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Sexually transmitted infections in pregnancy: a narrative review of the global research gaps, challenges, and opportunities

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Short summary: Curable sexually transmitted infections in pregnant women may cause poor maternal and newborn outcomes worldwide. Syndromic management is practiced in many settings yet fails to identify most infections. Etiologic screening has promise but further effectiveness and cost-effectiveness studies are needed.

Abstract

Background: Sexually transmitted infections (STI), such as chlamydial, gonorrheal, and trichomonal infection, are prevalent in pregnant women in many countries and are widely reported to be associated with increased risk of poor maternal and neonatal outcomes. Syndromic STI management is frequently used in pregnant women in low- and middle-income countries, yet its low specificity and sensitivity lead to both over- and undertreatment. Etiologic screening for chlamydial, gonorrheal, and/or trichomonal infection in all pregnant women combined with targeted treatment might be an effective intervention. However, the evidence base is insufficient to support development of global recommendations. We aimed to describe key considerations and knowledge gaps regarding chlamydial, gonorrheal, and trichomonal screening during pregnancy to inform future research needed for developing guidelines for low- and middle-income countries.

Methods: We conducted a narrative review based on PubMed and clinical trials registry searches through January 20, 2020, guidelines review, and expert opinion. We summarized our findings using the frameworks adopted by the World Health Organization for guideline development.

Results: Adverse maternal-child health outcomes of potential interest are wide-ranging and variably defined. No completed randomized controlled trials on etiologic screening and targeted treatment were identified. Evidence from observational studies was limited and trials of presumptive STI treatment have shown mixed results. Subgroups that might benefit from specific recommendations were identified. Evidence on harms was limited. Cost-effectiveness was influenced by STI prevalence and availability of testing infrastructure and high-accuracy/low-cost tests. Preliminary data suggested high patient acceptability.

Discussion: Preliminary data on harms, acceptability, and feasibility and the availability of emerging test technologies suggest that etiologic STI screening deserves further evaluation as a potential tool to improve maternal and neonatal health outcomes worldwide.

Key words: sexually transmitted diseases, pregnancy, screening, developing countries

1. Introduction

The curable sexually transmitted infections (STI) *Chlamydia trachomatis*, *Neisseria gonorrhoeae,* and *Trichomonas vaginalis* are common in pregnant women in many countries. Regional estimates of STI prevalence among pregnant women vary(1): *N. gonorrhoeae,* 1.2% (Latin America) to 4.6% (Southern Africa), *C. trachomatis,* 0.8% (Asia) to 11.2% (Latin America), and *T. vaginalis*, 3.9% (Latin America) to 24.6% (Southern Africa). While it is difficult to fully elucidate their relative impact, multiple studies have found associations between these three STIs and increased risk of poor maternal and neonatal outcomes (e.g., miscarriage, stillbirth, preterm birth, low birthweight, and mother-to-child HIV transmission).(2-6)

Few countries recommend routine screening for chlamydial, gonorrheal, or trichomonal infection in pregnant women.(7) The World Health Organization (WHO) recommends screening for HIV infection and syphilis(8) but has no specific guidelines for other STIs beyond syndromic management which limits treatment to symptomatic women.(9) The frequently asymptomatic nature of STIs in women is well established(10) and syndromic management fails to identify the majority of infected women. Syndromic management has modest sensitivity (40% to 75%) and specificity (54% and 76%) for detecting chlamydial and/or gonococcal infection.(10) A study of HIV-infected pregnant women in South Africa found that only 24% of women who tested positive for a chlamydial, gonococcal, or trichomonal infection had vaginal symptoms (sensitivity), whereas 47% of those with symptoms were negative for all three infections (specificity).(11) The poor specificity and sensitivity of syndromic management lead to both over- and undertreatment. Poor antimicrobial stewardship may increase the risk of antibiotic resistance.(12)

The prevalence of, and likely adverse outcomes associated with, curable STIs in pregnant women suggest that etiologic STI screening of all pregnant women followed by targeted treatment might be beneficial. However, the evidence base around that intervention is insufficient to support development of global recommendations. WHO uses a systematic process for developing guidelines(13) based, in part, on the Population, Intervention, Comparator, Outcomes (PICO) and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) frameworks for formulating the question and assessing the benefits, harms, and other relevant factors. This narrative review aimed to describe key considerations and knowledge gaps regarding etiologic STI screening during pregnancy using the PICO and GRADE frameworks. We also aimed to identify key studies in progress that may contribute to addressing these knowledge gaps. Our goal was to inform future research contributing to the evidence needed for developing guidelines, particularly for low- and middle-income countries.

2. Materials and Methods

This narrative review drew on focused PubMed literature searches, review of WHO and other agency guidelines, and expert opinion. International public health and clinical experts from academia, government, industry and community-based organizations met on July 14, 2019 in Vancouver, British Columbia, Canada to frame the initial inquiry. Presentations and discussion during the meeting were the initial source of information for the review. PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and clinical trials registry (https://clinicaltrials.gov and http://www.isrctn.com) searches conducted through January 20, 2020 were developed iteratively based on initial searches using the terms ‘pregnancy’ and ‘screening,’ and ‘sexually transmitted

infections,' 'chlamydia,' 'gonorrhea,' or 'trichomonas.' PubMed searches initially focused on review articles. Reference lists were examined to identify relevant studies. Randomized controlled trials, observational studies, modeling, and qualitative studies related to STI screening/treatment and presumptive STI treatment were examined. We limited our review to studies where the full-text was available in English. Since this was not a systematic review, literatures searches were not conducted systematically, and identified studies and articles were not assessed using standardized criteria.

We presented findings using the PICO and GRADE Evidence to Decision frameworks for health system/public health decisions(14) and for tests in clinical practice and public health.(15). The population (pregnant women in low- and middle-income countries), intervention (etiologic screening for *C. trachomatis*, *N. gonorrhoeae*, and/or *T. vaginalis* of all pregnant women followed by treatment and case management of those with positive test results), and comparator (syndromic STI management) were pre-determined by the authors to delineate the scope of the project. We examined the following GRADE domains: priority/importance, test accuracy, desirable effects (benefits), undesirable effects (harms), resource requirements/cost-effectiveness, equity, acceptability, and feasibility. We did not formally address the quality of available evidence or develop recommendations.

3. Findings

Formulating the key question using the PICO format and selecting outcomes are critical initial steps in the WHO guideline process.(13) (Figure 1) The population, intervention, and comparator were selected *a priori* by the authors. The adverse outcomes of potential interest were wide-

ranging. In meta-analyses of associations between chlamydial infection and adverse pregnancy outcomes, women with chlamydial infection had increased risk of preterm labor/birth, perinatal mortality, stillbirth, intrauterine fetal demise, and newborn low birthweight/birth size compared to those without chlamydial infection.(4, 5) The strength of those associations was attenuated in adjusted analyses and higher quality studies. Chlamydial infection was found to increase mother-to-child HIV transmission by almost 50% in one study.(3) A meta-analysis of trichomonal infection in pregnancy found that infected women had a 41% increased risk of preterm birth and 51% increase in having small for gestational age newborns compared to those without trichomonal infection.(2) We did not identify any meta-analyses on maternal gonococcal infection, however maternal gonococcal infection has been associated with preterm birth, low birthweight, and neonatal eye infections.(6)

Outcome definitions varied substantially among studies. Outcomes related to birth size have been examined using 1) mean birthweight,(16) 2) low birthweight categorization based in weight (<2500g)(17, 18) or chest/head circumference,(19) or 3) intrauterine growth restriction categorization based on weight or height (<10^{th} percentile).(18) In some studies gestational age was measured using ultrasound, a highly accurate method,(20) whereas others used self-reported date of last menstrual period or fundal height which is less accurate. Other outcome measures had similarly variable definitions across studies.

Subgroups: We identified several patient and population-level subgroups that might benefit from specific recommendations. Pregnant women living with HIV infection may have higher STI prevalence(21) and a higher risk of poor birth outcomes(22) than those without HIV

infection which may modify the effect of screening interventions. In malaria-endemic areas, sulfadoxine-pyrimethamine for intermittent preventive treatment in pregnant women may have some efficacy against CT and NG and associated adverse birth outcomes.(18) As such, local implementation of intermittent preventive treatment for malaria(23) could also influence the need for specific recommendations. Geographic heterogeneity in health systems and the distribution of STIs and HIV infection(1) might indicate other identifiers of sub-groups.

Figure 2 summarizes the GRADE Evidence to Decision domains.

Priority/importance: Improved maternal-child health is a primary target of the UN Sustainable Development Goals(24) and addressing STIs will contribute to meeting these targets. The high prevalence of STIs in pregnant women in low- and middle-income countries is established(1) and treatments are widely available and easy to administer.(25, 26) However, the magnitude of the impact of treating STIs in pregnant women on poor maternal-child outcomes has not yet been fully elucidated (see Benefits), a necessary step for establishing this area as a priority for intervention.

Benefits and desirable effects: The benefits of etiologic screening and treating curable STIs in pregnancy in low- and middle-income countries, apart from syphilis,(9) have not been rigorously examined. We did not identify any completed clinical trials on etiologic gonococcal, chlamydial, or trichomonal screening in pregnant women in low- and middle-income countries. Some observational studies from high-income countries support chlamydial screening for improving pregnancy outcomes but generalizability to low- and middle-income countries is unclear.(21) Multiple authors of reviews and meta-analyses reported that insufficient information on

confounders, including timing of infection versus testing/treatment, diagnosis of other infections, and other causes of poor maternal-child health outcomes, complicated interpretation of the available evidence.(4, 21, 27)

Trials of presumptive STI treatment in pregnant women to improve maternal/neonatal outcomes provide information that may help elucidate the potential impact of screening and treatment.(16, 17, 19) A cluster randomized controlled trial among ~4000 pregnant women in Uganda(19) found that one-time treatment with azithromycin 1g, cefixime 400mg, and metronidazole 2g, which were effective against NG, CT, TV, chancroid, and bacterial vaginosis, as well as several non-STI pathogens, resulted in a 17% decrease in early neonatal deaths and 47% improvement in birth weight compared with syndromic STI management. No effects on stillbirth, maternal deaths, or preterm delivery were identified. Three randomized trials of intermittent treatment for malaria in pregnancy were relevant. In Malawi,(17) pregnant women received sulfadoxine-pyrimethamine 1500mg/75mg for malaria prevention and azithromycin 1g, effective against NG, CT, and a variety of non-STI pathogens, during the second and third trimesters or placebo. The authors found a 34% decrease in preterm delivery and a 36% decrease in low birthweight among those that received azithromycin compared with placebo. No differences in perinatal or neonatal mortality were found. A second trial in Malawi(16) that compared presumptive azithromycin 1g + sulfadoxine-pyrimethamine 1000mg/50mg during the second and third trimesters with placebo + sulfadoxine-pyrimethamine found no significant impacts on preterm birth, gestational age at birth, mean birthweight, or perinatal death. In Papua New Guinea, presumptive azithromycin 1g + sulfadoxine-pyrimethamine 1500mg/75mg compared with sulfadoxine-pyrimethamine and

chloroquine 450mg–600mg in ~2000 pregnant women resulted in a 26% lower prevalence of low birthweight and 38% lower risk of preterm delivery.(28)

Insufficient knowledge of the effects of STIs at different gestational ages on birth outcomes limits our ability to optimize the timing of etiologic screening and treatment. Administration of presumptive STI treatment in the above trials varied from one-time treatment at any point during pregnancy(19) to monthly treatment during 14-26 weeks gestation until delivery.(17) Even if successfully treated, women can be re-infected during pregnancy if partners are not treated. Unfortunately, the effectiveness of partner management in these settings has not been fully examined. Additionally, the physiologic mechanisms by which chlamydial, gonococcal, and trichomonal infection impact birth outcomes are complex and unclear.(21, 29)

The Table shows the status of ongoing studies on the effectiveness of etiologic screening and treatment in pregnancy. Randomized controlled trials are underway in China(30) and Papua New Guinea,(29) and in the planning stages in Botswana and South Africa. A prospective cohort study was recently completed in Brazil.(31) A comparative-effectiveness study is in the planning stages in Ethiopia. Studies in Cameroon,(32) Kenya, Tanzania, and Malawi,(33) Mali,(34) and Zambia(35) are examining the impact of presumptive STI treatment, usually coupled with preventive malaria therapy.

Harm and undesirable effects: Evidence of harm from etiologic STI screening and treatment studies in low- and middle-income countries was limited. Publications of large clinical trials on presumptive STI treatment have not reported worse birth outcomes compared with control

interventions.(16, 17, 19, 28) In a trial of presumptive treatment in Papua New Guinea, numbers of adverse events were similar between in the control and intervention arms.(28) In one trial in the USA, treatment of asymptomatic trichomonal infection in pregnant women was associated with increased preterm birth(36) but the selected intervention (two 2g doses of metronidazole 48-hours apart at 16-23 weeks and 24-29 weeks gestation) was non-standard.

Harm attributable to antibiotic use during pregnancy is possible, however STI treatment guidelines were designed to minimize potential harm.(25, 26) While increasing antibiotic use can lead to increased antimicrobial resistance, treatment based on etiological test results rather than syndromic management should reduce overtreatment and decrease selective pressure for antimicrobial resistance. However, the effects on STI antimicrobial resistance have not been studied empirically. The presumptive STI treatment trial in Zambia(35) is investigating antimicrobial resistance in the vaginal microbiome.

STIs are often stigmatized(12) and have been associated with intimate partner violence(37) and fear of intimate partner violence.(38, 39) However, many studies have reported very high rates of acceptance of partner notification(38-41), suggesting that concerns about intimate partner violence and stigma around STIs were not a significant barrier for most women. The trial underway in Papua New Guinea(29) is examining intimate partner violence as an adverse event.

Test accuracy: Culture-based STI testing requires trained laboratory staff, specialized specimen transport and equipment, and has long turn-around times and low sensitivity.(42, 43) Consequently, STI diagnostics have moved toward molecular testing in many settings.(42) While

molecular tests also require specialized equipment, some can be conducted in low-resource clinical settings at or near the point-of-care rather than in a laboratory.(43, 44) Reported accuracy of those tests varied substantially but studies of some platforms (e.g., GeneXpert®, Cepheid®, Sunnyvale, CA, US) have shown accuracies of >95%.(42, 44) Studies in progress on etiologic STI screening are all using molecular methods for chlamydial and gonococcal screening.(Table) Tests for trichomonal infection are either molecular or immunochromatographic assays.

Resource requirements: Cheap antibiotics for STI treatment are widely available but accurate diagnostic tests are relatively expensive. In 2019, the Foundation for Innovative New Diagnostics negotiated a GeneXpert® *C. trachomatis/N. gonorrhoeae* test cartridge price of US$16.20/test for low- and middle-income countries,(45) which excludes specimen collection supplies and the test platform (US$17,000 one-time cost). Such pricing is well above the US$1/test threshold some experts have suggested is needed to implement etiologic STI testing in low- and middle-income countries.(43) Substantially lower test accuracies have been reported for more affordable test options.(42, 44)

Cost-effectiveness studies in Australia and the USA compared chlamydial screening in younger pregnant women with no screening.(46, 47) When considering costs associated with adverse outcomes averted, screening was cost saving at a chlamydial prevalence of 16.9% and 11%, respectively. Neither study considered overhead/capital costs or long-term population impacts of infections averted. Additionally, the evidence used in both studies to inform parameters related to short-term health outcomes was limited.

Different testing strategies could reduce costs and maximize impact. A modeling analysis of cost and effectiveness compared different antenatal chlamydial and gonococcal screening strategies in Botswana with syndromic management.(48) Having GeneXpert® equipment available at every antenatal care facility was the most expensive option but resulted in the most infections treated and cured. Syndromic management was the least expensive strategy, but it resulted in fewer infections cured and considerable overtreatment. A hub-and-spoke approach, where testing occurred at high-volume facilities and low-volume facilities collected specimens and sent them to high-volume facilities for testing, offered the optimal cost per infection averted. Further examination of the costs associated with etiologic screening and treatment in pregnancy are planned for the etiologic STI screening trials in Botswana, Papua New Guinea, and South Africa, as well as the comparative-effectiveness study in Ethiopia and presumptive STI treatment trials in Mali and Zambia.(Table)

Equity: A 2015-2016 survey of ministries of health found only fourteen countries, of which eleven were high income, with national antenatal screening policies for gonorrhea or chlamydia.(7) Given that pregnant women in low- and middle-income countries suffer from a disproportionate burden of STIs and poor maternal/neonatal outcomes,(24) access to etiologic STI screening could help improve health equity around reproductive health and maternal/neonatal outcomes. Although the potential magnitude of the impact global etiologic STI screening on health equity is unclear.

Acceptability: Etiologic STI screening and treatment has been shown to be highly acceptable to pregnant women in low- and middle-income countries. In a combined analysis of 1,817 pregnant

women from six different studies, 93.3% of women approached agreed to be tested.(49) Most participants preferred self-collected vaginal swabs over physician-collected vaginal swabs; same-day test results and treatment might have increased participation. In a Papua New Guinea pilot study using self-collected vaginal swabs, nearly all women approached wanted to participate.(50) Findings from a South African study also suggest very high (>95%) levels of acceptability.(51) Studies in Botswana, Brazil, and Papua New Guinea are examining acceptability among women, partners, and health care providers.(Table)

Including sex partners in etiologic screening and treatment is necessary to prevent re-infection. Partner notification and treatment has been acceptable to pregnant women in multiple settings in low- and middle-income countries.(38-41) In one study from Brazil, 97% of women reported feeling comfortable asking their partners to attend antenatal care and 54-56% of partners did attend.(40) A follow-up study to examine further partner involvement and etiologic screening was recently completed.(31)(Table)

Feasibility: Feasibility must be considered at both the facility and health system levels. Some etiologic STI tests can be conducted at or near the point-of-care, allowing for decentralized diagnostic services and enabling same-day testing and treatment in low-resource settings.(52) The six-study combined analysis discussed above reported high levels of feasibility across study sites (overall 96.7%) defined as the percentage of diagnosed women who received treatment.(49) The pilot in Papua New Guinea found that etiologic STI testing and treatment could be successfully implemented with same-day treatment.(50) In South Africa, 92% of 172 pregnant women with positive STI test results received same-day treatment.(51) While all of those studies

used molecular test platforms which require electricity, the findings suggest that etiologic STI screening and treatment can be operationalized in a variety of settings.

Despite successes in research studies, access to test technologies is a substantial barrier to implementing sustainable etiologic screening globally. WHO has recommended the GeneXpert® platform to diagnose tuberculosis in low- and middle-income countries since 2013.(53) As a result, many low- and middle-income countries have some laboratory infrastructure to support molecular testing using GeneXpert®(53) which could be applied to STI diagnosis. However, the costs associated with those tests remain high, making the need for cost-effectiveness studies critical for determining feasibility.

Studies in Papua New Guinea(29) and South Africa will examine operational feasibility of etiologic screening in select clinics.(Table) In Ethiopia investigators are examining feasibility at the regional health system level.(54)

4. Discussion

This review examined the evidence-gaps around etiologic STI screening in pregnancy in low- and middle-income countries for each of the GRADE criteria in order to guide ongoing research that could support the development of international guidelines. We did not find direct evidence on the impact of etiologic screening and treatment of gonococcal, chlamydial, and/or trichomonal infections on pregnancy outcomes in low- and middle-income countries. We found that differences in outcome definitions may contribute to future challenges with evaluating the evidence for eventual guidelines. Preliminary data on harms, acceptability, and feasibility

suggest that etiologic STI screening and treatment hold promise and merit further investigation, although a key challenge facing potential widespread implementation of this intervention is the high cost of and infrastructure needed for accurate etiologic STI tests. Potential harms should continue to be investigated but should not be considered a substantial barrier to further research. Current studies are further examining many of these challenges and knowledge gaps.

This review had several limitations. First, the focused search strategies and study selection processes of a narrative review might have missed some relevant studies. Second, we did not formally rate the quality of the existing evidence since our focus was on identifying current research gaps. Third, this review was limited to a subset of common curable STIs, gonorrheal, chlamydial, and trichomonal infection. Guidelines for the detection and treatment of other treatable STIs that impact maternal and neonatal outcomes, most notably *Mycoplasma genitalium* and bacterial vaginosis, are also lacking(12, 55) but were beyond the scope of this effort due to limited evidence and testing options, lack of complete understanding of pathophysiology, and/or limited treatment options,

Robust intervention trials examining the efficacy and potential harms of etiologic STI screening in antenatal settings are a priority. Additional research needs include:

- Development of consistent outcome measures, particularly for gestational age, birthweight, and pregnancy loss, that allow for comparisons across studies and in meta-analyses of individual-level data;

- Systematic recording of malaria prevalence and use of intermittent preventive therapy in affected areas given that such therapy may be protective against adverse birth outcomes among women with some STIs;
- Integration of partner notification and treatment into intervention trials to examine the role of re-infection and the effectiveness of strategies such as at-home testing, expedited partner therapy, and incentives for partner testing;
- Investigation of the influence of timing of etiologic STI screening and treatment during pregnancy as the ideal timing of STI screening during pregnancy is currently unknown and there is ongoing risk of re-infection;
- Collection of data on intimate partner violence at study enrollment and incidents of violence during studies since intimate partner violence is both a potential confounder and adverse effect;
- Collection of detailed cost data for performing cost-effectiveness analyses that consider STI prevalence, risk-based profile approaches to etiologic screening in low-resource settings, and availability of testing infrastructure to potentially guide the development of prevalence- or risk-based recommendations in resource-limited settings where the unit cost per test may otherwise be prohibitive;
- Collection and dissemination of population-based STI prevalence data to inform national estimates of STI burden in pregnancy;
- Collection of robust data on other factors associated with adverse pregnancy outcomes including other infections such as HIV, syphilis, *M. genitalium*, and bacterial vaginosis, maternal nutrition, maternal history of adverse birth outcomes, and anemia;

- Implementation research to examine operational and health system optimization for intervention delivery.

Global health inequities and the association between STIs and poor pregnancy and newborn outcomes support the need to continue to develop and evaluate more effective interventions to improve maternal and neonatal health worldwide. While the magnitude of the effect of STIs on poor maternal-child health outcomes in low- and middle-income countries is still unknown, there is potential for substantial population-level impacts given the high prevalence of STIs in pregnant women in low- and middle-income countries and the relative ease of treatment. The current syndromic approach to STI management in pregnant women in low- and middle- income countries leads to both under- and over-diagnosis and treatment. Emerging technologies have created new opportunities for implementing more effective STI screening and treatment approaches which are now being evaluated in large randomized controlled trials. Research focused on addressing key knowledge gaps identified here will be central to generating a robust evidence base to inform the development of effective and sustainable interventions aimed at reducing the burden and consequences of curable STIs in pregnancy in low- and middle-income countries.

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Figure 1. Population, intervention, comparison, and outcome model for etiologic screening for chlamydial, gonorrheal, and/or trichomonal infection in pregnant women in low- and middle-income countries

Population: All pregnant women in low- and middle-income countries

Intervention: Etiologic screening for *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and/or *Trichomonas vaginalis* infection followed by treatment and case management of those with positive test results

Comparator: Syndromic sexually transmitted infections (STI) management
- Purpose of the tests: Diagnose chlamydial, gonococcal, and/or trichomonal infection
- Role of the tests: Screen all pregnant women for these STIs using etiologic testing.
- Linked treatment: Antibiotics for specific diagnosed STI per established guidelines

Main outcomes: Adverse outcomes of potential interest are wide-ranging. Meta-analyses and systematic reviews have found associations between chlamydial, gonococcal, and/or trichomonal infection and pre-term labor/birth, neonatal/perinatal mortality, pregnancy loss, and newborn low birthweight, although it is difficult to clear delineate the magnitude of effect. Outcome definitions varied substantially among studies.

Perspective: Population-level

Subgroups: Pregnant women living with HIV infection; pregnant women living in regions with high malaria endemicity and/or widespread use of intermittent preventive treatment for malaria; other sub-groups that might benefit from specific recommendations depend on heterogeneity in health systems and distribution of STIs and HIV infection.

Background: The curable sexually transmitted infections (STIs) *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* are prevalent in pregnant women worldwide and are widely reported to be associated with increased risk of poor maternal and neonatal outcomes. The World Health Organization recommends syndromic management for curable STIs except syphilis, despite the low specificity and sensitivity of syndromic management and resultant over- and under- treatment of STIs.

Figure 2. Summary of GRADE Evidence to Decision characteristics for etiologic screening and treatment for chlamydial, gonorrheal, and/or trichomonal infection in pregnant women in low- and middle-resource countries

Characteristic	Assessment
Priority/importance	Maternal-child health is a high global priority; potential impact of etiologic STI screening on improving outcomes is unknown.
Desirable effects (benefits)	No randomized controlled trials identified; insufficient observational data; presumptive sexually transmitted infection (STI) treatment trials have had mixed results.
Undesirable effects (harms)	Evidence of harm is limited; presumptive STI treatment trials have not reported worse birth outcomes; concerns for stigma and intimate partner violence; possible risk of preterm birth associated with treatment of asymptomatic trichomonal infection; absence of evidence regarding antimicrobial resistance.
Test accuracy	Variable; very high with some molecular tests.
Resource requirements	Insufficient evidence to assess; accurate tests are high-cost; cost-effectiveness impacted by STI prevalence, availability of testing infrastructure, and cost of diagnostic tests.
Equity	Successful interventions could decrease global inequities in reproductive health and maternal and infant health outcomes.
Acceptability	Limited evidence shows high patient acceptability; no evidence on provider acceptability.
Feasibility	Limited evidence shows high feasibility in various settings; however, access to and cost of accurate tests is substantial barrier.

Table. Key characteristics of known studies in progress on non-syndromic management of chlamydia, gonorrhea, and/or trichomonas in pregnant women in low- and middle-income countries

PI (Country) [reference] Study name Status	**Study design and target sample size**	**Study population and inclusion criteria**	**Study groups and interventions**	**Outcomes**
Etiologic screening interventions				
Lee and Berhane (Ethiopia) ENAT Status: not yet recruiting	Pragmatic comparative effectiveness study 2x2 factorial design Target sample	Pregnant women with first ANC visit at study health centers at ≤24 weeks gestation based on last menstrual period and/or	**Health center randomization** Group 1: Strengthening Ethiopian MOH/WHO-recommended nutrition interventions, including iron, folate, iodized salt, and local corn soya blend supplement to women with MUAC <23 cm	Primary Birth weight; birth length Secondary Gestational age at delivery; preterm birth; small-for-gestational age; low birthweight; length-for age (at birth and 6 months); weight for age (at birth and 6 months); gestational weight gain; maternal anemia;

	size: 3600	fundal height	Group 2 (control): Nutrition standard of care **Individual randomization** All groups: Routine screening for HIV, syphilis, malaria Group 1: Urine culture and AST, molecular CT/NG testing (GeneXpert®[1]), symptomatic women screened for BV (BVBlue®[1]) and TV (OSOM®[1]) at enrollment using self-collected vaginal swabs; treat per test results; deworming in second and third	stillbirth; cost-effectiveness

			trimesters. Group 2: Standard of care screening urine dipstick; syndromic STI management	
Klausner, Morroni, Wynn (Botswana) Status: preparation	Cluster randomized controlled crossover trial in 2 antenatal clinics 500 women	Pregnant women ≥18 years old attending first ANC visit who are asymptomatic for CT/NG	Group 1: Molecular CT/NG (GeneXpert®) screening using self-collected vaginal swabs at first ANC visit and again after 27 weeks gestation; treat per test results; partner treatment provided when possible. Group 2 (control): Syndromic	Primary Mother-to-child CT/NG transmission; newborn eye infection; newborn pneumonia Secondary Preterm birth; low birth weight; premature rupture of membranes; maternal STI diagnosed and treated; incremental cost-effectiveness ratios, acceptability among

			STI management	women and healthcare workers
Medina-Marino and Klausner (South Africa) Status: not yet recruiting	3-arm (1:1:1) individually randomized-controlled hybrid-effectiveness trial with economic evaluation 2500 women (834 per arm)	Pregnant women age≥18 years attending first ANC visit at public antenatal clinic at <20 weeks gestation by ultrasound	All groups: Routine screening for HIV and syphilis Group 1: Molecular screening for CT, NG and TV (GeneXpert®) at first ANC visit using nurse-collection vaginal swabs; treat per test results; tests-of-cure at 3 weeks post-treatment Group 2: Molecular screening and treatment for CT, NG and TV (GeneXpert®) at first ANC	Primary Change in maternal STI status between first ANC visit and birth; composite outcome: low birthweight, premature rupture of membranes, preterm birth, stillbirth/spontaneous abortion Secondary Implementation process evaluation; STI risk factors; mother-to-child STI transmission; neonatal STI colonization; cost-effectiveness sub-study

			visit using nurse-collection vaginal swabs; repeat screening at 30–34 weeks gestation; treat per test results Group 3 (control): Syndromic STI management	
Tang (China) (30)[2] Status: recruiting	Individually randomized controlled trial in hospital-based antenatal clinic 200 women	Pregnant women 18-45 years old at first ANC visit to hospital-based clinic	Group 1: Molecular CT/NG screening (Cobas®) of urine or vaginal swab on enrollment and during 37-40 weeks gestation; azithromycin 1g as per test results; test of cure at 1 month, and 3 months after treatment as needed; patients	Primary: Composite outcome: stillbirth, spontaneous abortion, preterm labor, premature rupture of membranes, small for gestational age, low birth weight, infant death, birth defects, neonatal conjunctivitis Secondary:

			offered expedited partner therapy Group 2 (control): Syndromic STI management; molecular CT/NG testing (Cobas®) during 37-40 weeks gestation	Stillbirth; spontaneous abortion; preterm labor; premature rupture of membranes; infant death; birth defects; neonatal conjunctivitis and pneumonia; screening rate; treatment rate; cure rate; partner treatment; costs of testing and treatment
Vallely and Pomat (Papua New Guinea) (29) WANTAIM Status: recruiting	Cluster randomized controlled crossover trial in 10 health centers 4600 women	Women ≥16 years old attending ANC at ≤26 weeks gestation by ultrasound	All groups: HIV and syphilis screening Group 1: Molecular CT/NG and TV (GeneXpert®) and BV (BVBlue®) screening using self-collected vaginal swabs at 4 weeks post-enrollment and	Primary Composite outcome: preterm birth, low birthweight Secondary Premature rupture of membranes; maternal STI diagnosed and treated; incremental cost-effectiveness ratios; health system

			34-36 weeks gestation; treat per test results; partner treatment provided when possible Group 2 (control): Syndromic STI management	implementation requirements; acceptability among women and healthcare workers; newborn eye infection; newborn pneumonia; mother-to-child STI transmission; test accuracy for neonatal infection
Presumptive treatment interventions				
Chico and Chandramohan (Zambia) (35s) ASPIRE Status: recruiting	3-arm individually randomized controlled trial 5,436 pregnant women (1,812	HIV-negative pregnant women who have not yet started IPTp[3] 16-28 weeks gestation by	All groups: HIV and syphilis screening; syndromic STI management Group 1: Monthly IPTp-SP[3]; metronidazole 2g at first and second ANC visit	Primary Composite outcome: spontaneous abortion, stillbirth, small for gestational age, low birthweight, preterm delivery, neonatal mortality Secondary

	per group)	ultrasound		Individual components of composite
			Group 2: Monthly IPTp-DP[3]; metronidazole 2g at first and second ANC visit	outcome; neonatal length and stunting; clinical malaria; malaria parasitemia; placental malaria; maternal anemia; congenital anemia; congenital malaria; TV and BV treatment efficacy; GI side effects; maternal NG, CT, TV, and syphilis infection; maternal vaginal microbiota; inflammation markers; AST of cultured isolates from vaginal swabs in symptomatic women; intervention costs; maternal and healthcare preferences for treatments
			Group 3 (control): monthly IPTp-SP; placebo at first and second ANC	
Dionne-Odom (Cameroon) (32s)	Individually randomized controlled trial	HIV-positive pregnant women	Group 1: IPTp with daily trimethoprim-sulfamethoxazole DS; monthly	Primary *Plasmodium falciparum* peripheral parasitemia; composite outcome: CT, NG,

PREMISE Status: recruiting	310 pregnant women	16-55 <28 weeks gestation by dates/fundal height or ultrasound	azithromycin 1g x 3d Group 2 (control): IPTp with daily trimethoprim-sulfamethoxazole DS; monthly placebo x 3d	and syphilis infection Secondary Birthweight; symptomatic malaria; parasite density; placental malaria; maternal anemia; Group B streptococcus colonization; *Mycoplasma genitalium* infection; composite adverse birth outcome: low birth weight, miscarriage, preterm delivery, small-for-gestational age, congenital anomaly, early neonatal mortality; maternal adherence
Kotloff (Mali) (34s)	Three-cohort individually randomized	Pregnant women attending ANC	Groups 1 and 7 (cohorts 1 and 3, respectively): Maternal oral azithromycin 2g at 2nd and 3rd	Primary Infant mortality from 6 weeks through 6-12 months of age; composite outcome:

Status: not yet recruiting	controlled trial Cohort 1 (rural) 2x2 factorial design with mothers and infants randomized separately (Groups 1-4) Cohort 2 (rural infant-only): infants randomized (Groups 5 and	visit during 13-37 weeks gestation by fundal height and/or maternal report of quickening Unborn infants enrolled with mothers. Cohort 2 infants enrolled during routine vaccination visits	trimester ANC visits and during delivery; infant oral azithromycin at 6 and 14 week visits Group 2 (cohort 1): Maternal oral azithromycin 2g at 2nd and 3rd trimester ANC visits and during delivery; infant placebo at 6 and 14 week visits Group 3 (cohort 1): Maternal placebo at 2nd and 3rd trimester ANC visits and during delivery; infant oral azithromycin at 6 and 14 week	stillbirth, infant mortality through 6-12 months of age; Secondary Gestational age at birth; birth weight; incremental cost-effectiveness ratio

	6)		visits	
	Cohort 3 (urban): Mothers/infants randomized in tandem (Groups 7 and 8) 99,700 participants		Groups 4 and 8 (cohorts 1 and 3, respectively): Maternal placebo at 2nd and 3rd trimester ANC visits and during delivery; infant placebo at 6 and 14 week visits Groups 5 and 6 (cohort 2): No maternal intervention; infant oral azithromycin at 6 and 14 week visits versus placebo	
ter Kuile and Madanitsa	3-arm (1:1:1) individually	HIV-negative pregnant	Group 1: Monthly IPTp-DP; placebo at first ANC visit	Primary Composite outcome: spontaneous abortion,

(Kenya, Tanzania, Malawi) (33s) Status: done recruiting	randomized controlled trial 4,680 pregnant women (1,560 per group)	women 16-28 weeks gestation assessed by ultrasound who have not yet started IPTp	Group 2: Monthly IPTp-DP; azithromycin 2g at first ANC visit Group 3 (control): Monthly IPTp-SP at ANC	stillbirth, small for gestational age, low birthweight, preterm delivery, neonatal mortality Secondary Individual components of composite measure; neonatal length and stunting; clinical malaria; malaria parasitemia; placental malaria; maternal anemia; congenital anemia; congenital malaria; TV and BV treatment efficacy; GI side effects; maternal NG, CT, TV, and syphilis infection; maternal vaginal microbiota; inflammation markers; intervention costs
Other interventions				

Yeganeh, Brazil (31s) Status: completed, analysis ongoing	Prospective cohort 400 women and their partners	Pregnant women >18 years old with sexual partner for longer than 3 months seen at community antenatal care clinics[4]	Cohort: Women and partners screened for HIV, syphilis, hepatitis B and C (by lateral flow assay) and molecular CT/NG and TV (GeneXpert®) screening using self-collected vaginal swabs; STIs treated per test results	Primary: STI diagnosis; partner attendance at ANC visits for STI testing; gestational age; birthweight; congenital anomalies Secondary: Demographics and behavioral factors; acceptance of testing; partner presence at ANC visits; partner STI diagnosis; partner acceptance of treatment and referral

Abbreviations: AST: antimicrobial susceptibility testing; ANC: antenatal care visit; BV: Bacterial vaginosis; CT, *Chlamydia trachomatis*; DALY: disability-adjusted life year; NG: *Neisseria gonorrhea*; STI: sexually transmitted infection; TV: *Trichomonas vaginalis*

[1] GeneXpert®, Cepheid®, Sunnyvale, CA, US; BVBlue®, Gryphus Diagnostics, Knoxville, Tennessee, US; OSOM®, Sekisui Diagnostics, Burlington, Massachusetts, US; Cobas® Roche® Diagnostics, Rotkreuz, Switzerland

[2] Referenced protocol is for completed pilot study; authors are using same protocol for current randomized controlled trial.

[3] IPTp: intermittent preventive therapy for malaria in pregnancy; IPTp-SP: intermittent preventive therapy in pregnancy using sulfadoxine-pyrimethamine; IPTp-DP: intermittent preventive therapy in pregnancy using dihydroartemisinin–piperaquine. Sulfadoxine-pyrimethamine is recommended by WHO to protect against adverse birth outcomes attributable to malaria in endemic countries.(23) Sulfadoxine is a sulfanomide and may confer some protective effect against adverse birth outcomes among pregnant women with NG, CT, and TV and bacterial vaginosis.(18)

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Source: Studies were identified through searches of clinicaltrials.gov and ISRCTN.org, and co-author personal knowledge.

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