

# Perinatal morbidity and mortality associated with chlamydial infection: a meta-analysis study

## ABSTRACT

**Objective:** To evaluate the effect of *Chlamydia trachomatis* infection during pregnancy on perinatal morbidity and mortality. **Methods:** Systematic review and meta-analysis in an electronic database and manual, combining high sensitivity specific descriptors seeking to answer the research objective. The articles considered to be of high methodological quality (score above 6 on the Newcastle-Ottawa Scale) were assessed by meta-analysis. **Results:** Summary estimates of 12 studies were calculated by means of Mantel-Haenszel test with 95% confidence interval. It was observed that *Chlamydia* infection during pregnancy increased risk of preterm labor (relative risk (RR) = 1.35 [1.11, 1.63]), low birth weight (RR = 1.52 [1.24, 1.87]) and perinatal mortality (RR = 1.84 [1.15, 2.94]). No evidence of increased risk was associated with *Chlamydia* infection in regard to premature rupture of membranes (RR = 1.13 [0.95, 1.34]), abortion and postpartum endometritis (RR = 1.20 [0.65, 2.20] and 0.89 [0.49, 1.61] respectively). **Conclusion:** The diagnosis and treatment of *Chlamydia* cervicitis during pregnancy can reduce perinatal morbidity and mortality associated with this infection. However, clinical trials are needed to confirm these findings.

**Keywords:** *Chlamydia trachomatis*; perinatal mortality; morbidity; meta-analysis.

## INTRODUCTION

*Chlamydia trachomatis* (CT) is responsible for the most prevalent sexually transmitted bacterial infection worldwide.<sup>1-4</sup> The World Health Organization (WHO) estimates that 92 million new cases occur annually, four million in the United States and 10 million in Europe.<sup>1,3-5</sup> In Brazil an estimate from the Ministry of Health states approximately two million new cases only in 2001.<sup>6</sup>

Besides high prevalence, another concern is the high annual cost resulting from the sequelae of this infection, estimated at four billion dollars, thus achieving second place among the most expensive sexually transmitted diseases (STDs).<sup>1,7</sup> CT is usually asymptomatic and persistent, as well as widely distributed throughout the population; especially among the young.<sup>8,9</sup>

On the other hand, in Brazil CT detection is not a routine procedure: it is only recommended when patients show symptoms. This lack of diagnosis contributes considerably to the high prevalence of untreated CT leading to seriously damaging consequences.<sup>10</sup>

In women CT initially infects the cervix and urethra, eventually causing abnormal vaginal discharge and dysuria. When not treated the infection can reach the fallopian tubes, causing pelvic inflammatory disease and adhesions.<sup>11-13</sup> Abdominal pain, back pain, nausea, fever, dyspareunia, or menorrhagia affect up to 40% of untreated women. The sequelae resulting from CT include chronic pelvic pain, infertility and increased incidence of ectopic pregnancy.<sup>14-16</sup>

In pregnant women, CT is even more critical as it may affect normal intra- and extra-uterine development.<sup>17</sup> The pregnancy itself seems to increase the risk of CT colonization and alter immune response. It may also influence the clinical manifestations of disease in pregnant women.<sup>18,19</sup> In the United States, 2% to 13.7% of pregnant women are carriers of CT.<sup>18-22</sup> In Brazil some studies have shown prevalence rates of between 2.7% and 10%.<sup>2,10,23</sup> In this group, CT has been associated with an increased risk of preterm delivery, spontaneous abortion,<sup>24</sup> low birth weight, premature rupture of membranes (PROM) and perinatal mortality.<sup>25,26</sup> Moreover, children of mothers with CT

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may be infected during passage through the birth canal, developing conjunctivitis and pneumonia.<sup>27</sup>

That being said, studies conducted in pregnant women infected with CT show conflicting results regarding the risk of these events. Knowledge concerning the impact of infection in this group can improve counseling and treatment of infected pregnant women as a public health measure.

The objective of this meta-analysis was to evaluate perinatal morbidity associated with CT infection, determining the risk of preterm labor (PTL), PROM, low birth weight, perinatal mortality, endometritis and abortion.

## MATERIAL AND METHODS

Studies were selected through systematic review to determine the risk of perinatal morbidity and mortality associated with CT infection, and classified according to the outcomes: PTL (labor occurring before 37 weeks gestation), PROM, low birth weight (full term newborn weighing less than 2500 grams), perinatal mortality (mortality occurring between 20 weeks of gestation until 28 days after birth), endometritis (infection of the endometrium or decidua) and abortion (expulsion or fetal death before 20 weeks gestation). Searches were conducted on electronic databases such as PubMed, Embase, Lilacs, Cochrane, and Google Scholar. Manual searches were also conducted through gynecology journals and the bibliographies of reviewed articles.

The first part of the study involved examining major electronic databases. Results were acquired searching by keyword and specific descriptors determined by the database criteria, and combined to increase the sensitivity of the search for articles on the assessment of risk associated to CT infection in pregnancy (Box 1).

Articles were selected by means of eligibility criteria. To be included, a cohort study or case control study needed to be carried out on pregnant women diagnosed with CT during pregnancy who underwent medical follow-up

before and after childbirth. Publications from January 1980 to January 2010 were considered in English, Portuguese, Spanish or French. Articles were only included following the evaluation and agreement of two reviewers.

The Newcastle-Ottawascale was used to assess the methodological quality of studies. This scale varies between zero and nine points: studies with a score equal to or higher than six were considered methodologically sound.

Data collection of the primary studies was made using the appropriate instrument (the Newcastle scale) in order to obtain a summary measure flow chart. After calculating relative risk using the Mantel-Haenszel with a confidence interval of 95%, tabulation and interpretation of results ensued.

## RESULTS

After a manual search of the databases, 2695 articles were collected. Of these, 2550 articles were excluded when the titles and abstracts were not found to meet eligibility criteria (Box 1).

Among the 145 remaining items, the 12 selected had a score equal to or greater than 6 on the Newcastle-Ottawa scale (Table 1). The selected articles are risk assessment studies, carried out in populations of pregnant women who sought care in prenatal clinics at least until the end of the pregnancy. The diagnostic methods used included culture, molecular biology tests and/or IgM antibodies (Table 1).

CT prevalence ranged from 2.4% to 35.9%, depending on the characteristics of the population studied and the diagnostic methods used (Table 1). It was observed that CT infection during pregnancy increased the risk of PTL 1.51 [1.27, 1.80]. The test for heterogeneity was found to be significant when all items were considered in the evaluation. The analysis of funnel plot items from Gravett et al.,<sup>28</sup> Jain et al.<sup>29</sup> and Martin et al.<sup>30</sup> were removed for statistical re-evaluation, and as a result the relative risk (RR) decreased to 1:35 [1.11, 1.63] while heterogeneity lost its significance ( $p = 0.07$ ). (Table 2). The RR of CT infection and PROM was 1.13 [0.95 1:34] and the studies were found to be homogeneous for meta-analysis (heterogeneity  $p = 0.10$ ). Similar results were found with low birth weight, RR = 1.52 [1.24, 1.87], among the studies considered homogeneous for evaluation ( $p = 0.1$ ) (Table 2). Perinatal mortality was found to have a RR of 2.44 [1.63, 3.68], and items were shown to be heterogeneous ( $p = 0.02$ ). Following the evaluation of the funnel plot, the studies by Jain et al.<sup>29</sup> and Martin et al.<sup>30</sup> were removed, since their RR was 1.84 [1.15, 2.94]  $p = 1.0$ . (Figure 1).

Regarding endometritis and abortion, no significant correlation with CT in pregnancy was found, RR = 1.20 [0.65, 2.20] and RR = 0.89 [0.49, 1.61] respectively. Few studies of good quality have addressed such outcomes (Box 1).

### 2695 articles identified in electronic databases and manual search

2550 articles excluded after assessment of titles and abstracts

### 145 articles with full text assessment

77 excluded articles (did not present adequate study design - cohort or case control)

### 68 articles with full text assessment

56 excluded articles (did not meet the selection criteria)

### 13 articles

Loss = 1

### 12 articles

**Box 1:** Article selection process from the search to the quality assessment.

**Table 1. Characteristics of risk assessment studies included in meta-analysis**

Autor	Design	Local	Exclusion criteria	n	Loss	Time (months)	Diagnostic method	P ( <i>Chlamydia trachomatis</i> ) score	Newcastle-Ottawa
Andrews et al. <sup>20</sup>	Cohort nested trial	EUA	Pregnants (16 to 23) weeks	2570	214	12	LCR	9.9% (238/2398)	8
Berman et al. <sup>31</sup>	Retrospective cohort	India	Pregnants < 24 weeks	1203	104	36	Culture	22% (251/1152)	8
Blas et al. <sup>13</sup>	Retrospective cohort	EUA	Pregnants	4255	425*	12	PCR	-	7
Gravett et al. <sup>28</sup>	Prospective cohort	EUA	Pregnants 2-3 trimester	582	28	5	Culture	9% (47/534)	6
Harrison et al. <sup>32</sup>	Prospective cohort	EUA	< 32 weeks	1365	180	18	Culture	8% ( 94 /1185)	7
Jain et al. <sup>29</sup>	Case-control	India	Pregnants 3 <sup>rd</sup> trimester to labor	78	18	3	IgM	35.9% (28/78)	6
Kirk et al. <sup>17</sup>	Prospective cohort	London	Pregnants < 14 weeks	1101	295	4	Vaginal PCR	2.2% (18/806)	6
Kovacs et al. <sup>33</sup>	Prospective cohort	Hungary	Pregnants	6161		18	Gen probe	5.75% (362 /6161)	7
Martin et al. <sup>30</sup>	Prospective cohort	EUA	Pregnants < 19 weeks	304	36	12	Culture	6.7% (18/268)	7
Oakeshott et al. <sup>34</sup>	Prospective cohort	England cohort	Pregnants < 14 weeks	1216	15	24	PCR	2.4% (19/1214)	7
Silveira et al. <sup>35</sup>	Retrospective cohort	EUA	Pregnants > 20 weeks	2127	9	31	PCR	4.7%	6
Yu et al. <sup>36</sup>	Prospective cohort	China	Pregnants	300	0	10	PCR	11% (33/300)	7

n, number of subjects; loss, loss to follow-up; P, prevalence.

\* loss of approximately 10%.

## DISCUSSION

CT genital infection is considered a potential risk factor for perinatal complications and has been the subject of numerous studies in recent decades. In this review, risk of PTL was found to be associated with CT infection, with a measure of RR of 1.51 [1.27, 1.80]. A more conservative assessment including only articles considered statistically homogeneous lowered the risk, RR = 1.35 [1.11, 1.63], even though this assessment showed the highest risk of PTL delivery for pregnant women infected with CT. Blas et al. study<sup>13</sup> was significant to this review due to sample size and confirmed this association as also seen in smaller studies.<sup>20,28,30,32,35</sup> Studies suggest that treatment of CT in-

fection reduces the morbidity of pregnancy. However data from Andrews et al.<sup>20</sup> do not confirm this fact, suggesting that gestational age at treatment and re-infection may also influence perinatal morbidity.<sup>37</sup>

Similarly, PROM was also more common in pregnant women infected with CT, OR = 1.13 [0.95, 1.34]. However since the confidence interval includes the null value, the fact that CT infection increases the risk of PROM could not be confirmed. Kovacs et al. study,<sup>33</sup> which was the most significant among the included, showed no significant difference in the association between CT infection and PROM.<sup>13,28,33,36</sup> There is evidence that timely treatment of CT during antenatal care can significantly decrease the risk of PROM. That

**Table 2. Summary estimates of selected studies for association between Chlamydia infection and perinatal morbidity, according to the outcomes**

2.1 Preterm labor								
Study	Experimental		Control		Weight	Risk ratio		Risk ratio M-H, fixed, 95% CI
	Events	Total	Events	Total		M-H, fixed, 95% CI	M-H, fixed, 95% CI	
Andrews et al. <sup>20</sup>	24	233	191	2123	25.3%	1.14 (0.77, 1.71)		
Blas et al. <sup>13</sup>	76	735	181	2972	48.2%	1.70 (1.32, 2.19)		
Gravett et al. <sup>28</sup>	17	47	64	535	0.0%	3.02 (1.94, 4.71)		
Harrison et al. <sup>32</sup>	8	48	100	558	10.6%	0.93 (0.48, 1.79)		
Jain et al. <sup>32</sup>	2	21	0	39	0.0%	9.09 (0.46, 181.04)		
Martin et al. <sup>30</sup>	5	18	15	250	0.0%	4.63 (1.90, 11.30)		
Silveira et al. <sup>35</sup>	11	97	254	1988	15.9%	0.89 (0.50, 1.57)		
Total (95% CI)	1113		7641		100.0%	1.35 (1.11, 1.63)		
Total events	119		726					
Heterogeneity: $\text{Ch}^2 = 7.07$ , $\text{df} = 3$ ( $p = 0.07$ ); $I^2 = 58\%$ Test for overall effect: $Z = 3.06$ ( $p = 0.002$ )							0.1 0.2 0.5	2 5 10
							Experimental	Control

2.2 Premature rupture of membrans								
Study	Experimental		Control		Weight	Risk ratio		Risk ratio M-H, fixed, 95% CI
	Events	Total	Events	Total		M-H, fixed, 95% CI	M-H, fixed, 95% CI	
Blas et al. <sup>13</sup>	49	839	130	3378	27.1%	1.50 (1.09, 2.06)		
Gravett et al. <sup>28</sup>	11	47	54	487	0.0%	2.11 (1.94, 3.75)		
Harrison et al. <sup>32</sup>	4	39	50	447	4.2%	0.92 (0.35, 2.41)		
Kovacs et al. <sup>33</sup>	70	352	1162	5809	68.8%	0.99 (0.80, 1.23)		
Yu et al. <sup>36</sup>	10	33	33	267	0.0%	2.45 (1.33, 4.50)		
Total (95% CI)	1240		9634		100.0%	1.13 (0.95, 1.34)		
Total events	123		1342					
Heterogeneity: $\text{Ch}^2 = 7.07$ ; $\text{df} = 3$ ( $p = 0.07$ ); $I^2 = 56\%$ Test for overall effect: $Z = 1.34$ ( $p = 0.18$ )							0.01 0.1	10 100
							Experimental	Control

2.3 Low birth weigh								
Study	Experimental		Control		Weight	Risk ratio		Risk ratio M-H, fixed, 95% CI
	Events	Total	Events	Total		M-H, fixed, 95% CI	M-H, fixed, 95% CI	
Berman et al. <sup>31</sup>	11	149	37	2123	25.3%	1.34 (0.70, 2.57)		
Blas et al. <sup>13</sup>	40	848	114	2972	48.2%	1.41 (0.99, 2.00)		
Gravett et al. <sup>28</sup>	15	47	73	535	0.0%	2.12 (1.33, 3.38)		
Harrison et al. <sup>32</sup>	4	39	51	558	10.6%	1.03 (0.39, 2.79)		
Jain et al. <sup>29</sup>	6	21	1	38	0.6%	10.86 (1.40, 84.24)		
Kovacs et al. <sup>33</sup>	24	359	303	5802	30.0%	1.28 (0.86, 1.91)		
Martin et al. <sup>30</sup>	5	18	19	238	2.3%	3.48 (1.47, 8.23)		
Total (95% CI)	1481		11141		100.0%	1.52 (1.24, 1.87)		
Total events	105		598					
Heterogeneity: $\text{Ch}^2 = 10.69$ ; $\text{df} = 6$ ( $p = 0.10$ ); $I^2 = 44\%$ Test for overall effect: $Z = 3.06$ ( $p < 0.0001$ )							0.01 0.1	10 100
							Experimental	Control

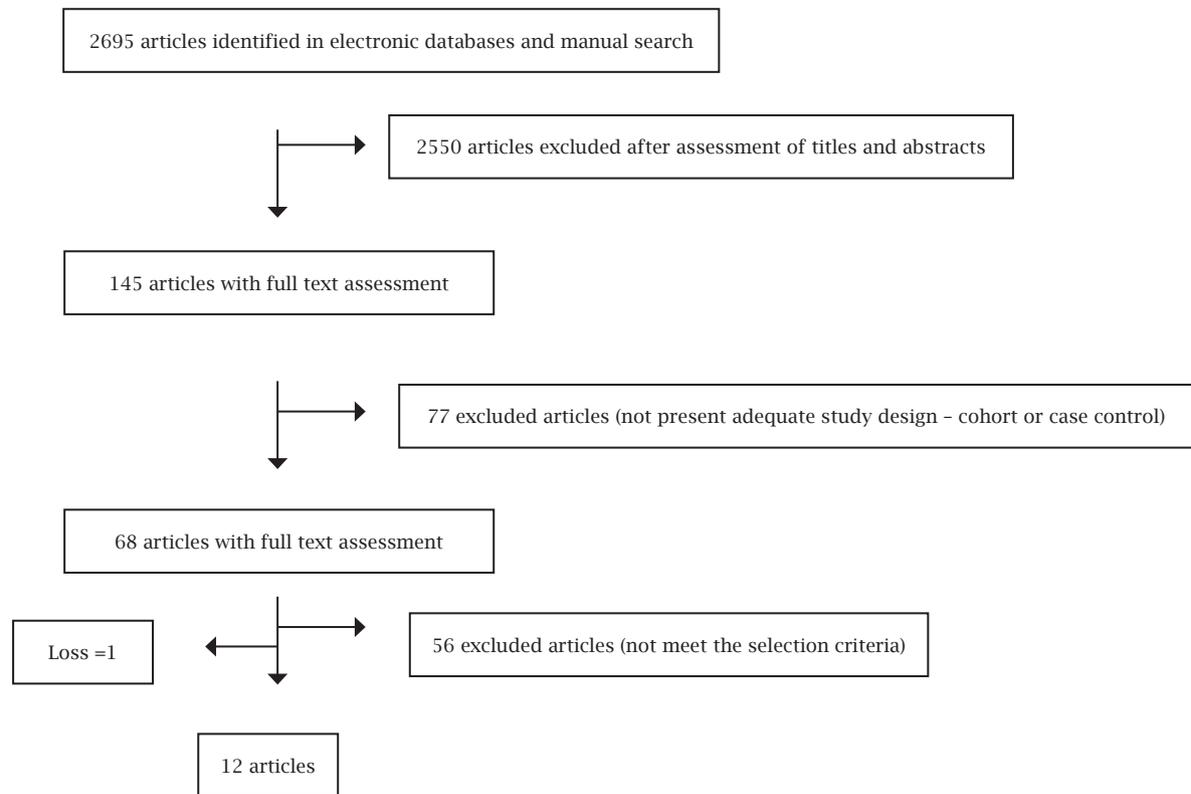
cont.

**Table 2. Summary estimates of selected studies for association between Chlamydia infection and perinatal morbidity, according to the outcomes (Cont.)**

2.4 Perinatal mortality									
Study	Experimental		Control		Weight	Risk ratio		Risk ratio	
	Events	Total	Events	Total		M-H, fixed, 95% CI	M-H, fixed, 95% CI		
Blas et al. <sup>13</sup>	7	851	15	3304	28.0%	1.87 (0.76, 4.56)			
Harrison et al. <sup>32</sup>	0	37	3	430	2.6%	1.62 (0.09, 30.79)			
Jain et al. <sup>29</sup>	3	21	0	39	1.7%	12.73 (0.69, 235.31)			
Kovacs et al. <sup>33</sup>	13	349	118	5799	62.6%	1.83 (1.04, 3.21)			
Martin et al. <sup>30</sup>	6	18	8	246	5.1%	10.25 (3.99, 26.35)			
Total (95% CI)	1276		9918		100.0%	2.44 (1.63, 3.68)			
Total events	29		144						
Heterogeneity: $\text{Ch}^2 = 11.52$ ; $\text{df} = 4$ ( $p = 0.02$ ); $I^2 = 65\%$ Test for overall effect: $Z = 4.29$ ( $p < 0.0001$ )								0.01 01	10 100
								Experimental	Control

2.5 Endometritis									
Study	Experimental		Control		Weight	Risk ratio		Risk ratio	
	Events	Total	Events	Total		M-H, fixed, 95% CI	M-H, fixed, 95% CI		
Berman et al. <sup>31</sup>	11	229	30	800	76.9%	1.28 (0.65, 2.52)			
Harrison et al. <sup>32</sup>	2	76	25	869	23.1%	0.91 (0.22, 3.79)			
Total (95% CI)	305		1669		100.0%	1.20 (0.65, 2.20)			
Total events	13		55						
Heterogeneity: $\text{Ch}^2 = 0.18$ ; $\text{df} = 1$ ( $p = 0.67$ ); $I^2 = 0\%$ Test for overall effect: $Z = 0.58$ ( $p = 0.56$ )								0.01 0.1	10 100
								Experimental	Control

2.6 Abortion									
Study	Experimental		Control		Weight	Risk ratio		Risk ratio	
	Events	Total	Events	Total		M-H, fixed, 95% CI	M-H, fixed, 95% CI		
Harrison et al. <sup>32</sup>	3	32	21	353	17.2%	1.58 (0.50, 5.00)			
Kirk et al. <sup>17</sup>	5	16	235	782	46.3%	1.04 (0.50, 2.17)			
Martin et al. <sup>30</sup>	0	18	12	259	8.4%	0.55 (0.03, 8.89)			
Oakeshott et al. <sup>34</sup>	1	29	120	1185	28.2%	0.34 (0.05, 2.35)			
Total (95% CI)	95		2579		100.0%	0.89 (0.49, 1.61)			
Total events	9		388						
Heterogeneity: $\text{Ch}^2 = 2.17$ ; $\text{df} = 3$ ( $p = 0.54$ ); $I^2 = 0\%$ Test for overall effect: $Z = 0.37$ ( $p = 0.17$ )								0.01 0.1	10 100
								Experimental	Control



**Figure 1:** Process used in the selection of articles from the search to the quality assessment.

being said, the effectiveness of treatment during pregnancy is 97% (92.9-99.2) using azithromycin, 95% (76.2-99.9) with amoxicillin and 64% (44.1-81.4) with erythromycin. Such antibiotics are considered safe for use during the prenatal period.<sup>38</sup>

Pregnant women with CT infection also increased the risk of low birth weight, RR = 1.52 [1.24, 1.87]. All items involved in this review demonstrated an increased risk of CT infection during pregnancy, a fact statistically reinforced after the effect of the summary measure. Despite the fact that low birth weight may be brought about by several other causes, this data suggest that early diagnosis and treatment of CT infection during pregnancy can minimize the occurrence.<sup>13,29,30,32,33</sup> However, even with appropriate treatment, 10-20% of infections persist or recur during the prenatal period, contributing to the emergence of adverse events in pregnancy even with appropriate treatment. Thus, follow-up tests may be needed to monitor infection.<sup>37</sup>

The rate of perinatal mortality, defined as a death from 20 weeks gestation until 28 days after birth, was significantly higher in pregnant women with CT infection, with a risk of 1.84 [1.15, 2.94]. All articles showed increased risk, which supported the statistical significance after the summary measure and analysis of heterogeneity.<sup>13,29,30,32,33</sup>

With regard to abortion and endometritis associated with CT, summary measure did not show significant increased risk. Few papers have studied these factors and have shown opposing results. CT infection is highly prevalent among pregnant women. It can be assumed that studies with high methodological quality associated CT infection with an increased risk of prematurity, low birth weight and perinatal mortality. The publication of new studies could possibly strengthen the link being suggested in current studies. The significance of screening for this infection in pregnant women should be considered, especially when dealing with younger populations and risk factors for STDs. Thus, randomized clinical trials in treatment of CT infection in pregnant women are needed to evaluate the possibility of reducing this risk.

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