

Abstract Pregnancy and Lyme Disease; Analysis of the Literature and Guidelines; Tick Bite Diseases Foundation Netherlands; 2018

The Dutch Tick Bite Disease Foundation Netherlands (Stichting Tekenbeetziekten, STZ) commonly receives questions about the risks and what to do during pregnancy when the mother has Lyme disease, and we also frequently hear of incidents of transfer during pregnancy. We have therefore investigated what the scientific literature actually claims and which articles are important and which are not. Personally, we also wanted an answer to the question why the risk is surprisingly underestimated, sometimes resulting in harmful consequences. Most of the articles were available to us in PDF format and we have read them in full.

The literature also confirms that Lyme disease is transmissible. However, the discussion about the *chance* of transfer is influenced by numerous medical-scientific factors. We describe how the literature and these factors have been incorporated in the guidelines (Dutch CBO, IDSA, Ilads, DBG), but this appears to be rather cursory.

What is described as a 'small chance' by the Dutch Quality Institute for Healthcare, the CBO, is based on a limited number of sources: autopsy research of stillborn babies or babies who died shortly after birth or miscarriages (Schlesinger 1985, Gardner 2000, Shirts 1983, MacDonald 1987, Weber 1988) and four population studies, two of which are prospective studies (Maraspin 1996, Lakos 2010) and two retrospective studies (Gerber 1994, Strobino 1999). It is remarkable that the following prospective studies have not been included in the 2013 CBO guideline (Markowitz 1986, Nadal 1989, Strobino 1993, Williams 1995). **The first conclusion with regard to the CBO guideline is that the population studies included are not sufficient (often for statistical reasons) or not applicable to the Dutch situation (Conclusion 1).**

Neither does the CBO guideline provide direct and clear treatment advice for pregnant women with Lyme disease (only with regards to prophylaxis). But then no gynaecologists were involved. The website of the Dutch National Institute for Public Health and the Environment, the RIVM, does not clarify any issues either and we also do not know what actually happens in practice. **When it comes to treatment, the 2013 CBO guideline states that treatment limits the risk of transfer even further, but the relevant literature discusses IV (!) treatment in an EM (!!)** and on the contrary, shows that **oral treatment with, for example, Amoxicillin, such as for non-pregnant women 500 mg 3 times a day for 14-30 days, is not sufficient (Conclusion 2).** Experience has likewise shown that this is not adequate. The "pharmacokinetics" are influenced in a different way during pregnancy. Continuing treatment during pregnancy with 2 types of antibiotics or two weeks of IV Ceftriaxone appears to yield better results. An American paediatrician reports that virtually no transfer occurs with two types of oral antibiotics.

Based on four 'case studies' (Shirts 1983, Schlesinger 1985, MacDonald 1987, Weber 1988), the 2013 CBO guideline states that "*spirochetes are rarely detected*". But the 1990s only produced 5 case studies. Despite the limited amount of literature, a number of case studies were not included in the CBO guideline (Önk 2005, MacDonald 1986, Lavoie 1987). **After analysing the limited amount of literature available on cases, it seems to us that 'spirochetes are rarely searched for in deceased babies' (Conclusion 3).**

To illustrate that for instance other *Borrelia* species than *B. burgdorferi* can also cause foetal disease, a number of publications about transfer of *B. hermsii* and *B. duttonii* are briefly described without any desire of completeness. Congenital Lyme has also been described in animal studies that include putting down foetuses for the research (in particular PCR).

Transfer can occur through the placenta, the amniotic fluid and the uterus wall.

Various studies have demonstrated either spirochetes in the placenta and / or foetus or a statistical relationship with clinically determined Lyme disease and a poor outcome without either the mother or the foetus being seropositive. It also seems that infection in the uterus or through the placenta leads to little tissue inflammation. For comparison, seronegativity also exists in approximately 20% of babies with congenital syphilis. There is also a tendency for seronegativity in the mother during pregnancy (immunotolerance / immunosuppression). If the mother is IgG positive, the baby will be as well until they are six or seven months old. These are antibodies from the mother that pass through the placenta. The

only way to determine if the new-born baby has Lyme is by examining available tissue, such as the placenta. It is wrongly thought that infected babies are IgM positive at birth. Repeated blots provide more information about an active infection. For an indication of whether transfer has taken place, the placenta and the umbilical cord blood, blood and urine of the baby can be examined with various types of tests. **This brings us to the fourth conclusion: It is wrongly thought that infected babies are IgM positive from birth. Repeated blots and direct tests are needed to determine whether the new-born has Lyme disease (Conclusion 4).**

The amount of damage that vertical transfer causes during pregnancy depends on the trimester of the pregnancy in which the transfer takes place. There are indications that longer-existing Lyme disease in the pregnant woman does not lead to problems more often than acute Lyme disease during pregnancy. Several authors state that no 'specific syndrome' can be distinguished. Babies with congenital Lyme can display disorders early on, but can also have symptoms that only become apparent later on.

A normal delivery is of course always preferred over a C-section. STZ believes that transfer through blood is a potential risk and supports the WHO in the donor discussion (see <https://www.tekenbeetziekten.nl/donor-en-Lyme/>).

One article states that PCR has found spirochetes in breastfeeding milk. Appropriate antibiotics can be used all through breastfeeding to reduce the risk of transfer (L1 and L2).

The Deutsche Borreliose Gesellschaft (DBG) and ILADS physicians in the US, who see a relatively large number of pregnant women and young children with Lyme disease, believe in a high oral dose during the entire pregnancy; though the opinions vary in the matter of which type of antibiotics (Amoxicillin and/or Azithromycin). The DBG guideline adheres to 3-6 g/day of Amoxicillin. The ILADS guideline does not offer any recommendations for pregnancy.

Because guidelines conclude that congenital Lyme is rare instead of 'rarely investigated', a curious evidence-based circular logic is triggered, since it means congenital Lyme cases are not recognized, monitored or documented by the medical sector, and parents' concerns are not acknowledged. For all that, the discussion about the *chance* of transfer is influenced by numerous medical-scientific factors.

On the one hand, large prospective studies are necessary for an improved risk assessment. For a comparison of risk subgroups, a prospective study of at least 20,000 risk pregnancies and births is required. And on the other hand, research is needed into untreated Lyme pregnancies. It is estimated that there can be around 250 a year in the Netherlands.