STIs & WOMEN'S HEALTH: INFERTILITY & ADVERSE PREGNANCY OUTCOMES

PHASES 1 & 2 SUMMARY PRESENTATION

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START CENTER
STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER

PHASE I

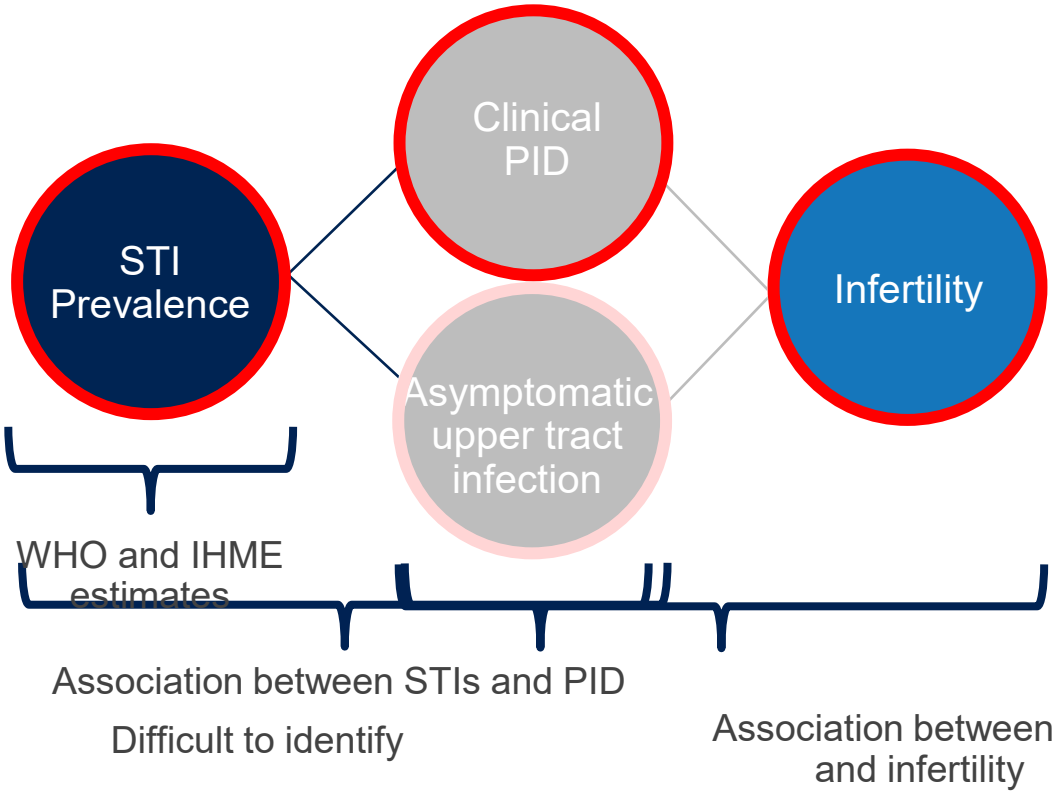
PROJECT OBJECTIVES

Understand the extent to which STIs contribute to infertility in LMIC settings

Assist in building the case for increased resource allocation to STI prevention, diagnostics, and treatment

ESTIMATING ASSOCIATIONS

Pathway between STIs and Tubal-Factor Infertility



SUMMARY OF EVIDENCE

Chlamydia	• Overall evidence suggests that chlamydia is an important cause of PID • Two randomized trials provide evidence that screening and treatment may reduce PID • Need additional clinical trials to evaluate effects of screening and treating on incidence of chronic pelvic pain and infertility

Existing Clinical Trials – Screening for Chlamydia to Reduce PID Incidence

1. Scholes 1996

- RR = 0.44 (95% CI: 0.20-0.90)
- Incidence of PID among women screened = 8 per 10,000 woman-months
- Incidence of PID among controls = 18 per 10,000 woman-months

2. Oakeshott 2010

- RR = 0.65 (95% CI: 0.34-1.22)
- Incidence of PID among women screened = 1.3%
- Incidence of PID among controls = 1.9%

SUMMARY OF EVIDENCE

Chlamydia	• Overall evidence suggests that chlamydia is an important cause of PID • Two randomized trials provide evidence that screening and treatment may reduce PID • Need additional clinical trials to evaluate effects of screening and treating on incidence of chronic pelvic pain and infertility
Gonorrhea	• Evidence of an association between gonorrhea and PID, but less compared to chlamydia • Limited ability to determine impact of historical infections due to lack of gonorrhea antibody tests • No clinical trials to date evaluating gonorrhea prevention strategies to reduce incidence of PID
M. genitalium	• Moderate evidence of an association between *M. genitalitum* and infertility • Mixed evidence of an association between *M. genitalium* and PID • Need initial clinical trials to examine effect screening and treating on PID and related outcomes
T. vaginalis	• Low quality epidemiological studies in literature review • Potential for high impact given elevated prevalence of *T. vaginalis* in SSA and SEA
Syphilis	• No demonstrated association between syphilis and PID • Limited evidence of association between syphilis and infertility with low quality evidence

CONCLUSIONS

Strong evidence to support focusing investments on chlamydia

- Strongest evidence for association with PID and with infertility
- Only randomized trial evidence among five key STIs

Modest evidence for gonorrhea as cause of PID

- Mixed evidence for gonorrhea as cause of infertility
- Lower prevalence and concentration among key populations may position gonorrhea as a lower priority for investment

M. genitalium may be an important emerging priority for research

- Prevalence close to that of chlamydia
- Unique opportunity to compare screen & treat vs. SOC approach for multiple outcomes as screen & treat is not currently recommended

CONCLUSIONS

Need to clarify association between *T. vaginalis* and PID/infertility

- Potential for large impact given elevated prevalence of *T. vaginalis* in sub-Saharan Africa and Southeast Asia

Limited evidence for associations between syphilis and PID/infertility

- Remains an important cause of long-term health consequences for women and infants (e.g. congenital syphilis)

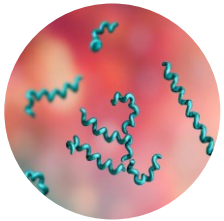
PHASE II

PROJECT GOALS

OVERARCHING OBJECTIVE: to build a comprehensive case regarding the impact of STIs on women's health.

- **Building on Phase I findings focusing on the impact of STIs as a cause of infertility.**
- **Broadening this scope to adverse pregnancy outcomes.**

SUMMARY OF FINDINGS: SYPHILIS & APOs



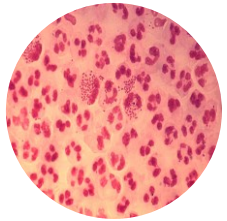
1. There is strong evidence of an increased risk of **stillbirth**, **preterm birth,** and **low birth weight** following maternal syphilis infection

2. Clearly established strong association between **preconception syphilis** and spontaneous abortion

3. **Congenital syphilis** is prevalent among infants born to mothers with syphilis. **Prevalence of congenital syphilis has been shown to** increase with progression of pregnancy (with higher proportions being detected in the later trimesters)

4. There were **limited findings** in recent literature for its association with **SGA** and **no recent evidence** for **PROM, PPROM** and **ectopic pregnancy**

SUMMARY OF FINDINGS: GONORRHEA & APOs



1. Overall, the evidence establishing a significant association between gonorrhoea and all the APOs is less consistent. There evidence is moderate for **preterm birth**, **low birth weight**, and **stillbirth**

2. Gonorrhea had a consistent positive association with **PROM**. There was a significantly high risk of **PPROM following maternal gonorrheal infection** (Whelan 2021), suggesting that gonorrhea has a substantial impact on the likelihood of PPROM

3. There is an established increased risk of **SGA infants** following maternal gonorrhea infection (Heumann, 2017), however with **limited** findings in recent literature for its association with **spontaneous abortion,** and **lack** of recent evidence for its association with **neonatal infection** and **ectopic pregnancy**

SUMMARY OF FINDINGS: CHLAMYDIA & APOs

1. Higher number of studies, though primarily of lower quality, are readily available and inform increased risk of *Chlamydia* for all adverse pregnancy outcomes studied (particularly with **spontaneous abortion** where data was more limited, but significant association seen)

2. Positive association seen among **preterm birth**, **PPROM** & **low birth weight,** with lower association established for **small for gestational age** among neonates

3. Lack of recent data for association with **neonatal infection**, with recommendation for screening and treatment in pregnancy, and **ectopic pregnancy**

SUMMARY OF FINDINGS: M. GENITALIUM & APOs

1. Among smaller pool of findings, studies show inconsistencies in association with adverse pregnancy outcomes. More evidence based required for significant takeaways

2. Absence of evidence requiring screening/treatment during pregnancy could allow for future opportunities for innovative research design

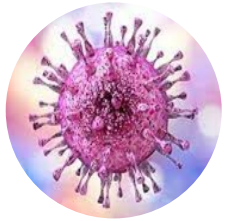
SUMMARY OF FINDINGS: TRICHOMONIASIS & APOs

1. There are inconsistent findings between trichomoniasis and various APOs. Further evidence-based studies are needed

2. There was a moderate to high association between *T. Vaginalis* and PTB, PROM/PPROM, LBW, spontaneous abortion, and SGA

3. The strength of the association between T. Vaginalis & APOs (particularly SAB & PROM) was attenuated after adjusting for co-infection with other STIs

SUMMARY OF FINDINGS: HSV & APOs

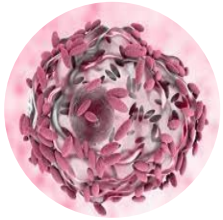


1. There are inconsistent findings between HSV and different APOs. More evidence-based studies are warranted

2. There was a moderate to strong association between HSV and PTB, PROM, LBW, and SB

3. Although no recent literature was included, HSV is a very well known neonatal infection with devastating consequences. Serological tests for HSV-2 and vaccines are needed

SUMMARY OF FINDINGS: BV & APOs



1. Clear association between *BV* and **PTB** in all three systematic reviews & meta-analyses examined and **preterm PROM** in one systematic review & meta analysis

2. Studies examining the effect of treating *BV* on reducing the rate of PTB, however, have all yielded null results (including RCT published in 2023)

3. Pre-conception *BV* was associated with very PTB (gestational age 28-32 weeks), but this association was attenuated when stratifying by co-infection status and examining independent infection with *BV*

4. Evidence regarding the association between BV and other APOs is mixed

CONCLUSIONS

1

Strong Evidence for Syphilis & APOs:

- The link between syphilis and nearly every APO is well-established.
- Treating syphilis reduces these outcomes, but in lower resource settings, screening and treatment is implemented poorly.

2

Moderate to Mixed Evidence for Chlamydia, Gonorrhea, BV & APOs:

- Chlamydia, gonorrhea, and BV are all associated with certain APOs, but no clinical trials showing that screening and treating these STI reduces the risk of APOs.

3

Limited Evidence for Trichomoniasis, HSV, M. gen & APOs:

- Trichomoniasis, HSV, and M. gen show inconsistent results, with some studies indicating significant risks for preterm birth, PROM, and low birth weight, and others reporting null findings.

4

Quantification of the association between STIs and APOs, and determining whether these associations are causal, is limited by a lack of RCTs, variably defined outcomes, mixed study results, and limited data on coinfection and other confounding factors.

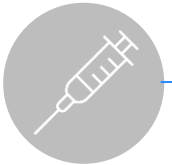
FUTURE OPPORTUNITIES

Clinical trials showing that screening and treating gonorrhea, chlamydia, and BV reduces APOs.

- However, there are several study design challenges that must be considered including whether single screen and treat will be adequate, ethical considerations, etc.

Building the evidence base for M. gen & trichomoniasis and APOs.

- Evidence is currently insufficient to recommend screening/treatment so filling in these gaps in the literature could be essential to informing recommendations.



Vaccines for syphilis and HSV

- Given the well-established relationship between syphilis and nearly all APOs and HSV and neonatal herpes, there is a huge need for syphilis and herpes vaccines to avert poor neonatal and maternal health outcomes

Better understanding how coinfection with BV (and other STIs) impacts risk of APOs.

- Evidence suggesting that *BV* with other STIs might result in different outcomes than BV alone or other STIs alone.