Ophthalmia Neonatorum

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4.1 Introduction

Ophthalmia (*Latin*: inflammation of the membranes or coats of the eye) Neonatorum (*Latin*: of the newborn), is also known as neonatal conjunctivitis. Ophthalmia Neonatorum (ON) is defined as an acute, mucopurulent conjunctivitis, presenting in the first 4 weeks of life [1, 2]. Initially ON was used only for cases due to *Neisseria gonorrhoeae* [3], but it now encompasses any inflammation due to any entity (e.g., chlamydia trachomatis, chemical, etc.) [4].

ON is a clinical diagnosis and may involve the eyelids, conjunctiva, cornea, and/or lacrimal apparatus. Therefore, dacryocystitis cases which usually present with purulent recurrent conjunctivitis should also technically fall within the definition of ON. Both conditions can be coded under the term "neonatal conjunctivitis and dacryocystitis" [5]. Therefore, any infant presenting with signs of external eye infection within the first 4 weeks of life should be treated as ON unless proven otherwise [6].

4.2 Incidence

The incidence of ON varies between 1.6 and 24% according to different studies from varying geographical locations, and depends on the socioeconomic character of the area. Under-notification of infectious diseases [6] and limitations in reporting suggest numbers are an underestimate; nearly 85% of combined chlamydial and gonococcal cases in infants less than 1 year do not report the specimen source so are not counted among cases [7]. With a broader definition including cases with unknown, other, or missing specimen sources, the prevalence of gonococcal ON, for

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example, may possibly be as high as 1.1–1.6 cases per 100,000 live births from 2010 to 2015 [7].

Neisseria gonorrhoeae and *Chlamydia trachomatis* were major causes of microbial neonatal conjunctivitis before the twenty-first century. The prevalence [8] and incidence of neonatal conjunctivitis has decreased because of the development of antibiotics, more widespread use of prepartum examination, and increased number of cesarean section [9].

Since the institution of neonatal ocular prophylaxis, the incidence of gonococcal conjunctivitis, for example, has decreased dramatically in the Western world [10, 11] with a reduction from 10 to 0.3% [11]. In the United States, ON caused by *N. gonorrhoeae* has an incidence of 0.3 per 1000 live births, while *Chlamydia trachomatis* represents 8.2 of 1000 cases [12]. In another study, when defined as gonorrhea in infants less than 1 year with a specimen source of "eye" or "conjunctiva," there were an estimated 0.4 cases or fewer per 100,000 live births per year during 2013–2017 [13].

The geographic variation is illustrated by the fact that rates in New Zealand are 145.9 per 100,000 births per year for Chlamydial infections and 3.79 per 100,000 births per year for Gonorrhea infections [14], while in Pakistan 17% of 1010 babies developed neonatal conjunctivitis with Staphylococcus aureus (65% of all positive cultures) which was the most causative agent [15].

A global study investigating the incidence of ON cases presenting to members of the American Association of Pediatric Ophthalmology and Strabismus (AAPOS) found that ophthalmologists encountered 0–5 cases per year per practitioner, with *Chlamydia trachomatis* being the most common reported organism (35%) [4].

4.3 Etiology

The specific cause of neonatal conjunctivitis can be correlated to the onset of conjunctivitis [10, 11, 16, 17].

- First 24 h of life: Chemical causes (silver nitrate drops or from prophylactic eye drops like erythromycin drops, gentamicin drops).
- 24–48 h of life: Bacterial causes are most likely (*Neisseria gonorrhoeae*, *Staphylococcus aureus*).
- 5–14 days of life: *Chlamydia trachomatis*.
- 6–14 days of life: Herpes keratoconjunctivitis.
- 5–18 days: *Pseudomonas aerugi*nosa.

Etiology can also be classified as either sexually transmitted or non-sexually transmitted. An association between neonates with purulent conjunctivitis and mothers with vaginal discharge was first described in 1750 [1]. Sexually transmitted causes tend to include *N. gonorrhoeae* and *Chlamydia trachomatis*. *N. gonorrhoeae*

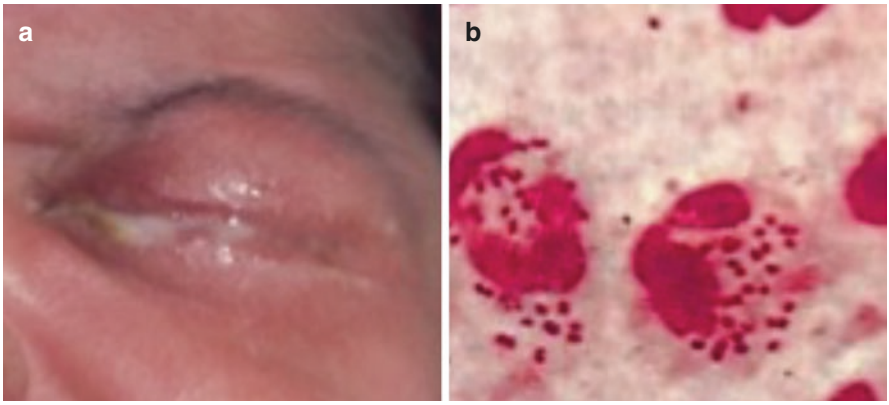

Fig. 4.1 Composite figure showing a neonate with purulent discharge and swollen lids (**a**). The gram stain shows gram-negative intracellular diplococci, suggesting *N. gonorrhea* as the causative organism (**b**)

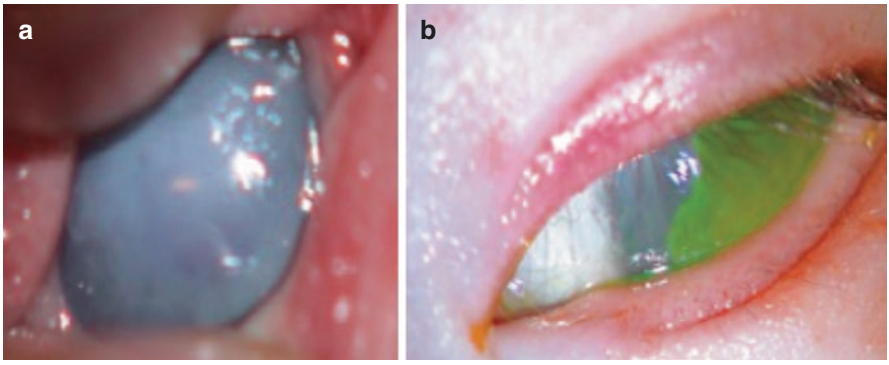

Fig. 4.2 Infant with geographic ulcer due to HSV, prior to (**a**) and after staining with topical fluorescein (**b**)

accounts for less than 1% of ophthalmia cases worldwide; however, of the babies born to mothers infected with *N. gonorrhoeae,* up to 48% develop ophthalmia neonatorum (Fig. 4.1). While *Chlamydia trachomatis* accounts for 2–40% of ophthalmia neonatorum cases [18]. Non-sexually transmitted bacteria, like *Staphylococcus aureus*, *Streptococcal* species, gram-negative bacteria (*Haemophilus spp.*, *Escherichia coli*, *Pseudomonas aeruginosa*), and *Haemophilus*, account for 30–50% of ON cases [19, 20]. Much less commonly, neonatal conjunctivitis is caused by viral infections (herpes simplex, adenovirus, enteroviruses) (Fig. 4.2). Unusual organisms causing neonatal conjunctivitis like *Serratia marcescens* (*S. marcescens*) are usually seen as nosocomial infections associated with significant morbidity and mortality in the neonatal intensive care units (NICU) [21]. Chemical conjunctivitis can be seen after silver nitrate prophylactic treatment.

4.4 Clinical Symptoms

ON caused by *N. gonorrhoeae* typically presents in the first 3–4 days of life. The neonate may present with mild conjunctival hyperemia and discharge. In severe cases, there is marked chemosis, copious discharge, and potentially rapid corneal ulceration and perforation of the eye. Systemic infection can cause sepsis, meningitis, and arthritis.

Chlamydia trachomatis is an obligate intracellular bacterium that causes neonatal inclusion conjunctivitis. The onset of conjunctivitis usually occurs around 1 week of age [22], although onset may be earlier, especially in cases with premature rupture of membranes. ON due to *Chlamydia* can have a delayed peak at around the age of 2-week-old. This is explained by the fact that the first-line empirical therapy with topical eye drops is not sufficiently effective against chlamydia and may not eradicate the infection, hence delaying the onset of symptoms and diagnosis [22]. Eye infection is characterized by minimal to moderate discharge, mild swelling of the eyelids, and hyperemia with a papillary reaction of the conjunctiva. Severe cases may be accompanied by more copious discharge and pseudomembrane formation. *Chlamydial* infection in infants differs from that in adults in several ways: in infants, there is little to no follicular response, membrane formation may occur, and there is greater mucopurulent discharge.

Herpes simplex virus (HSV) infection is usually secondary to HSV type 2 and typically presents later than infection with *N. gonorrhoeae* or *C. trachomatis*, frequently in the second week of life. Any child diagnosed with HSV ON must have a full systemic evaluation to exclude pneumonitis, hepatitis, and encephalitis.

Chemical conjunctivitis refers to a mild, self-limited irritation and redness of the conjunctiva occurring in the first 24 h after instillation of silver nitrate, a preparation used for prophylaxis against ophthalmia neonatorum. This condition improves spontaneously by the second day of life.

4.5 Pathophysiology

The causative organism usually infects the infant through direct contact during passage through the birth canal. Infection can ascend to the uterus, especially if there is prolonged rupture of membranes, so even infants delivered by a cesarean section can be infected.

4.6 Diagnosis and Investigation

Diagnosis of ON is a clinical diagnosis supported by appropriate laboratory investigations. This should include immediate conjunctival scraping with Gram stain to look for gram-negative intracellular diplococci to exclude or confirm a presumptive diagnosis of *N. gonorrhoeae* infection, since this organism can cause rapid corneal ulceration if left undiagnosed and therefore untreated (Fig. 4.1).

Culture on chocolate agar or Thayer Martin for *N. gonorrhoeae* and culture on blood agar for other bacteria are performed. Additionally, a conjunctival scraping should be done to rule out chlamydial infection by using antigen immunodetection and polymerase chain reaction. If the corneal epithelium is involved, a culture and polymerase chain reaction for herpes simplex virus is indicated.

In *Chlamydia trachomatis* infection, polymerase chain reaction (PCR) [23], direct fluorescent antibody staining, and Giemsa-stained epithelial cells from conjunctival scraping can be useful and essential in some cases to make the diagnosis [12]. Serology is not informative in these local epithelial infections [24]. Attempts at DNA sequencing of *Chlamydia* positive samples were successful and the results revealed multiple genotypes with a clear 48% dominance of genotype E contributing to both neonatal and adult conjunctivitis. The dominance of genotype E may be due to the different tissue tropism of these strains for the conjunctival mucosa of neonates or is a reflection of the actual dominance of circulating urogenital strains among humans [25].

The standard diagnostic tests for the isolation of the virus in herpetic conjunctivitis are virus culture and viral DNA detection by PCR. Patients with signs of systemic infection that look unwell may have spread disease manifesting as meningitis, bacteremia, arthritis, or sepsis; on those cases, additional investigation including blood culture, cerebrospinal fluid for gram stain or joint are warranted [26]. Evaluation of meningitis, bronchitis, and hepatitis with systemic disease is mandatory in cases of neonatal herpetic conjunctivitis.

4.7 Prophylaxis

The concept of ON prophylaxis is the best method adapted ever since Credes introduced it in 1884 to control ON disease burden and complications [19, 27]. Prevention of ophthalmia neonatorum can be effectively practiced through antenatal care by treating sexually transmitted infections in pregnant women, newborn screening, and ocular prophylaxis. A combination of these three will reduce the ocular morbidity and blindness in the pediatric population, particularly in underdeveloped nations [1].

In the absence of ocular prophylaxis, studies have estimated transmission rates of gonococcal infections of 30–50% from the mother to the newborn [4]. Neonatal ocular prophylaxis is mandated in most states and is considered most effective when administered up to 1 h after birth.

A 2.5% povidone-iodine has been used immediately after birth [28]. A clinical trial for ophthalmia neonatorum conducted in Kenya showed that a 2.5% solution of povidone-iodine was more effective and less toxic than erythromycin or silver nitrate ointment. Povidone-iodine is particularly useful in developing countries because of its low cost and ease of application [29]. Chemical conjunctivitis has been reported with use of silver nitrate but not 2.5% povidone-iodine solution.

Erythromycin ophthalmic ointment is currently the only FDA-approved prophylactic agent available in the United States [30]. Failure of prophylaxis may be due to either poor compliance of protocols or reinfection.

4.8 Management

ON is an acute emergency and requires immediate treatment and referral because of the significant risk of corneal perforation and intraocular infection that can very quickly lead to blindness, if the cause is *N. gonorrhoeae* [1]. Since a mother may have multiple sexually transmitted diseases, infants with one type of ON should be screened for other such diseases. Public health authorities should be contacted to initiate evaluation and treatment of other maternal contacts in cases of sexually transmitted diseases.

Ideally, a swab of the discharge should be obtained in order to determine which organism is responsible. In the absence of easy access to laboratory diagnosis, the World Health Organization recommends that babies should be treated for both gonococcal and chlamydial infections.

World Health Organization (WHO) treatment recommendations for ON due to *C. trachomatis* include oral erythromycin, while topical erythromycin is recommended as an adjunct therapy. The purpose of the systemic therapy is to decrease the risk for pneumonitis and also prevent the relapse of conjunctivitis.

For gonococcal ON, the recommended treatment is a single dose of intramuscular ceftriaxone injection (50 mg/kg of body weight, maximum 125 mg). An alternative regimen is cefotaxime 100 mg/kg in a single dose [14] others are kanamycin and spectinomycin [2].

For chlamydial ON, the recommendation is 50 mg/kg of erythromycin syrup per day, divided into 4 doses, for 14 days. Topical erythromycin can be used as adjunct therapy as well. Conjunctivitis secondary to *Staphylococcal* species and pseudomonas requires treatment with systemic antibiotics. On the other hand, patients with herpes simplex conjunctivitis should have treatment with systemic antiviral therapy, along with topical ophthalmic drugs, including 0.15% ganciclovir or 1% trifluridine for 14 days [3, 4, 30].

Recommendations about management in asymptomatic babies born to mothers infected with *Chlamydia trachomatis* infection exist; these babies require close monitoring for the appearance of clinical symptoms suggestive of chlamydia ocular or respiratory infections [31, 32].

4.9 Complications

These may be immediate, long term, or treatment related. Immediate ones are usually seen in cases of gonococcal ON which is associated with a high risk of corneal perforation [33] and untreated gonococcal ophthalmia neonatorum can result in corneal scarring, ocular perforation, and blindness as early as 24 h after birth [34, 35, 36].

Late ones include corneal opacity which contributes to a significant proportion of blinding eye diseases in Asia and Africa [37]. Sixty percent of blindness that occurs in children under 12 years is due to corneal opacity mostly from infections resulting in huge social and economic burden to the family and society in India [38]. There

are no published contemporary estimates of gonococcal ON-related blindness in the US; it is considered rare in industrialized countries [39]. Even historical information about gonococcal ON-related blindness is limited. In the late nineteenth century, prior to Crede's prophylaxis with silver nitrate, ON, primarily caused by gonorrhea, was considered a major cause of childhood blindness; in Europe at that time, the prevalence of ophthalmia neonatorum among live births in maternity hospitals was greater than 10%, resulting in corneal damage in 20% and blindness in approximately 3% of these infected infants [39, 40]. An observational study from Nairobi, Kenya in the 1980s reported that 16% of a series of 64 infants with gonococcal ON had corneal involvement [37].

Treatment-related complications are rare but oral erythromycin is associated with an increased risk of developing pyloric stenosis [41]. The risk of chemical conjunctivitis with erythromycin is between 10 and 13% [3, 42] and chemical conjunctivitis is a well-known side effect of prophylactic topical agents used at birth such as silver nitrate.

4.10 Prognosis

Detection and timely treatment of infected mothers is essential to prevent permanent ocular damage; if left untreated or partially treated, corneal ulceration, perforation, and blindness can occur. Approximately 10,000 cases of blindness per year are secondary to ophthalmia neonatorum worldwide [43]. Fortunately, in most cases, neonatal ophthalmia neonatorum caused by non-gonococcal bacteria is a mild disease and has a good prognosis; however, up to 50% of babies born to mothers with chlamydia infection may develop neonatal conjunctivitis [30], and from those, up to 20% are at risk of having pneumonia [44]. Chemical conjunctivitis secondary to silver nitrate or other topical prophylactic agents is self-limiting.

References

1. Rapoza PA, Quinn TC, Kiessling LA, Green WR, Taylor HR. Assessment of neonatal conjunctivitis with a direct immunofluorescent monoclonal antibody stain for Chlamydia. JAMA. 1986;255(24):3369–73.
2. Teoh DL, Reynolds S. Diagnosis and management of pediatric conjunctivitis. Pediatr Emerg Care. 2003;19(1):48–55.
3. Zuppa AA, D'Andrea V, Catenazzi P, Scorrano A, Romagnoli C. Ophthalmia neonatorum: what kind of prophylaxis? J Matern Fetal Neonatal Med. 2011;24(6):769–73.
4. Zloto O, Gharaibeh A, Mezer E, Stankovic B, Isenberg S, Wygnanski-Jaffe T. Ophthalmia neonatorum treatment and prophylaxis: IPOSC global study. Graefes Arch Clin Exp Ophthalmol. 2016;254(3):577–82.
5. International Statistical Classification of Diseases and Related Health Problems (ICD-10). https://icd.who.int/browse10/2010/en.
6. Pilling R, Long V, Hobson R, Schweiger M. Ophthalmia neonatorum: a vanishing disease or underreported notification? Eye. 2009;23(9):1879–80.

7. Kreisel K, Weston E, Braxton J, Llata E, Torrone E. Keeping an eye on chlamydia and gonorrhea conjunctivitis in infants in the United States, 2010-2015. Sex Transm Dis. 2017;44(6):356–8.
8. Pak KY, Kim SI, Lee JS. Neonatal bacterial conjunctivitis in Korea in the 21st century. Cornea. 2017;36(4):415–8.
9. Di Bartolomeo S, Mirta DH, Janer M, Rodríguez Fermepin MR, Sauka D, Magariños F, de Torres RA. Incidence of Chlamydia trachomatis and other potential pathogens in neonatal conjunctivitis. Int J Infect Dis. 2001;5(3):139–43.
10. Smolkin T, Roth-Ahronson E, Kranzler M, Geffen Y, Mashiach T, Kugelman A, Makhoul IR. Optimizing accessibility of a hand-wash gel to infant's cradle: effect on neonatal conjunctivitis. Pediatr Infect Dis J. 2019;38(1):e7–11.
11. Jin J. Prevention of gonococcal eye infection in newborns. JAMA. 2019;321(4):414.
12. Castro Ochoa KJ, Mendez MD. Ophthalmia neonatorum. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020.
13. Centers for Disease Control and Prevention. STDs in Women and Infants. https://www.cdc.gov/std/stats17/womenandinf.htm.
14. Newlands S, Dickson J, Pearson J, Mansell C, Wilson G. Neonatal conjunctivitis in the New Zealand Midland region. N Z Med J. 2018;131(1486):9–17.
15. Gul SS, Jamal M, Khan N. Ophthalmia neonatorum. J Coll Physicians Surg Pak. 2010;20(9):595–8.
16. Zikic A, Schünemann H, Wi T, Lincetto O, Broutet N, Santesso N. Treatment of neonatal chlamydial conjunctivitis: a systematic review and meta-analysis. J Pediatric Infect Dis Soc. 2018;7(3):e107–15.
17. Singh G, Galvis A, Das S. Case 1: eye discharge in a 10-day-old neonate born by cesarean delivery. Pediatr Rev. 2018;39(4):210.
18. Moore DL, MacDonald NE, Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Preventing ophthalmia neonatorum. Can J Infect Dis Med Microbiol. 2015;26(3):122–5.
19. Matejcek A, Goldman RD. Treatment and prevention of ophthalmia neonatorum. Can Fam Physician. 2013;59(11):1187–90.
20. Prevention of neonatal ophthalmia. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS (eds). Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. American Academy of Pediatrics Elk Grove Village (IL): American Academy of Pediatrics; 2012. pp. 880–882.
21. Yeo KT, Octavia S, Lim K, Lin C, Lin R, Thoon KC, Tee NWS, Yung CF. Serratia marcescens in the neonatal intensive care unit: a cluster investigation using molecular methods. J Infect Public Health. 2019; S1876-0341(19)30384-3.
22. Darville T. Chlamydia trachomatis infections in neonates and young children. Semin Pediatr Infect Dis. 2005;16(4):235–44.
23. Rafiei Tabatabaei S, Afjeiee SA, Fallah F, Tahami Zanjani N, Shiva F, Tavakkoly Fard A, Shamshiri AR, Karimi A. The use of polymerase chain reaction assay versus cell culture in detecting neonatal chlamydial conjunctivitis. Arch Iran Med. 2012;15(3):171–5.
24. Balla E, Petrovay F, Erdősi T, Balázs A, Henczkó J, Urbán E, Donders GGG. Distribution of Chlamydia trachomatis genotypes in neonatal conjunctivitis in Hungary. J Med Microbiol. 2017;66(7):915–8.
25. Gallo Vaulet L, Entrocassi C, Corominas AI, Rodríguez Fermepin M. Distribution study of Chlamydia trachomatis genotypes in symptomatic patients in Buenos Aires, Argentina: association between genotype E and neonatal conjunctivitis. BMC Res Notes. 2010;3:34.
26. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:RR–03): 1-137.
27. Recommendations for prevention of neonatal ophthalmia. Infectious diseases and immunization committee, Canadian Paediatric Society. Can Med Assoc J. 1983;129(6):554–5.
28. MacDonald N, Mailman T, Desai S. Gonococcal infections in newborns and in adolescents. Adv Exp Med Biol. 2008;609:108–30.

29. Fransen L, Nsanze H, Klauss V, Stuyft PV, D'Costa L, Brunham RC, Piot P. Ophthalmia neonatorum in Nairobi, Kenya: the roles of Neisseria gonorrhoeae and Chlamydia trachomatis. J Infect Dis. 1986;153(5):862–9.
30. Hammerschlag MR. Chlamydial and gonococcal infections in infants and children. Clin Infect Dis. 2011;53(Suppl-3):S99–S102.
31. Kapoor VS, Whyte R, Vedula SS. Interventions for preventing ophthalmia neonatorum. Cochrane Database Syst Rev. 2016;2016(9):CD001862.
32. World Health Organisation. Guidelines for the management of sexually transmitted infections 2004. https://apps.who.int/medicinedocs/en/d/Jh2942e/.
33. Tarabishy AB, Jeng BH. Bacterial conjunctivitis: a review for internists. Cleve Clin J Med. 2008;75(7):507–12.
34. U.S. Preventive Services Task Force. Ocular prophylaxis for gonococcal ophthalmia neonatorum: reaffirmation recommendation statement. Am Fam Physician. 2012;85(2):195–8.
35. Snowe RJ, Wilfert CM. Epidemic reappearance of gonococcal ophthalmia neonatorum. Pediatrics. 1973;51(1):110–4.
36. Woods CR. Gonococcal infections in neonates and young children. Semin Pediatr Infect Dis. 2005;16(4):258–70.
37. Fransen L, Klauss V. Neonatal ophthalmia in the developing world. Epidemiology, etiology, management and control. Int Ophthalmol. 1988;11(3):189–96.
38. Aruljyothi L, Radhakrishnan N, Prajna VN, Lalitha P. Clinical and microbiological study of paediatric infectious keratitis in South India: a 3-year study (2011-2013). Br J Ophthalmol. 2016;100(12):1719–23.
39. Schaller UC, Klauss V. Is Credé's prophylaxis for ophthalmia neonatorum still valid? Bull World Health Organ. 2001;79(3):262–3.
40. Stephenson S. Ophthalmia neonatorum with especial reference to its causation and prevention. London: George Pulman and Sons Ltd, The Ophthalmoscope Press; 1907.
41. Eberly MD, Eide MB, Thompson JL, Nylund CM. Azithromycin in early infancy and pyloric stenosis. Pediatrics. 2015;135(3):483–8.
42. Isenberg SJ, Apt L, Wood M. A controlled trial of povidone-iodine as prophylaxis against ophthalmia neonatorum. N Engl J Med. 1995;332(9):562–6.
43. Isenberg SJ, Apt L, Wood M. The influence of perinatal infective factors on ophthalmia neonatorum. J Pediatr Ophthalmol Strabismus. 1996;33(3):185–8.
44. Hammerschlag MR, Chandler JW, Alexander ER, English M, Koutsky L. Longitudinal studies on chlamydial infections in the first year of life. Pediatr Infect Dis. 1982;1(6):395–401.