Influence of infection with *Chlamydia trachomatis* on pregnancy outcome, infant health and life-long sequelae in infected offspring

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This chapter deals with genital chlamydial infections in pregnancy and postpartum. There is increasing evidence that *Chlamydia trachomatis* infection may result in a number of adverse pregnancy outcomes, including early and late abortion, intrauterine infections of the fetus, stillbirth, prematurity, premature rupture of the membranes (PROM) and postpartum endometritis. Ectopic pregnancy is commonly associated with a previous tubal chlamydial infection where immunological reactions seem to play a role. *C. trachomatis* infection may be acquired as an intrauterine infection, as well as during transit through the birth channel, and this may result in neonatal conjunctivitis and/or pneumonia. The role of chlamydial infection in the sudden death syndrome has also been considered, but evidence so far is minimal. Neonatal chlamydial infection may cause life-long sequelae, such as obstructive lung disease. Genital chlamydial infections have been associated with problems in insemination and attempts at in vitro fertilization. The chapter also deals with screening of pregnant women for *C. trachomatis* and the treatment of infected mothers and their offspring.

**Key words:** *Chlamydia trachomatis*; pregnancy; abortion; stillbirth; prematurity; intrauterine infections; postpartum endometritis; postpartum salpingitis; neonatal infection; neonatal pneumonia; neonatal conjunctivitis.

Until recent years, interest in *Chlamydia trachomatis* infection in pregnant women focused mainly on transfer of the agent to their offspring (generally believed to occur at delivery during the passage through the birth channel) and on the possibility of conjunctivitis and pneumonia in the infant. The triad of ‘inclusion conjunctivitis’ in an infant with concomitant cervicitis in the mother and eye infection in the father was described almost a century ago. While these data suggested transfer of an infectious agent, the lack of any curative therapy made the observation only a notation in the medical history book — although of interest ‘in the light of present knowledge’. During the 1970s, the development of diagnostic techniques allowed isolation of chlamydia in tissue cell cultures. Some of these techniques could be widely applied, and this meant a breakthrough in our understanding of the epidemic proportion of genital chlamydial infection, particularly in young adults, almost wherever studies were performed. Culture and serological studies confirmed the correlation between genital chlamydia...
infection in mothers and conjunctivitis in their infants. The diagnosis of chlamydial infection in pregnant women had also become highly relevant as it had been demonstrated that *C. trachomatis* is a bacterium which is sensitive to erythromycin – an antibiotic that could be given to pregnant women and their infants. The drug could be used for treating lactating women who might have developed postpartum endometritis. In the 1970s it was also revealed that intrauterine fetal chlamydial infection could occur in women with premature rupture of the membranes (PROM). During the 1980s it was shown that *C. trachomatis* was responsible for a number of adverse pregnancy events, i.e. early and late abortion as well as stillbirth. In recent years it has also become evident that intrauterine infection with *C. trachomatis* can also occur in mothers with intact membranes.

Complications following chlamydial infection in the offspring may, in turn, result in life-long and even life-threatening sequela, for example, *asthma and obstructive lung disease* (COL) (see further below under ‘Neonatal infections’).

**ADVERSE PREGNANCY OUTCOMES**

**Early and late spontaneous abortion**

In a study from India, 25 of 77 women with early and late spontaneous abortion during the 6–24th week of gestation had chlamydial antigen detected in endometrial curettage samples. This was in contrast to only one of 25 controls (in the 6–16th week of gestation) who did not differ in parity. Curettage may reveal the characteristic histological picture of chlamydial endometritis dominated by a massive plasma cell infiltration. Other studies also suggest a role for *C. trachomatis* in late spontaneous abortion. In cases of abortion, signs of placentitis, with evidence of a chlamydial infection, have also been described.

Seroepidemiological studies also suggest a correlation between infection with *C. trachomatis* and recurrent spontaneous abortion. However, other studies have denied such a correlation. If one intends to perform microbiological tests in the work-up in cases with a history of recurrent spontaneous abortion it may be relevant to include antigen tests for *C. trachomatis* along with tests for, for example, β-haemolytic streptococci group B (GBS), *Listeria monocytogenes*, *Toxoplasma gondii* and syphilis.

**Post-abortal endometritis and salpingitis**

A number of studies indicate a correlation between post-abortal pelvic inflammatory disease (PID) and genital chlamydial infection. In 943 women in whom elective abortion was performed, post-abortal PID was significantly associated with the presence of *C. trachomatis* before the intervention (*P* < 0.04). In another study, eight of 29 (28%) women with a genital chlamydial infection developed post-abortal PID; this was in contrast to 24 of 241 (10%) women without evidence of such an infection (*P* < 0.025). In yet another study, *C. trachomatis* was isolated from the cervix in 70 (14%) of 507 women admitted for abortion. Of the *C. trachomatis*-positive women, 20% developed PID versus only 2% of cases negative for *C. trachomatis*.

The collected evidence of the risk of developing post-abortal PID in chlamydia-infected women suggests that, prior to performing elective abortion, tests for *C. trachomatis* ought to be performed in any woman considered to be at any risk of being a carrier of the organism. Such a test may also be indicated in women who have recently experienced a spontaneous abortion.
Intrauterine infection; stillbirth

Serum antichlamydial IgM antibodies detected by enzyme-linked fluorescence and enzyme-linked immunosorbent assays, as well as the demonstration of elevated serum levels of IgM in newborns, have indicated that intrauterine chlamydial infections may occur in utero. The finding of IgM antibodies to \( C. \text{trachomatis} \) in cord blood of 10.4% of infants of mothers who have delivered preterm (10 weeks before term) also demonstrates that fetuses may be infected by \( C. \text{trachomatis} \).\(^{10} \)

DNA amplification tests for \( C. \text{trachomatis} \) in amniotic fluid were positive in 6.7% of women with pre-labour amniorrhexis.\(^{23} \)

In cases of stillbirth, chlamydial antigen has been demonstrated by the polymerase chain reaction (PCR) in lung and liver tissue; this suggests that disseminated intrauterine fetal infection with \( C. \text{trachomatis} \) does occur. This was the case in stillbirth, which had occurred in the 20–30 gestational weeks.\(^{13} \) Such infections are probably also common in relation to other infections seen in cases of stillbirth, such as those caused by cytomegalovirus.

Perinatal death was significantly correlated to a positive culture of \( C. \text{trachomatis} \) in a study of 6161 Hungarian women.\(^{24} \)

PROM; premature birth

Studies\(^{25,26} \) have postulated an association between premature rupture of the membranes (PROM) and infection with \( C. \text{trachomatis} \).\(^{27,28} \) Intrauterine lung infection with \( C. \text{trachomatis} \) was demonstrated in an infant with premature birth in a case with PROM. As the diagnosis of infection had been made just after birth it suggested that the pneumonia had been contracted in utero, possibly after PROM.\(^{9} \) Infections with \( C. \text{trachomatis} \) in infants have also been correlated in other studies to a history of PROM in their mothers\(^{29} \) (Figure 1).

The Hungarian study previously referred to\(^{24} \) demonstrated a statistical correlation between chlamydial infection in the mother and the premature birth of infants with an extremely low birth weight.

Gravett and co-workers\(^{30} \), in a case–control study, found that infection with \( C. \text{trachomatis} \) in mothers was associated with premature birth at <37 weeks of gestation with an odds ratio (OR) of 4.4 (1.7–9.2 CI, 95%) and with birth at or after this week with an OR of 4.3 (2.1–8.8 CI, 95%). The study was of particular value as it had adjusted for age, race, parity, marital and welfare status, smoking, prior abortion, prior pre-term delivery, anaemia, third trimester bleeding and urinary tract infection with current pregnancy. Others have not found a correlation between adverse pregnancy outcome in general and cervical chlamydial infection in the mother. One reason for various findings may be that studies were performed when there were differences in gestational times. Statistical correlation between genital chlamydial infection in mothers has generally been performed late in pregnancy and often not adjusted for other known aetiological factors for prematurity, including infectious agents other than \( C. \text{trachomatis} \).

A correlation has been demonstrated between adverse pregnancy outcome and antichlamydial serum IgM (but not IgG) antibodies, on the one hand, and adverse pregnancy outcome on the other. That is, this was the case in 13 of 67 IgM-positive versus eight of 99 negative women (\( P < 0.03 \)).\(^{26} \) The authors assumed that women with a recent and probably acute ongoing chlamydial infection were at risk of preterm delivery.
Causal relationships between pregnancy and postpartum conditions and adverse pregnancy outcomes on the one hand and genital infection with *C. trachomatis* on the other:

- Cervicitis
- Urethral syndrome
- Arthritic conditions, e.g. sexually acquired reactive arthritis (SARA)
- Early abortion
- Late abortion
- Post-abortal PID
- Premature delivery
- Stillbirth
- Intrauterine infection
- Premature rupture of the membranes (PROM)
- Postpartum endometritis
- Postpartum salpingitis

Figure 1. Chest X-ray of an infant who had been infected *in utero* by *Chlamydia trachomatis* and who developed signs of pneumonia shortly after birth.
• Ectopic pregnancy
• Postpartum conjunctivitis

The above-mentioned observations stress the value of screening pregnant women for *C. trachomatis* in order to reduce the rate of prematurity and other adverse pregnancy outcomes.

**Postpartum infections**

Pregnant women may have contracted a chlamydial infection before they conceive and this may result in chlamydial endometritis. However, such an infection can also develop after delivery if it has been contracted during pregnancy. The infection can then spread to the uterine tube postpartum, resulting in salpingitis. Pregnant women who have been infected with *C. trachomatis* during pregnancy may, as a sequela, develop infertility; this is one explanation of ‘one-child sterility’. The infection may spread per continetatum to the abdominal cavity, causing perihepatitis, periselitis, perisigmoititis and peritonitis (cf. ref. 33). Chronic abdominal pain may occur as a sequela of chlamydial PID contracted after delivery and is often believed to relate to the development of intraperitoneal adhesions (cf. ref. 33) – in intra-abdominal chlamydial infection this is often referred to as ‘violin string adhesions’.

*C. trachomatis* has been associated with late postpartum endometritis if occurring within 2 days of delivery. In one series, late postpartum endometritis occurred in 22% of *C. trachomatis*-positive cases but in only 5% of the chlamydia-negative cases studied. Culture from the cervix detected *C. trachomatis* from 60% and from the endometrium in 23% of postpartum endometritis patients.

The diagnosis of postpartum chlamydial infections on clinical grounds is generally even more difficult than in non-pregnant women. The minimal criteria for PID released by the Centres for Disease Control (CDC), Atlanta, had, in one study of 651 American patients, a sensitivity of 83 versus 95% for adnexal tenderness exclusively (*P* = 0.01). Among CDC’s proposed supportive criteria for PID, a positive test for *C. trachomatis* (and/or for *Neisseria gonorrhoeae*) increased the probability that the woman had endometritis.

The risk for developing a postpartum complication stresses the value of screening for *C. trachomatis* late in pregnancy.

**Ectopic pregnancy**

A number of observations have linked a past tubal infection with *C. trachomatis* to ectopic pregnancy. Antichlamydial antibodies are more common in women with ectopic pregnancy than in controls. For example, in one study 75% of 112 women with ectopic pregnancy had antichlamydial IgG antibodies, in contrast to 21% of controls with intrauterine pregnancies. In the ectopic pregnancy cases, the geometric mean titre of immunofluorescence antibodies was higher than in controls. Histological evidence supports a correlation between ectopic pregnancy and chlamydial infection of the Fallopian tubes. Subepithelial lymphocytic and plasma cell infiltration can be seen in such cases. Demonstration of chlamydial antigenic material in ectopic pregnancy samples adds to the evidence for a link between *C. trachomatis* and this condition.

It has been postulated that tubal cell damage caused by chlamydial PID may lead to impaired ability to express heat shock proteins (hsp), i.e. hsp27. Women with this inability more often also have chlamydial hsp60 antibodies. A correlation between
the ability to conceive and the lack of hsp60 antibodies in patients with a history of ectopic pregnancy has also been demonstrated.45

The rate of ectopic pregnancy has decreased in communities where the prevalence of genital chlamydial infection has been shown to have decreased, for example in Sweden46 and Norway.47 There is a time lag between the ectopic pregnancy rate and that of genital chlamydial infection in females. The delay between a documented chlamydial PID and ectopic pregnancy was 5 years in a Swedish study.48

INFERTILITY; INSEMINATION; IN VITRO FERTILIZATION

Chlamydial vasteitis and epididymitis49 may reduce the fertility of males by blocking the vas deferens, as shown in experimental infections in an animal model50 or by interference with sperm production. Chlamydial elementary bodies (EBs) can attach to sperm51 and thereby, at least theoretically, hitch-hike to the upper female genital tract after sperm have been deposited in the vagina by a chlamydia-infected male. Chlamydia may also penetrate into spermatozoa. Incubation of EBs of serovar E of C. trachomatis decreased the motility of spermatozoa after 60 minutes, when the proportion of dead spermatozoa was increased (as indicated by hypo-osmotic swelling tests), as compared to non-infected control samples co-incubation of Chlamydia trachomatis EBs with sperms also increased lysosine phosphorylation of the 80- and 90-kDa sperm proteins. This suggests that a genital chlamydial infection might influence sperm capacitation.52,53

Chlamydia may persist alive in semen samples treated for insemination by cryopreservation and stored at −196 °C for up to 3 weeks. Thus, four of five semen samples from 21 men with chlamydial urethritis were still chlamydia-positive after such handling.54 Chlamydial infection in sperm donors and egg recipients may also interfere with the success rate in in vitro fertilization trials.55

These in vitro observations may not only suggest a role for C. trachomatis in couples with infertility and subfertility problems – they may also open up speculation about a possible role for the organism in genetic transfer etc.

NEONATAL INFECTIONS

Conditions and sequelae of intrauterine and infant infection with Chlamydia trachomatis:
- Prematurity
- Neonatal conjunctivitis
- Neonatal pneumonia
- Otitis media
- Sudden infant death
- Apnoea
- Asthma
- Chronic obstructive lung disease (COL)

Conjunctivitis

Epidemiology

The eyes of infants born to mothers infected with C. trachomatis are probably more likely to be transiently colonized by the agent than to develop conjunctivitis. When
using cultures of eye secretion on cycloheximide-treated McCoy cells\textsuperscript{5} it was found that five (22.5\%) of 23 women had infants whose eyes were chlamydia-positive.\textsuperscript{56} However, none of these children developed either neonatal conjunctivitis or subsequent pneumonia, which might be explained by the fact that eye secretion has strong antichlamydial activity.\textsuperscript{57} This activity is unrelated to immunological reactions. IgG antichlamydia immunofluorescence (MIK) antibodies were detected in cord blood of 35 (25\%) of the 139 infants studied. Obviously, transient colonization of infants’ eyes is common.

It is of note that half of the cases of neonatal chlamydial pneumonia run without signs of ‘inclusion’ conjunctivitis.\textsuperscript{58} This stresses the importance of diagnosing genital chlamydial infections in pregnant women. Figure 2 shows chlamydial conjunctivitis.

The incubation period of neonatal chlamydial conjunctivitis varies from days to a few weeks.\textsuperscript{59} The conjunctivitis is generally caused by \textit{C. trachomatis} serotypes D–K and less often by serotype Ba. The condition is often misdiagnosed, as illustrated by the fact that affected children have most often been seen by two or more physicians before the

\begin{figure}[h]
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\caption{Chlamydial conjunctivitis. Courtesy of B. Moller.}
\end{figure}
infants had their chlamydial infection definitely diagnosed.\textsuperscript{59} Exclusion of a concomitant gonococcal infection is, however, of the utmost importance as blenorrhoea can rapidly degrade the cornea, leading to blindness. Although most chlamydial conjunctivitis cases self-heal, there have been some indications that chlamydial eye infections in children can, although rarely, result in pathological changes corresponding to those seen in the early stages of trachoma (generally caused by \textit{C. trachomatis} serotypes A–C). However, such observations date back in time\textsuperscript{60} and may have represented children who were never treated with antibiotics. Nowadays children often get antibiotic therapy, for example, for respiratory tract infections, that ‘en passant’ may cure any persisting chlamydial eye infection.

The various possible routes of spread of \textit{C. trachomatis} to infants are shown in Figure 3. As shown, chlamydial infection may spread not only from the mother to the child at delivery, but also directly from the father to the infant as well as from any other chlamydia-infected care-taker with chlamydial conjunctivitis (by means of infected fingers, towels etc.). Such transmission may occur when nursing the infant both in hospitals and other institutions as well as in the child’s home. Siblings and other children suffering from chlamydial conjunctivitis may also be the source of the infant’s eye infection.\textsuperscript{61} It is notable that chlamydial conjunctivitis has also been seen in infants delivered by Caesarean section.\textsuperscript{62}

Neonatal chlamydial conjunctivitis generally starts mono-ocularly. The fellow eye becomes affected after 2–7 days in 75% of infants, in comparison to adults in whom the fellow eye generally becomes affected later, i.e. after 5–30 days in approximately one-third of cases.\textsuperscript{59} The nasopharynx was culture-positive for \textit{C. trachomatis} in up to two-thirds of conjunctivitis cases, for example, in 67% of a series of Swedish neonates.\textsuperscript{59}

History, signs and result of laboratory tests in neonatal chlamydial conjunctivitis:
- Debut mono-ocularly at 5–14 days after delivery
- Usually becomes bilateral, if untreated
- Scant or copious eye discharge
- Oedema and erythema of eyelids
- Conjunctiva may bleed at examination or at sampling procedure

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure3}
\caption{Possible transmission routes of \textit{Chlamydia trachomatis} that could result in neonatal conjunctivitis.}
\end{figure}
• EB in eye secretion detected at microscopy, using monoclonal antibody to C. trachomatis or in Giemsa-stained smears
• Concomitant signs of pneumonia
• Antichlamydial serum antibodies
• Chlamydial genital (or eye) infection in parents (or other sexual consort of mother)

Chlamydial secretion in cases of neonatal conjunctivitis generally contains a large number of elementary bodies (EBs), making most chlamydial diagnostic methods useful, for example, immunofluorescence (IF), culture and nucleic-acid-based tests. IF tests have the advantage of allowing the diagnosis to be settled quickly after sampling. If there is no access to an IF-microscope and monoclonal antibodies to C. trachomatis, Giemsa staining can be employed to reveal the presence of any chlamydial inclusion in infected cells. The inherent autofluorescence of chlamydial EBs can also be used to diagnose neonatal conjunctivitis, provided that UV microscopy is available.

In a comparison of ELISA, IF and culture in the diagnosis of chlamydial conjunctivitis, we found predictive positive values of 98, 96 and 94% for these methods respectively, while the negative predictive values were 93, 89 and 92%.63

Pneumonia

Chlamydial neonatal pneumonia does not initially appear until the infant has developed cellular immunity to C. trachomatis. This usually occurs first after (4)–6–(12) weeks of age.

Pneumonia in newborns caused by C. trachomatis is difficult to diagnose as the condition often causes only minimal symptoms, such as slight tachypnoea and subfebrility.1,64 Parents may have little or no experience of how an infant breathes, which makes it difficult for them to suspect that their child may be suffering from pneumonia. They may believe that tachypnoea is the normal way of breathing for a newborn. The child may, however, also present with wheezing, discrete cough and congestion. Rules can be heard at auscultation.

Direct aspiration of infected genital secretion during delivery is suggested to be the common cause of chlamydial pneumonia. Pneumonia may also follow chlamydial conjunctivitis,265–68 but concomitant conjunctivitis occurs in only every second case. This further highlights the difficulty of recognizing chlamydial neonatal pneumonia. Therefore, it is obviously a great risk that chlamydial pneumonia will often go untreated (if the child does not develop other infections leading to therapy with antibiotics active against C. trachomatis). It is notable that pregnant women may develop chlamydial conjunctivitis even if prophylactic therapy with either topical erythromycin or tetracycline have been given. This further stresses the need to be observant for signs of chlamydial conjunctivitis and pneumonia in newborns.

History, signs and laboratory test results suggestive of neonatal pneumonia:
• Onset at the mean of 6 weeks of age (range 4–12 weeks)
• Non-febrile or subfebrile
• Cough and congestion
• No wheezing
• Rules at lung auscultation
• Tachypnoea
• Increased total serum levels of IgM (in all cases) and of IgG, IgA and IgE in most cases
• Antichlamydial serum IgM antibodies (pathognomonic)
• Eosinophilia (> 300 mm³)
• Chest X-ray shows diffuse infiltrates and hyperinflation
• Genital and/or eye chlamydial infection diagnosed in parents (or other sexual partner of mother) or other care-taker of child

Neonatal chlamydial pneumonia has been correlated with low birth weight. It has also been hypothesized that not only the eye, but also the nasopharynx can be the source of a chlamydial lung infection. Recovery of \textit{C. trachomatis} from eye and nasopharyngeal secretions and also from the genital tract from a newborn support the occurrence of a chlamydial pneumonia.

A very early onset suggests that the infection may even start as an intrauterine chlamydial infection.

Laboratory findings in neonatal chlamydial pneumonia indicate that the child has a non-specific B-cell stimulation with elevated serum levels of IgG, IgM, IgA and IgE. Detection of antichlamydial IgM antibodies is considered a pathogenetic sign of neonatal chlamydial pneumonia. Similarly, a large number of blood eosinophilic granulocytes is a powerful diagnostic parameter.

Radiographic examination shows hyperinflation and diffuse bilateral infiltrates, which may be more advanced than suggested by chest auscultations. Histological findings in neonatal chlamydial pneumonia have been reported from only a few cases. These have shown diffuse interstitial and alveolar infiltrates of monocytes and neutrophils. A chest X-ray of chlamydial pneumonia in a child is shown in Figure 4.

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\includegraphics[width=0.8\textwidth]{figure4.png}
\caption{Chest X-ray of child with chlamydial pneumonia.}
\end{figure}
Concurrent infection by viruses in cases of chlamydial neonatal pneumonia seems to be common, e.g. with cytomegalovirus, respiratory syncytial virus, rhinovirus, enterovirus and adenoviruses.  

Sudden infant death syndrome

In a study of 166 cases of sudden death in Danish infants, 22 (19.4%) had a positive immunofluorescence test for *C. trachomatis* in formaldehyde-fixed sections of lung tissue. Histology of the lungs did not reveal any characteristic picture in any of the 31 cases that had signs of pneumonia. Thus, further data are required for confirmation of a causal relationship between sudden death and a chlamydial infection in infants, if any.  

Persistence of neonatal chlamydial infections

A neonatal chlamydial infection may persist for many years, at least up to school age. The possibility of such chronic infections has been brought up as an issue in instances where the father has been prosecuted for incest. It is of note that a chlamydial infection contracted during the neonatal period, if untreated, may persist for years at extragenital sites, such as the nasopharynx. Antichlamydial antibodies are not uncommon, a finding in children where genital chlamydial infections are common in women.  

Therapy of neonatal chlamydial infections

Even if the newborn child concomitantly has chlamydial conjunctivitis and pneumonia, there is a remarkable delay until the parents consult with affected children. Delay in therapy is not only due to the patient’s (parents’) delay, but often also to the doctor’s delay. Also, adult patients with chlamydial conjunctivitis have often seen two or three doctors before the diagnosis is finally established, which may take several months.  

It is important to stress that topical therapy of neonatal conjunctivitis should not be used. Thus, topical chloramphenicol treatment has no curative effect on chlamydial conjunctivitis. Apart from being ineffective, antibiotic eye ointments will not cure extraocular sites, such as the nasopharynx, which may be colonized. General therapy of neonatal chlamydial conjunctivitis is also not least important as it may also cure a concomitant chlamydial pneumonia or genital chlamydial infection.  

Not only the choice of antibiotic for general therapy, but also the correct dose and length of course are important for successful eradication of *C. trachomatis* from the eyes in cases of neonatal conjunctivitis. With a 10-day-course of either 200 mg erythromycin ethylsuccinate or 50 mg roxithromycin (divided into two doses) given daily to 28 neonates (all less than 2 months of age) an unexpected failure rate was seen. Thus, 29 and 43% remained positive for *C. trachomatis* at follow-up after these therapies, respectively. With a repeated 14-day-course of erythromycin and the same dose regimen, 98% of those positive at the follow-up were healed. All children who had been given a repeated course were culture-negative at follow-up after 1 year. The diagnoses in all the chlamydial conjunctivitis cases cited were based on culture on cycloheximide-treated McCoy cells. It is essential to note that nucleic acid tests may be positive for up to 3 weeks after finishing therapy and may represent the presence of as yet unshed, dead organisms.  

Silver nitrate is not effective against eye infection with *C. trachomatis*. Children given such prophylactic therapy for gonorrhoea need an antibiotic course if they develop signs of post-gonococcal chlamydial conjunctivitis.
Table I. Therapy of neonatal chlamydial conjunctivitis and pneumonia.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Dose regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis</td>
<td>Erythromycin base (syrup)</td>
<td>50 mg/kg orally four times a day for 14 days</td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Dose regimen not yet established</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Erythromycin base (syrup)</td>
<td>25 mg/kg orally a day for 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Experience limited</td>
</tr>
</tbody>
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Experience of antibiotic therapy with chlamydial pneumonia is limited.\textsuperscript{57,81} Clinical relapse does occur, even when a 2-week antibiotic course has been given, i.e. with erythromycin ethylsuccinate (40 mg/kg/day).\textsuperscript{2} This is also the case if sulfisoxazole (150 mg/kg/day) is prescribed.\textsuperscript{1} The role of azithromycin in the therapy of neonatal chlamydial pneumonia is still not defined\textsuperscript{81} but this drug is likely to be a therapeutic alternative.

There are psychological aspects to consider if a chlamydial infection has been diagnosed in an infant. The mother may be severely stressed when she becomes aware that she has a sexually transmitted infection which she may have transferred to her child. Furthermore, her relationship with her consort (presumably the father) may also be severely disturbed if she suspects that he has been unfaithful during her pregnancy. To diagnose a chlamydial infection post partum however, the mother may, of course, have contracted the infection before she had conceived or even before establishing her relationship with the father of the child. If neonatal chlamydial infection is diagnosed, therapy for both parents must not be forgotten.\textsuperscript{82}

Sequelae of neonatal chlamydial infection

Although chlamydial conjunctivitis is usually self-limiting, corneal pannus formation, i.e. neovascularization, corneal scarring and visual impairment, may occur as sequelae.\textsuperscript{60,76} However, such manifestations seem to be rare.

Significant limitation of expiratory airflow have been found in children 7–8 years of age in cases with proven neonatal pneumonia.\textsuperscript{64} Also, abnormal elevated volumes of trapped air, i.e. an altered functional residual capacity and residual volume/total lung capacity ratio, may be found. Persons who have had neonatal chlamydia pneumonia may develop chronic obstructive lung disease\textsuperscript{83} which may first appear clinically during later life and even cause early death due to respiratory failure. Serological findings suggest a correlation between chronic lung disease and intrauterine chlamydial infection in extremely-low-weight premature born infants.\textsuperscript{67–69} Chlamydial neonatal pneumonia cases are over-represented in adults developing asthma.

It is notable that, beyond infancy, \textit{C. trachomatis} as an aetiological agent of pneumonia seems to be uncommon, although serological evidence of such infections has been reported in cases with no evidence of any concomitant infection.\textsuperscript{84} It may be speculated that \textit{C. trachomatis} infection in adult cases is rare because it is never searched for. Anyway, as in neonates, a person must have developed a cellular immune response to the agent before being taken ill.

Chlamydial pneumonia in adults is usually caused by \textit{Chlamydia pneumoniae}. However, such an aetiology can also be seen early in life. \textit{C. pneumoniae} can cause endothelial dysfunction in animal models\textsuperscript{85} – a phenomenon that may influence the rate of many vascular phenomena later in life if affecting very young persons.
Neonatal chlamydial pneumonia often coincides with other infectious agents, such as EMV and respiratory syncytial virus\textsuperscript{58} – agents which are also known to correlate with chronic pulmonary disorders. However, most reports on neonatal chlamydial pneumonia lack studies on possible concomitant non-chlamydial aetiologies to the condition.

**Chlamydia screening of pregnant women**

There are a number of means for screening for genital infections with *C. trachomatis*, some of which may also be used for pregnant women.\textsuperscript{86} The urine of pregnant women has been suggested to contain components which interfere with ligase chain reaction (LCR) assays more often than does urine of non-pregnant women.\textsuperscript{87} Testing introital samples may avoid this interference.

The screening of pregnant women for *C. trachomatis* is still performed in only a few clinical settings. One unsolved problem is to determine the optimal time to screen for *C. trachomatis* during the gestational period – and also to determine whether more than one screening is needed. ‘Extramarital’ sexual contacts by the male partner are not too uncommon during his partner’s pregnancy and are considered to become more common as the gestational time passes. If only one screening is chosen, it is likely to be most optimal at the end of the second trimester; this reduces any adverse pregnancy outcome but still catches most of the newly contracted chlamydial infections. The choice of one-time screening during pregnancy must be considered in relation to social, ethnic and cultural traditions in the cohort to be screened.

**Therapy of pregnant women**

Apart from avoiding the risk of transferring a chlamydial infection to the offspring,\textsuperscript{88} therapy of a chlamydial infection in a pregnant woman will reduce the chance for her to develop chlamydial endometritis and PID after delivery (see above).

Therapy of pregnant and lactating women involves specific management issues\textsuperscript{81,89,90}, for example, in the choice of antibiotic drug. Erythromycin\textsuperscript{88} or azithromycin\textsuperscript{81} are recommended for the therapy of genital infections in pregnancy. For lactating women the same drugs can be used as in pregnancy. A comparison of therapy with 500 mg of amoxicillin three times daily for 7 days with 1 g of azithromycin as a single dose showed that these therapies are equally effective in a study of prenatal clinic attendees positive for *C. trachomatis*, according to tests for cure 4 weeks after starting the therapy.\textsuperscript{91} Resolution of symptoms after treatment of urogenital infection with *C. trachomatis* may vary with the drug used, i.e. being quicker after azithromycin than after tetracycline therapy. However, the dose regimen also has an influence. For example, 500 mg of azithromycin given for 6 days were more efficient than 1 g given as a single dose.\textsuperscript{92}

Antichlamydial antibiotic therapy in pregnant women has both been and not been reported to decrease the rate of preterm delivery and growth retardation of fetuses may also influence future possibilities for conceiving.\textsuperscript{39,45,93–95} However, as already discussed, studies of these conditions with regard to chlamydial infections have often not considered the large number of other aetiologies of adverse pregnancy outcomes.

In the therapy of post-abortional PID, not only the risk for a chlamydial infection but also a concomitant infection by anaerobic bacteria should be considered.\textsuperscript{96,97}

As in neonates, general antibiotic therapy should be given to pregnant women with chlamydial conjunctivitis as sites other than the eyes may be affected.\textsuperscript{98}
It has been questioned whether treatment should be based on risk assessment rather than performing universal screening of both gonorrhoea and genital chlamydia infections in pregnant women in the third trimester before institution of therapy.\(^9\)

The absence of risky behaviour had a negative predictive value for the presence of these agents. The women tested had been screened before during the first trimester, and this could have had an impact on behaviour change and thus influenced the study outcome until retest. Such an approach (any time during pregnancy) may, however, make partner notification impossible – a key procedure in preventing the spread of these infections.

Matters that remain to be solved with regard to chlamydial therapy include the question of whether all infants of non-treated women with a proven genital chlamydial infection should be given therapy independent of symptoms and signs. Furthermore, is re-screening of chlamydia-positive pregnant women (and their infants) needed and, if so, by which test(s) and at which time(s) after delivery?

**SUMMARY**

The role of genital chlamydial infection in adverse pregnancy outcome, for example, in abortion, stillbirth, prematurity, intrauterine infections and in postpartum endometritis and salpingitis, is likely to have been underscored. Such infection may also interfere with the future chance to conceive. The role of such infection in ectopic pregnancy, both in women with and without a documented history of chlamydial PID, is well established. Chlamydial infection in infants contracted from the mother is often overlooked, with a risk of life-long sequelae – such as obstructive lung disease; this increases the motivation to screen pregnant women for *C. trachomatis*. The high rate of chlamydia-positive pregnancy women stresses the need for partner notification and the need to be aware of pharmacokinetic, compliance and antibiotic-resistance problems in chlamydia therapy also in this group of women.

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**Practice points**

- perform screening for *C. trachomatis* in pregnant women
- test for *C. trachomatis* in cases of adverse pregnancy outcome
- check-up for effectiveness of therapy against genital, eye and other types of infection with *C. trachomatis*
- do not forget partner notification in cases of genital chlamydia infection, but be aware of psychological problems if highlighting a sexually transmitted infection to a pregnant woman
- test for *C. trachomatis* infections in infants as a differential diagnosis in cases of conjunctivitis, pneumonia and genital infections

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**Research agenda**

- better characterize the long-term effects of *C. trachomatis* infection in infancy, for example, the effect of such infection on lung function and the haemodynamic system
- define the optimal time for chlamydia screening during gestation
REFERENCES


