UK National Screening Committee Policy Review

Chlamydia screening in pregnancy: an evidence review

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1. Introduction

Genital *Chlamydia trachomatis* is the most common sexually transmitted infection (STI). Between 70% and 90% of women and 50-70% of men with genital *C. trachomatis* (subsequently referred to as chlamydia) have asymptomatic infection. Treatment of chlamydia infection with antibiotics is effective, although reinfection rates appear to be high, particularly among young women (1;2).

In England, the National Chlamydia Screening Programme (NCSP) was established in 2003 with an opportunistic screening strategy of offering tests to all sexually active women and men aged 25 years or less across a range of health care settings. The aims were to control high rates of chlamydia infection in this age group through the early detection and treatment of asymptomatic infection and to prevent the development of sequelae and reduce onward disease transmission (http://www.chlamydiascreening.nhs.uk). The reproductive sequelae of chronic infection in women can include pelvic inflammatory disease (PID), caused by ascending infection in the genital tract, together with ectopic pregnancy and tubal factor infertility (3-6). However, the probabilities of a woman with untreated chlamydia infection going on to develop chronic reproductive problems are not well understood. In the recent POPI (Prevention of Pelvic Infection) trial, PID incidence was considerably lower than previously estimated (1.6% overall) and although the risk of clinical PID was reduced by 35% in women receiving chlamydia screening and treatment compared with controls (deferred screening), this was not statistically significant (7); of note, nearly 80% of PID cases overall occurred in women negative for chlamydia at baseline, highlighting the importance of incident infections (7;8).

Recent guidance from the National Institute of Health and Clinical Excellence (NICE) in the 2008 Routine Antenatal Care Guideline includes the recommendation that chlamydia screening should not be offered as part of routine antenatal care but that health care professionals should inform pregnant women aged less than 25 years about the high prevalence of chlamydia in their age group and provide information on their local NCSP (9)

The main justification for introduction of an antenatal screening programme for an infection is to prevent any adverse pregnancy outcomes caused by the infection and to reduce the risk of infants becoming infected and developing associated morbidities; there may also be indirect benefits for the woman. The main aims of the NCSP are reduction of the incidence of sexually transmitted Chlamydia infection and the related sexual and reproductive health morbidities such as infertility and ectopic pregnancy. This review addresses a range of issues relating to chlamydia infection in pregnancy and focuses on its consequences for the index pregnancy and the newborn.

2. Is *Chlamydia trachomatis* an important health problem?

2.1 Population prevalence

Large-scale population based studies of chlamydia are sparce and its prevalence in the general sexually active population uncertain; however, available data suggest that prevalence in men and women aged 15-24 years in Europe and the USA is 1-6% (10-13).

In the UK an estimated 217,570 new diagnoses of chlamydia made in genitourinary medicine clinics and community settings in 2009 were reported, including 130,333among females (13). In the Chlamydia Screening Studies (ClaSS) prevalence study, which involved active screening of 16-39 year olds randomly sampled from general practices in the Birmingham and Bristol areas in 2001-2002, estimated chlamydia prevalence was 3.2% (95% CI 2.8-4.2%) overall (3); among women, prevalence declined with increasing age, from 6.2% among those aged 16-19 years and 20-24 years, to 3.3% among those aged 25-29 years and 0.4% among those aged 26-39 years. Recent data reported to the NCSP for the period April 2009 to December 2009 indicated that, among females aged less than 25 years in England (all testing venues) the screen positive rate was 6.7%, this ranged from 2.8% in education venues to 9.2% in Contraceptive and Sexual Health Services (14). In the POPI trial, which took place in London, the study population (n=2529) were female, aged less than 28 years, not pregnant and sexually active: chlamydia prevalence was 5.4% and 5.9% in the intervention and control (deferred screening) groups respectively at baseline (7).

Higher prevalence of chlamydia among young people has been reported in numerous studies, with the peak age group for infection in women being 16-19 years (3). Other groups of women identified with higher chlamydia prevalence include those with other STIs, some ethnic groups and single women, reflecting factors such as sexual behaviours including higher rates of unprotected sexual intercourse, of concurrent partnerships and of sexual partner change, health-seeking behaviours and access to health care (3;15;16;17). In the ClaSS study, chlamydia infection was associated with the number of new sexual partners in the past year; individuals with one new partner had a 2.6-fold increased risk of infection compared with no new partner, increasing to a 4.2-fold increased risk for those with two new partners (3).

2.2 Chlamydia prevalence in pregnant women

There are limited data on prevalence of chlamydia in pregnant women and reported rates vary widely across settings, ranging from 2% to 26% (Table 1). In a systematic review and analysis of UK-based chlamydia prevalence studies published up to mid 2002, mixed effect models and meta-analysis techniques were used to obtain estimated prevalence across different populations and age groups (18). Prevalence was highest in genitourinary medicine (GUM) clinics and in the youngest age groups, e.g. an estimated 17% in women aged less than 20 years in GUM clinics. The crude overall mean prevalence in antenatal clinics was 8.5% (95% CI 6.6-10.6) overall (n=803), which is substantially higher than more recent reports from the UK, which have indicated chlamydia prevalence of around 2% (Table 1).

Several of the UK-based antenatal studies have provided age-stratified chlamydia prevalence and findings have been consistent with the non-pregnant population, with the highest prevalence seen in the youngest age groups (Table 2). Of note, the studies by Oakeshott et al and Kirk et al were among women in the first trimester of pregnancy; although the study by Oakeshott et al was community-based, the study of Kirk and colleagues was based on an unselected population of women attending an Early Pregnancy Unit and thus may not be representative of the general antenatal population (16;19).

Table 1: Results from chlamydia prevalence studies in pregnant women

Setting	N screened	Chlamydia prevalence (%)	Reference
Australia	420	2.7% overall; 9.1% in indigenous population	(20)
Australia	239	3.3% overall (95%CI 1.1-5.6) 9.4% in <25 year olds (95% CI 2.2-16.5)	(21)
Australia	1044	3.2% (95% CI 1.8-5.9) in 16 – 25 year olds	(22)
Brazil	3003	9.4% (median age 24 years)	(23)
China	504	10.1%	(24)
Congo	529	1.7%	(25)
Finland	8000	10.6% (<23 years) 12.5% (23-28 years)	(26)
Germany	31856 18169	3.26% (cervical swabs) 2.93 (urine samples)	(27)
Ghana	261	3.4%	(28)
Ireland	945[1]	3.7%	(29)
Mongolia	2000	19.3%	(30)
Mozambique	~1000	4.1%	(31)
Pacific Region	1618	26.1% in <25 year olds 11.9% in ≥25 year olds	(32)
Thailand	182	10%	(33)
United Kingdom	1214	2.4% (95% CI 1.5 – 3.3)	(16)
United Kingdom	806	2.2% (95% CI 1.4 – 3.5)[2]	(19)
United Kingdom	511	1.96% (95% CI 0.9 – 3.6)[2]	(34)
USA	1587	2.0%	(35)
USA (New Orleans)	752	17.8%	(36)

[1] 83% pregnant women, 10% female infertility clinic attenders, 7% female family planning clinic attenders

[2] unselected population from Early Pregnancy Unit (reasons for attendance include vaginal bleeding, pain, anxiety and uncertain dates)

Table 2

Estimated chlamydia prevalence in antenatal populations in the UK, stratified by age group

Age group	Adams et al 2004 (18)		Oakeshott et al 2002 (16)	Kirk et al 2008 (19)
	Estimates from logistic regression model in meta-analysis	Estimated prevalence from meta-analysis	GP and FP clinics in London, women <10 weeks gestation, 1998-2000	Early Pregnancy Unit in London, women <15 weeks gestation, 2004
<20 years	12.6 (95% CI 6.4-23.2)	13.5 (95% CI 9.5-19.1)	14.3 (95% CI 3.7-24.9)	7.5 (95% CI 2.6-19.9)
20-24 years	8.3 (95% CI 4.2-15.7)	6.5 (95% CI 3.5-10.4)	6.4 (95% CI 2.6-12.7)	9.1 (95% CI 5.0–15.9)
25-29 years	4.1 (95% CI 2.0-8.2)	7.2 (95% CI 2.4-14.2)	-	0.7 (95% CI 0.1–3.6)
≥25 years	-	-	1.5 (95% CI 0.9-2.4)	-
≥30 years	2.2 (95% CI 1.1-4.6)	0.0 (95% CI 1.2-1.2)	-	-
30-34 years	-	-	-	1.5 (95% CI 0.6–3.7)
≥35 years	-	-	-	0.0 (95% CI 0.0–1.6)

Age-stratified data for antenatal prevalence of chlamydia in a recent German study showed broad comparability with UK data. Among more than 50,000 pregnant women, prevalence was generally slightly lower among women tested on the basis of urine samples compared with cervical swabs (both estimates provided for urine and cervical samples respectively): 10.9% and 10.2% among pregnant women aged 20 years or less, 4.5% and 5.7% among those aged 21-25, 1.6% and 2.3% among those aged 26-30, 0.9% and 1.8% among those aged 31-35, 0.7% and 1.3% among those aged 35-39 and 0.4% and 0.8% among those aged 40 or older (27). High prevalence of chlamydia has been reported in studies specifically focussed on pregnant adolescents and young women, including a rate of 13% among 107 African American pregnant adolescent girls in the USA (37) and 13.7% among 212 pregnant young women aged less than 20 years in Australia (38).

Few data on time trends in chlamydia prevalence in the antenatal population are available, and none from the UK. In a large Finnish study with retrospective testing of stored serum samples from the Finnish Maternity Cohort taken between 1983 and 2003, a decreasing chlamydia seroprevalence among pregnant women over calendar time was found: for women aged <23 years prevalence halved, decreasing from 20.8% in 1983-1989 to 10.6% in 1997-2003, with declines also seen among 23 to 28 year olds (from 19.1% to 12.5%) (26); however this in the context of increasing numbers of diagnosed chlamydia infections reported nationally and no chlamydia screening programme in Finland.

Prevalence of chlamydia has been investigated in specific groups of pregnant women. Among women seeking a pregnancy termination, rates of 15.7% have been reported from Denmark (39), 4.4% in legal residents and 13% in undocumented migrants in Switzerland (40) and 5.0% from Norway (41). In the UK, in a large study of nearly 1000 women undergoing a termination of pregnancy there was a chlamydia prevalence of 8.5% (95% CI 7.6-10.5) (17). In a study in the USA, chlamydia prevalence was 12% among nearly 1500 women attending family planning services for pregnancy testing overall (median age 22 years); 64% were pregnant and no difference in chlamydia infection rate was seen by pregnancy status (42).

Chlamydia rates have also been reported from pregnant women seeking care from sexual health services: in one study in Baltimore, USA, 9.9% of pregnant women (half of whom knew of their pregnancy at presentation) had chlamydia compared with 7.7% of non-pregnant women (matched for clinic and year) in 1996-2002 (43). Although data from such studies provide important information on rates and risks of chlamydia infection in specific populations, they should not be used to extrapolate to the general antenatal population.

2.3 Consequences of perinatally-acquired chlamydia infection in infants

It is difficult to estimate the burden of neonatal infection with chlamydia as infected infants are usually asymptomatic and the most common manifestations of neonatal chlamydia (conjunctivitis and pneumonia) are non-specific. Furthermore, chlamydial disease in newborns is normally of a mild-to-moderate nature and easily treated (see sections 3.3 and 4.3). In the UK, ophthalmia neonatorum (conjunctival infection presenting in the first 28 days of life, usually applied to infections caused by chlamydia or *N.gonorrhea*) was a notifiable disease until 2010. The Health Protection Agency (HPA) reported a total of 85 cases in England and Wales in 2004, 87 in 2005 and 100 in 2006. However, these figures are likely to be under-estimates. A recent study in Leeds demonstrated considerable under-notification of ophthalmia neonatorum, with only around one in five cases (based on positive laboratory samples) notified to the HPA (44). Although chlamydia is the primary cause of ophthalmia neonatorum, the fact that it is not specific to chlamydial infection and the problem of under-notification makes it difficult to interpret HPA data.

Chlamydia is understood to be a major cause of neonatal conjunctivitis, although robust supportive population-based data are lacking, partly reflecting the fact that most infants with conjunctivitis are managed within the primary care setting. In a recent prospective study in the Netherlands (where there is no policy for antenatal screening for chlamydia), 23 infants, median age one week, presenting to hospital with bacterial conjunctivitis were tested to determine the underlying pathogen, with 61% found to have chlamydia (45). These data are

based on a hospital population and thus biased towards severe or prolonged cases, as most infants with conjunctivitis would usually be treated in the primary care setting.

In a further, retrospective study from the same Dutch group, stored samples from infants aged less than six months who presented at hospital with respiratory tract infections were tested for chlamydia; 7% of infants were found to have chlamydia although it was not possible to determine whether this was the causative pathogen for the respiratory infection or a coincidental finding (46).

- Chlamydia is the most common STI affecting men and women in the UK. Signs of infection can include urethritis and cervicitis. The effects of chronic infection in women may include pelvic inflammatory disease which can result in infertility and ectopic pregnancy.
- The precise current epidemiological picture of chlamydia in the general antenatal population in the UK is incomplete, but it is estimated that overall antenatal prevalence of chlamydia is in the range of 2-4%
- Highest prevalence of chlamydia is found in the youngest age groups in both pregnant and non-pregnant women
- Although women aged <25 years have the highest chlamydia prevalence within the antenatal population (in range of 6 – 14%), they only contribute 25% of all national deliveries in England and Wales.
- As evidence is lacking on the burden of symptomatic chlamydial infection in neonates, it is not possible to determine whether or not neonatal chlamydial infection is an important public health problem in the UK

3. Is the natural history of the condition understood?

Although chlamydia infection in women is usually asymptomatic, among those with symptoms the most common manifestation is local mucosal inflammation associated with a discharge and urethritis, vaginitis and/or cervicitis. Approximately half of all women with chlamydia have the infection in both the cervix and the urethra, around a third in the cervix only and the remainder in the urethra only (47). Around one in five women with diagnosed and treated chlamydia are estimated to become reinfected within 10 months after initial treatment (2).

3.1. Pregnancy outcomes

There is a limited understanding of the potential mechanisms by which chlamydia might lead to adverse pregnancy outcomes, but these may include ascending infection in pregnancy resulting in premature rupture of membranes and chorioamnionitis (48). The impact of chlamydia on pregnancy outcome requires clarification, as current evidence is limited and conflicting. Although several studies have reported associations between chlamydia infection and adverse pregnancy outcomes, including spontaneous abortion, preterm delivery, premature rupture of membranes and low birth weight (49-51), no such associations have been described in other studies (52-53). In a prospective study involving more than 3000 pregnant women screened for chlamydia infection in late pregnancy, of whom 6% had chlamydia (based on chlamydial antigen detection), there was no effect of chlamydia infection on pregnancy outcome including preterm delivery (53). Many studies have been limited by small numbers, poorly described methods (especially regarding selection of the study population) and/or by a lack of adjustment for confounding factors (49;50;54;55). Women with chlamydia have been found to be at increased risk of being co-infected with other genital tract infections and of late attendance for antenatal care compared with women without chlamydia (56); both these factors are also associated with adverse pregnancy outcomes, highlighting the need for adjustment for confounding in analyses investigating chlamydia.

More recent studies investigating whether there is an association between adverse pregnancy outcomes and chlamydia are complicated by taking into account timing of chlamydia diagnosis and treatment and they vary in their ability to address these factors in the analyses. Additionally, several studies were not specifically designed to address this research question but have used stored samples and existing databases. In a nested case-control study within the Preterm Prediction Study (57), women with chlamydia in pregnancy were retrospectively identified through testing stored samples; although these women may have received chlamydia screening and treatment in pregnancy, treatment data were unavailable in the study database. A two-fold increased likelihood of preterm delivery associated with chlamydia infection detected on the sample taken at 24 weeks gestation (AOR 2.3 95% CI 1.01-4.78) was reported, adjusting for a large number of known risk factors for preterm delivery. Of note, although a two-fold increased risk of preterm delivery was reported, this only just achieved statistical significance. However, a subsequent study by the same authors had conflicting findings: this later study was another secondary analysis, involving retrospective chlamydia testing of stored urine samples from women participating in two concurrent randomised controlled trials (RCTs) of treatment for bacterial vaginosis or *Trichomonas vaginalis*, with sampling at randomisation (median 19 weeks gestation) and at a third trimester follow-up visit (median 26 weeks gestation). Overall prevalence of chlamydia was 10% in this selected population of women who had at least one other genital infection. Preterm delivery rates were 14% versus 13% for women with and without chlamydia infection at randomisation and 13% versus 11% respectively at follow-up; receipt of antibiotics effective against chlamydia in pregnancy was not associated with a lower rate of preterm delivery in women with or without positive chlamydia tests (58).

The role of chlamydia in preterm delivery was investigated in a recently published case-control study including 2127 pregnant women delivering between 2005 and 2008 in a single study site in the USA. Prevalence of chlamydia among cases (women who delivered before 37 weeks gestation) was 4.2% compared with 4.7% among controls. Adjusted analysis of risk factors for

preterm birth found no significant association with chlamydia, although data were not provided on the timing of diagnosis or treatment of chlamydia in the study population (59).

It has been suggested that women with acute chlamydia infection (as indicated by IgM seropositivity) may be at increased risk of adverse pregnancy outcomes than women with chlamydia who are IgM seronegative and women without chlamydia infection (52;60). However, in contrast, others have suggested that reinfection or persistent infection rather than acute infection is associated with increased risk of adverse reproductive outcomes (2).

3.2 Perinatal transmission

Transmission of chlamydia from an infected pregnant woman to her infant is thought to occur via exposure of the infant to infected maternal secretions during passage through the birth canal. There is very limited evidence suggesting that in utero transmission may also take place with several studies documenting infection in infants born to infected mothers who delivered by elective caesarean section with intact membranes (who have thus avoided exposure in the birth canal) (61-63). There is no evidence to support postnatal transmission from mother to infant.

There have been few prospective birth cohort studies of infants born to women with chlamydia infection and many have been limited by small numbers. Further limitations include a lack of follow-up of all infants of mothers identified with chlamydia, which introduces potential for bias. For example, Schachter et al followed up only 131 infants of 262 pregnant women with chlamydia (64). Vertical transmission rates reported in the literature range from 25-50% (61;62). Risk factors for vertical transmission of chlamydia have not been well elucidated, although higher rates of transmission (60-70%) among infants born vaginally to mothers with symptomatic infection (chlamydial cervicitis) have been reported (64;65), which may reflect higher chlamydial carriage.

3.3 Consequences for the infant

Manifestations of chlamydia infection in infants are usually easily recognised and treated. The most common complications are conjunctivitis and pneumonia. In a prospective cohort study of 174 infants born to mothers with chlamydial infection in the UK, Preece and colleagues found that 25% of infants had vertically acquired the infection. Of these, 44% had no symptoms, 40% had conjunctivitis, 7% conjunctivitis and pneumonia, 7% pneumonia only and 1% otitis media (62). In this cohort, which involved follow-up to age 24 weeks, in untreated children there was a gradual loss of chlamydial carriage over time.

Table 3 summarizes results on reported rates of chlamydial conjunctivitis from studies of infants born to mothers with confirmed chlamydia diagnosis (limited to those with study populations of more than 20 infants). These studies suggest that one in five to ten infants of infected mothers develop chlamydial conjunctivitis. Chlamydial conjunctivitis appears at 5-14 days postpartum (usually later than gonococcal conjunctivitis) and is usually mild, characterised by oedema and erythema of the eyelids, with a unilateral or bilateral watery discharge, which may become purulent. Corneal or conjunctival scars appear to be a very rare outcome (65).

The nasopharynx is the most common site of vertically acquired chlamydia. Nasopharyngeal chlamydia infection is usually asymptomatic although up to one in six infants of mothers with chlamydia are estimated to go on to develop pneumonia (Table 4). Chlamydial pneumonia has several characteristic features, including usual onset of symptoms at 3-12 weeks of age, with infants tending to be afebrile and presenting with tachypnoea and a distinctive cough. Some studies have reported considerable overlap between conjunctivitis and pneumonia in exposed infants, for example, Preece et al found that half of the infants with pneumonia also had conjunctivitis (62). In the absence of treatment, chlamydial pneumonia shows a gradual improvement over four to eight weeks (55).

Table 3: Rates of chlamydial conjunctivitis among infants born to mothers with chlamydia infection

	No. of infants with conjunctivitis over no. exposed	**%**	**95% CI**
Heggie et al 1981 (66)	20/95	21	13, 31
Hammerschlag et al 1982 (67)	12/60	20	11, 32
Schachter et al 1986 (64)	23/131	18	11, 25
Skejeldestad et al 1987 (68)	3/35	9	2, 23
Laga et al 1988 (69)	18/210	9	5, 13
Datta et al 1988 (70)	4/49	8	2, 20
Preece et al 1989 (62)	20/174	11	7, 17
Hammerschlag et al 1989 (71)	35/230	15	11, 20

Table 4 : Rates of chlamydial pneumonia among infants born to mothers with chlamydia infection

	No. of infants with pneumonia over no. exposed	**%**	**95% CI**
Heggie et al 1981 (66)	3/95	3	1, 9
Hammerschlag et al 1982 (67)	4/60	7	2, 16
Schachter et al 1986 (64)	21/131	16	10, 23
Skejeldestad et al 1987 (68)	0/35	0	10*
Datta et al 1988 (70)	3/49	6	1, 17
Preece et al 1989 (62)	6/174	3	1, 7

* one-sided 97.5% confidence limit

Webley and colleagues recently demonstrated that *C.trachomatis* as well as *C.pneumoniae* could be isolated using polymerase chain reaction (PCR) from bronchoalveolar lavage specimens from 182 children with severe persistent airway disease that was non-responsive to therapy; 52% of the children aged less than 2 years were PCR positive for *C.trachomatis*, decreasing with increasing age to 29% of those aged more than 15 years (72). This is the first study to suggest an association between *C.trachomatis* and chronic respiratory disease in childhood and confirmatory research is needed.

- Whether or not chlamydia directly causes adverse pregnancy outcomes remains uncertain
- A minority of infants born to women with chlamydia develop symptomatic disease (conjunctivitis and/or pneumonia)
- These conditions tend to have a characteristic presentation, are usually not severe and are treatable

4. Does early detection and treatment have benefit over later detection and treatment? Are treatments or interventions effective?

4.1 Treatment of chlamydia in pregnancy: background

Effective and low cost treatment for chlamydia in pregnancy is available and is based on use of specific antibiotics, as some commonly used for treatment of chlamydia outside pregnancy (including doxycycline and ofloxacin) are contraindicated in pregnancy. In the treatment of chlamydia in general, test of cure (ToC) is not recommended, but pregnancy is an exception

given the potential for exposure of the infant in cases where the infection did not respond to treatment, or where re-infection occurs.

Treatment of chlamydia in pregnancy is less straightforward than treatment outside pregnancy because the range of antibiotics is more limited. There is also potential for pregnancy to exacerbate the recognised problems of gastro-intestinal intolerance associated with some antibiotics recommended for use in pregnancy (e.g. erythromycin) which may increase the likelihood of non-completion of the regimen. In some studies, fewer than half of the pregnant women have adhered to their antibiotic regimen (73). In addition to the problem of adherence, it has been suggested that pregnancy-related haemodilution may partly explain the relatively high treatment failure rates seen in some studies (74). Resistance to macrolides (including azithromycin and erythromycin) appears to be rare.

Another factor requiring consideration when treating pregnant women is the impact of the drug on the developing fetus, particularly as erythromycin, amoxicillin and azithromycin all cross the placental barrier (75). A recent follow-up study of children whose mothers participated in the ORACLE II trial has highlighted the potential for long-term adverse events associated with exposure to antibiotics in utero. In the trial, erythromycin and/or amoxicillin-clavulanate (co-amoxiclav) was compared to placebo for women in spontaneous labour with intact membranes, with no improvement in neonatal morbidity or mortality found with use of either antibiotic (76). The follow-up study took place when the children had reached seven years of age and reported a significant increase in functional impairment in children exposed to erythromycin (with or without co-amoxiclav) (OR 1.18 95% CI 1.02-1.37); there was also an increased prevalence of cerebral palsy in children in either antibiotic arm compared with those in the placebo arm (77). Although these results cannot be easily extrapolated to the situation of antibiotic treatment of chlamydia in pregnancy, they highlight the potential for unexpected, long-term adverse events associated with in utero antibiotic exposure and the need for long-term safety data.

Only half of infants born to women with chlamydia are likely to acquire infection and fewer than half will develop symptoms associated with the infection. In a systematic antenatal screening programme for chlamydia, a substantial proportion of infants who would not be expected to develop any morbidity would be exposed in utero to antibiotics.

In a Cochrane review of 11 clinical trials of treatment of chlamydia in pregnancy published in 2000, amoxicillin was found to be as effective as erythromycin in terms of achieving a microbiological "cure" (78). In a recent meta-analysis of eight clinical trials involving 587 patients, "treatment success" (i.e. negative cultures for chlamydia DNA obtained 2–6 weeks after treatment completion) of azithromycin versus erythromycin did not differ, with treatment success rates of 72-93% for erythromycin or amoxicillin compared with 94-100% for azithromycin (intention to treat analysis); compliance to treatment across the eight trials ranged from 44% to 100% (73). In an observational cohort study of 277 pregnant women with chlamydia selected from a managed care organisation in the USA, initial treatment started at a median of 15 gestational weeks with 69% of women receiving azithromycin, 9% amoxicillin and 19% erythromycin. Negative ToC was used as a proxy for treatment effectiveness. Overall, 81% of women had ToC results available at least 7 days after treatment. A significantly higher proportion of women receiving azithromycin had a negative ToC than erythromycin (97.2% v 64.3%); 95.2% of women receiving amoxicillin had negative ToC which was also significantly more than among the women on erythromycin (79).

Azithromycin has a long-half life allowing single dosing which, together with the lower incidence of gastrointestinal side effects compared with erythromycin, makes it a potentially attractive choice for treatment of chlamydia in pregnancy. Initially azithromycin was substantially more expensive than erythromycin or amoxicillin (three to eight times more), but the availability of generic azithromycin has now reduced costs (80). Although azithromycin is recommend by WHO for use in pregnancy, the British National Formulary only recommend use of azithromycin in pregnancy if no alternative is available, on the basis of the lack of adequate and well-controlled safety studies in pregnant women.

Recommended regimens for treatment of chlamydia in pregnancy (Grade A recommendation)

(BAASH 2006)

- Erythromycin 500mg four times a day for 7 days

or

- Erythromycin 500 mg twice a day for 14 days

or

- Amoxicillin 500 mg three times a day for 7 days

or

- Azithromycin 1 gm stat

4.2 Impact of maternal treatment on pregnancy or infant outcomes

There is very limited evidence to demonstrate a beneficial impact of antenatal chlamydia screening and treatment on pregnancy outcomes. In a double-blind placebo-controlled trial of erythromycin treatment of chlamydia in pregnant women in the USA, women with endocervical cultures positive for chlamydia and who had successfully completed a 7 day "placebo run-in" were randomised at 23 to 29 gestational weeks (74). Treatment (with erythromycin 333mg three times daily) continued until completion of the 35th week of pregnancy, to cover reinfections. Overall, there was no statistically significant difference in rates of adverse pregnancy outcomes between arms, with 8% versus 11% in the treatment versus placebo arm having low birth weight infants, 13% versus 15% preterm delivery (<37 weeks) and 3% versus 4% PROM. Adherence data (by pill count) were available for most women, with no significant difference between arms (23% in the treatment arm and 16% in the placebo arm took less than two-thirds of their pills). Mid-study cultures were performed 2-4 weeks after randomisation for an unselected sub-group of women. Results from these cultures indicated a high treatment failure rate in the treated women (20%) and a relatively low persistence of chlamydia in the placebo arm (37% had negative cultures at this time), which could not be completely explained by use of non-study antibiotics.

In a retrospective study in the USA, although the prevalence of PROM and of small for gestational age (SGA) infants were significantly lower among pregnant women successfully treated for chlamydia with erythromycin (7 days) compared with pregnant women receiving the same treatment but who remained infected at the end of pregnancy (7% versus 20% for PROM and 13% versus 25% for SGA), there was no statistically significant difference when comparing the former group with chlamydia-uninfected matched controls. The prevalence of preterm delivery was 3% in the chlamydia-positive women successfully treated, 14% in those with treatment failure and 12% in control women (81).

In a single-site observational study in the USA, Ryan et al used women with untreated chlamydia (n=1110) cared for before the establishment of an antenatal chlamydia screening and treatment programme as historical controls in an investigation of the impact of erythromycin for 7 days on pregnancy outcomes in women with chlamydia (n=1323). In unadjusted analysis there was a significantly higher rate of PROM and low birth weight among the historical controls than among the women successfully treated (6% versus 3% and 20% versus 11% respectively). In adjusted analysis, treatment remained significantly associated with a decreased risk of PROM. No statistically significant difference in perinatal mortality between the two groups was found (82). In contrast, in a more recent small prospective study of women with chlamydial cervicitis, there was no significant difference in PROM or preterm delivery between women with chlamydia who received erythromycin treatment for one week (n=23) and 58 infected women who remained untreated (of note, these women were participants in a diagnostic accuracy study and had false negative antigen detection tests but were culture positive, with their clinicians blinded to culture results – hence the lack of treatment); in addition, no difference in conjunctivitis or pneumonia was seen by treatment group (83), although statistical power was limited due to the small sample sizes.
In another observational study, involving 184 women with chlamydia and their infants (32 women who refused treatment and 152 treated with erythromycin at 36 weeks gestation), 12% of the 24 infants of untreated mothers with follow-up had chlamydial infection compared with 7% of the 59 infants of treated mothers, a significant difference (64). This observational

study is limited by the fact that no infant follow-up was available for nearly a third of treated women. Furthermore, the finding that 7% of infants of treated women developed infection indicates that the strategy of treatment with erythromycin at 36 weeks is only partially successful.

First trimester screening (at booking) is recommended by the US guidelines, with repeat testing recommended in the third trimester for women with positive first trimester tests and for those women with new or multiple sexual partners. A recent, population-based study in Washington State, USA used data on maternal chlamydia status routinely recorded on birth certificates, although information on maternal treatment was lacking; women who were diagnosed with chlamydia in pregnancy and thus had the opportunity for treatment (although receipt of antibiotics could not be confirmed) remained at higher risk of preterm delivery (RR 1.50 95%CI 1.03-2.17) and PROM (RR 1.50 95%CI 1.03-2.17) compared with women without chlamydia (56). Such findings provide additional, although indirect, evidence that antenatal screening for chlamydia does not necessarily result in improved pregnancy outcomes

Recent studies have also demonstrated that neonatal chlamydial conjunctivitis and pneumonitis continue to occur where maternal chlamydia was detected and treated in pregnancy. For example, in a retrospective cohort study comparing the effectiveness of different antibiotics in pregnancy for treatment of chlamydia, which documented an overall treatment success rate of 92% (based on negative ToC) with most treatment taking place in the first or early second trimester (mean gestation at treatment 15 weeks), the prevalence of conjunctivitis and pulmonary infection in the infants was 11% overall (79). Although there was no microbiological confirmation that these infections were chlamydial in origin, the proportion of infants presenting with these conditions is within the range seen in natural history studies (Tables 3 and 4).

4.3 Treatment of symptomatic chlamydial infection in infants

Chlamydia conjunctivitis should be treated with systemic antibiotic treatment (oral erythromycin), as topical treatment alone is less effective. Systemic treatment has the additional benefit of treating infection in other body sites, including the respiratory tract. Erythromycin is also the recommended treatment for chlamydial pneumonia. Efficacy of systemic erythromycin therapy is approximately 80-90% and thus a second course may be required in a small proportion of cases. One small study has demonstrated the effectiveness of azithromycin in infants with conjunctivitis (84).

Most infants will initially be and/or entirely managed and treated in primary care. In a Dutch study of infants referred to hospital with conjunctivitis, although two-thirds had chlamydia, only 12% had received antibiotics that were active against chlamydia (45). As chlamydia is the major cause of ophthalmia neonatorum, general practitioners should have a high index of suspicion of neonatal chlamydial infection and respond promptly with the appropriate treatment. It is likely that prompt treatment of infants with chlamydial conjunctivitis will also result in fewer infants developing pneumonia.

With regard to safety aspects of infant treatment, an association between erythromycin therapy in the first few weeks of life and hypertrophic pyloric stenosis has been identified, with the highest risk apparent in the first two weeks of life (85); it is therefore recommended that erythromycin should only be used in the first month of life when the therapeutic benefits outweigh the risks and no alternative agent is available (86).

- Antibiotics are an effective treatment for chlamydia in pregnant women, with an estimated 64-95% successfully treated with their first antibiotic regimen (varies according to the specific drug used and adherence to treatment)

- Chlamydial conjunctivitis and pneumonia in infants respond well to antibiotic treatment
- However, there is insufficient evidence of benefit from screening for chlamydia in pregnancy over the clinical management of infants with symptomatic infection
- The potential harms associated with in utero exposure to antibiotics have yet to be clearly defined

5. Is the screening test valid and reliable? Is there a safe and acceptable screening test? Are there adequate facilities for confirming test results and resources for treatment?

5.1 Testing: background

Culture of endocervical swab specimens was traditionally considered as the reference test for chlamydia diagnosis. Although culture has a high specificity, it has a low sensitivity and is thus an inadequate gold standard. Cell culture is expensive and time-consuming and not suitable as a screening test. Other tests for chlamydia include antigen detection tests and nucleic acid amplification tests (NAATs), which can be performed on a variety of samples, including urine and cervical or vulvovaginal swabs. NAATs include PCR tests and ligase chain reaction (LCR) tests; the latter test is no longer used. In sexual health clinics in the UK, use of NAATs now predominates, with 81% of women in such clinics tested using a NAAT on a cervical specimen in 2007 (80) and use of NAATs on first-catch urine, cervical, vulvovaginal and urethral specimens are the test of choice recommended in current BAASH guidelines (87).

5.2 Diagnostic accuracy of tests: studies in pregnant women

In a review carried out for the NICE Antenatal Care guidelines (88), prospective cohort studies with results on the diagnostic accuracy of a range of tests on pregnant asymptomatic women were identified. In summary, antigen detection tests – that is, enzyme immunoassay (EIA) and

direct fluorescent antibody (DFA) tests were found to have 86-96% and 85-98% sensitivity, 93-96% and 95-99% specificity, 69-79% and 78-93% PPV and 98-100% and 97-99.5% NPV respectively in endocervical samples, with a true positive defined as a positive initial or repeat culture (89;90).

Renton et al tested cervical, vaginal and urine samples separately by DFA and LCR, and considered a true positive as a positive test on any test at any site: results indicated that sensitivity was lowest in urine samples (78% for DFA and 83% for LCR) and similar for cervical and vaginal swabs (respectively 93% and 92% for DFA and 97% and 94% for LCR) (17). Specificity of 100% was reported for EIA and LCR of endocervical swabs, for LCR of vaginal swabs and for LCR of urine samples in another study where a true positive was defined as ≥1 test from any site confirmed positive by two independent tests (with confirmation of LCR by another LCR test for major outer membrane protein (MOMP-LCR); sensitivity was 82% for EIA and LCR of endocervical samples, 100% for LCR of vaginal samples and 91% for LCR of urine samples (91). Garland et al determined diagnostic accuracy of PCR and LCR testing in first-catch urine, self-inserted tampon and endocervical swabs, with a true positive defined as a positive culture of endocervical specimen and/or positive PCR and LCR on at least one of the sites: sensitivity for endocervical samples was 45.5% for culture, 82% for PCR and 88% for LCR (92). In another study, LCR was performed on urine and culture and LCR on endocervical samples, with a true positive defined as a positive culture or a negative culture with a positive LCR test with confirmation with a MOMP-LCR or DFA: specificity of LCR testing was very high (99.5% for urine and 100% for endocervix) with sensitivity of 84% for urine and 90% for endocervix, compared with 30% sensitivity and 100% specificity for culture (93).

There are limited data available on the diagnostic accuracy of the DNA probe test (nucleic acid hybridisation test), with two studies indicating sensitivity of 86-94%, specificity of 99-100%, PPV of 94-100% and PNV of 99% (94;95). Gram staining of cervical mucus was found to have a high sensitivity (91%) but low specificity (18%) for detecting chlamydial infection, using a DNA probe test as a reference standard (96).

5.3 Current recommendations for testing pregnant women

Current BAASH guidelines for chlamydia screening do not recommend the use of EIAs, point of care tests or DNA probe tests for diagnosis owing to their inferior sensitivity and specificity compared with NAATs (87). Other than making the recommendation that ToC is performed for pregnant women, the guidance for tests or testing sites for pregnant women are as for non-pregnant women (i.e. NAAT on first-catch urine, cervical, vulvovaginal and urethral specimens). Of note, ToC using NAATs should take place at least 5 weeks after treatment (6 weeks for azithromycin) to avoid the detection of residual genetic material from dead chlamydia organisms. The only test recommended for confirming a positive NAAT is a different NAAT. The HPA recommend that all positive tests should be confirmed with an equally sensitive but different NAAT, ideally with a different target.

5.4 Acceptability

Endocervical specimens require a speculum examination, but chlamydia testing can also be performed on urine samples or self-taken vaginal swabs, which are non-invasive and thus is usually more acceptable. No studies could be identified that have explored the acceptability of screening tests for chlamydia in pregnant women. However, in one study involving screening over 1000 pregnant women in their first trimester with self-administered vaginal swabs and urine samples, women were asked to indicate their preference regarding type of sample: 47% indicated a preference for urine specimens, 5% for swabs and 48% had no preference (16).

- NAATs are the recommended test for all population groups
- NAATs have high sensitivity and specificity for detection of chlamydia in pregnant women
- Test of cure is recommended in pregnancy

6. Organizational considerations

Prevention of vertical transmission of chlamydia from mother to infant requires that the infection is identified and successfully treated before delivery, and that either the mother remains free of infection for the remainder of her pregnancy or that any subsequent maternal re-infection is identified and treated. If chlamydia screening were to take place in early pregnancy (e.g. at the booking visit) then there would be potential for re-infection before delivery when exposure of the infant takes place. The earlier in pregnancy that screening takes place, the greater the potential for a sexually active pregnant woman to acquire infection after screening. Thus screening and treatment of women late in pregnancy would seem the more appropriate hypothetical approach for prevention of infection and reducing morbidities in infants of mothers with chlamydia. However, if screening were to take place in the third trimester then the opportunity to avert any adverse pregnancy outcomes potentially resulting from chlamydia infection in pregnancy, such as preterm labour or PROM, would be lost as these would hypothetically require early detection and treatment.

Information is lacking on the incidence of chlamydia infection in pregnancy in general and there are no data on the UK population. In one study of more than 700 pregnant women in the USA, with an overall chlamydia prevalence of 18%, 5% of women with a negative test in early pregnancy were found to be infected in a repeat test at 34 gestational weeks and 13% of women with a positive test in early pregnancy were either re-infected or had a treatment failure (i.e. their repeat test was also positive) (36). In another large (n=2470) study in the USA, 4% of women with a negative chlamydia test in the second trimester of pregnancy had a positive test in the third trimester (58). In a medical record review of 40 mothers of infants with chlamydial infection in the USA, most (63%, n=25) had been tested for chlamydia in pregnancy, of whom 64% had received a negative test (three-quarters of whom were tested in the first trimester) (97).

In the scenario of a pregnant woman with chlamydia being detected through antenatal testing and successfully treated, several factors may place her at increased risk of acquiring the infection again. The most important is likely to be whether or not her sexual partner is also successfully treated. No data are available on partner treatment in the context of pregnancy in the UK, but nearly 75% of programme areas in the NCSP did not meet the recommended standards for partner treatment (98). No studies have been carried out to investigate compliance with current recommendations on abstinence from sexual intercourse until completion of treatment. In a recent systematic review of published studies in non-pregnant populations, the median re-infection rate was 14% among women and modelling provided estimated re-infection rates of 8% at 3 months, 15% at 6 months, peaking at 21% at 13 months; re-infection was associated with young age, but not with treatment type (2).

7. Would the objectives of screening justify the costs?

There is insufficient evidence to address this question in depth. In Table 5, age-specific prevalence estimates have been applied to live birth data for England and Wales stratified by age groups in order to estimate the approximate number of chlamydia-exposed infants delivered in a year in the scenario of no antenatal screening and treatment for chlamydia. Between 2000 and 5500 cases of conjunctivitis and 800-4000 cases of pneumonia would be expected in a year, based on low and high estimates from natural history studies. Of note, up to half of the pneumonia cases may present initially with conjunctivitis. The benefits of performing routine antenatal screening of around 700,000 women annually in order to prevent this number of easily treated neonatal complications are likely to be out-weighed by the costs, but there have been no formal evaluations of cost-effectiveness in the context of pregnancy. In the scenario of 100% effective antenatal screening and treatment of chlamydia, but where antenatal screening was limited to women aged less than 25 year old, it is estimated that 11,000 chlamydia-exposed infants (or two in five) would be missed in England and Wales (Table 5).

Conclusion

- There is insufficient evidence to recommend the offer of chlamydia screening during pregnancy

- The evidence linking maternal chlamydia infection to adverse outcomes of pregnancy and to the overall neonatal disease burden is limited. Furthermore, a strategy which focuses on the under 25 age group would miss a significant number of affected newborns born to women outside this group.

- The issues relating to the screening and treatment of chlamydia infection during pregnancy differ significantly to the non pregnancy context in terms of the timing of the test and the need for a test of cure following treatment. These require a more systematic approach than the opportunistic, ad hoc, model of delivery employed by the NCSP.

- The range of antibiotics available for use in pregnancy are limited and pregnancy is associated with exacerbated gastro-intestinal intolerance and non-completion of treatment. Following the ORACLE study, there are also concerns about the long term effect of antibiotics in pregnancy where the balance of benefit and harm is uncertain. These issues complicate further the treatment of chlamydia in pregnancy.

- Collaborative work should be undertaken to develop guidance for health professionals who are approached by pregnant women requesting Chlamydia testing.

- Research is needed on the effectiveness of chlamydia screening and treatment in pregnancy with respect to prevention of adverse pregnancy outcomes and infant complications, particularly regarding optimal timing in pregnancy and repeat testing.

Table 5

Illustrative example of burden of neonatal complications of maternal chlamydial infection, England and Wales

Maternal age (years)	Live births[1]	Chlamydia prevalence[2]	Chlamydia exposed infants	Infants with conjunctivitis (low estimate - 8%)[3]	Infants with conjunctivitis (high estimate - 21%)[3]	Infants with pneumonia (low estimate - 3%)[4]	Infants with pneumonia (high estimate - 16%)[4]
<20	44691	12%	5363	429	1126	161	858
20-24	135971	7.5%	10198	816	2142	306	1632
25-29	192960	4%	7718	617	1621	232	1235
>=30	335089	1%	3351	268	704	101	536
Totals	**708711**		**26630**	**2130**	**5592**	**799**	**4261**

[1] Based on 2008 data

[2] Based on data in Table 2

[3] Based on data in Table 3

[4] Based on data in Table 4

NB Up to half of the pneumonia cases are likely to have presented initially with conjunctivitis (i.e. overlap between cases, so summing the conjunctivitis and pneumonia cases will over-estimate the infant burden of disease)

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Literature search for chlamydia screening in pregnancy (2003-2009)

October 2009

Background.
Previous literature searches have been produced on this topic by University of Oxford in 2006 and 2007. The results from those searches have been included in this list.

Sources searched: Medline, Embase, Cochrane Library.

Dates of search: Medline 2003 – October Week 2 2009; Embase 2003-2009 Week 42, Cochrane Library 2009 Issue 4.

Search strategy.
Medline (OVID interface)

1 Chlamydia trachomatis/
2 chlamydia/
3 trachomatis.tw.
4 chlamydia*.tw.
5 exp Chlamydia Infections/
6 1 or 2 or 3 or 4 or 5
7 exp pregnancy/ or exp pregnancy complications/
8 (pregnan* or ante?natal* or ante natal* or pre?natal* or pre natal*).mp.
9 exp Infant, Newborn/
10 exp fetus/
11 exp "congenital, hereditary, and neonatal diseases and abnormalities"/
12 perinatal care/ or postnatal care/ or preconception care/ or prenatal care/
13 exp Prenatal Diagnosis/
14 8 or 7 or 10 or 9 or 13 or 12 or 11
15 6 and 14
16 limit 15 to yr="2003 -Current"

Embase (OVID interface)

1 exp chlamydia/
2 exp chlamydiasis/
3 chlamydia*.tw.
4 trachomatis.tw.
5 or/1-4
6 exp pregnancy/
7 exp pregnancy complication/
8 (pregnan* or ante?natal* or ante natal* or pre?natal* or pre natal*).mp.
9 newborn/
10 fetus/
11 exp newborn disease/
12 exp obstetric care/
13 7 or 10 or 6 or 12 or 9 or 8 or 11
14 13 and 5
15 limit 14 to yr="2003 -Current"

Cochrane Library (Wiley Interscience interface)
#1 chlamydia* or trachomatis
#2 MeSH descriptor Chlamydia, this term only
#3 MeSH descriptor Chlamydia trachomatis explode all trees
#4 MeSH descriptor Chlamydia Infections explode all trees
#5 (#1 OR #2 OR #3 OR #4)
#6 pregnan* or antenatal* or ante natal* or prenatal* or pre natal*
#7 neonat* or infant* or newborn*
#8 fetus or foetus or foetal or fetal
#9 MeSH descriptor Pregnancy explode all trees
#10 MeSH descriptor Pregnancy Complications explode all trees
#11 MeSH descriptor Infant, Newborn explode all trees
#12 MeSH descriptor Fetus explode all trees
#13 MeSH descriptor Congenital, Hereditary, and Neonatal Diseases and Abnormalities explode all trees
#14 MeSH descriptor Perinatal Care explode all trees
#15 MeSH descriptor Postnatal Care explode all trees
#16 MeSH descriptor Preconception Care explode all trees
#17 MeSH descriptor Prenatal Care explode all trees
#18 MeSH descriptor Prenatal Diagnosis explode all trees
#19 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)
#20 (#5 AND #19), from 2003 to 2009

Results.
All results were downloaded into an Access database, and 424 duplicates removed.
A total of 1183 citations remained.

Database	**No. citations retrieved**	**Exclusive**
Medline	647	647
Embase	898	502
Cochrane Library	62	34
	1607	**Total = 1183**

The title and abstracts of these citations, and where necessary and available the full text, were examined for relevance to chlamydia screening in pregnancy. Articles commenting on other papers are listed with the original paper.
212 citations remained, and have been classified as follows (Articles lacking original data, such as editorials and non-systematic reviews are separated):

Category	**No. of citations**
Editorials	1
Non-systematic reviews	22
Systematic reviews	9
Guidelines	8
Incidence/prevalence	74
Adverse pregnancy outcomes	28
Adverse neonatal outcomes	22
Complications	1

Identification or screening tests	32
Treatment	14
Total	212