 y, or Lyme within 1 y before pregnancy: resp. 1.5 - 3 times more abnormalities.
- However, risk subgroups too small: not significant.
- 7 of 1000 diagnosed + treated for Lyme + <1 of 1000 seroconversion (untreated).
- Their conclusion: main concern is untreated LD but risk of untreated Lyme Disease is small.

Williams 1995: 5011 babies, 2504 in endemic and 2507 in non-endemic area: at birth and 6 months after birth: serology and questionnaire about Lyme risk factors and abnormalities in the baby.

- In the endemic group more treated LD before pregnancy, more tick bites during pregnancy, and more positive serology of umbilical cord
- Cardiac malformation 2.4x more often in endemic group then in non-endemic group
- Undetected Lyme can be present in endemic group + risk subgroups too small (n=6-67) to differ significantly compared to endemic group as a whole
- Six months follow up too short; often malformations will surface after 1 year

Conclusions based on the population studies

1. Population studies lack power in risk-subgroups or are not comparable to Dutch situation

2. The guideline states that the risk for vertical transmission is further reduced by treatment, but

- There is no treatment advice for LD in pregnancy
- Gynecologists did not participate
- No estimate of the risk; whereas literature clearly shows elevated adverse outcomes in risk groups (despite lack of the power for significance)
- Literature shows that e.g. 500 mg Amoxicillin 3x daily 14-30 days (the normal) will not be sufficient and that IV Ceftriaxon has a much better result

4 Case studies in the Dutch guideline

- Mother contracted LD in first trimester of pregnancy
- Babies still-born or died within 39 hours after birth
- Deformities heart and brains + spirochetes in babies

(Shirts 1983, Schlesinger 1985, MacDonald 1987, Weber 1988)

- CBO conclusion: “only seldom spirochetes are found”
- BUT: in the 1990ties only 5 case studies are done!
- AND: case studies of adverse outcomes of MacDonald 1986, Lavoie 1987, Trevisan 1997, Önk 2005 are not included

Conclusion should be: "Seldom affected fetuses, placentas and infants are investigated on the presence of spirochetes."

Risk estimates

Gardner review in 3rd, 4th and 5th edition of "Infectious Diseases of the fetus and newborn infant":

- 263 cases in 21 references - 66 adverse outcome (25%)
- 20/66 fetal deaths in 2nd trimester of pregnancy; 15/66 (23%) cardiologic ;10/66 (15%) neurologic
- Infection in 1st trimester 32%, 2nd 25%, 3rd 16% / overall 25%
- Little relation with serology
- Besides miscarriages/fetal death: 1. early severe congenital LD with sepsis, 2. early mild congenital LD within 1-2 months, 3 late subacute congenital LD within 2 y.

To estimate the risk: large prospective studies of all Lyme-pregnancies are needed with a long-term follow up of life babies and pathological research of affected fetuses, placentas and infants that died around birth (Gardner, 2002).

! CBO guideline based on this same reference: *"Proven transmissions are rare. In study of placentas and obduction of death fetus of women with LD only seldom spirochetes are found". "Congenital LD even in endemic areas is rare, and the relation between incidental adverse outcomes and LD during pregnancy is often not clear (Gardner, 2002)"*

Serology

Several case studies find spirochetes in placenta and/or fetus (Schlesinger et al., 1985; MacDonald et al., 1987; MacDonald 1989) or a statistical relation between clinically diagnosed LD and adverse outcome (Williams, 1995; Lakos 2010) without positive serology in mother or fetus.

It seems that infection in the uterus or through the placenta does not lead to inflammation or is less pronounced (MacDonald, 1989; Duray & Steere, 1988; Williams, 1995).

Factors:

- Immature immune system of fetus and neonatal
- Early treatment of LD of the mother
- Immunosuppression in the mother during pregnancy

For comparison: also 20% congenital syfilis cases are seronegative

Conclusions Serology

It is wrongly thought that the just born baby can or must have IgM for Borrelia

Repeated blots and direct tests are needed to determine whether the baby has LD

Part 2: What to do during pregnancy?

- CBO guideline (implicit): 500 mg Amoxicillin 3x daily 14-30 days
- Deutsche Borreliose Gesellschaft: 3-6 g/die during pregnancy
- UK NICE guideline: treat pregnant women similar (no Doxycycline)
- ILADS guideline: treat pregnant women similar (no Doxycycline)
- DBG / ILADS physicians: high dosage of Amoxicillin and/or Azithromycin during pregnancy

Treatment during pregnancy

”During pregnancy, amoxicillin has lower plasma concentrations and more rapid elimination(…). The pharmacokinetics of ceftriaxone, however is not significantly influenced by pregnancy”. “Our present data definitely support the superiority of high dose IV, penicillin or parenterally administered ceftriaxone over the oral antibiotic treatment” (Lakos, 2010)

- Amoxicillin: reaches fetus without consequence
- Azithromycin: transfer through placenta unknown
- Gardner 2002: use of AB reduces chance from 67% to 15%
- Jones 2011: 1 type of AB: chance 50/50; 2 types of AB: close to no transmission at all

Delivery and breastfeeding

- Preference for normal birth
  - No information about delivery complications in case of LD
  - Risk on transmission by blood C-section
  - See WHO blood donor advice for Lyme Disease

- Breastfeeding
  - With L1 (most safe) and L2 (safe) antibiotics
  - L1-L5 classification for safety of medicines during lactation
  - Amoxicillin (L1), Azithromycin (L2), Plaquenil (L2)

PART 3: TO CHECK FOR INFECTION WHEN THE BABY IS BORN?

Placenta: PCR and microscopy

Umbilical cord blood: PCR, Western Blot and cellulair test
(arrange in advance for cellulair test through private lab)

Baby blood:

- Antibodies of mother visible up to 6-9 months old
- Don't expect IgM of baby
- Repeat Western Blots every 3-6 months to see if bands change: proof for active infection (cooperation of pediatrician needed)

Baby urine:

- Pharmacy sells small bags to catch baby urine ($0.60 / €0.80 per piece)
- PCR urine: IGeneX USA has urine test kits for Borrelia that can be mailed

RISK ESTIMATES

Discussion about the risk or chance on congenital LD is influenced by a number of uncertainties

..neonatal IgM? / mother immuntolerance? / composition serological tests / suppression of Bb antigen presentation / hardly any investigation of placenta, fetus, stillborn, neonates that die / differences of AB treatments in population studies / different pharmacokinetics in pregnancy not accounted for / no proper control groups / specialists report 'no syndrom' / no. of investigated risk pregnancies too small for statistic evidence…

INTERNATIONAL UPDATE

WHO: December 2018:

7 years into the development of ICD-11:

Congenital Lyme Disease slipped from the list!

CDC: 29 January 2020:

"Untreated Lyme disease during pregnancy can lead to infection of the placenta. Spread from mother to fetus is possible but rare. Fortunately, with appropriate antibiotic treatment, there is no increased risk of adverse bit outcomes. There are no published studies assessing developmental outcomes of children whose mothers acquired Lyme disease during pregnancy."

www.cdc.gov/lyme/transmission/

Prof. Christian Perronne & Dr. John Lambert write an open letter to the WHO: Time to recognise Congenital Lyme; June 2020

RESEARCH NEEDED!

1. Large prospective studies of Lyme pregnancies, to be able to statistically compare risk sub-groups (tick bite before and during pregnancy; LD (EM, 2nd, 3rd phase, chronic) before and during pregnancy; treated orally or IV; and in which trimester): approx. 20.000 pregnancies / births are needed
2. Together with:
   A. More extensive investigation of fetuses, placentas, still-borns, neonates
   B. Long-term follow up of alive babies (7 yr of age?)
3. Investigate untreated Lyme pregnancies (because of sero negativity through e.g. immunosuppression, women are not easy to find, <1 on 1000)