North American Society for Pediatric and Adolescent Gynecology (NASPAG) Fellows
Research Consortium

**Protocol Title:** Retrospective review of pelvic inflammatory disease (PID) in pediatric and adolescent virgins through the NASPAG Fellows Research Consortium (FRC).

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**Background/Justification:**
Pelvic inflammatory disease (PID) is an infection of the female upper genital tract leading to inflammation of the uterus, fallopian tubes, and ovaries, and timely management of this condition is critical for prevention infertility, ectopic pregnancy, and chronic pelvic pain. While PID classically occurs in sexually active women, rare cases occur in virginal pediatric and adolescent patients. The majority reports of virginal PID are published as a case report or series, although one single-center retrospective review exists.

Most reports describe patients presenting initially with vague symptoms including abdominal or pelvic pain, fever, nausea, vomiting, dizziness, diaphoresis, dysuria, and leukocytosis. Tubo-ovarian abscess has been observed in some cases, but not all. Additionally, long-term complications include severe secondary dysmenorrhea requiring surgical intervention. Due these vague symptoms, as well as the rarity of virginal PID, cases are often initially misdiagnosed as other more common conditions, such as appendicitis or pyelonephritis.

Although *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are commonly identified as the source of infection in sexually active women, virginal PID cases report a wide variety of pathogens, including *Escherichia coli*, *Streptococcus pneumoniae*, *Bacteroides uniformis*, *Streptococcus milleri*, coagulase negative *Staphylococcus*, *Fusobacterium Nucleatum*, and *Abiotrophia/Granulicatella* species. Many cases are polymicrobial, and in some cases culture results are negative.

Several hypotheses exist for mechanism of infection in virginal pediatric and adolescent PID, and the most common theories include ascending vaginal infection, pooling of urine during urinary tract infection or due to obesity, and GI origin, including hematogenous bacterial seeding, Crohn’s Disease, and bowel translocation. Additional theories include a change in cervical secretion composition, pooling of urine due to labial agglutination, post-surgical infection, and infection secondary to reciprocal oral sex. Clinical details, as well the microorganism cultured, provide insight on the mechanism in specific patients, and variation in microorganism and clinical history between cases suggests that multiple mechanisms may be responsible for virginal PID. The exact mechanism of infection is unconfirmed in most cases, highlighting a need for a more comprehensive understanding of the virginal PID pathology.

Because PID presentation in virginal patients is uncommon, pathophysiology is poorly understood, and diagnosis is often missed at initial presentation, leading to a delay in treatment.
Due to the serious long-term sequelae of PID, sexually active women suspicious for PID are treated quickly with antibiotics; however, specific guidelines do not exist for virginal pediatric and adolescent patients. Most existing case reports describe initial presentation in the emergency department, and describe management with surgical intervention in addition to broad spectrum antibiotics, suggesting there may be a need for more aggressive management in virginal cases due to late diagnosis. Furthermore, little data exists on long term fertility and pain prognosis in virginal pediatric and adolescent PID patients. More information is needed to understand the mechanism of infection in this unique patient population, as well as to determine treatment methods used and and their efficacy, time to diagnosis, and incidence of long term PID sequelae. The NASPAG Fellows Research Consortium is an ideal a program for data collection in virginal PID cases due to its large patient population and multiple sites; thus, we propose to use this platform to further investigate virginal PID pathophysiology, treatment, and outcomes.

**Hypothesis:**
While a variety of mechanisms can cause virginal PID, the most common mechanisms are pooling of urine due to obesity or urinary tract infection, bowel or GU translocation, or ascending vaginal infection due to poor perineal hygiene.

**Research Goals and Objectives:**

**Primary Aim:**
Determine the most common mechanisms of action leading to PID in virginal pediatric and adolescent patients, including an assessment of the association of virginal PID with the onset of menses in the setting of medical co-morbidities such as history of radiation, GI pathology such as Crohn’s Disease and history of ruptured appendix, and poor perineal hygiene.

**Secondary Aims:**
1. Determine most common presentation of virginal PID in pediatric and adolescent patients
2. Determine time from initial presentation to diagnosis including reasons for delay in diagnosis
3. Determine treatments most often used and their efficacy in patients with virginal and adolescent PID
4. Investigation into long-term outcomes for virginal patients diagnosed with and treated for PID including recurrence, infertility, ectopic pregnancy, dysmenorrhea, and chronic pelvic pain

**Methods:**
Retrospective chart review through the NASPAG Fellows Research Consortium will evaluate demographic data such as race and age, as well as clinical variables, including comorbidities, medical history, surgical history, pubertal status, menstrual history, and symptoms apparent at initial presentation. We will also collect information regarding medical and surgical management, microbial organism identified, pathology documented, and time from initial
presentation to PID diagnosis. Finally, if available, we will collect information on long-term outcomes, including instance of recurrence, infertility, ectopic pregnancy, dysmenorrhea, and chronic pelvic pain.

Data will be entered by each site into RedCap database and managed by Medstar Health Research Institute’s Department of Biostatistics and Bioinformatics to ensure the same variables are being collected across all sites. Data will be de-identified and study number keys will be stored in locked drawers in the PI office at each site. Data collection sheets will be destroyed once the data is entered into RedCap.

**Participants:** Member institutions of the NASPAG Fellows Research Consortium if they choose to participate will obtain local institutional IRB approval for this study.

**Study Design:** A retrospective chart review study

**Inclusion Criteria:** All virginal females from birth to 25 years who have been diagnosed with PID.

**Exclusion Criteria:** Patients who are not virgins, patients older than 25, and patients without a documented PID diagnosis.

**Statistical Analysis:** This is planned as multi-site longitudinal retrospective study based on the data from the chart review of virginal PID patients. We are anticipating participation from 3 sites, and a preliminary query from these sites suggests approximately 10 cases per site; thus, we anticipate that our sample size will be 30. We do not

After collection of data from participating sites, appropriate statistical analysis will be performed on all patients included.

**Data Management:** Data will be entered into RedCap database and managed by Medstar Health Research Institute’s Department of Biostatistics and Bioinformatics in compliance with HIPAA regulation. All data will be de-identified as no personal identifiers will be collected.

**Confidentiality of Data**

All data collected via retrospective chart review will be de-identified. We will use secure data entry via Research Electronic Data Capture (REDCap) set up through the MedStar Health Research Institute. Data will be exported to institutional password protected computers and the survey will only be accessed by registered investigators with individual logon and password. A unique subject code will be developed to enable researchers to link the de-identified data base to the identified charts. Each site will maintain its own, separate code. We will use the medical record number linked to an individual subject number in the order that patients are identified (ie Subject 1, 2, 3, etc.). No patient identifiers will be collected. Any information exchanged between institutions will be done over secure, institution-based electronic mail and will not contain patient information or identifiers.
De-identified data will only be made available to investigators of the study. Site specific data will only be available to individual site investigators. Any additional studies performed using data collected under this protocol will require a separate, IRB approved protocol prior to data evaluation.

All keys linking PHI to study number will be stored in the PI's office in a locked cabinet and destroyed after all data has been collected and entered in the database. Paper forms linking PHI with participant study code will be discarded in a hospital designated trash can for shredding of confidential papers.

**Consent**
There will be no consent process for this retrospective chart review as many patients no longer receive care at the institutions where they were diagnosed. Thus, contacting patients for consent is not a viable option.

**Risks and Benefits**
Breach of data security is an important risk to consider when performing a retrospective chart review. Data de-identification and storage will be performed as outlined above with care not to bring any identifiable information into the data set as well as to protect the security of the data set and unique data set code.

The research subjects whose charts are reviewed are not likely to benefit directly from this research. However, future pediatric and adolescent virginal patients diagnosed with PID, as well as the health care professionals delivering medical care, will benefit from added knowledge regarding virginal PID.

**Compliance:** The trial will be conducted in compliance with our written protocol, the mandates of Health and Human Services (HHS), and all applicable institutional, state and local requirements.

**Feasibility:**
Given that the project is a retrospective chart review, RedCap database is made available to all Medstar affiliated fellows through the Graduate Medical Education, therefore creation and upkeep will be at no cost to investigators. We anticipate that IRB approval at various sites will be completed by Fall 2018. We anticipate given the overall small sample size, that data entry and analysis should not be time intensive and will likely be completed by Winter 2018. We understand that unanticipated difficulties may arise, and our timeline may be adjusted as appropriate. Also, the cost of this project will be minimal as it consists only of chart review and no additional research staff are necessary.
References

Proposed Data Collection for RedCap (to be completed by check-box, numerals, or few word answer for ease of collection over multiple sites; may be revised based on input from collaborators)

1. Age at diagnosis
2. Race
3. Pubertal status
   a. Pre-menarcheal
   b. Post-menarcheal
      i. Age at menarche
   c. Tanner stage
      i. Breast
         1. I
         2. II
         3. III
         4. IV
         5. V
      ii. GU
         1. I
         2. II
         3. III
         4. IV
         5. V
4. Medical History and Comorbidities
   a. Inflammatory bowel disease
   b. Obesity
   c. Lichen sclerosis
   d. Bowel obstruction
   e. Appendicitis
   f. Recurrent urinary tract infection
   g. Immunocompromised
   h. Other
5. Surgical History
   a. Abdominal surgery
   b. Pelvic surgery
6. Presentation
   a. Abdominal pain
   b. Pelvic Pain
   c. Nausea
   d. Emesis
   e. Fever
   f. Constipation
   g. Dysuria
   h. Urinary retention
   i. Diaphoresis
7. Gross Pathological Findings
   a. Cervical Discharge
b. Vaginal Discharge
   i. Present
   ii. Absent
   iii. Not reported

c. Pyosalpinx
   i. Unilateral
   ii. Bilateral
   iii. Absent
   iv. Not reported

d. Uterine Inflammation
   i. Present
   ii. Absent
   iii. Not reported

e. Vulvar Inflammation
   i. Present
   ii. Absent
   iii. Not reported

f. Peritoneal Exudate
   i. Present
   ii. Absent
   iii. Not reported

8. Microorganism Identified
   a. Number
      i. No organism identified
      ii. Single organism cultured
      iii. Polymicrobial
   b. Organisms Identified (genus and species)

9. Management
   a. Medical
      i. Number of antibiotics used
      ii. Duration of antibiotic course (in days)
      iii. Type of antibiotics used
      iv. Any other pharmacological intervention
   b. Surgical
      i. Laparoscopic exploration
      ii. Abscess drainage
      iii. Hysterectomy
      iv. Salpingectomy
      v. Appendectomy
      vi. Adhesion removal
      vii. Ovarian resection
      viii. Bowel resection

10. Time from initial presentation to diagnosis
a. Date of presentation
b. Date of diagnosis

11. Delay in diagnosis/Misdiagnosis
   a. Appendicitis
   b. Pyelonephritis
   c. IBD
   d. Pelvic tumor

12. Short-Term Complications
   a. Tubo-ovarian Abscess
   b. Sepsis
   c. None

13. Long-Term Complications
   a. None Known
   b. Recurrence within 12 months
   c. Dysmenorrhea
   d. Chronic Pelvic Pain
   e. Infertility
   f. Ectopic Pregnancy

14. Perineal Hygiene
   a. Good
   b. Poor
   c. Not Reported

15. Suspected Mechanism of Action
   a. Ascending vaginal infection
   b. Bowel or GU translocation
   c. Inflammatory bowel disease
   d. Complication of prior surgery
   e. Urinary tract infection and pooling of urine
   f. Pooling of urine due to obesity
   g. Other (write in)