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Sexually Transmitted Infections in Pregnancy and Reproductive Health: Proceedings of the STAR Sexually Transmitted Infection Clinical Trial Group Programmatic Meeting

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Abstract: The goal of the STAR Sexually Transmitted Infection Clinical Trial Group (STI CTG) Programmatic meeting on Sexually Transmitted Infections (STIs) in Pregnancy and Reproductive Health in April 2018 was to review the latest research and develop recommendations to improve prevention and management of STIs during pregnancy. Experts from academia, government, nonprofit, and industry discussed the burden of STIs during pregnancy; the impact of STIs on adverse pregnancy and birth outcomes; interventions that work to reduce STIs in pregnancy, and the evidence, policy, and technology needed to improve STI care during pregnancy. Key points of the meeting are as follows: (i) alternative treatments and therapies for use during pregnancy are needed; (ii) further research into the relationship between the vaginal microbiome and STIs during pregnancy should be supported; (iii) more research to determine whether STI tests function equally well in pregnant as nonpregnant women is needed; (iv) development of new lower cost, rapid point-of-care testing assays could allow for expanded STI screening globally; (v) policies should be implemented that create standard screening and treatment practices globally; (vi) federal funding should be increased for STI testing and treatment initiatives supported by the Centers for Disease Control and Prevention (CDC), the Centers of Excellence in STI Treatment, public STD clinics, and the President's Emergency Plan for AIDS Relief (PEPFAR).

STAR STI CTG PROGRAMMATIC MEETING

The goal of the STAR STI CTG Programmatic meeting on STIs in Pregnancy and Reproductive Health was to review the latest research and develop recommendations to improve prevention and management of STIs during pregnancy. Experts from academia, government, nonprofit, and industry discussed the burden of STIs during pregnancy; the impact of STIs on adverse pregnancy and birth outcomes, interventions that work to reduce STIs in pregnancy; and the evidence, policy, and technology needed to improve STI care during pregnancy.

CURABLE STIs ARE COMMON

Sexually transmitted infections are common globally and disproportionately affect women and pose a large public health burden. In 2012, there were 6 million new cases of syphilis, 78 million *Neisseria gonorrhoeae* (NG), 131 million *Chlamydia trachomatis* (CT), and 143 *Trichomonas vaginalis* (TV) infections globally.[1] A recent systematic review found that the prevalence of curable STIs was particularly high among pregnant women in low- and middle-income countries.[2] The TV prevalence was highest in Southern Africa

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(24.6%) followed by Asia (13.6%); syphilis prevalence (7.2%) was highest in East Africa; NG prevalance (4.6%) was highest in Southern Africa; and CT prevalence was very high in Latin America (11.2%).[2]

Untreated STIs Are Associated With Adverse Pregnancy and Neonatal Outcomes

Curable STIs are associated with maternal morbidity,[3] preterm birth, low birth weight, and stillbirth.[4–6] Preterm birth is the leading cause of under-five mortality globally.[7] A World Health Organization (WHO)-led study in 2013 found that prematurity and its associated complications were the largest contributor to mortality in children globally accounting for 1 million of the 6 million under-five deaths.[8] According to the March of Dimes, in the United States, the rate of preterm birth increased to 1 in 10 babies (9.9% of live births), and the rate is highest among black infants (13.4%).[9] In addition, there are around 2.6 million stillbirths per year of which 7% to 30% are caused by STIs or other infections.[10–12]

About 50% of untreated maternal CT and NG infections are transmitted to the neonate during birth,[13] which can cause eye and lower respiratory tract infections.[14] Gonococcal eye infections can result in corneal damage and blindness if untreated.[15] Pneumonia due to CT develops in 10% to 20% of infants born to women with untreated CT infection.[16] Curable STIs are also associated with increased mother-to-child transmission of HIV.[17]

Antenatal STIs Are Often Suboptimally Diagnosed and Treated

Despite the large burden and risk to maternal and infant health posed by STIs, in most countries, routine antenatal testing for CT, NG, and TV infections is not offered.[18] In 2015, only 14 countries had policies recommending that pregnant women be tested for CT and/or NG infections.[18] In the United States (US), the CDC recommends CT testing for all pregnant women and NG testing for pregnant women who are at increased risk or who live in areas where NG is highly prevalent.[19] Diagnostic testing for TV is recommended for pregnant women seeking care for vaginal discharge and should be considered in high-prevalence settings.[19]

Countries without STI testing guidelines rely on an approach called syndromic management,[20] which uses algorithms to manage patients with specific STI syndromes (e.g., vaginal discharge syndrome) based on patient symptoms, clinical signs and select risk factors.[21] Patients are then treated with standardized drug regimens for the possible causes of their syndromes, without testing for the etiologic organism. Syndromic management has a number of benefits, including timely treatment at the point-of-care, and no requirement for laboratory resources. Although the syndromic approach has high sensitivity for symptomatic persons, because most STIs are asymptomatic the approach fails to detect the large majority of pregnant women with infection.[21,22] The syndromic approach also lacks specificity, potentially unnecessarily exposing pregnant women to antibiotics and undermining antimicrobial stewardship.[21,22] A recent systematic review and meta-analysis of the performance of abnormal vaginal discharge flowcharts used for syndromic management found that summary diagnostic performance estimates were consistently low for all flowcharts, regardless of whether risk assessments or clinical examinations were included.[23] The authors recommended that future WHO guidelines exclude syndromic management of abnormal vaginal discharge to detect cervical infection.[23] Currently, the WHO is in the process of revising its STI care guidelines.

Although antenatal syphilis testing is recommended by the WHO and available in most countries, there continues to be challenges related to uptake. Globally, only a few countries have reached at least 90% coverage during first antenatal care visits and in 26 countries, less than 50% of antenatal care attendees are tested for syphilis (data unavailable from the US).[24] Further, in the US where syphilis testing is a routine part of antenatal care, the number of congenital syphilis cases more than doubled between 2013 and 2017.[25]

Rates of Partner Notification and Treatment Are Low

Partner notification is a process where sex partners of an index patient with an STI are identified, notified about their exposure, counseled, and treated.[26] Treating partners reduces the likelihood of re-infecting the index patient,[27] and decreases the burden of infection in communities because the partners are often asymptomatic and otherwise unlikely to access care.[28]

Partner notification is governed by country-specific policies related to the control of communicable diseases.[29] There is variation between countries; however, voluntary, patient-based partner notification is the most common method globally.[30] [31] Some countries allow for expedited partner therapy, which is the clinical practice of treating partners by providing medications to the index patient to give to a partner prior to an examination of the partner by a healthcare provider.[32] Regardless of the strategy, partner notification is often low.[33, 34] A systematic review of partner notification strategies in low- and middle-income countries found that the median proportion of sex partners notified in the 39 included studies was 54%.[33] Limited prior research has found that although pregnant women report higher rates of willingness to notify partners about an STI, this willingness does not always translate to higher rates of partners receiving treatment.[33, 35]

Innovations May Allow for Improvements in STI Testing, Treatment, and Prevention of Reinfection

Innovations in diagnostics may allow for the expansion of STI testing and improved management, particularly in low resource settings. Characteristics of new diagnostics include: easy to use, multiplex, and patient-collected samples.[36] Additionally, STI diagnostic platforms are available that allow for patient diagnoses outside of clinical laboratories, have high sensitivity and specificity, and allow for rapid results (while the patient is still present).[36] Rapid tests have the potential to dramatically reduce the time between testing, results, and treatment, which may increase the likelihood of STI treatment and ultimately improve cure rates.[37]

Several studies have found that routine, rapid, antenatal syphilis, CT, NG, and TV testing is acceptable, feasible, and cost-effective in certain circumstances. A recent short report found that uptake of antenatal STI testing was high across diverse settings ranging from 85.2% in the Democratic Republic of Congo to 99.3% in Vietnam. Further, treatment was also high and ranged from 91.7% to 100%.[38]

In terms of cost-effectiveness, two recent studies evaluated testing pregnant women for chlamydial infections.[39, 40] An Australian study looked at antenatal CT testing among women aged 16 to 25 years compared with women with no testing and found that testing cost AU $183 more per case detected than no testing.[39] A US-based study comparing testing all pregnant women to no testing found that testing cost US $19 more per case detected and treated.[40] Although both studies found that testing was more costly than no testing, when considering adverse outcomes averted due to testing and treatment (e.g., preterm birth and low birth weight infants averted) testing resulted in cost savings at higher CT prevalence rates (e.g., Australia study threshold was 11% and US-study was 16.9%). Those studies had several limitations that may change the cost-effectiveness ratio: only short-term outcomes and costs were assessed and benefits among partners were not examined.

Antenatal syphilis testing has been found to be cost effective even in low prevalence settings and cost-saving after adjusting for averted medical care.[41] However, questions remain about how

to increase testing and treatment uptake. Several studies have looked at the issue of whether to use point-of-care versus centralized testing and have different results depending on the setting. A study in Mongolia found that point-of-care testing reduced rates of congenital syphilis compared with centralized testing.[42] However, a study in South Africa found that point-of-care testing did not increase treatment rates, but reduced the time to treatment.[42] A study in Zambia found that more women were tested using a point-of-care strategy compared with centralized testing, but treatment rates were not different.[43] In addition, utilizing dual point-of-care testing for syphilis and HIV infection has the potential to simplify training and procurement and reduce burdens on laboratories and patients. Dual testing has been shown to be cost-effective.[44]

PATHOGENESIS OF ADVERSE MATERNAL, PREGNANCY AND NEONATAL OUTCOMES

Mechanisms for Adverse Impact of Perinatal Infectious on Pregnancy Outcomes

Sexually transmitted infections are associated with increased inflammation,[45] which may play a role in adverse perinatal and infant outcomes. Intrauterine infection/inflammation is associated with about 40% of preterm deliveries.[46] An animal model where intrauterine inflammation was induced by injection of agonists into amniotic fluid,[47] found that the cytokine interleukin-1 (IL1) is a critical mediator in perinatal inflammation. This result suggests that IL1 is a potential therapeutic target. A cord blood study conducted in Cincinnati found that intrauterine inflammation was associated with adverse pulmonary outcomes at 6 to 12 months in moderate/late preterm infants.[48] Adverse outcomes associated with low lung function at birth can continue well into the fourth decade of life.[49, 50]

MYCOPLASMA GENITALIUM IN PREGNANCY

In women *M. genitalium* is common and associated with adverse outcomes of pregnancy, including preterm birth, and is a contributor to perinatal mortality and morbidity.[51, 52] A multisite study in the United States of 1139 women at risk for STIs found the prevalence of *M. genitalium* was 20.5%.[53] Another study in the United States among pregnant women receiving routine antenatal care demonstrated a prevalence of 8.4%. Research is needed to understand if *M. genitalium* infects the placenta, chorion and/or amnion, and/or causes inflammation and sequelae, such as neonatal conjunctivitis or respiratory distress. [51, 52]

Additional research is also needed to better understand the impact and optimal regimen of *M. genitalium* treatment. Treatments for *M. genitalium* have been hampered by antibiotic resistance and some treatments, such as doxycycline, moxifloxacin, and clarithromycin, are contraindicated or lack sufficient human data in pregnancy. Azithromycin is a treatment option; however, resistance is increasing and it is an FDA pregnancy category B drug. Lefamulin may be a future treatment option as phase 2 clinical trials of Lefamulin[54] have provided some safety data in pregnancy.

VAGINAL MICROBIOME AND PREGNANCY

Research of the human microbiome and its diversity has helped to elucidate its role in health and human disease.[55] A normal vaginal microbiome is primarily dominated by *Lactobacillus* species.[56] Lactobacillus species produce lactic acid to maintain a normal vaginal pH and may play a role in preventing urogenital diseases, such as bacterial vaginosis (BV), vaginal yeast infections, and urinary tract infections, as well as in acquiring or transmitting STIs. Hence, disruption or modulation of the normal vaginal microbiota may contribute to increased susceptibility to infectious disease and adverse outcomes.

A study conducted by Ravel et al examined the vaginal microbiome species composition of 396 asymptomatic, reproductive aged, North American women.[57] Investigators were able to subdivide vaginal microbiomes into five community state types (CST) including CST I: *Lactobacillus crispatus*, CST II: *Lactobacillus gasseri*, CST III: *Lactobacillus iners*, CST IV: *Lactobacillus jensenii*, and CST V: *Lactobacillus*-poor.[57] The proportion of CST varied by race (i.e., white, black, Hispanic, and Asian) but not by age. It was determined that *L. crispatus* was most associated with stable vaginal microbiota and that an abnormal vaginal microbiome was associated with loss of lactic acid-producing lactobacilli, higher Nugent scores (used in BV diagnosis; associated with preterm birth), higher proportion of *Gardnerella vaginalis,* and the presence of strict anaerobes.

A longitudinal analysis of the vaginal microbiome in pregnancy was conducted by collecting lateral vaginal wall swabs during the first, second, and third trimester from 100 pregnant women in Belgium.[58] From that study, 77 (77%) women were found to have normal or Lactobacillus-dominated vaginal microflora during the first trimester. Of these 77 women, 64 (83.1%) maintained normal vaginal microbiota throughout their pregnancy, whereas 13 (16.9%) women converted to abnormal vaginal microbiota during the second or third trimester. Women with *L. gasseri* and/or *L. iners* were 10 times (RR = 9.49, 95% CI 1.30–69.40; $P = 0.009$) more significantly likely to convert from normal to abnormal vaginal microbiota during pregnancy compared with women with *L. crispatus*-dominated vaginal microbiota. Overall, it was concluded that the species composition affects the stability of the vaginal microbiome in pregnancy.

Romero et al extended these findings by conducting a retrospective case-control longitudinal study of 22 healthy, pregnant women (delivering at term) and 32 healthy, nonpregnant women to characterize the vaginal microbiota during normal human pregnancy. They found that pregnant women had a higher abundance of *L. crispatus*, *L. gasseri*, and *L. jensenii* and a lower abundance of 22 other phylotypes (many associated with CST IV-A and IV-B) over time compared with nonpregnant women.[59] In this study, CST IV-B or CST IV-A were characterized by a high relative abundance of species of the genus *Atopobium* as well as *Prevotella*, *Sneathia*, *Gardnerella*, *Ruminococcaceae*, *Parvimonas*, *Mobiluncus,* and other taxa previously shown to be associated with BV. The authors of this study hypothesized that maintaining a CST dominated by *Lactobacillus* spp. during pregnancy may confer a protective role against ascending infection of the genital tract during this time.

These same investigators subsequently conducted a nested case-control study of pregnant women delivering at term (controls) versus those with spontaneous preterm delivery before 34 weeks of gestation (cases) to determine if any significant differences could be found within the vaginal microbiome of women with preterm versus term delivery.[60] Interestingly, the authors found no difference in the relative abundance of bacterial taxa in the vaginal microbiome between women with spontaneous preterm delivery and those who delivered at term. In addition, no differences in the frequency of vaginal CSTs between women with spontaneous preterm delivery and those who delivered at term. However, the results of this study were limited by a small sample size (i.e., only 18 patients with preterm delivery were included). In contrast, a prospective case-control study [61] of 49 pregnant women by DiGiulio found that prevalence of a *Lactobacillus*-poor vaginal community state type (CST 4) with high levels of *Gardnerella* or *Ureaplasma* was inversely correlated with gestational age at delivery ($P = 0.0039$). The study also found that most women experienced a postdelivery disturbance in vaginal microbiota characterized by a decrease in

Lactobacillus spp. and an increase in diverse anaerobes such as *Peptoniphilus, Prevotella*, and *Anaerococcus* spp. This disturbance was unrelated to gestational age at delivery and persisted for up to 1 year after delivery. Reasons for the discordance between the results of this study and that of Romeo et al[59] are likely multifactorial including differences in the racial composition of the study cohorts, the timeframe of pre-term birth cases, and whether or not pre-term birth was spontaneous or nonspontaneous.[61] Identifying signatures/markers in the vaginal microbiota for predicting premature birth should be a focus of future research efforts.

Hyman et al have also assessed the diversity of the vaginal microbiome and its potential association with preterm birth in a prospective study of 88 pregnant women.[62] *L. crispatus* was found to be highly abundant in the vaginal microbiome of white women, whereas *L. iners* was highly abundant in African American and Hispanic women. Species diversity was greatest among African American women. The investigators found that diversity of the vaginal microbiome correlated with preterm birth and that race and ethnicity were important variables. Of the 19% of women with preterm birth (among the 88 women followed), 15% were Hispanic, 18% were white, 25% were African American, and 25% were Asian.

Overall, studies conducted to-date have revealed that the vaginal microbiome becomes less diverse and more stable during pregnancy and is largely dominated by *Lactobacillus* spp.[59] Data collected thus far suggest that the distribution of predominate vaginal CSTs during pregnancy varies by population, race, and ethnicity. It is not clear, however, what precipitates the shift from normal vaginal microbiota to abnormal vaginal microbiota. Whether such shifts in CSTs are a result of (i) the initial loss of vaginal lactobacilli, potentially caused by behavioral activities or other inciting events, (ii) sexual acquisition of a sexually transmitted pathogen that leads to complex changes in the vaginal microbiota or (iii) sexual acquisition of a polymicrobial consortium of microorganisms is not clear.[63] Further, the influence of sexual activities on the vaginal microbiota during pregnancy is not well defined.

VAGINAL MICROBIOME: NEXT STEPS

Much previous research related to the vaginal microbiome are limited by small sample sizes, and thus more research is needed. Further, research is needed to identify biomarkers associated with adverse pregnancy outcomes in both uninfected women and those infected with STIs. Future cohort or banked sample studies will assess the species composition and regulation of the vaginal microbiome during pregnancy, and will examine the severity of STIs and pregnancy outcomes. Those studies are necessary to define the relevant endpoints and clinical outcomes in both pregnant and nonpregnant populations and examine variables such as race and sexual behavior. However, the lack of standardization with regard to vaginal microbiome testing platforms is a challenge that must first be addressed.[63, 64] From that work, greater insight will be gained into STI etiology in pregnancy and biomarkers/predictors of various outcomes including preterm labor, membrane rupturing, still birth, early neonatal infections, and immune modulation. A number of clinical studies of vaginal probiotic supplementation with or without antimicrobials to improve vaginal dysbiosis or pregnancy outcomes are either underway or planned (https://clinicaltrials.gov/ct2/results?cond=&term=vaginal+probiotics&cntry=&state=&city=&dist=) however vaginal probiotics are not currently recommended for vaginal dysbiosis in the CDC STD Treatment Guidelines.[65]

GAPS AND CLINICAL ISSUES IN STI PREVENTION/CONTROL

Gaps in Prevention and Control of Congenital Syphilis

Congenital syphilis cases are on the rise in the United States, and in 2017, there were 918 cases of congenital syphilis reported to the CDC. To address the rise in syphilis among pregnant women, as well as men who have sex with men, the CDC issued a call to action[66] for communities impacted by congenital syphilis and other groups who have a role to reduce the burden of infection through research, treatment, and outreach. The CDC call to action encourages key stakeholders to: Create new tools to detect and treat syphilis and increase testing in order to control the further spread of syphilis, and to improve electronic medical records in order to improve patient outcomes. In the call to action, the CDC also published a list of stakeholders that they believe need to take action. The CDC Division of Sexually Transmitted Disease (STD) Prevention (DSTDP) is undertaking a number of activities including, ongoing epidemiological research and analysis of surveillance data; convening local, state, and national partners to foster connectivity and the promotion of best practices; developing and applying care cascade and case review board practices to support in-depth analysis of medical care gaps and congenital syphilis rates.

There are also state-level activities taking place. In 2017, the CDC awarded nine state and local health department STD programs a total of US $4 million in order to enhance their congenital syphilis responses. The goals of that program were to make sustainable improvements to congenital syphilis related activities, strengthen prevention through prospective information gathering and interventions and retrospective activities to identify opportunities for change. Key activities included improving data collection of maternal and fetal epidemiologic and clinical risk factors; improved ascertainment of pregnancy status among female syphilis cases; strengthening congenital syphilis morbidity and mortality case review boards; matching syphilis surveillance data with vital statistics; and strengthening partnerships with maternal and child health programs and healthcare providers.

In addition to resources provided directly by the CDC, funding is provided to support the National Network of STD Clinical Prevention Training Centers (NNPTC) to assist clinicians in the United States with the skills, knowledge, and experience that they need to address and prevent STDs in their patients. The NNPTC provides regional based in-person clinical training, as well as online resources, including the STD clinical consultation network (CCN (www.STDCCN.org)) and the national STD curriculum that can be found at www.std.uw.edu. The curriculum includes seven self-study modules with an individual progress tracker and provides free continuing education credits.

CLINICAL ISSUES RELATED TO STIs AND PREGNANCY

Bacterial and viral STIs have an influence on pregnancy outcomes and pregnancy can modify the manifestation of some STIs. Thus, the timeliness of treatment during pregnancy is essential to avoid adverse outcomes.

Neonatal herpes simplex virus (HSV) infection occurs in anywhere from 1 in 3,000 to 1 in 10,000 pregnancies.[67] An estimated 1,500 cases of neonatal HSV occur each year in the US and more than 100 babies die from neonatal herpes.[67] Neonatal HSV can be caused by either HSV-1 or HSV-2; however, two-thirds of cases in the Americas are caused by HSV-1.[67] Worldwide neonatal HSV occurs in 10.3 per 100,000 live births and two-thirds of

cases are caused by HSV-2.[67] Among pregnant women in the US, HSV-2 has a seroprevalence between 20% and 30% and HSV-1 has a seroprevalence of 60%.[68] Approximately 10% of HSV-2 seronegative women have a seropositive partner, while up to one-third of women of childbearing age are seronegative for HSV-1 and HSV-2 and 3.7% of those women will acquire either virus during pregnancy.[68]

Eighty-five percent of babies who develop neonatal HSV acquire the disease during labor and delivery.[69] Most transmissions occur during asymptomatic shedding and most women have no signs or symptoms. A study conducted on women giving birth found that in recurrent HSV infection the risk of mother-to-child transmission (MTCT) is quite low and that the risk of MTCT is highest during the first episode of genital HSV.[69] Although most benign forms of neonatal HSV occur in the skin, eyes or mouth, 1 in 4 neonates will have a life-threatening disseminated infection.[70] Incorporation of antiviral drugs during pregnancy, especially during the third trimester, can reduce the clinical occurrence of maternal HSV at the time of delivery by 75%.[71] Antiviral suppression can also reduce the number of cesarean deliveries by 40% and can reduce viral shedding at the time of delivery by 90%.[71] There is insufficient evidence about whether antiviral suppression late in the third trimester can prevent neonatal herpes. Other strategies to reduce neonatal HSV include routine screening and better diagnostic tools to confirm whether a suspicious legion is herpes. Rapid point-of-care tests for HSV shedding would be helpful in reducing cesarean deliveries and would allow neonatologists to implement early antiretroviral therapy in infants born to mothers with HSV shedding at the time of birth.

There are approximately 2 million cases of syphilis in pregnant women worldwide and syphilis is associated with adverse pregnancy outcomes.[6] Over the last 5 years, there has been an 87% increase in congenital syphilis worldwide.[25] Timely treatment is essential in preventing congenital syphilis, as over one half of pregnancies in women with untreated syphilis will result in adverse outcomes.[72] Implementation of point-of-care testing and/or rapid tests are essential in order to detect syphilis earlier in pregnancy and to reduce/prevent congenital syphilis worldwide.[73, 74] In addition, standard of care treatment for pregnant women with syphilis is the same as the standard of care treatment for non-pregnant women. Penicillin is the recommended treatment to prevent MTCT of syphilis and for treating neonatal infection. Alternative treatments for syphilis can also be problematic; for instance, there is limited data about the use of ceftriaxone in pregnant women to prevent congenital syphilis.[75] Additional barriers to treatment of syphilis especially in pregnant women include penicillin shortages and failure by insurers to cover fully penicillin for syphilis treatment.[76] There are also concerns about the impact of the opioid epidemic on syphilis and individuals who are unable or unwilling to seek care.

Neisseria gonorrhoeae infections during pregnancy increase the risk for preterm birth, premature rupture of membranes, intraamniotic infection, low birth weight, and postpartum endometritis.[77–79] Screening pregnant women who are at risk for NG infections could help to reduce MTCT of both HIV infection and NG infection.[17] Researching alternative treatments is also important as the only currently recommended regimen for NG in pregnancy is ceftriaxone and azithromycin and there are limited options for alternative regimens for patients with allergies or those with antibiotic resistance.[19]

Antenatal CT infection is also associated with preterm birth, low birth weight, intrapartum fever, and late postpartum endometritis.[80] Alternative treatment regimens are also urgently needed especially for those with intolerance or allergies to current treatment regimens.

Trichomonas vaginalis infection is associated with vaginal and systemic immune activation, as well as preterm delivery and low birth weight.[81] However, questions remain about whether at-risk pregnant women should be screened for TV infection. For example, a previous study of screening and treating asymptomatic TV during pregnancy did not reduce preterm delivery.[82]

In summary, because STIs in pregnancy may have serious adverse consequences, timely diagnosis and treatment are important. The data on some STIs in pregnancy are limited and dated. There is a lack of data on comorbidities. Advances in diagnostics should be used to optimize screening for, and treatment of STIs in pregnancy to prevent maternal morbidity, adverse pregnancy outcome, and, transmission to the neonate. Finally, effective anti-infective therapies are needed to address issues such as antimicrobial resistance and must be studied in pregnant women.[83]

GLOBAL ALLIANCE TO PREVENT PREMATURITY AND STILLBIRTH BIOREPOSITORY

The mission of the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) is to reduce the burden of preterm birth and stillbirth by advancing collaborative research in order to identify, develop, and implement evidence-based solutions.[84] The GAPPS Biorepository was created in 2009 and opened in 2012 through philanthropic support. The GAPPS Biorepository provides a unique and widely accessible international biobank with comprehensive maternal and newborn phenotypic data linked to high-quality tissue biospecimens at several timepoints from early pregnancy through childbirth and postpartum, which includes diverse populations and geographies. The GAPPS Biorepository model supports many types of research ranging from parturition to adverse pregnancy outcomes including origins of chronic disease, genetics/biology, pathophysiology, molecular etiology, epidemiology, diagnostics and biomarkers, translational science, health care delivery, and new therapies/prevention solutions. Participants are enrolled early in pregnancy with ultrasound dating of gestational age and receive period follow-up during each trimester of pregnancy, and at birth and during the postpartum period. Standardized clinical, nutritional, and demographic data linked to biospecimens and pregnancy case records with standardized classification of complications and adverse outcomes are collected. The GAPPS Biorepository provides state of the art systems for the collection, preservation, managed access, and quality assurance of robust standardized data for pregnancy and newborn cohorts that buildout and support a global network of biorepositories in order to enable data sharing and/or specimen transfer and accelerate research. In addition, efforts continue to develop new, harmonized international repositories for underrepresented populations. To date, the GAPPS Biorepository has enrolled more than 4,500 women in Bangladesh, 3,000 women in the US and 1,500 women in Zambia.

The GAPPS Biorepository program is designed to be self-sustainable, by addressing challenges to biobanking, including up-front collection costs, regulatory burdens, participant retention, supply chain, maintenance of technical equipment and data management, and anticipating needs to design relevant specimen/data collections. The GAPPS Biorepository provides many collaborative opportunities and a unique value proposition by improving efficiencies, shortening research throughput, and reducing research costs while providing the potential for follow up study of children born to enrolled mothers and creating agnostic infrastructure for future clinical trials and emerging multidiscipline research that ultimately benefit public health.

CLINICAL RESEARCH PRIORITIES MOVING FORWARD

Three main clinical research priorities were identified (Table 1). There is an urgent need to identify more STI treatments, especially for

TABLE 1. Identified Clinical, Laboratory, and Policy Priorities to Address STIs in Pregnancy

Clinical Research Priorities
1. Alternative treatments for STIs during pregnancy
2. Routine screening with point-of-care rapid diagnostic testing for STIs during pregnancy globally
3. Further research into the vaginal microbiome
Laboratory Priorities
1. Assess STI test performance in pregnant vs. nonpregnant women
2. Develop further point-of-care tests
3. Develop microbial based biomarkers for adverse pregnancy outcomes
4. Research in pathogenesis of intrauterine infection/inflammation and the link between vaginal dysbiosis and intrauterine infection/inflammation
Policy Priorities
1. Create Office of STI Research at the NIH.
2. Increase national policies that create and require monitoring of standard antenatal care screening recommendations and treatment practices
3. Include congenital syphilis in Infant Fetal and Infant Mortality Reviews
4. Expand Federal funding for STD clinics to increase access
5. Increase STI screening and treatment in PEPFAR-supported programs
6. Add STI screening and treatment as part of integrated antenatal care packages globally

pregnant women. A starting point is with studies of drugs that are known to be safe and efficacious in nonpregnant adults. The use of animal models and/or conducting retrospective trials in countries where alternative therapies are used could provide useful preliminary data. Cord blood studies and ex vivo studies may serve as possible avenues to improve the treatment of STIs in pregnancy.

Adequate infrastructure, personnel capacity, and cost-effectiveness remain challenges to the implementation of routine STI screening in pregnant women. Point-of-care rapid diagnostic testing could provide solutions to some challenges, particularly in low- and middle-income settings, because they are easy to use and patients can collect their own samples. More evidence is needed demonstrating the feasibility of application, scale-up, and cost-effectiveness of STI screening during pregnancy, particularly studies that compare point-of-care versus off-site testing and multiple versus single STI testing.

Finally, there is a need for greater understanding about the relationship between the vaginal microbiome and STI transmission and acquisition.

LABORATORY PRIORITIES

There are also four main laboratory priorities (Table 1). There is an urgent need to develop novel point-of-care rapid diagnostic tests that target pregnant women. Novel point-of-care rapid diagnostic tests should be handheld, easy to operate, cost effective, and should return results quickly so that patients may be quickly treated. Development of such novel point-of-care tests could help reduce transmission of STIs and be used as a triage tool or confirmatory device to help reduce overtreatment. To reduce costs, improve the ability to detect and treat comorbidities, and improve maternal and perinatal outcomes, new STI tests should be designed to be able to detect multiple pathogens.

Studies have shown some promise related to the use of the vaginal microbiome as a predictor of pregnancy outcomes; however, markers have shown a very small impact in terms of public health. Larger studies are needed to validate before testing studies are implemented. Further, it is necessary to move from exploratory studies toward longitudinal studies. Finally, more research is needed in to the pathogenesis of intrauterine infection/inflammation and how vaginal dysbiosis can cause intrauterine infection/inflammation.

POLICY PRIORITIES

In the US, the creation of an Office of STI Research at the National Institutes of Health (NIH) would allow for better integration of STI research policies and priorities, especially as relevant to HIV research while working in conjunction with the Office of AIDS Research. Policies should be implemented that create and require the monitoring of standard antenatal care screening recommendations and treatment practices across the US. Given the recent upsurge in STIs in the US, funding increases for the CDC's STD prevention efforts and the Centers of Excellence in STI Treatment are needed. In the context of a congenital syphilis crisis, it would be useful to expand the Fetal and Infant Mortality Review to include congenital syphilis. Utilizing federal funding to expand the number and hours of local STD clinics could better serve communities at risk. Highlighting jurisdictions that are doing well with STI screening and treatment, especially during pregnancy, could incentivize improvements in care. Furthermore, PEPFAR supported initiatives should increase STI screening, testing and care programs, and at least 20% of funding from PEPFAR and the Global Fund should be focused on STIs.

Routine STI screening during pregnancy should be included in the WHO guidelines. The WHO recently published antenatal care guidelines that include HIV, syphilis, urinary tract infection, malaria, and anemia screening, depending on the geographic location.[85] If enough evidence is not available to do so, the WHO should convene a meeting including relevant experts to identify research gaps and plan a program to address those gaps. Providers and researchers also need to continue to request an integrated approach to antenatal and postnatal care inclusive of STI screening and treatment in policy and practice.

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