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Factors associated with pelvic inflammatory disease: A case series analysis of family planning clinic data

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Abstract

Background: We aimed to better understand factors associated with pelvic inflammatory disease in an outpatient setting.

Methods: We analysed the characteristics of pelvic inflammatory disease cases diagnosed in an outpatient setting during 2018. There were 72 cases included in the final analysis.

Results: Of the pelvic inflammatory disease cases analysed, 55% were idiopathic, 22.2% were related to a sexually transmitted infection, and 22.2% had onset of symptoms within 6 weeks of a gynaecological procedure. Of the sexually transmitted infection–positive pelvic inflammatory disease cases, *Chlamydia trachomatis* was present in 56%, *Mycoplasma genitalium* was present in 38%, and *Neisseria gonorrhoeae* was present in 12.5% of cases. Many pelvic inflammatory disease cases had evidence of vaginal dysbiosis or features associated with vaginal flora disruption (recent antibiotic usage and/or vulvovaginal candidiasis).

Conclusion: This case series highlights the burden of *Mycoplasma genitalium* pelvic inflammatory disease, and clinicians should be aware to include testing for this when diagnosing pelvic inflammatory disease. Our findings also support the hypothesis that host dysbiotic microbiota may contribute to pelvic inflammatory disease pathogenesis, with further research required to explore this proposition.

Keywords

pelvic inflammatory disease, sexual health, sexually transmitted infection, women's health

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Introduction

Pelvic inflammatory disease (PID) is a clinical syndrome of ascending infection and inflammation of the female reproductive tract. Long-term sequelae of PID can include tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. It is a spectrum of disease with clinical presentation ranging from subclinical infection to severe acute symptoms.[1] In approximately 60% of cases with PID, no causative pathogen is identified.[2] Where a pathogen is identified, the sexually transmitted pathogens *Neisseria gonorrhoea* (NG), *Chlamydia trachomatis* (CT), and *Mycoplasma genitalium* (MG) may be implicated.[3] It may also be associated with gynaecological procedures such as intrauterine device (IUD) insertion and termination of pregnancy, and sexual behaviour risk factors such as recent change in partner, history of multiple sexual partners, and early age of sexual debut.[4,5]

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Given that PID can be associated with some bacterial vaginosis (BV)-related organisms and can occur in the absence of a sexually transmitted infection (STI), a dysbiotic microbiota may also be implicated in the development of this condition.[6,7] Molecular testing for known BV organisms has identified the endometrial presence of microbiota such as *Sneathia* (Leptotrichia) *sanguinegens, Sneathia amnionii, Atopobium vaginae*, and BV-associated bacteria 1 (BVAB1) in women with PID.[8,9] This frequent association with dysbiosis supports the hypothesis that evidence of dysbiosis (BV) and/or factors impacting the reproductive tract microbiota (such as recent antibiotic usage or recent vaginal candidiasis) could be risk factors for PID.

Our study aimed to analyse the characteristics of PID cases diagnosed at an outpatient family planning clinic during 2018.

Methods

We undertook a retrospective file audit of all PID cases diagnosed across five fixed Family Planning NSW clinic sites in New South Wales, Australia, during 2018 (1 January 2018 to 31 December 2018, with some follow-on analysis of early 2019 records). The clinics are outpatient settings in metropolitan and regional locations, providing sexual and reproductive healthcare services to people of all ages, including a dedicated youth drop in clinic at one regional site. Files were audited from 12 months prior to the diagnostic presentation and for 3 months after to exclude a subsequent alternative diagnosis and to assess the response to PID treatment. Audit was conducted *by the clinical investigator team members S.S. and W.H.* with consensus on interpretations reached. Audits were conducted every 3–6 months. A standardized criterion was used to extract data from case files which were entered into an audit tool spreadsheet. These data included age, ethnicity, symptoms at diagnosis, clinical examination findings at diagnosis, investigation results at diagnosis, response to treatment at follow-up, number of sexual partners in the preceding 12 months, any change in sexual partner in the preceding 3 months, antibiotic use in the preceding 12 months, vaginal symptoms typical of thrush or BV in the preceding 12 months, STI in the preceding 12 months, gynaecological procedure in the preceding 12 months, contraceptive use in the preceding 12 months, and relevant medical or medication history.

PID diagnosis was guided by the criteria outlined by the European Guideline for the Management of PID[10] and the Australian STI Management Guidelines.[3] Cases were included in the analysis if standardized diagnostic criteria were met and an alternative diagnosis was excluded. For the purpose of this audit, cases were grouped separately if the onset of symptoms occurred within 6 weeks of a gynaecological procedure.

Statistical analysis

The study was conducted as a pilot chart audit, so no power analysis was conducted to determine the sample size. The data were analysed by sub-groups to show frequency within each group, and due to the low numbers, chi-square tests were used to determine statistically significant differences in frequencies of variables between groups (single-variable analysis for each variable).

Ethical approval for this research was obtained from Family Planning NSW (FPNSW) Ethics Committee (R2016-07) and University of Technology Sydney (ETH16-0658). Consent requirements do not apply to this study, as identifiable data are not required. Data for this study were confidentially retrieved and de-identified by a sole FPNSW investigator.

Results

A total dataset of 298 files where PID had been identified as a reason for consultation via data collection software (DME Client®) was provided. After removal of duplicate files and exclusion of files with no evidence of a PID presentation, 96 medical records were audited.

A further 24 were excluded from the analysis. In most cases, this was because standardized diagnostic criteria were not met for diagnosis of PID, an alternative diagnosis was made at follow-up (e.g. appendicitis), or the case was lost to follow-up after initial diagnostic presentation.

This resulted in a total of 72 PID cases analysed. In all, 55.6% of these cases were of idiopathic aetiology (n = 40), 22.2% were STI pathogen–related (n = 16), and 22.2% were within 6 weeks of gynaecological procedure (n = 16) (summarized in Figure 1).

The 16 STI-associated cases included 5 MG (2 of which were azithromycin-resistant), 7 CT, 1 NG, 1 *Trichomonas vaginalis*, 1 with both CT and MG, and 1 with both CT and NG. Overall, 56% (9 cases) were associated with CT, 38% (6 cases) with MG, and 12.5% (2 cases) with NG.

Post-procedure PID included cases following IUD insertion (n = 15) or medical termination of pregnancy (n = 1), and were included in this group if they had onset of PID symptoms within 6 weeks of the procedure.

Over 50% of people with PID reported a single sexual partner in the 12 months preceding diagnosis, and 27% reported a recent sexual partner change in the 3 months preceding diagnosis. Recent sexual partner change was significantly associated with STI-related PID cases in our series, with 68.8% having had a recent partner change compared with only 18.8% in the post-gynaecological procedure groups and 15% in the idiopathic group (Table 1, $p = 0.001$, chi-square statistic).

Associated demographic, contraceptive, sexual behavior, and medical history features are presented in Table 1.

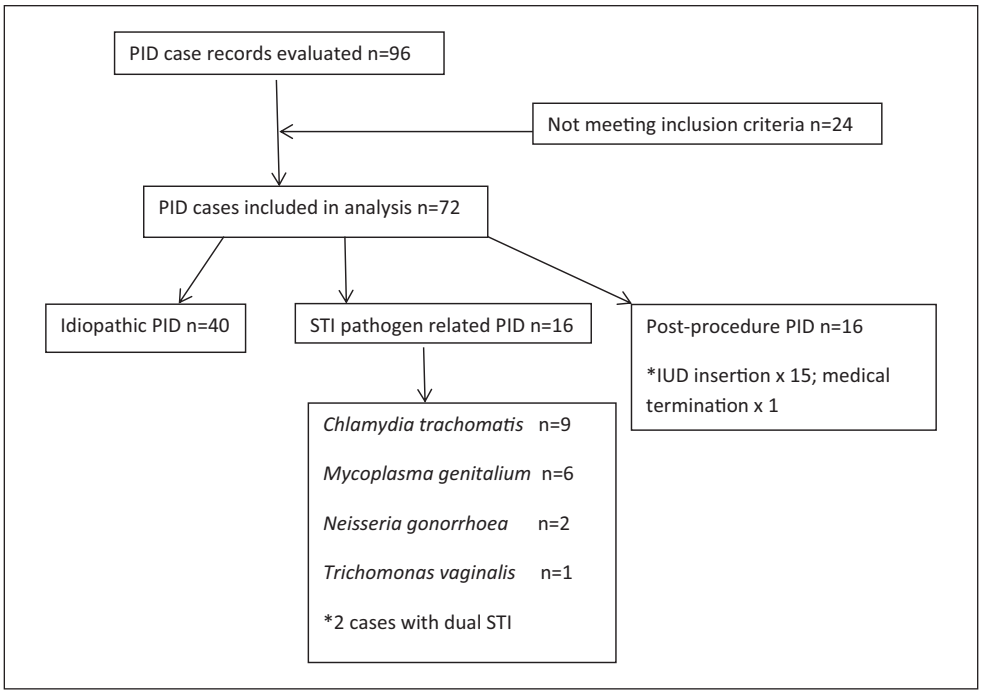

Figure 1. Flowchart of PID cases.

We observed that one in five PID cases had self-reported, or had an encounter in the medical record of, vaginal symptoms consistent with candidiasis or BV in the 12 months prior to PID diagnosis. This was lowest in the post-procedural group (12.5%) and highest in the STI-associated group (31.3%). Overall, just under one in four PID cases reported antibiotic usage in the 12 months prior to PID diagnosis. Just over 40% had vaginal symptoms at the PID diagnostic visit. These associations did not reach statistical significance.

Discussion

Our analysis provides valuable insights into factors associated with PID cases diagnosed and managed in an outpatient setting. This case series demonstrates that idiopathic PID (55%) continues to represent a large disease burden, which is in line with previously published findings.[2,11] This supports the hypothesis that factors other than currently recognized STIs and gynaecological procedures are involved in PID aetiology, including reproductive tract microbiome factors,[12] or that the infection has ascended and therefore pathogens are not isolated on samples from the lower reproductive tract.[13] Our group is working to further evaluate how these host and microbial factors are involved in PID.[14] Understanding more about these factors may lead to future improved diagnostic tools, targeted therapies based on host microbial and pathogenic factors, and preventive strategies such as optimization of the vaginal microbiota. In the meantime, it is important for clinicians to ensure PID is included as differential diagnosis in presentations of pelvic pain in the absence of an STI and be aware that a negative STI result does not exclude PID.

A finding from our analysis relates to the pathogens identified in STI-related PID cases, with CT being present in 56% of cases, MG in 38% of cases, and NG in 12.5% of cases. There was one case of PID associated with trichomonas and two cases with dual STI infection present – one with NG and CT, and one with CT and MG. Two of the MG cases were macrolide-resistant infections. Overall, MG was present in 8.3% of total PID cases, a finding consistent with secondary analysis of the English POPI (prevention of pelvic infection) study where 9.4% of PID was attributable to MG infection.[15] It is imperative that clinicians diagnosing PID include testing for MG in their investigations in line with European, UK, and Australian guidelines for people presenting with PID.[1,10,16] Moxifloxacin is recommended as first-line treatment for women with MG PID.[1,10] Antimicrobial resistance is a rapidly evolving challenge in the management of MG, and consideration of a laboratory which offers resistance testing is important.[1]

Recent sexual partner change was significantly associated with STI-related PID cases in our series, with 68.8% in this group reporting recent partner change. However, sexual behaviour risk factors were not associated with other PID types. Over 50% of people with PID reported a single sexual partner in the 12 months preceding diagnosis, and 27% overall reported a recent sexual partner change in the 3 months preceding diagnosis. This is in

Table 1. Features associated with PID cases.

	Total PID, n = 72	Idiopathic PID, n = 40	STI-related PID, n = 16	Post-procedure PID, n = 16	p value*
Age mean (range)	26.1 (15–47)	26.8 (16–47)	25.3 (17–40)	26.4 (18–43)	
Contraception at diagnosis, n (%)					
No contraception	9 (12.5)	4 (10)	5 (31.3)	0	0.004
Oral Contraception	13 (18.1)	8 (20)	3 (18.7)	1 (6.25)	
Levonorgestrel 52 mg IUD (Mirena®)	23 (31.9)	10 (25)	3 (18.7)	12(75)	
IUD – copper	10 (13.9)	7 (17.5)	1 (6.3)	3(18.75)	
Contraceptive implant (Implanon NXT®)	5 (6.9)	4 (10)	0	0	
Depot medroxyprogesterone acetate injection	4 (5.6)	3 (7.5)	0	0	
Unknown	8 (11.1)	4 (10)	4 (25)		
Sexual partners in the preceding 12 months, n (%)					
1	41 (57)	24 (60)	6 (3.5)	11 (68.8)	0.187
2	14 (19.4)	7 (17.5)	5 (31.3)	2 (1.3)	
3 and above	9 (12.5)	3 (7.5)	4 (25)	2 (1.3)	
Unknown	8 (11.1)	6 (15)	1 (6.3)	1 (6.3)	
Partner change in the preceding 3 months	20 (27.4)	6 (15)	11 (68.8)	3 (18.8)	0.001
Clinical features at PID diagnosis, n (%)					
Recent-onset pelvic pain	65 (90)	35 (87.5)	14 (87.5)	16 (100)	0.455
Deep dyspareunia	36 (50)	24 (60)	7 (43.8)	5 (31.3)	0.261
Abnormal vaginal bleeding	41 (57)	21 (52.5)	10 (62.5)	10 (62.5)	0.696
Vaginal symptoms[a]	31 (43)	17 (42.5)	6 (37.5)	8 (50)	0.857
Lower abdominal tenderness	31 (43)	18 (45)	6 (37.5)	7 (43.8)	0.935
Bimanual tenderness					
Adnexal	44 (61.6)	24 (60)	10 (62.5)	10 (6.3)	0.790
Uterine	35 (48.6)	19 (47.5)	7 (43.8)	9 (56)	0.617
Cervical	42 (58.3)	28 (70)	9 (56)	5 (31.3)	0.209
Cervicitis	49 (68.1)	24 (60)	11 (68.8)	14 (87.5)	0.331
Fever	6 (8.3)	2 (5)	2 (12.5)	2 (12.5)	0.209
Factors noted in the preceding 12 months, n (%)					
Vaginal symptoms (candidiasis, BV)	15 (20.8)	8 (20)	5 (31.3)	2 (12.5)	0.766
Any antibiotic use	18 (24.7)	11 (27.5)	3 (18.8)	4 (25)	0.924
Indications for antibiotic use in the preceding 12 months					
STI treatment (% of total group)	7 (38)	5 (12.5)	1 (6.3)	1 (6.3)	0.947
Previous PID	4 (22)	3 (7.5)	1 (6.3)		
Vaginal infection	3 (16)	1 (2.5)	1 (6.3)	2 (12.5)	
Other	4 (22)	2 (5)		1 (6.3)	

PID: pelvic inflammatory disease; STI: sexually transmitted infection; IUD: intrauterine device; BV: bacterial vaginosis.
[a]Any vaginal symptoms other than abnormal bleeding self-reported in the medical record at the diagnostic visit.
*Statistical test for differences in frequency between the groups, chi-square statistic, not adjusted for multiple variables.

line with previous research which has demonstrated that pathogen-negative PID is less likely to be associated with sexual risk and recent partner change.[11] This may challenge traditional clinician thinking that PID always directly correlates to STI risk and supports a move towards considering PID in the differential diagnosis even in the absence of traditional STI and sexual behaviour risk factors.

Cases were grouped separately if the onset of symptoms occurred within 6 weeks of a gynaecological procedure to avoid confounding. Given the PID–IUD relationship is complex, meaningful interpretation for this group is beyond the scope of this small observational series.[17]

In the 12 months preceding PID diagnosis, 24.7% of patients self-reported having had, or had a documented provision in the medical record of, antibiotic therapy for any reason including an STI or BV. It was relatively common for PID cases to report symptoms suggestive of vaginal flora disruptions such as vulvovaginal candidiasis and/or BV at the time of diagnosis, in the 12 months prior to a PID diagnosis, or to have had an attendance recorded within the preceding 12 months for these conditions. The pathophysiology and potential risks associated with the development of PID are likely distinct for these different dysbiotic conditions; however, the observation additionally supports the hypothesis that host dysbiotic microbiota

may contribute to PID pathogenesis,[12] and further research is required to explore this proposition.

Strengths and limitations

This case series represents a small dataset and relies on self-reporting for some associated clinical factors including a prior history of symptoms typical of candidiasis or BV and antibiotic use in the 12 months prior to PID diagnosis. The case series nature of this audit meant that calculation (power analysis) of the sample size selected in this study was not performed. We also acknowledge that the clinical diagnosis of PID is challenging and that diagnostic threshold may vary between clinicians. However, the specialized nature of family planning consultations and high levels of clinician experience as well as the strict inclusion criteria are likely to have minimized the chance of misdiagnosed cases in the dataset.

Conclusion

Our key findings include showing MG as an important pathogen in STI-related PID, and that dysbiotic host reproductive tract microbiota likely contributes to PID pathogenesis. Importantly, our findings reinforce the guidance that clinicians should include testing for MG at the time of PID diagnosis in line with current national and international guidelines. Further research is required to more clearly define the role of vaginal dysbiosis in PID and its implications for improved diagnosis, management, and potential prevention.

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Author cotribution(s)

Sally Sweeney: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing.
Deborah Bateson: Formal analysis; Supervision; Writing – review & editing.
Kirsteen Fleming: Formal analysis; Writing – review & editing.
Wilhelmina Huston: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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Ethical approval, consent to participate, and consent to publication

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Data availability statement

De-identified raw audit data can be supplied upon request.

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