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Sexually transmitted infections in pregnancy – An update on *Chlamydia trachomatis* and *Neisseria gonorrhoeae*

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ABSTRACT

Routine screening for Chlamydia and gonococcal infection in pregnancy is not widespread, especially in low- and middle-income countries (LMICs), despite their potential adverse consequences on pregnancy outcome. We conducted a systematic literature search of three major databases to review current literature surrounding *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in pregnancy. We discuss the epidemiology and burden of both infections, detection methods, potential adverse feto-maternal and infant outcomes and provide an overview of treatment options. A total of 67 articles met the inclusion criteria. The prevalence of *C. trachomatis* and *N. gonorrhoeae* across all trimesters ranged between 1.0%–36.8% and 0–14.2% worldwide, respectively. The most common diagnostic method is the Nucleic acid amplification test (NAAT). In pregnancy, chlamydia is associated with preterm birth, spontaneous miscarriage, stillbirth and neonatal conjunctivitis, while gonorrhoea is mainly associated with preterm birth and stillbirth. Amoxicillin, erythromycin and azithromycin showed similar efficacy in the treatment of chlamydia in pregnancy, while ceftriaxone and cefixime were effective in treating gonorrhoea in pregnancy. Being largely asymptomatic infections in women, we opine that detection strategies with locally appropriate tools should be combined with the syndromic approach in LMICs, where there is a high burden of disease.

Introduction

A public health concern

Chlamydia trachomatis (CT) and *Neisseria gonorrhoeae* (NG) are the commonest bacterial sexually transmitted infections (STIs) in pregnancy [1]. They are curable and cause significant morbidity if left untreated. With over one million STIs occurring daily worldwide [2], it is vital for countries to tackle this challenge, in order to achieve the Sustainable Development Goal 3 on universal access to sexual and reproductive healthcare services [3]. To this end, the World Health Organisation (WHO) developed a global strategic roadmap to ensure that "*every newborn, mother and child not only survives, but thrives*" [4]. Unfortunately, STIs, particularly during pregnancy, are neglected health issues despite the negative impact on feto-maternal and infant outcomes.

The WHO estimated about 127.2 million and 86.9 million new cases of chlamydial infections and gonorrhoea respectively, globally in 2016. In women aged 15−49years, the estimated pooled prevalence was 3.8 % (95 %UI: 3.3–4.5) for CT and 0.9 % (95 % UI: 0.7–1.1) for NG. The highest prevalence for gonorrhoea was reported from WHO Africa Region while that for chlamydia was from the Americas [5].

CT and NG infections in women may result in pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, preterm labour, post-abortal and postpartum endometritis, neonatal conjunctivitis and neonatal pneumonia [6,7]. There is increased frequency in pregnancy, younger women, and low educational or socioeconomic status [8–10]. They often coexist with HIV infection [11]. Unlike the viral STIs (HIV, Hepatitis B and C), routine antenatal screening for Chlamydial and gonococcal infections is rarely done in low- and middle-income countries

Abbreviations: aOR, adjusted odds ratio; CI, Confidence interval; CT, *Chlamydia trachomatis*; LBW, low birth weight; NAAT, nucleic acid amplification test; NG, *Neisseria gonorrhoeae*; OR, odds ratio; PCR, polymerase chain reaction; PROM, prelabor rupture of membranes; PTB, preterm birth; PTL, preterm labor; SGA, small for gestational age; STI, sexually transmitted infections; UI, uncertainty interval.

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(LMICs). Even in countries with national guidelines for routine STI screening of all pregnant women, under-screening still occurs [12]. This is despite the known effects of these infections on pregnancy outcome, and the fact that they are curable with antibiotics that are available and safe in pregnancy.

Mechanism of Chlamydia trachomatis *and* Neisseria gonorrhoeae *infection*

Chlamydia is an obligate intracellular bacterium that exists in both resting and infectious forms within the epithelium of an infected host, sometimes making detection and elimination difficult [6]. The commonest species implicated in STI is *C. trachomatis* (CT), whose serovars D–K have affinity for the epithelial cells of the urogenital tract, migrating from the cervix to the uterus and fallopian tubes, causing a chronic, asymptomatic infection. The release of pro-inflammatory cytokines and interferon-γ prevents intracellular replication of the organism but it remains viable in a state of persistence [13]. In this form, most of the genes that code proteins for cell division and maintenance are inactive, except that coding for the chlamydial 60 kDa heat shock protein (hsp60) which aids survival in stressful conditions. The synthesis and release of this protein into the extracellular compartment is increased, with stimulation of a localized inflammatory response of the immune system. In the fallopian tube, this causes tissue damage, adhesions and tubal occlusion. Chronic presence of chlamydial hsp60 in the maternal immune system results in production of cross-reacting antibodies between chlamydial and human hsp60, which can cause maternal rejection of the embryo [14].

Neisseria gonorrhoeae is an obligate human pathogen that infects mucosal surfaces of the human reproductive tract, including the rectum, pharynx and conjunctiva. In women, it causes endoluminal damage of the fallopian tubal epithelium, resulting in loss of ciliated cells and fibrosis by inducing an inflammatory immune reaction. This can lead to tubal scarring and occlusion, with subsequent infertility or ectopic pregnancy [15]. NG is asymptomatic in about 45 % of infected women [16], but can cause symptoms of endocervicitis and urethritis, and can be disseminated haematogenously to other organs. In pregnancy, NG is associated with prelabour rupture of membranes, preterm birth, postpartum endometritis and neonatal infections, with increased odds of having a low birth weight (LBW) or small-for-gestational-age baby [17,18].

Pathogen detection

Genital swabs from the vagina or endocervix, first void urine and samples from liquid-based cervical cytology can be collected for *Chlamydia* and Neisseria detection. Non-urogenital samples such as rectal and pharyngeal swabs may be collected as indicated [19]. Vaginal and urine specimens are often preferred by women because they are less invasive and can be self-collected with minimal discomfort [20,21]. However, endocervical swabs are superior to other urogenital samples when culture is required. To optimize isolation of *C.trachomatis* and *N.gonorrhoeae on culture*, specimen collection swabs should have shafts made of plastic or wire (not wood), with tips of Dacron or rayon (not cotton) [22]. A cytobrush may also be used for *C.trachomatis* collection during a pap smear. A sucrose-phosphate based transport medium is used for *C.trachomatis* culture samples, while direct inoculation on a growth medium or use of a swab transport system is required for *N. gonorroheae* specimen transport. Due to the fastidious nature of *N. gonorrhoeae,* a CO2-enriched environment in the growth medium helps to optimize its recovery [22].

Laboratory diagnosis of *Chlamydia* and Neisseria is done using culture or non-culture techniques. The non-culture methods are mainly immunoassays for antigen or antibody detection, and nucleic acid amplification testing (NAAT) for RNA or DNA detection. *C.trachomatis* detection methods via cell culture differ among laboratories, though all require significant technical expertise and are relatively expensive [22]. *N.gonorrhoeae* culture is done on either non-selective chocolate agar or selective media such as the modified Thayer-Martin, New York City or Martin-Lewis medium [23]. The current gold standard for testing is the NAAT [24], though confirmatory culture is recommended in Neisseria detection where possible, for antibiotic sensitivity testing [25].

Screening and treatment guidelines

Screening for STIs in pregnancy is necessary, as chlamydial and gonococcal genital infections in women are largely asymptomatic [26,27] and up to 50 % of infected pregnant women could be asymptomatic [28]. Women with asymptomatic, untreated STI in pregnancy have 3.3 times higher risk of a preterm delivery compared to those that received treatment [29].

The Centres for Disease Control and Prevention recommends *C. trachomatis* screening for all pregnant women. At-risk women (i.e. having multiple sex partners or <25years of age) should have a repeat test done in their third trimester. Women at risk of NG infection should be screened early in pregnancy, and have a repeat *N.gonorrhoeae* test during their third trimester if such risk is still present [30].

Several antibiotics are used for treating CT and NG in pregnancy with relatively similar efficacy and tolerability. They include erythromycin, clindamycin, amoxicillin and azithromycin for CT [31], while ceftriaxone, cefixime, amoxicillin plus probenecid and spectinomycin have been used for NG treatment [32]. WHO recommends single dose Azithromycin 1 g orally as first choice treatment for chlamydia [26], while second-line drugs include erythromycin (base or ethylsuccinate), amoxicillin and sulfamethoxazole. A single dose of intramuscular ceftriaxone 250 mg or oral cefixime 400 mg is recommended for the treatment of gonorrhoea [27]. However, as co-infection of gonorrhea with chlamydia often occurs, dual treatment for both infections is frequently done.

Dual therapy of either ceftriaxone or cefixime plus azithromycin is also recommended in settings without local data on gonococcal resistance patterns [27]. This approach has a dual benefit of addressing possible gonococcal resistance and treating chlamydia co-infection if present [33]. It is important to trace and treat sexual partners, and upon completion of treatment a week of sexual abstinence is advised. Test of cure is recommended six weeks after treatment [25]. Retreatment with Ceftriaxone and Azithromycin is advocated in suspected treatment failure, as a reinfection is quite likely. However, culture (including NAAT where available) and antibiotic sensitivity testing are also advised [34].

Due to changes in epidemiology and advancements in diagnostic and treatment modalities, updated information is required for locally appropriate STI management strategies in pregnancy. Routine screening for Syphilis in pregnancy is already a WHO recommendation, but *Chlamydia* and Gonorrhoea are not included, even though a 90 % reduction in incidence of gonorrhoea (compared to the 2018 baseline) is one of the global targets for 2030 [4]. This review provides an update on the epidemiology, diagnosis and treatment of CT and NG in pregnancy. We also evaluate the effect of these infections on pregnancy outcome.

Method

We conducted a literature search of PubMed, HINARI and Cochrane CENTRAL databases from January 2000 till 30th April 2020. We used a combination of key words and Medical Subject Headings (MeSH terms) to identify studies assessing the

prevalence of CT and/or NG including their effects on predefined health outcomes. The search terms used include: "Sexually transmitted infections"; "Gonorrhoea"; "*Chlamydia*"; "Maternal"; "Pregnancy"; "outcomes"; "complications". We restricted our search to observational and experimental studies on CT and/or NG in pregnancy, and attempted to identify all relevant studies in English language without prejudice to publication status.

One author (AO) conducted a literature search and independently screened titles and abstracts of the search results with OB, for potentially relevant studies and obtained the full reports of such studies. We independently applied the eligibility criteria (see supplementary table S1) to the full reports using an eligibility form and ensured each study was included in the review only once. We resolved disagreements through discussion with another team member (BA). Reference lists of retrieved studies were reviewed for additional relevant studies. The PRISMA guidelines [35] were adapted to report the search and selection of studies.

AO and OB extracted data from eligible studies using a predefined data extraction form, and independently evaluated the publications using the STROBE [36] and CONSORT [37] checklists for observational and experimental studies respectively. Due to the diversity of the study designs and laboratory methods, a meta-analysis was not done. The outcomes of interest include prevalence and adverse pregnancy and infant outcomes (miscarriage, stillbirth, preterm delivery, LBW, perinatal mortality, ophthalmia neonatorum, neonatal pneumonia, infant death).

We summarize our findings as a narrative synthesis [38] evaluating the epidemiology, risk factors, adverse pregnancy and infant outcomes, detection methods and treatment options for *C. trachomatis* and *N. gonorrhoea* in pregnancy.

Results and discussion

The search output of the two databases yielded 1038 titles, in addition to 34 titles from additional sources from which 156 duplicate publications were removed using EndNote (version X6 PDF Tron™ Systems Inc. 2001–2014). Eight hundred and forty-two (842) publications were screened out at the title and abstract stage, leaving 74 articles eligible for review; of which seven full text articles could not be retrieved and were thus excluded. A total of 67 publications were evaluated for this review. A detailed flow diagram of the selection process according to the PRISMA guidelines is provided in Fig. 1.

There were 57 observational studies and 10 randomized controlled trials (RCT) included in this review, with a total of 544,782 participants. The studies all investigated sexually

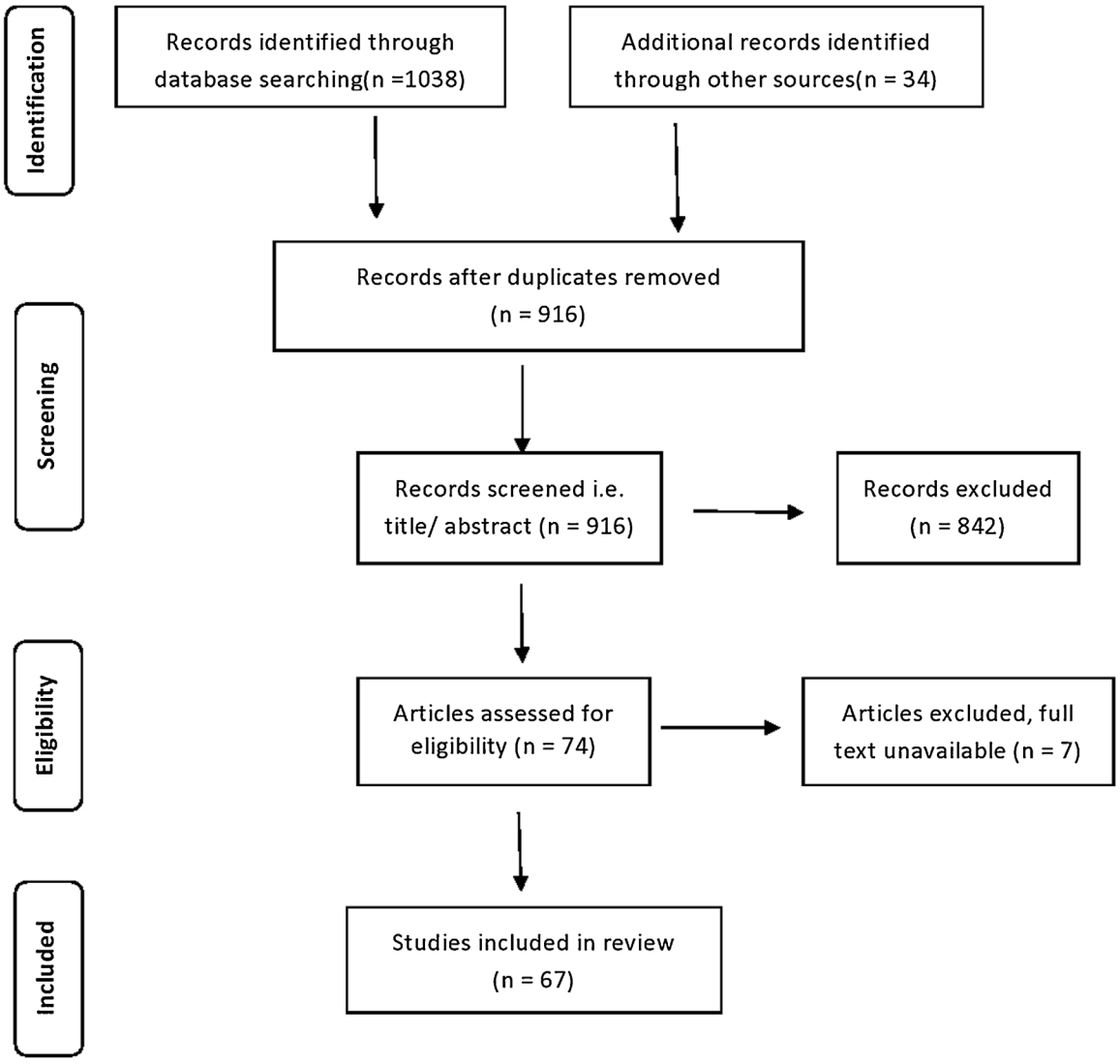

Fig. 1. Flow diagram of identified studies.

Table 1
Characteristics of included studies.

Author	Year	Country	CT/NG test	Setting
Abdelaziz[52]	2013	Sudan	CT&NG	200 pregnant women in the 2nd and 3rd trimester attending routine ANC
Abdelrahim[54]	2016	Sudan	CT	308 pregnant women of low socioeconomic class (monthly family income <$50) attending routine ANC
Adachi[86]	2015	Brazil, Argentina, South Africa (SA)& USA	CT&NG	1373 pregnant women diagnosed of HIV-infection at labor/delivery
Adachi[91]	2016	Brazil, Argentina, SA& USA	CT&NG	1373 pregnant women diagnosed of HIV-infection at labor/delivery with infant follow-up till 6months
Aliyu[53]	2019	Nigeria	CT	Cases = 83 women with spontaneous miscarriage; Control = 83 pregnant women at >28 weeks' gestation
Badman[59]	2016	Papua New Guinea	CT&NG	125 pregnant women at first antenatal clinic visit (1 st & 2nd trimester)
Badrakh[62]	2017	Mongolia	CT&NG	National survey (ANC records)
Baer[93]	2019	USA	NA	15,860 women diagnosed with STI in pregnancy, with matched controls. Obtained from birth records
Bagheri[83]	2018	Iran	CT	Cases = 97 women with spontaneous miscarriage (<24weeks GA); Control = 60 pregnant women
Baldeh[89]	2019	Gambia	NA	280 pregnant women at routine ANC
Bilardi[87]	2010	Australia	NA	100 pregnant women aged 16–25yrs in ANC
Blas[72]	2007	USA	NS	851 CT + ve women & 3404 CT -ve women obtained from birth certificate data registry
Borges-Costa[71]	2011	Portugal	CT&NG	204 pregnant adolescents before and after delivery
Bristow[79]	2017	Haiti	CT&NG	300 pregnant women in clinic
Burton[92]	2019	Australia	NA	Cases = 380 singleton preterm births; Controls = 380 singleton births at 37 gestational weeks or more
Carter[98]	2011	USA	NA	Cases = 12,158 children with birth defects; Controls = 5913 children obtained from the National Birth Defects Prevention Study (1997–2004). Information on genital tract infections in the first trimester and one month preceding pregnancy were obtained during interviews of the mothers.
Casillas-Vega[80]	2017	Mexico	CT	662 women first-time attendees of O&G clinics
Causer[45]	2014	Australia	NS	198 samples from community STI screening
Chaponda[40]	2016	Zambia	CT&NG	1086 pregnant women at first ANC visit
Chow[94]	2009	USA	NA	Birth records (1997–1999) matched with CT case reports of women = 10,917
Contini[68]	2018	Italy	CT	200 pregnant women at $\leq$ 12 weeks pregnancy (100 with spontaneous miscarriage as cases and 100 with voluntary termination as control).
Dionne-Odom[36]	2019	USA	CT&NG	432 women: 210 HIV + ve and 222 HIV-ve that delivered in a study hospital btw 2000–2014
Gadoth[51]	2019	DR Congo	CT&NG	Pregnant women attending ANC
Gray[90]	2001	Uganda	NS	study group = 2070 pregnant women given presumptive STI treatment once in pregnancy; Control group = 1963 mothers given iron/folate
Hill[95]	2015	USA	NS	1120 pregnant women from retrospective chart review
Jacobson[100]	2001	USA	NA	129 pregnant women enrolled at two university clinics
Johnson[73]	2011	USA	CT&NG	730 pregnant women from STD clinic medical records and state birth records (1996–2002)
Jones[44]	2007	South Africa	CT&NG	626 women aged 14–25 years from 2 community based youth groups and 2 clinics
Joseph Davey[11]	2019	South Africa	CT&NG	242 pregnant women at first ANC visit (44 % were HIV + ve)
Kacmar[101]	2001	USA	NA	39 pregnant women before 33 weeks gestational age
Kataoka[64]	2006	Japan	CT&NG	877 pregnant women with singleton pregnancy <11 weeks
Kiguen[43]	2019	Argentina	CT	509 pregnant women (14–45yrs) at 35–37weeks gestation within the community.
Lippman[42]	2007	Brazil, Argentina, SA, USA	NA	818 women from general and gynecologic clinics
Liu[56]	2013	Australia	CT&NG	354,217 primiparous women whose singleton birth occurred 1999–2008.
Martens[46]	2013	Gambia	CT& NG	1838 women in the SurePath phase and 2164 women for the PreservCyt phase in 11 locations of of varying prevalence
Marx[38]	2010	Kenya	CT&NG	441 pregnant HIV-1-infected women recruited from ANCs (1999–2002) at 32weeks gestation, followed-up till 12months post-partum
Masha[49]	2017	Kenya	CT&NG	202 pregnant women at ANC who were tested for curable STIs
Menéndez[39]	2010	Mozambique	CT&NG	262 women (14–61yrs) recruited at the ANC, family planning clinic and community. Pregnant women = 151
Moodley[27]	2017	South Africa	CT&NG	615 pregnant women at ANC booking
Morikawa[21]	2018	South Africa	CT&NG	430 HIV infected pregnant women <34 weeks
Mudau[41]	2018	South Africa	CT&NG	247 HIV infected pregnant women at booking visit
Nadafi[83]	2005	Iran	NA	92 CT positive (IgG & IgM) pregnant women at 2 antenatal clinics
Otgonjagala[63]	2017	Mongolia	CT&NG	200 healthy pregnant women and their newborns in 4 hospitals
Ovalle[81]	2012	Chile	CT	255 pregnant women at antenatal clinic
Panaretto[57]	2006	Australia	CT&NG	456 pregnant women at antenatal clinic
Pereboom[70]	2018	Netherlands	CT	383 pregnant women and 282 partners at primary midwifery care practices
Pourabbas[84]	2018	Iran	CT&NG	239 pregnant women delivering in 2 hospitals
Rahimkhani[85]	2018	Iran	CT	119 pregnant women in first trimester
Rantsi[69]	2016	Finland	NA	2950 women with ectopic pregnancy (800), miscarriage (800) or preterm delivery (1350) from registry records
Rastogi[66]	2003	India	CT&NG	350 pregnant women attending antenatal clinic

Table 1 (*Continued*)

Author	Year	Country	CT/NG test	Setting
Reekie[58]	2018	Australia	CT	101,558 women with singleton births from national data registries
Romoren[48]	2004	Botswana	CT&NG	703 pregnant women at primary healthcare clinics
Romoren[50]	2007	Botswana	CT&NG	703 pregnant women attending antenatal clinics
Scheidell[74]	2018	Haiti	CT&NG	200 pregnant women at antenatal clinic
Schmidt[10]	2015	Brazil	NA	323 pregnant women with preterm birth
Sethi[67]	2017	India	CT	1000 pregnant women at <24weeks gestation attending antenatal clinics
Shannon[99]	2018	Botswana, DRC, Haiti, SA, Vietnam, Peru	NA	1957 pregnant women at antenatal clinics
Sheffield[75]	2005	USA	CT	1953 pregnant women at 16-<24weeks gestation with asymptomatic CT infection diagnosed by urine ligase chain reaction
Silveira[78]	2017	Brazil	CT	562 pregnant women admitted during labor into maternity hospitals
Somboona[47]	2018	Thailand	NA	130 women aged 15–54 years
Stevens-Simon[76]	2002	USA	CT&NG	102 pregnant 13–21 year olds attending 2 teen clinics
Suguira-Ogasawara[91]	2005	Japan	CT	658 women (504 pregnant women with history of recurrent miscarriage and 154 non-pregnant controls)
Teasdale[1]	2018	South Africa, Zimbabwe	CT&NG	4549 women from Methods for Improving Reproductive Health in Africa (MIRA) study, of which 766 were pregnant
Travassos[77]	2012	Brazil	CT	63 HIV positive attendees of a high-risk antenatal clinic
Vallely[60]	2016	Papua New Guinea	CT&NG	765 pregnant women attending antenatal clinics
Vallely[61]	2017	Papua New Guinea	CT&NG	1764 women from antenatal clinics, sexual health clinic and well women clinic
Wynn[101]	2015	Botswana	NA	200 pregnant women <35weeks gestation at antenatal clinic

transmitted infections (including CT and/or NG) in pregnancy and some of them included HIV-infected pregnant subjects [39–45]. They were mostly hospital- based studies, though participants were drawn from the community in some studies [42,46–49] (Table 1).

Epidemiology of Chlamydia trachomatis *(CT) and* Neisseria gonorrhoeae *(NG) in pregnancy*

The studies reviewed were conducted across all continents within the last 2 decades; Africa (23/68), North America (14/68), South America (5/68), Australia (6/68), Europe (4/68) and Asia (11/68). Four (4) were multinational studies conducted in countries located in several continents. It appears that pregnancy may be a risk factor for CT and NG infection [8,9,39], and pregnant women likely have higher rates of such infections compared to non-pregnant women [6].

The reported prevalence of CT in pregnancy worldwide is 1 %–36.8 %, while NG prevalence in pregnancy is 0%–14.2%. Individual studies among pregnant women in the WHO AFRO (Botswana, Democratic Republic of Congo, Gambia, Kenya, Nigeria, Mozambique, South Africa, Sudan, Uganda, Zambia, and Zimbabwe) reported NG prevalence range of 0–8% [1,21,33,40–44,47,49–55] and prevalence of CT ranging from 3.1 to 36.8% [1,21,33,40–44,47,49,51–57]. Chico et al. [58] reported pooled CT prevalence rates in East and Southern Africa (excluding South Africa) as 6.9 % (95 %CI 5.1 %–8.6 %) while NG was 3.7 % (95 %CI 2.8 %–4.6 %). West and Central Africa pooled prevalence estimates for CT and NG were 6.1 % (95 % CI 4.0 %–8.3 %) and 2.7 % (95 %CI 1.7 %–3.7 %), respectively.

Individual studies of CT and NG prevalence among pregnant women in other WHO regions are as follows: Western Pacific (Australia, Papua New Guinea, Mongolia, Japan) CT 1 %–22.9 %, NG 0.1–14.2% [59–68]; Southeast Asia (Thailand, India) CT 1.6–18.8 %, NG 0% [50,69,70]; Europe (Portugal, Italy, Netherlands, Finland) CT 1.9 %–11.8 %, NG 4.9 % [71–74]; the Americas (USA, Brazil, Mexico, Haiti, Argentina, Chile) CT 5.9 %–14.8 %, NG 0 %–7.1 %. [39,47,75–84]. Studies in the Eastern Mediterranean region (Iran) suggest CT prevalence of 6.7 %–27.6 % and NG prevalence of 1.3 % [85–88].

One in five women attending ANC had a curable STI [5] while a CT prevalence of 8.3 % was reported in non-pregnant women [60]. The prevalence of CT in partners of pregnant women was 2.6 % [73]. In studies that conducted newborn assessment, CT and NG prevalence was 7.5 %–11.7 % and 0% - 0.4 % respectively [66,87].

Risk factors for CT and NG infections in pregnancy

Various sociodemographic and behavioural factors have been associated with occurrence of CT and NG in pregnancy. Modifiable risk indicators identified in most studies include poor education, low socioeconomic status, previous STI, tobacco smoking and lack of prenatal care in pregnancy [41,46,62,75,89,90]. The strongest predictor of risk for cervical infections was age, with the highest prevalence in teenagers [53], though an association is seen with advanced maternal age ≥40 years [47], possibly due to the cumulative risk of multiple infections that increases with age [72].

The odds of having an STI are doubled in women with low educational levels (aOR: 2.09; 95 % CI: 1.14–3.84) and poverty (aOR: 2.01; 95 % CI: 1.00–4.01) [91]. Some studies suggested no association between low educational level and STI (aOR: 0.04; 95 % CI: 0.01 – 0.35), but unemployment significantly increased the risk of STI acquisition (aOR: 21.97; 95 % CI: 1.57–306.65) [92]. Other risk factors for CT infection include previous preterm birth, previous ectopic pregnancy and CT genotype E [41,83]. Presence of genital ulcers, bacterial vaginosis, urogenital schistosomiasis, hygiene practices and early sexual debut are predisposing factors for CT/NG infections [52,54].

During pregnancy, infection rate increases with advancing gestation; a three-fold higher risk of infection in the third trimester compared to earlier trimesters has been reported [55]. HIV-infected women have 3–7 times increased odds of having STI during pregnancy compared to HIV negative women, and more commonly have multiple infections [39,40]. HIV co-infection with CT/NG is highly prevalent in some settings, with increased risk of mother-to-child-transmission of HIV during pregnancy [89] and cervical neoplasia in 12 % of women [42]. There is a strong association between STI and malaria co-infection, including HIV infection [43]. The presence of other STIs increases the risk of

Table 2
Studies on *Chlamydia trachomatis, Neisseria gonorrhoeae* and adverse pregnancy outcomes.

CT/NG and adverse pregnancy outcomes (n = 21)					
Study	Continent	Country	Support association		Findings
			CT	NG	
CT/NG and miscarriage (studies = 7)					
Abdelaziz 2013	Africa	Sudan	No		Evaluated 200 pregnant women having symptomatic and asymptomatic vaginal infections. Tested vaginal and cervical swabs for CT (including NG, BV, TV, Candida albicans and mycoplasma spp). No significant association (p = 0.7) between history of abortions and CT infections.
Aliyu 2019	Africa	Nigeria	No		Compared 83 women with spontaneous miscarriage with 83 women with on-going pregnancy beyond 28 weeks' gestation (control). There was no significant difference in CT IgG seropositivity in both groups (P = 0.192; OR = 0.41, CI 0.10– 0.63).
Bagheri 2018	Asia	Iran	Yes		Compared 97 women that had recent miscarriage with 60 pregnant women without any miscarriage history (control). There was a significantly higher rate of CT infection in the study group using PCR (11.3 vs. 0%, P = 0.007), but not with anti-CT IgG and IgA antibody evaluation (p > 0.05).
Contini 2019	Europe	Italy	No		Compared chorionic villi tissue and peripheral blood mononuclear cells from 100 women with miscarriage and 100 women that had voluntary interruption of pregnancy (control). No significant difference in CT prevalence or DNA load (p > 0.05).
Rahimkhani 2018	Asia	Iran	No		Evaluated first void urine of 119 pregnant women at 12–14 weeks gestation for CT (including *M. genitalium* and HPV). The association between CT and miscarriage was not significant (p = 0.93)
Rantsi 2016	Europe	Finland	No		Compared cases of ectopic pregnancy (800), miscarriage (800), and PTB (1350) with equal number of pregnant women without these diagnoses (control). Anti-CT IgG antibodies were associated with two-fold odds of ectopic pregnancy (aOR, 2.31; 95 %CI 1.53; 3.47). Incidence of miscarriage and PTB were similar between both study groups.
Sugiura-Ogasawara 2005	Asia	Japan	No		Prospectively evaluated 504 women with recurrent abortion for CT antibodies (IgG and IgA). Miscarriage rates between women with positive and negative CT antibody was not significantly different (33.3 % vs 23.9 %). Also no difference in incidence of ectopic pregnancy.
CT/NG and stillbirth (studies = 4)					
Liu 2013	Oceania	Australia	Yes	No	Retrospectively compared 3658 and 196 birth records linked to maternal CT and NG notification respectively, with 350,363 CT/NG negative records (control). CT was associated with spontaneous PTB (aOR 1.17, 95 %CI 1.01; 1.37) and stillbirth (aOR 1.40 95 %CI 1.00; 1.96). NG was associated with spontaneous PTB (aOR 2.50 95 %CI 1.39; 4.50) but not stillbirth (aOR 2.35 95 %CI 0.58; 9.56). There was no effect of CT or NG on SGA.
Moodley 2017	Africa	South Africa	No	No	Retrospectively evaluated 615 pregnant women out of the total participants in a study on STIs and pregnancy outcomes. There was no association reported between occurrence of stillbirth, PTB or LBW and the presence of CT, NG and T.vaginalis. Occurrence of PTB was 3 times more likely in asymptomatic untreated women (CT/NG/TV) compared to those treated while pregnant (33.3 % vs 13.2 %; p = 0.042)
Rastogi 2003 (see below)	Asia	India	Yes		
Reekie 2018 (see below)	Oceania	Australia	No		
CT/NG and prelabor rupture of membranes (PROM), preterm labor (PTL), preterm birth (PTB) (studies = 11)					
Baer 2019			No	Yes	Compared 15,860 women having an STI in pregnancy with equal number of women without STI (exact propensity score-matched control). No increased odds of PTB were reported with CT. Women with NG had increased odds of PTB and early term delivery (OR 1.2−1.8).
Blas 2007	North America	USA	Yes		Retrospectively compared a cohort of 851 women having CT infection with 3404 women without CT (control). Compared to CT-negative women, the CT-infected women had increased risk of PTB (RR 1.46, 95 % CI 1.08–1.99) and PROM (RR 1.50, 95% CI 1.03–2.17). The risk of infant death and LBW was not significantly different in both groups.
Burton 2019	Oceania	Australia	No	Yes	Retrospectively evaluated 380 pregnant women that had singleton preterm birth (i.e. < 37 weeks gestation) with 380 pregnant women that had singleton term births (control) tested for CT, NG (including TV and Syphilis). NG-infected women had an increased risk of PTB (aOR 2.92, 95 %CI 1.07–7.97); but there was no such association with CT infection (aOR 1.38, 95 %CI 0.63–3.04)
Chow 2009	North America	USA	Yes		Retrospectively evaluated 10,917 birth records that were matched to a maternal CT positive report in pregnancy. An increased odds of PROM (aOR 1.2, 95 % CI 1.0, 1.3) and LBW (aOR 1.2, 95 % CI 1.1, 1.3) with CT infection was reported. PTB was not associated with prenatal CT infection.
French 2006	North America	USA	Yes		Secondary data analysis of 1038 pregnant black women screened for CT, NG (including BV, TV, Mycoplasma hominis, and GBS). 42 % of PTB were attributable to the presence of CT, BV or TV alone or in combinations.
Hill 2015			No	No	Retrospectively compared 187 pregnancies affected by gonorrheal and chlamydial cervicitis (GCC) with 933 unaffected controls. No significant differences found between GCC-negative and positive pregnancies for PTB (17.79 % vs 16.58 %), Preterm PROM (3.97 % vs 2.67 %) and PTL (8.25 % vs 8.02 %). There was a higher risk of PTB but not PTL when infection occurred earlier trimesters, but it was not significant.
Johnson 2011	North America	USA	Yes	Yes	Retrospectively matched 163 pregnant women who delivered preterm and/or LBW newborns with 567 women who did not (control). Conducted tests for CT, NG (including BV, TV and syphilis). NG increased odds of PTB 2-fold (aOR2.01, 95 %CI 1.01–3.97), especially with a first trimester diagnosis (aOR: 2.95, 95 % CI: 1.30–6.70). CT was associated with LBW (aOR: 2.09, 95% CI: 1.01–4.24)
Liu 2013 (see above)			Yes	Yes	
Moodley 2017 (see above)	Africa	South Africa	Yes	Yes	
Adachi 2016 (see below)			Yes	Yes	
Silveira 2009	South America	Brazil	No	–	Retrospectively evaluated clinical records of 2127 pregnant women. Found that CT diagnosis was not associated with preterm birth.

acquiring HIV infection due to underlying risky sexual behavior, and genital mucosal barrier breach from inflammation and ulcers. In HIV-infected persons with other STI co-infection, the risk of HIV transmission is increased through viral shedding.

Effects of chlamydial and gonococcal infections on pregnancy outcome

Over half of the pregnant women with chlamydial and/or gonococcal infection in the studies reviewed were found to be asymptomatic [32,40,44]. The odds of mothers with CT/NG infection having an adverse fetal outcome was 1.35 times more than those without (OR 1.35, 95 % CI 1.03–1.76) [89], while a reduction of CT and NG infection in pregnancy significantly improved pregnancy outcome (Rate Ratio 0.43; 95 % CI 0.27 – 0.68) [93].

Studies suggest that CT may cause adverse pregnancy outcomes by direct infection of the fetus, damage to the placenta, or through severe maternal illness. Though the mechanism is still poorly understood, immunology plays a key role in this process, as inflammatory responses in the fetus to CT infection with release of cytokines may result in miscarriage, PROM, or preterm labor [6].

Spontaneous miscarriage and ectopic pregnancy

In addition to direct tissue damage by infection of the organism, cell-mediated immunity to human hsp60 can adversely affect subsequent pregnancy outcomes [14]. However, evidence on association of CT infection with the occurrence of spontaneous miscarriages is mixed [55,56,68,71], with more studies reporting no significant association between CT infection and miscarriage (Table 2). Among women that had a history of recurrent miscarriage, presence of serum antibodies to CT was not associated with miscarriage in subsequent pregnancy [94]. Rantsi et al. [72] reported a two-fold increased risk of ectopic pregnancy in the presence of anti-chlamydial IgG antibodies (aOR 2.31; 95 %CI 1.53; 3.47). Tubal stenosis or occlusion that results from pelvic inflammatory disease caused by CT infection lays the platform for a possible ectopic pregnancy, as the fertilized ovum is trapped within a damaged fallopian tube.

Preterm labour, prelabour rupture of membranes (PROM) and preterm birth

CT/NG co-infection in HIV-infected pregnant women was associated with a higher incidence of preterm births compared to those without CT/NG infection (28.6 % vs 10.2 %) [95]. An increased risk of preterm birth has been found in pregnant women with NG [59,76], especially before 32 weeks gestational age [96,97] but not with CT infection [59,61,75,76,96]. Reports show an association between CT infection in pregnancy and PROM [75,98] but not with NG infection [99] (Table 2).

Stillbirth

Worldwide, there are about 2.6 million stillbirths annually, with LMICs bearing 98 % of this burden [100]. Although scant data exists on CT and NG association with stillbirth, maternal infection is a known preventable cause of stillbirth [100]. Two large retrospective cohort studies that addressed this outcome reported divergent

Table 3
Studies on *Chlamydia trachomatis, Neisseria gonorrhoeae* and adverse infant outcomes.

CT/NG and adverse infant outcomes (total studies = 9)					
Study	Continent	Country	Support association		Findings
			CT	NG	
CT/NG and vertical transmission (studies = 1)					
Pourabbas 2018	Asia	Iran	Yes	Yes	Evaluated 239 women during vaginal delivery and their newborns. The vertical transmission rates of NG and CT to the neonates were 75.6 % and 33.3 % respectively.
CT/NG and neonatal ophthalmia/pneumonia (studies = 1)					
Adachi 2016 (see below)	Africa	South Africa	Yes	Yes	
CT/NG and other adverse infant outcomes (studies = 6)					
Adachi 2016	Africa	South Africa	Yes	Yes	Evaluated HIV-infected pregnant women on different antiretroviral regimens to prevent intrapartum vertical transmission of HIV. Higher incidence of adverse outcomes (neonatal sepsis, pneumonia, congenital syphilis, conjunctivitis, LBW, PTB, death) were reported among infants of mothers with CT/NG co-infection compared to those of CT/NG uninfected women (65.7 % vs 37 %, $p = 0.001$). Also found higher rates of death (11.4% vs 3%, $p = 0.02$), LBW (42.9% versus 16.9%, $p = 0.001$), and PTB (28.6% vs 10.2%, $p = 0.008$) among infants of CT/NG co-infected mothers compared to infants of CT and NG negative mothers. Odds of an adverse outcome were 1.4times higher in infants of CT and/or NG positive mothers (OR 1.35, 95% CI 1.03–1.8)
Blas 2007	North America	USA	No		Retrospectively compared a cohort of 851 women having CT infection with 3404 women without CT (control). The risk of infant death (RR 1.02 [0.37–2.80]) or LBW (RR 1.12, [0.74–1.68]) with CT was not increased.
Borges-Costa 2012	Europe	Portugal	Yes	Yes	Evaluated 163 pregnant adolescents prospectively for CT, NG (including TV, BV and GBS). CT and/or NG infection was significantly associated with LBW (p = 0.021)
Panaretto 2006	Oceania	Aboriginal	Yes	Yes	Evaluated 403 pregnant women for CT, NG (including TV and 432 women for syphilis). LBW and perinatal death were associated with the occurrence of STI in pregnancy.
Reekie 2018	Oceania	Australia	No		Retrospectively evaluated 101,558 birth records, and linked 40,424 of them to a maternal CT report. Reported no significant association between a positive CT test and spontaneous PTB (aOR 1·08 [0·91–1·28]; p = 0·37), SGA (aOR0·95 [0·85–1·07]; p = 0·39), or stillbirth (0·93 [0·61–1·42]; p = 0·74).
Warr 2019	Africa	Kenya	Yes	Yes	Evaluated 1221 HIV-uninfected pregnant women in a study on peripartum HIV acquisition in Kenya, with testing for CT, NG (including BV, TV, Candida and Syphilis). Maternal NG infection was associated with infant death (aHR = 3.83, 95 % CI1.16 to 12.68, p = 0.028). Maternal CT was also associated with infant death. Reported no association of other genital infections with stillbirth or infant death.

results – one found an association of CT with stillbirth (aOR: 1.40, 95 %CI: 1.00–1.96) [59], while the other reported no significant association (0·93, 95 %CI 0.61–1.42; p = 0.74) [61]. A smaller cohort study found that women with untreated CT infection are more likely to have stillbirths compared to those without CT infection (11.5 % vs 4.7 %, p < 0.05), and no stillbirth was reported among the treated CT-infected women [59,69]. No significant association between NG infection and stillbirth was reported [59] (Table 2).

Adverse infant outcomes

The association of infant death with CT and/or NG co-infection is unclear. Though some prospective studies reported a higher incidence of infant deaths in CT/NG infected mothers compared to uninfected mothers [60,95,101], a retrospective cohort study found no increased risk of infant death with maternal CT infection [75]. Several studies indicate an association between LBW incidence and the presence of NG/CT infections in pregnancy [74,76,95,97] but two studies found no such association [33,75]. There was no significant association between small for gestational age (SGA) babies and CT/NG infections in pregnancy [59,61,75].

One study showed a reduced rate of CT/NG infection (rate ratio, 0.43; 95 %CI, 0.27−0.68) and infant ophthalmia (rate ratio, 0.37; 95 %CI, 0.20−0.70) following presumptive STI treatment of 2070 pregnant women [93]. In a randomized trial of HIV-infected pregnant women, Adachi et al. [95] reported no significant difference in neonatal pneumonia incidence between CT/NG infected and non-infected women. The association of maternal genital tract infections with congenital defects such as bilateral renal agenesis or hypoplasia, cleft lip and/or cleft palate, and transverse limb defects require further investigation [102] (Table 3).

Detection methods

Studies that evaluated the usefulness of syndromic approach in the management of STI have found it to be of poor predictive value, with sensitivity of 45 % and positive predictive value of 30 % in different clinical settings [41]. Symptoms such as abdominal pain and vaginal discharge were neither predictive of the risk of CT or NG, nor the presence of STI [42,53,57]. Most women (71.6 %) were asymptomatic [62] with symptoms reported by only 29.7 % and 47.1 % of women with CT and NG infection, respectively [44].

The acceptability of STI screening among pregnant women was high in several studies, with 85–99 % consenting to testing during their antenatal visits [82,103,104]. Self-testing was preferred to provider testing [45,47] and sample collection done at home rather than by the provider in the clinic [47]. Vaginal swab was preferred to urine specimens [47]. The commonest specimen used for laboratory diagnosis was genital swabs (38/52). Other specimens include urine (14/52) and blood (4/52).

Table 4 shows the various diagnostic methods used in the studies reviewed, and the diagnostic performance of some techniques. The loop-mediated isothermal amplification with gold nanoparticle probe (LAMP-AuNP) method may be preferred for CT detection in resource-poor settings as it is cheaper, requires little technical knowledge and easier to use compared to polymerase chain reaction (PCR)-based methods [50]. The results are rapidly obtained within an hour with a sensitivity of 96 % and specificity of 99−100% [50].

Treatment options

CT and NG infections in pregnancy are curable with feasibility of treatment in 91–100 % of cases [101]. However, in a trial conducted to assess spontaneous resolution of asymptomatic *Chlamydia trachomatis* infection in pregnancy, 44 % (61/140) of the CT-positive participants had spontaneous resolution of the infection during follow up [78]. Medications evaluated for treatment of CT in pregnancy include amoxicillin, azithromycin and erythromycin.

The efficacy of amoxicillin (500 mg thrice a day for 7 days) is similar to azithromycin (1 g single dose) or erythromycin (500 mg 4 times a day for 7 days) for CT treatment in pregnancy [105,106]. However, erythromycin is more effective for chronic CT infection [82]. Erythromycin for CT treatment reduces stillbirth rates and increases mean duration of gestation in preterm deliveries, but with no significant effect on LBW incidence [69]. Patient

Table 4
Distribution of diagnostic methods for *C. trachomatis* and *N. gonorrhoeae* among included studies, with diagnostic performance of selected methods.

Laboratory method	*C. trachomatis* (n = 52)[a]	*N. gonorrhoeae* (n = 37)[a]
Nucleic Acid Amplification Test (NAAT) including PCR	47	30
Enzyme Linked Immunoabsorbent Assay (ELISA)/ peptide-specific Enzyme Immune Assay technique (EIA)	4	–
Direct Fluorescence Assay (DFA)	3	
Culture	1	7
Gram stain		2
Immunoassay	1	–
Immunofluorescence	1	–
Hybrid capture technique	1	–
Immunochromatographic Tests (ICT)	1	1
LAMP-AuNP, LAMP-GE, PCR-GE, LOD	1	–

	Diagnostic performance			
	C.trachomatis		*N.gonorrhoeae*	
Laboratory method	Sensitivity	Specificity	Sensitivity	Specificity
GeneXpert[45]	100 %	99.5 %	100 %	100 %
Diaquick (ICT)[45]	27.3%	66.7 %	–	–
*DFA[80]	96 %	97.3 %	–	–
Gonorrhoea Card (ICT)[45]	–	–	66.7 %	76.9 %
SurePath# (Qx Amplified DNA assay)[46]	95 %	99.7 %	100 %	100 %
PreservCyt# (Qx Amplified DNA assay)[46]	94.1%	99.8 %	95.3 %	99.95 %
LAMP AuNP[47]	96 %	99−100%	–	–

[a] n = total number of publications in which laboratory method was specified; LAMP- loop-mediated isothermal amplification; PCR – polymerase chain reaction; GE - agarose gel electrophoresis; AuNP – gold nanoparticle probe; LOD – limit of detection; ICT – Immunochromatographic test; DFA – Direct Fluorescence Assay: *Positive predictive value - 86.5 %; Negative predictive value - 99.3 %; Accuracy – 97.3 %; #Liquid-based cytology media.

Table 5
Studies on *Chlamydia trachomatis and Neisseria* gonorrhoeae treatment in pregnancy to prevent adverse pregnancy and infant outcomes.

CT& NG screening/treatment to prevent adverse pregnancy and infant outcomes (total studies = 3)					
Study	Continent	Country	Support association		Findings
			CT	NG	
CT/NG treatment to prevent adverse pregnancy outcomes (studies = 3)					
Gray 2001	Africa	Uganda	Yes		Compared 2070 pregnant women with 1963 pregnant controls in a cluster-randomized trial evaluating the presumptive treatment of genital infections using azithromycin, cefixime, and metronidazole versus placebo. CT/NG reduction reported (RR 0.43, 95 % CI 0.27 – 0.68), including TV and BV. Found reduced risk of PTB (RR 0.77, 95 % CI 0.56–1.05), LBW (RR 0.68, 95% CI 0.53–0.86), neonatal death, (RR 0.83, 95% CI 0.71 – 0.97), and infant ophthalmia (RR 0.37, 95% CI 0.20 – 0.70) in the treatment group.
Rastogi 2003	Asia	India	Yes		Compared 17 CT-positive pregnant women given Erythromycin with 42 CT-positive but untreated women lost to follow-up and 269 CT-uninfected women. The babies of the treated CT-positive mothers had larger birth weights (2200 vs 2113.3 g, $p > 0.05$) and were delivered at later gestation (Mean 35.5 vs 33.1 weeks, $p < 0.05$) compared to untreated women. Untreated CT-infected women had more still births compared to CT-uninfected women (11.5 % vs 4.7 %), with none reported among CT-infected but treated women.
Romorenl 2004	Africa	Botswana	No	Yes	Compared CT prevalence among 116 pregnant women that were prescribed erythromycin based on syndromic STI diagnosis with 557 pregnant women that had no such prescription (control). NG prevalence was also evaluated among 110 pregnant women prescribed ceftriaxone for syndromic diagnosis and 561 women that were not prescribed the drug (control). Found no difference in CT prevalence in study and control groups (7% vs 8%). NG prevalence was 0% in ceftriaxone group and 4% in control group.
CT treatment to prevent adverse outcomes in infants (studies = 0)					
No studies identified					

compliance with azithromycin was higher than for amoxicillin [105], though there were fewer side effects reported with amoxicillin use compared to azithromycin and erythromycin [85,106]. The commonest side effects reported were gastrointestinal symptoms [106].

There is a paucity of studies evaluating the treatment of NG in pregnancy. Medications shown to be effective include a single dose of intramuscular Ceftriaxone 250 mg or 125 mg, as well as oral Cefixime 400 mg [51,107] (Table 5).

Conclusion and recommendation

CT and NG infections in pregnancy were generally associated with increased risk of preterm births and stillbirths. However, the mixed reports on their association with other adverse pregnancy outcomes such as PROM, spontaneous miscarriages and LBW highlight a need for further research into the effects of CT and NG on these pregnancy outcomes.

The poor diagnostic value of the syndromic approach for diagnosing STI in pregnancy, and the high prevalence of asymptomatic CT and NG infection may result in many missed opportunities to avert some adverse pregnancy outcomes. This buttresses the need to strengthen detection strategies with locally appropriate tools in combination with the syndromic approach.

The availability of several detection methods, acceptability of routine screening for CT/NG to pregnant women and availability of affordable, tolerable and effective medications are justifiable reasons to consider routine antenatal screening for these conditions. Early detection and prompt treatment will likely reduce the risk of feto-maternal morbidity and mortality. Larger high-quality research is needed to ascertain feasible, locally appropriate detection and management strategies for CT and NG infections in pregnancy.

Author contributions

BA and AO designed the study. AO carried out the literature search and conducted the data analysis with OB. OB and AO wrote the first draft of the manuscript. BA and FO and CO revised the draft and contributed to the development of the full manuscript. All authors have read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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None

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.10.002.

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