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A Commentary on Current Diagnostic Challenges and Research Needs for Evaluating Reproductive Sequelae of Sexually Transmitted Infections

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Abstract

Advancing the understanding of pelvic inflammatory disease (PID) requires access to advanced diagnostic approaches for evaluating reproductive sequelae of sexually transmitted infections (STIs). Current limitations of clinical criteria and advanced imaging technologies for diagnosing reproductive sequelae make diagnosis and surveillance of PID a challenge. We summarize and comment on major challenges in diagnostic evaluation of reproductive sequelae: limited point-of-care clinical diagnostic options for reproductive sequelae, economic and geographical obstacles to accessing state-of-the-art diagnostics, an expanding list of STIs that may cause reproductive sequelae and the complexities in evaluating them, and the need for coordinated research efforts to systematically evaluate biomarkers with gold-standard, well-defined specimens and associated clinical data. The future use of biomarkers in readily accessible mucosal or blood-derived specimens as a non-invasive approach to determining STI etiologies may be fruitful and requires more research. Biomarkers under consideration include cytokines, STI-specific antibody responses and mRNA transcriptional profiles of inflammatory markers.

Keywords

pelvic inflammatory disease; infertility; diagnosis; sexually transmitted infection; biomarker

Current Diagnostic Approaches for Sexually Transmitted Infection (STI) Sequelae Using Clinical Criteria and Imaging

Pelvic inflammatory disease (PID) diagnosis [1] relies on minimum clinical criteria from pelvic examination, with additional use of limited laboratory testing, basic imaging

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approaches, and/or endometrial biopsy to increase PID diagnosis specificity. Greater diagnostic sensitivity and specificity might be achieved by advancing imaging technologies [2] and the exploration of biomarkers for inflammation, STI, and reproductive sequelae [3–10]. This commentary summarizes challenges and obstacles for PID and infertility diagnosis and presents a list of research questions that may help overcome these challenges and advance the field.

Diagnostic Challenges

Historic and current obstacles to accurate PID and infertility diagnoses are schematically summarized in Figure 1.

Diagnostic Challenges During Acute Presentation

PID often presents in younger women with acute pelvic pain who seek care in emergency departments, often after business hours, with a need for immediate diagnosis and care. In such cases, a pelvic examination for determining PID diagnosis followed by presumptive antibiotic treatment is often the prescribed course of action despite low specificity of the exam, and there is often limited laboratory testing or imaging performed. Several obstacles to accessing more specific diagnostic tools under such circumstances exist: unavailability of advanced imaging technologies and/or needed specialized personnel after hours, and economic, geographic, and time constraints to obtaining advanced diagnostic testing to define the underlying causes of the presumptive PID diagnosis.

Access to infertility services

Women with untreated symptomatic PID or subclinical PID may develop infertility. Access to state-of-the-art diagnostic testing for infertility requires time with a specialist and is expensive; it also sometimes requires long-distance travel for some women. Infertility evaluation is mainly accessed by older women who often have more time availability and economic resources; however, there is still a great need and benefit for younger women to have access to infertility services.

Stigma

There is stigma associated with evaluation of STIs and reproductive sequelae. Sexual history questions, pelvic examinations, and invasive procedures can result in healthcare avoidance and normalization of pain. Non-invasive accurate tests for STI sequelae (e.g., tests performed on blood, urine, or even self-collected vaginal swabs) could help overcome stigma-related diagnostic challenges.

Overlapping syndromes with reproductive implications

Endometritis, salpingitis, tubo-ovarian abscess, pelvic peritonitis, and any combination thereof can be part of the spectrum of inflammatory disorders of the upper female genital tract comprising PID [1, 11]. These overlapping conditions are currently best diagnosed with specific imaging technologies, but they may also be associated with specific biomarkers or STIs. Differential associations are currently incompletely understood;

however, understanding these complexities better may be necessary for advances in PID diagnostics.

Multiple Possible STI Etiologies of Reproductive Sequelae

There are now multiple sexually transmitted pathogens associated with PID and infertility, and diagnostic testing for active infection with these pathogens may not capture infection that has resolved but causes persisting inflammation leading to these reproductive sequelae. While use of serology as evidence of past infection in women with reproductive sequelae for *C. trachomatis* is promising [3, 12], there are not good serological assays available for the other pathogens of interest (e.g., *N. gonorrhoeae* [4] and *M. genitalium* [5]). It may thus be difficult to develop a complete panel for serological evaluation for all STIs associated with reproductive complications.

Lack of validated biomarkers

There is an obvious need for and value of easily measured, validated biomarkers for PID, STI or both in accessible specimen types (i.e., mucosal and blood specimens) for diagnosing reproductive sequelae of STIs. Thus, future research activities will undoubtedly focus on progress in this area. In particular, hypotheses and ideas for exploring inflammatory factors or gene transcriptional signatures associated with syndromes are emerging and show much promise in addition to identifying pathogen etiologies [5, 6, 8–10].

Lack of validated specimen repositories

There is a previously identified and continuing need for accessible specimen repositories with associated clinical data [13, 14]. Such reference materials could be shared among researchers to compare and contrast new technologies, when used with gold-standard comparator data (i.e., associated with expert agreed-upon clinical diagnosis based on current state-of-the-art imaging technologies). Although specimen repositories exist, research studies using these repositories have been done in the past decade and they in general had small sample sizes. Larger studies using the repository samples and promising diagnostic approaches, such as measuring specific biomarkers, are needed.

Key research questions that will advance the field

In light of these challenges, we have summarized research needs and open questions for researchers in this field of study. Answers to these questions will advance this field and overcome these challenges with approaches grounded in evidence and science. They are:

1. PID diagnosis: Is there a need to amend or modify the currently recommended clinical criteria for PID diagnosis by including laboratory testing in the criteria for PID diagnosis? If so, what laboratory tests are supportive of a diagnosis of PID? Is there a need for more research on laboratory tests that predict PID? If so, what biomarkers or other laboratory tests should be evaluated? What best practices or standardization of laboratory tests are needed?
2. Can imaging technologies be further strengthened and standardized for the diagnosis of PID? Which imaging methods reflect best practices or could be

further strengthened? What is the evidence for the performance (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) of imaging in diagnosing PID and what is its added value (in performance and cost considerations) over clinical criteria and laboratory tests in diagnosing PID?

3. Diagnosing STI etiologies of PID – While nucleic acid amplification tests (NAATs) for *C. trachomatis, N. gonorrhoeae*, and *Trichomonas vaginalis* are already routinely performed for evaluating STI etiologies of PID, what is the added value for molecular testing for other potential STIs? What is the evidence for the role of these other etiologies in PID: *M. genitalium, Ureaplasma urealyticum*, Herpes Simplex Virus-1/2 (HSV-1/2), *Gardnerella vaginalis*, etc.? How would availability of point-of-care testing for *C. trachomatis* and *N. gonorrhoeae* and even *M. genitalium* impact treatment of women with clinical PID?

4. Diagnosing STI etiologies of infertility – Is there a need to modify current infertility diagnostic practices to include more laboratory testing for STIs? If so, what laboratory tests (e.g. serology, molecular tests, etc.) are most contributory in determining the STI(s) etiology of infertility? Is there a need for more research on laboratory tests for diagnosing STI etiologies for infertility? What is the added value of including laboratory testing for STI in those with infertility? What best practices or standardization of laboratory tests for STI in infertility are needed?

5. Is this field ready for development of target product profiles to guide laboratory testing for PID and infertility across multiple applications and populations? What technical and statistical methods need to be developed and applied for assay evaluation and analysis of laboratory test findings?

6. There is a need for a standardized repository of well characterized specimens (serum and other specimens from the reproductive tract) with associated, available clinical data to facilitate assay development and evaluation for PID and infertility. What populations and clinical data need to be included? Are there available cohorts? What considerations should guide development of cohorts?

Conclusions

A substantial research effort is needed to advance current diagnostic methods for PID and infertility. Such advances are expected to come from development of STI-specific biomarkers for these reproductive sequelae, such as immune or immunogenetic markers that can be readily measured in blood or genital specimens. Identification and validation of such biomarkers, used alone or in combination, is a research gap of the highest priority because of their potential to contribute to preventing or improving the management of reproductive sequelae of STIs.

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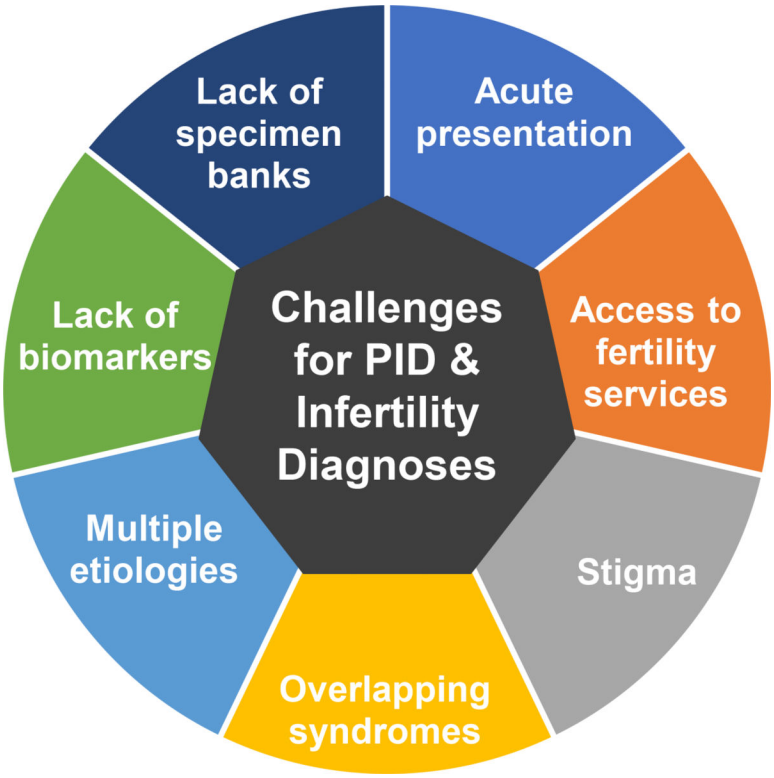

Figure 1.

Key challenges to pelvic inflammatory disease (PID) and infertility diagnosis: 1) limited clinical diagnostic options when patients present with acute symptoms of PID in the emergency department, 2) economic and geographical limitations in accessing diagnostic services for evaluating reproductive sequelae, 3) stigma of STI and reproductive sequelae serving as obstacles to diagnostic testing, 4) an expanding list of potentially causative sexually transmitted infections (STIs) and overlapping differential syndromes with reproductive sequelae, 5) and the need for a coordinated research effort to systematically evaluate accessible, affordable, and non-invasive biomarkers of STI-induced reproductive sequelae using gold-standard, well-defined specimens and associated clinical data.