The treatment of mild to moderate pelvic inflammatory disease with a short-course azithromycin based regimen versus ofloxacin plus metronidazole: results of a multicentre, randomised controlled trial

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Abstract (word count 299)

Objective: A multicentre, randomised non-inferiority trial compared the efficacy and safety of 14-days of ofloxacin and metronidazole (standard-of-care [SoC]) versus a single dose of intramuscular ceftriaxone followed by 5-days of azithromycin and metronidazole (intervention arm [IA]) in women with mild to moderate pelvic inflammatory disease (PID).

Methods: Women with a clinical diagnosis of PID presenting at sexual-health services were randomised to the SoC or IA arms. Treating clinicians and participants were not blinded to treatment allocation but the clinician performing the assessment of primary outcome was blinded. The primary outcome was clinical cure defined as ≥70% reduction in the modified McCormack pain score at day 14-21 after starting treatment. Secondary outcomes included adherence, tolerability and microbiological cure.

Results: Of the randomised population 72/153 (47.1%) reached the primary end point in the SoC arm, compared to 68/160 (42.5%) in the IA (difference in cure 4.6% (95% CI -15.6,6.5%). Following exclusion of 86 women who were lost to follow-up, attended outside the day 14-21 follow-up period, or withdrew consent, 72/107 (67.3%) had clinical cure in the SoC arm compared to 68/120 (56.7%) in the IA, giving a difference in cure-rate of 10.6% (95% CI -23.2-1.9%). We were unable to demonstrate non-inferiority of the IA compared to SoC arm. Women in the IA took more treatment doses compared to the SoC group ((113/124 [91%] cf. 75/117 [64%], p=0.0001), but were more likely to experience diarrhoea (61% compared to 24%, p<0.0001). Of 288 samples available for analysis, *M. genitalium* was identified in 10% (28/288), 58% (11/19) of which had baseline antimicrobial resistance-associated mutations.

Conclusion: A short-course azithromycin based regimen is likely to be less effective than the standard treatment with ofloxacin plus metronidazole. The high rate of baseline antimicrobial resistance supports resistance testing in those with *M. genitalium* infection to guide appropriate therapy.

Key words: Pelvic inflammatory disease, azithromycin, *Mycoplasma genitalium*, ofloxacin.

Trial registration: European Clinical Trials database (EudraCT number 2010-023254-36)

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INTRODUCTION

Pelvic inflammatory disease (PID) is the most significant complication of sexually transmitted infections (STI) in women, causing serious reproductive morbidity and chronic pelvic pain[1,2]. Recommended antibiotic regimens for PID are taken for 14-days and have a clinical cure rate up to 90-97%[3]. However, treatment success rests with the patients' ability to adhere to therapy. Previous studies show that a 14-day course of doxycycline is completed in only 30-70% of cases[4,5] with side-effects and symptom resolution being the main reasons for non-adherence. The recommended alternative to doxycycline in UK and European PID guidelines, is twice-daily ofloxacin[6,7]. Whilst better tolerated, 7-31% of women still experience side-effects[8,9] and it also requires a 2-week course with a high tablet burden. Thus, of all women starting a 14-day course of antibiotics, only approximately 70-80% will experience full resolution of symptoms by the end of treatment[8,10,11]. Guidance from the European Medicines Agency (EMA) restricting the use of quinolone antibiotics[12], further increases the need to evaluate alternative regimens.

PID is associated with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* with studies in the 1980s and 1990s detecting these organisms in 50-77% of cases[13,14,15]. However, more recent literature suggests that only 17-35% of women with PID test positive for either pathogen, and many cases have an unidentified microbiological aetiology[16,17].

Mycoplasma genitalium is associated with a significantly increased risk of PID[18], and despite guidelines recommending testing all women with suspected PID, this has not yet been widely adopted [19]. This is important because current recommended therapies specify antibiotics with low efficacy against *M. genitalium*[7,20]. Clearance of mycoplasma after doxycycline is poor and older fluoroquinolones, including ofloxacin, have limited activity[21]. Azithromycin has demonstrated efficacy against mycoplasma, is well tolerated, and its long half-life allows shorter-course regimens which may improve adherence. However reports of treatment failure suggest the rapid emergence of antibiotic resistance, with global resistance reported in 30-100% of cases[21,22,23,24]. Despite this an extended course of azithromycin remains recommended for *uncomplicated* urogenital *M. genitalium*

infection where the organism remains macrolide-susceptible[19]. Few studies have examined the efficacy of an extended azithromycin regimen in the treatment of *complicated* urogenital infection.

Our aim was to assess the clinical efficacy and safety of a two-week course of treatment (standard-of-care [SoC]) compared to a short-course azithromycin-based regimen (intervention arm [IA]) in women presenting with mild-moderate PID.

METHODS

Trial design

This was a multicentre, open-label, non-inferiority, randomised controlled trial comparing SoC (14-days of twice-daily ofloxacin 400mg and metronidazole 400mg – total of 56 tablets), with IA (one intramuscular ceftriaxone injection 500mg followed by 5-days of azithromycin [1g day one, 500mg once daily days 2-5] plus twice-daily metronidazole 400mg – total of 16 tablets plus 1 injection) for the treatment of mild to moderate PID. All agents could be taken with or without food, although women were advised to take metronidazole with food if they experienced gastrointestinal upset. The study protocol was approved by Brighton & Sussex University Hospitals NHS Trust ethics committee (EC Reference Number: 10/H1107/70). Written informed consent was obtained from participants.

Eligibility criteria

Women with a clinical diagnosis of PID attending one of nine UK sexual health outpatient clinics from November 2011-August 2015 were invited to participate.

Inclusion criteria were a clinical diagnosis of PID based on pelvic pain for less than 30-days with adnexal tenderness on examination. Exclusion criteria were: age <16-years; severe PID requiring hospitalisation; positive pregnancy test or breast-feeding; urinary tract infection (positive leucocytes/nitrites on urinalysis); intracellular gram-negative diplococci on microscopy or contact of gonorrhoea within 3-months; antibiotics within previous 7-days; known allergy to study drugs; ultrasound scan showing other pelvic pathology; history of epilepsy/severe depression.

Two substantial protocol amendments were made prior to the start of recruitment (increase in ceftriaxone dose (250mg to 500mg) in-line with national guidelines; incorporating nucleic acid amplification tests (NAATs) for *N. gonorrhoeae* identification (Aug 2011)) and several amendments were made during the trial period (additional study sites (2012-15); simplifying inclusion criteria from 'direct lower abdominal tenderness (with or without rebound tenderness) and adnexal tenderness'

to ‘adnexal tenderness’ (Nov 2012); removal of the exclusion criterion 'absence of cervical pus cells’ (Nov 2012); addition of £20 travel reimbursement at day 14-21 visit (Mar 2015).

Study assessment: Baseline demographic and medical history data were collected. Examination included an assessment of pelvic and abdominal tenderness using the modified McCormack pain-score[25] (Table 1).

Table 1: Modified McCormack signs and scoring system for abdominal and pelvic tenderness[25]

Twelve parameters are used to calculate the pain score:
• DIRECT tenderness in each abdominal quadrant (4)
• REBOUND tenderness in each abdominal quadrant (4)
• cervical motion tenderness (1)
• uterine tenderness (1)
• right and left adnexal tenderness (2)
Each parameter is scored as follows:
0 tenderness absent
1 tenderness described by the patient but not manifested by changes in facial expression or muscle tone
2 tenderness resulting in altered facial expression or muscle tone
3 tenderness causing observable, marked distress
Total score is a sum of the values. The maximum score is 36.

Vaginal specimens were examined for bacterial vaginosis (BV) using light microscopy, tested for *C. trachomatis*, *N. gonorrhoeae* using NAATs (BD ProbeTec™ CT/GC Qx SDA assay), and *M. genitalium* using in-house real-time PCR assay targeting the MgPa adhesion gene [26]; endocervical specimens were sent for gonorrhoea culture/susceptibility.

Following treatment women were advised to have sexual abstinence for 14-days and return if symptoms worsened within 48-72 hours. Partner notification was initiated. Women taking ofloxacin and subsequently found to have gonorrhoea on NAATs were switched to the IA if clinical response was considered inadequate.

14-21 day follow-up: Repeat clinical examination and sampling for *N. gonorrhoeae* (if culture positive at baseline) was undertaken. If symptoms persisted after this visit then clinical review was arranged according to local protocols. Adverse events were documented.

If *C. trachomatis*, *N. gonorrhoeae* and/or *M. genitalium* were diagnosed at baseline, the participant was invited for a test-of-cure at 6-8 weeks. Mycoplasma positive samples were tested for molecular markers of macrolide and fluoroquinolone antimicrobial resistance (AMR) at the national reference laboratory (Public Health England). Molecular resistance assays targeted the 23S rRNA, *gyrA* and *parC* genes[27].

Outcomes:

The primary outcome was clinical cure at 14-21 days, defined as ≥70% reduction in the modified McCormack pain-score compared to baseline. Any woman who required a treatment switch prior to 14-days (e.g. due to side-effects), did not complete therapy or did not return for the 14-21 day assessment was also considered to have experienced treatment failure. The secondary outcome measures were adherence (residual pill-count, self-reported adherence), tolerability (incidence of nausea, vomiting, bloating, fatigue, dizziness, rash, diarrhoea), and microbiological clearance. An additional secondary outcome was to identify AMR in cases where *M. genitalium* was identified.

Sample size:

The sample size was calculated based on 80% of women in the SoC arm achieving a reduction in modified McCormack score of ≥70%. Non-inferiority was defined as a lower 95% confidence interval of no more than 10% difference in response rate for the IA compared to the SoC, requiring a sample size of 198 women in each treatment arm (396 in total, 80% power, one-sided alpha=5%). As women who failed to return for the 14-21 day assessment were assumed to be treatment failures in the analyses, no inflation was made for loss-to-follow-up.

In August 2015 the trial was terminated by the Drug Safety Monitoring Board because slow recruitment and a higher than expected loss-to-follow-up rate which meant that the required sample-size was unlikely to be reached.

Randomisation

Blocked randomisation, with blocks of varying size and stratified by study site, was used to generate randomisation lists. Medication allocation was kept in sealed, sequentially numbered, identical opaque containers by an independent company thus concealing the assignment from the research team.

This was not a blinded trial since use of placebo would have removed the potential benefits of the IA. Thus, to reduce assessment bias, the clinician performing the 14-21 day assessment of outcome was blinded to the treatment allocation, and women were asked not to reveal this information to the examining clinician.

Statistical methods

The intent-to-treat population included all randomised patients, regardless of whether the treatment was taken or participants returned for follow-up. This allowed a comparison to be made between the efficacy of the two drug treatment strategies incorporating any difference in adherence, which had been postulated to be a potential benefit of the IA. A conservative approach was taken by classifying all treatment switches and discontinuations as 'failures'.

The difference in the primary endpoint or 'cure' was calculated between the two groups and a 95% confidence interval was calculated for the difference. These analyses were performed in both the intent-to-treat (defined above) and per-protocol populations (defined as excluding women who switched, discontinued or failed to return for the 14-21 day assessment).

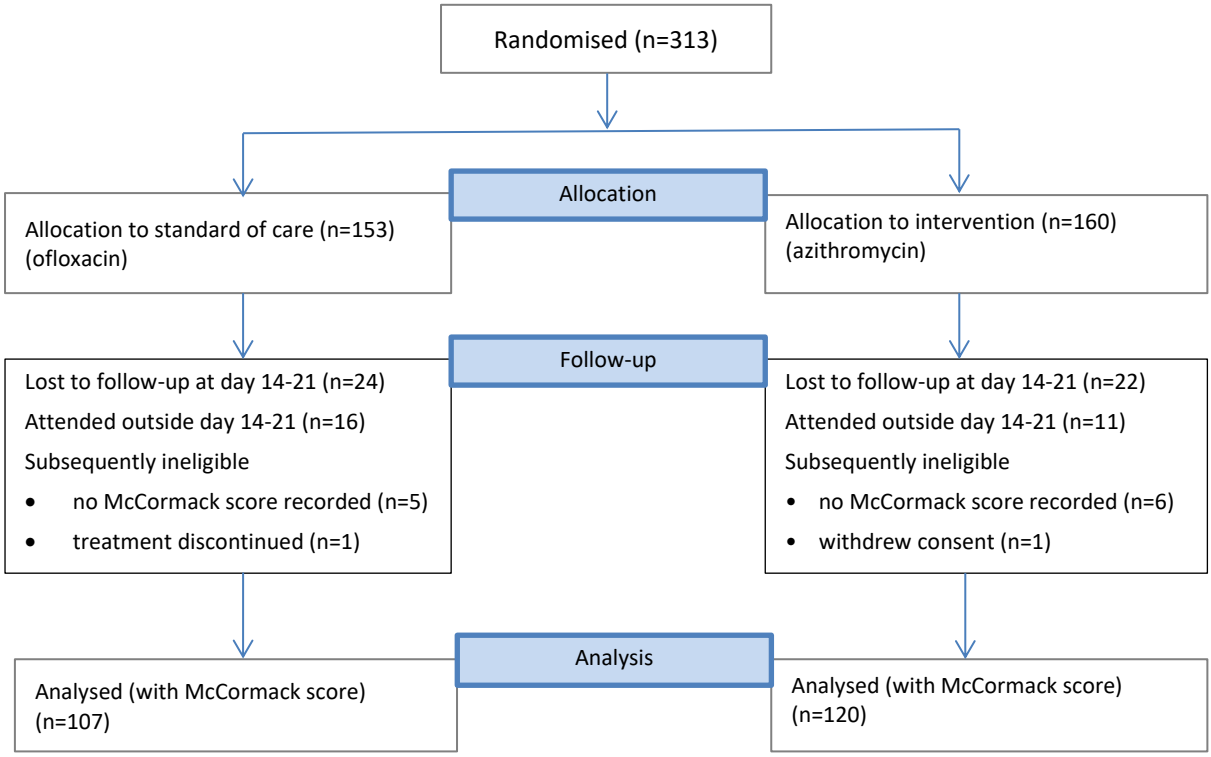
Secondary endpoints in the intent-to-treat population were compared between the two treatment arms using Chi-squared tests. Non-attending women were assumed not to have any side-effects. We did not impute data on adherence and therefore the proportions reporting complete/good adherence were calculated in the subgroup of women who reported adherence data.

RESULTS

Patient recruitment

A total of 313 women with PID were randomised across nine UK sites of whom 227 had primary outcome data available for analysis (Figure 1).

Figure 1: Randomised and eligible populations in standard of care and intervention arms



Patient characteristics

Participant baseline characteristics were similar between the treatment groups (Table 2).

Table 2: Demographic characteristics, baseline symptoms and microscopy

	Ofloxacin (SoC) (n=153)	Azithromycin (IA) (n=160)
Age (years), median (range)	25 (17-47)	25 (16-52)
Ethnicity, n (%)		
White UK / non UK / other	114 (74.5)	124 (78.1)
Black African / other	20 (13.1)	23 (14.4)
Previous PID, n (%)		
Yes	45 (29.4)	45 (28.1)
No	97 (63.4)	109 (68.1)
Unknown	11 (7.2)	6 (3.8)
Previous chlamydia, n (%)		
Yes	49 (29.4)	54 (33.8)
No	93 (60.8)	100 (62.5)
Unknown	11 (7.2)	6 (3.8)
Number sexual partners last 3 months median (range)	1 (0-50)	1 (1-130)
Lower abdominal pain (%)	147 (96.1)	150 (93.8)
Vaginal Discharge (%)	99 (64.7)	103 (64.4)
Deep dyspareunia (%)	75 (49.0)	91 (56.9)
Intermenstrual bleeding (%)	41 (26.8)	35 (21.9)
Dysuria (%)	36 (23.5)	40 (25.0)
Post coital bleeding (%)	27 (17.7)	38 (23.8)
Bacterial vaginosis (%)	45 (29.4)	51 (31.9)
Cervical pus (>30 PMNLs/hpf)*		
Present (%)	119 (77.8)	124 (77.5)
Absent (%)	24 (15.7)	21 (13.1)
Urine dip		
Nitrites (%)	1 (0.7)	2 (1.3)
Leucocytes (%)	41 (26.8)	30 (18.8)
Median McCormack scores (range)	9 (1-26)	8 (2-20)
Number positive ***N gonorrhoeae***	0	1
C. trachomatis	15	12
M. genitalium	13	15

*PMNLs/hpf: polymorphonuclear lymphocytes per high power field

Of the randomised population 72/153 (47.1%) reached the primary endpoint in the SoC arm, compared to 68/160 (42.5%) in the IA, giving a difference in cure of 4.6% (95% CI -15.6, 6.5%). Proportions in the per-protocol population were 72/107 (67.3%) and 68/120 (56.7%), respectively (difference: -10.6%, 95% CI -23.2, -1.9%). As the lower limit of each confidence interval fell below -10%, we were not able to demonstrate non-inferiority of the IA.

Information on adherence was available for 241 individuals. Among these, women in the IA were more likely to take all treatment doses (113/124 (91.1%)) compared to the SoC arm (75/117 (64.1%), p=0.0001). Similar proportions took $\geq$5-days of metronidazole (107/110, 97.3% SoC; 105/113, 92.9% IA; p=0.23), however only 69.1% (76/110) completed all 14 days of metronidazole in the SoC arm.

Safety

Two hundred and thirty three participants (111 in the control arm and 122 in the IA) provided safety data and, as noted above, women without follow up safety data available were assumed not to have side-effects in this analysis. There were no significant differences in reported side-effects between the groups (Table 3) with the exception of diarrhoea which was more common in the IA (98/160 (61.3%)) compared to the SoC arm (37/153 (24.2%), p<0.0001).

Table 3: Incidence of side effects among women randomised to SOC or IA arms.

	Ofloxacin (SOC) n=153 n (%)	Azithromycin (IA) n=160 n (%)	P value*
Nausea	77 (50.3)	80 (50.0)	1.00
Vomiting	23 (15.0)	19 (11.9)	0.51
Bloating	52 (34.0)	51 (31.9)	0.78
Fatigue	66 (43.1)	56 (35.0)	0.17
Dizziness	55 (36.0)	44 (27.5)	0.14
Rash	9 (5.9)	17 (10.6)	0.19
Diarrhoea	37 (24.2)	98 (61.3)	0.0001

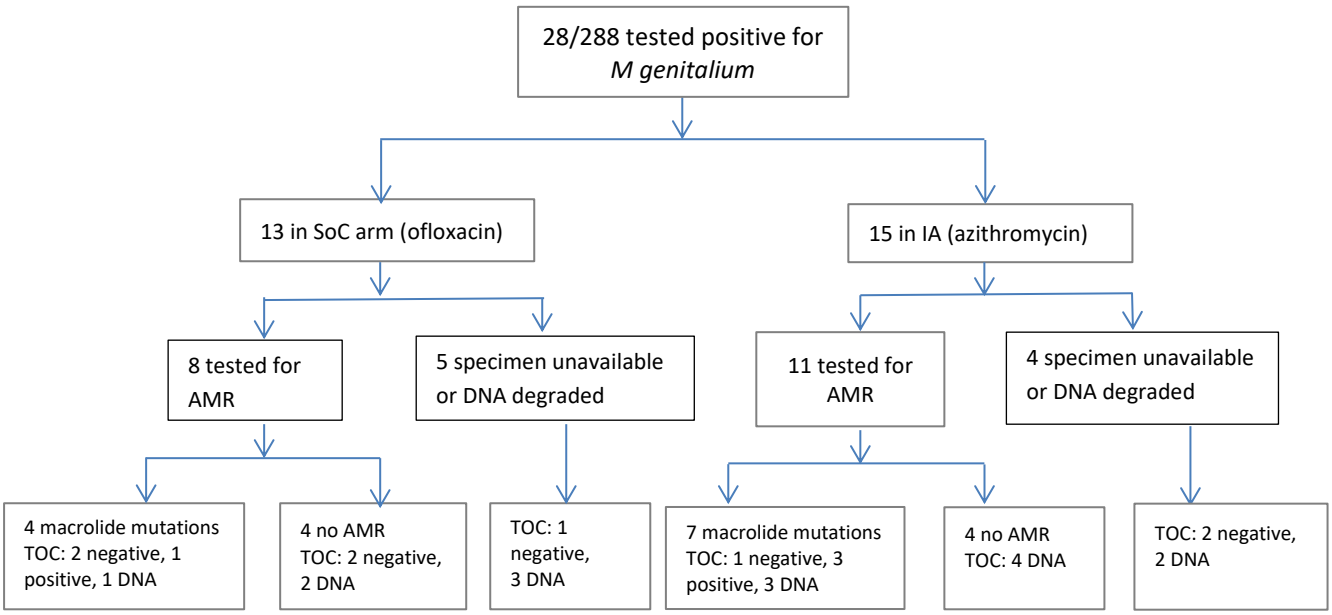
*P value using Chi-squared test

Patients with diarrhoea were asked to grade the severity (one woman in each group failed to grade severity). A higher proportion reported moderate to very severe diarrhoea in the IA (72% (69/97)) compared to those in the SoC arm (27% (10/36)).

Microbiology

Eighty-per-cent of participants had no pathogen identified. Twenty-seven women tested positive for *C. trachomatis* (9.6%) and one woman for *N. gonorrhoeae* (0.4%). Specimens for *M. genitalium* testing were received at the reference laboratory for 288 (92%) women. Twenty-eight of these tested positive for *M. genitalium* (9.7%), and 10 of these women (3.4%) were co-infected *C. trachomatis*. Of the 28 M.genitalium positive specimens, 23S rRNA sequencing data were available for 19 (70.4%)of which 11 (57.9%) carried macrolide AMR-associated mutations at baseline, prior to receiving any study drugs. Test-of-cure samples were received for 12 of these cases (63.2%) of which 8 (66.7%)) were negative and 4 (33.3%) remained positive (3 randomised to IA; 1 to SoC) (Figure 2).

Figure 2: *M genitalium* results including follow-up and test of cure (TOC)



*DNA = did not attend for follow-up

Two women (1 from each arm) who remained positive for MG following treatment subsequently received moxifloxacin and became symptom free. The remaning 2 were lost to follow-up. There was no evidence that AMR developed during the study period. A specimen from one patient in the SoC arm was found to contain *M. genitalium* harbouring resistance mutations in both the 23S rRNA and *parC* genes that have been associated with clinical treatment failure to both macrolide and quinolone antibiotics[28,29,30,W1]. This patient reported resolution of symptoms but was lost-to-follow-up before a test-of-cure specimen was received.

DISCUSSION

This is the first trial to assess a regimen based on a short-course of azithromycin in women with mild-moderate PID, using a pragmatic approach which reflects usual clinical practice. Whilst the primary outcome was defined as a ≥70% reduction in pain at 14-21 days, overall **treatment success** also reflected compliance with the protocol *and* engagement in care. Thus the definition of treatment failure included not only persistent pain, but also antibiotic switches, failure to re-attend, and follow-up outside the specified window of 14-21 days, which allowed us to incorporate adherence to the **treatment strategy** into our endpoint. This pragmatic approach was chosen to better reflect routine clinical care in Sexual Health Services (SHS). Consequently the proportion of women 'cured' in this study (47.1% SOC; 42.5% IA) was lower than observed in other PID trials[3,8,10,w2,w3]. Disappointingly 23.3% of women either did not return for evaluation at 14-21 days (14.7%), or were ineligible due to attending outside day 14-21 (8.6%). In retrospect the follow-up window of 7-days may have been too restrictive for a young population. To allow comparison with previous trials, we also analysed the subgroup of women who returned for evaluation within the predefined time period (the per-protocol population). Whilst cure rates were higher (SoC: 67.3%, IA: 56.7%), they remained below other published trials[3,8,10,w2,w3], possibly reflecting the mild nature of PID in this study (median McCormack scores 8-9). A limitation of the modified McCormack pain-score is the difficulty in achieving a 70% reduction in pain if a woman starts with a low baseline score. Possibly as a consequence of not reaching the planned sample size, we were unable to demonstrate that the short-course was non-inferior to the standard longer course of antibiotics although our findings suggested that the azithromycin based-treatment may be inferior to the control treatment.

Adverse events were reported by a high proportion of women compared to other studies. Gastrointestinal side-effects predominated: 50% of women in both groups recorded nausea compared to 2-20% in the literature[8,w4,w5]. We were particularly interested in tolerability of the increased dose and duration of azithromycin, and therefore women were required to record any issues on a questionnaire and were also asked by the research nurse if they had experienced specific

side-effects, and this specific enquiry may have contributed to a higher rate of reporting. Rates of diarrhoea were also higher than previously described, especially in the IA (61% vs 24%), with more women grading it as moderate to very severe (72% vs 27%). Despite these side-effects, levels of adherence were high, with more women in the IA taking all treatment doses (91% vs 64%), which is consistent with other studies comparing similar PID regimens[w5].

This multi-centre randomised study recruited relatively high numbers of women despite falling rates of PID diagnoses seen in SHS over the study period [w6]. Baseline characteristics were similar and the high rates of previous chlamydia (33%) and PID (29%) suggest a population at ongoing risk. The study did however fail to meet the target sample-size despite increasing the number of sites and a time extension. During the study period there were significant challenges to national SHS provision[w7,w8]. In April 2013 responsibility for commissioning of services was transferred to local government through the Health and Social Care Act[w9]. Subsequent financial pressures at a time of growing demand, along with service fragmentation, impacted on the research capability of participating centres. Tendering resulted in clinics being destabilised either by procurement or integration with Contraception Services e.g. change in service provider where research was not prioritised, services split onto multiple sites in less convenient locations, introduction of new electronic patient records resulting in lengthier waiting-times for prospective participants. A weakness of the study was the high loss-to-follow-up reflecting a young and often mobile population in inner-city locations. Whilst ethical approval was received to introduce a travel-reimbursement to increase retention, this was implemented too late to have an impact.

We found low rates of *C. trachomatis* (9.6%) and *N. gonorrhoeae* (0.4%) consistent with declining rates in some other studies. In 2011, Burnett et al found only 4.4% gonorrhoea, 10% chlamydia, and 2.6% with both organisms in women diagnosed with PID[16]. Price et al [17] estimated the overall population excess fraction of PID due to C*. trachomatis* was 20% (decreasing from 53.5% in women aged 16-19 years to 11.5% in women aged 35-44 years) leaving a high proportion of women with unexplained or non-STI aetiology, including microorganisms associated with BV. Goller et al[w10]

highlighted that women with clinical PID but no identified pathogen were older, less likely to have vaginal inflammation, or report recent unprotected sex. They comment that either these women had PID caused by as yet unidentified organisms, or they didn't have PID at all. In our study, 80% of women had no identifiable microbiological aetiology, although, in-line with other PID studies, 30% had BV at baseline. BV has been noted to be frequently present in women with PID (up to 70%), but whether BV-associated bacteria independently cause PID, whether they facilitate the ascension of known pathogens, or whether they are simply innocent bystanders is yet to be determined.

This study has provided one of the first estimates of how much PID is associated with *M. genitalium* in the UK. We found similar rates of *M. genitalium* (9.7%) to *C. trachomatis* (9.6%), adding to the growing body of evidence that mycoplasma is a significant aetiological organism. National guidelines strongly recommend mycoplasma testing to guide choice of appropriate therapy[6]. Moxifloxacin has activity against most cases of mycoplasma, gonorrhoea, chlamydia, and several implicated anaerobes (*G.vaginalis, Prevotella* species, *A.vaginae*) and appears to be a good first-line single agent in women aged ≥18 years[w11]. However following the 2018 EMA guidance restricting the use of quinolones[12], options for outpatient management of PID are increasingly limited. At the beginning of the study there was confidence that a short-course of azithromycin would not only adequately treat chlamydia, but also be a robust approach for PID caused by *M. genitalium.* However in many countries macrolide resistance is now reported in over half of diagnosed mycoplasma infections, having been rare only 10-years ago[23,24]. In this study 58% of women with *M. genitalium* had baseline macrolide resistance, adding to the growing literature calling for baseline AMR testing to guide appropriate therapy[19].

Whilst the short azithromycin course undoubtedly has limitations, once reliable near-patient tests for suspected pathogens are available and combined with baseline AMR tests, it may have a place in treating *M. genitalium* negative PID, or cases where macrolide resistance is absent. We did not find any evidence of AMR developing *during* the study period, which whilst reassuring and consistent with the conclusions of Horner et al[w12] and recent observations by Durukan et al[w13], would not

negate the need for comprehensive test-of-cure and further AMR assessment in treatment failures[19]. Despite the higher rates of gastrointestinal adverse events, the side-effects of the short-course may be considered by some to be more acceptable than taking antibiotics for two-weeks. This approach may be particularly useful for individuals with chaotic lifestyles, those pregnant or at risk of pregnancy or younger women where adherence can be more challenging.

In summary, current PID guidelines encourage clinicians to have a low threshold for empiric therapy, although the first line option is now limited to a two-week course of doxycycline and metronidazole, with a single dose of intramuscular ceftriaxone. The short-course azithromycin regimen described in this study may offer an alternative option in future when near patient STI testing and AMR become available.

Total word count: 2996

KEY MESSAGES:

- A 5-day course of oral azithromycin and metronidazole, with stat IM ceftriaxone, was less effective than a 14 day course of oral ofloxacin and metronidazole
- *M genitalium* was associated with ~10% of cases of PID in this study
- For women with macrolide sensitive *M. genitalium*, or who are pregnant or unable to adhere to a 2 week antibiotic course, the short azithromycin course may be an alternative choice

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COMPETING INTERESTS:

JR reports personal fees from GSK Pharma, Hologic Diagnostics, Mycovia and Janssen Pharma as well as ownership of shares in GSK Pharma and AstraZeneca Pharma; and is author of the UK and European Guidelines on Pelvic Inflammatory Disease; is a Member of the European Sexually Transmitted Infections Guidelines Editorial Board; is a Member of the National Institute for Health Research Funding Committee (Health Technology Assessment programme); was previously a Member of the National Institute for Health Research HTA Primary Care, Community and Preventative Interventions Panel (2013-2016). He is an NIHR Journals Editor and associate editor of Sexually Transmitted Infections journal. He is an officer of the British Association for Sexual Health and HIV (vice-president), and the International Union against Sexually Transmitted Infections (treasurer), and a charity trustee of the Sexually Transmitted Infections Research Foundation.

PATIENT CONSENT: Obtained

CONTRIBUTORS: GD, SS, JW were involved in the design and writing the manuscript. GD and JW were involved in conducting the study. CS was involved in the study design and performed the statistical analysis, as well as reviewing the manuscript. RP conducted Mycoplasma genitalium tests

and reviewed the manuscript. JR advised on the conduct of the study and revised the manuscript before submission.

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REFERENCES

1. Weström L, Joesoef R, Reynolds G, Hagdu A, Thompson SE. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. *Sex Transm Dis.* 1992;19:185–92

2. Hillis SD, Joesoef R, Marchbanks PA, Wasserheit JN, Cates W, Westrom L. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. *American Journal of Obstetrics and Gynecology* 1993;168:1503–9

3. Haggerty CL, Ness RB. Newest approaches to treatment of pelvic inflammatory disease: a review of recent randomized clinical trials. *Clin Infect Dis.* 2007;44:953-60

4. Dunbar-Jacob J, Sereika SM, Foley SM, Bass DC, Ness RB. Adherence to oral therapies in pelvic inflammatory disease. *Journal of Women's Health* 2004;13: 285–91

5. Brookoff D. Compliance with doxycycline therapy for outpatient treatment of pelvic inflammatory disease. *South Med J.* 1994 Nov;87:1088-91

6. Ross J, Cole M, Evans C et al. 2018 United Kingdom National Guidelines for the Management of Pelvic Inflammatory Disease: British Association for Sexual Health & HIV. (https://www.bashhguidelines.org/media/1170/pid-2018.pdf) (Accessed 25th November 2019)

7. Ross J, Guaschino S, Cusini M, Jensen J. 2017 European guideline for the management of pelvic inflammatory disease. *Int J STD & AIDS* 2017;29:108-114 doi.org/10.1177/0956462417744099

8. Ross JD, Cronjé HS, Paszkowski T et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. *Sex Transm Infect*. 2006;82:446-451 doi: 10.1136/sti.2005.019109

9. Martens MG, Gordon S, Yarborough DR, Faro S, Binder D, Berkeley A, Ambulatory PID Research Group. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. *South Med J.* 1993;86:604-10

10. Savaris RF, Teixeira LM, Torres TG et al. Comparing Ceftriaxone plus Azithromycin or Doxycycline for Pelvic Inflammatory Disease. *Obstet Gynecol*. 2007;110:53-60

11. Piyadigamage A, Wilson J. Improvement in the clinical cure rate of outpatient management of pelvic inflammatory disease following a change in therapy. *Sex Transm Infect*. 2005;81:233-235

12. European Medicines Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. EMA/175398/2019. (https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products). (Accessed 25th November 2019).

13. Bowie WR, Jones H. Acute pelvic inflammatory disease in outpatients: association with Chlamydia trachomatis and Neisseria gonorrhoeae. *Annals of Internal Medicine* 1981;95:685–8

14. Bevan CD, Johal BJ, Mumtaz G, Ridgway GL, Siddle NC. Clinical, laparoscopic and microbiological findings in acute salpingitis: report on a United Kingdom cohort. *British Journal of Obstetrics and Gynaecology* 1995;102:407–14

15. Soper DE, Brockwell NJ, Dalton HP, Johnson D. Observations concerning the microbial etiology of acute salpingitis. *American Journal of Obstetrics and Gynecology* 1994;170:1008–14

16. Burnett AM, Anderson CP, Zwank MD. Laboratory-confirmed gonorrhea and/or chlamydia rates in clinically diagnosed pelvic inflammatory disease and cervicitis. *American Journal of Emergency Medicine* 2012;30:1114–1117

17. Price MJ, Ades AE, Soldan K, Welton NJ, Macleod J, Simms I, DeAngelis D, Turner KME, Horner PJ. The natural history of Chlamydia trachomatis infection in women: a multi-parameter evidence synthesis. *Health Technol Assess*. 2016;20(22) DOI: http://dx.doi.org/10.3310/hta20220

18. Lis R, Rowhani-Rahbar A, Manhart LE. Mycoplasma genitalium Infection and Female Reproductive Tract Disease: A Meta-Analysis. *Clin Infect Dis*. 2015;61:418–426

19. Soni S, Horner P, Rayment M, Pinto-Sander N, Naous N, Parkhouse A, Bancroft D, Patterson C, Fifer H. British Association for Sexual Health and HIV national guideline for the management of infection with Mycoplasma genitalium(2018) https://www.bashhguidelines.org/media/1198/mg-2018.pdf (Accessed 25th November 2019)

20. CDC guidelines for Pelvic Inflammatory Disease (PID). 2015 http://www.cdc.gov/std/tg2015/pid.htm (Accessed 25th November 2019)

21. Jensen JS, Bradshaw C. Management of Mycoplasma genitalium infections – can we hit a moving target? *BMC Infectious Diseases* 2015;15:343

22. Lau A, Bradshaw CS, Lewis D, Fairley CK, Chen MY, Kong FY, Hocking JS. The efficacy of azithromycin for the treatment of genital Mycoplasma genitalium: A systematic review and meta-analysis. *Clin Infect Dis.* 2015;61:1389-1399

23. Pitt R, Fifer H, Woodford N, Alexander S. Detection of markers predictive of macrolide and fluoroquinolone resistance in Mycoplasma genitalium from patients attending sexual health services in England. *Sex Transm Infect.* 2018;94:9-13

24. Dionne-Odom J, Geisler WM, Aaron KJ, Waites KB, Westfall AO et al. High prevalence of multidrug-resistant Mycoplasma genitalium in human immunodeficiency virus-infected men who have sex with men in Alabama. *Clin Infect Dis*. 2018;66:796–798

25. McCormack WM, Nowroozi K, Alpert S, Sackel SG, Lee YH, Lowe EW, Rankin JS. Acute pelvic inflammatory disease: characteristics of patients with gonococcal and nongonococcal infection and evaluation of their response to treatment with aqueous procaine penicillin G and spectinomycin hydrochloride. *Sex Transm Dis*. 1977;4:125-31

26. Jensen JS, Björnelius E, Dohn B, Lidbrink P. Use of TaqMan 5' nuclease real-time PCR for quantitative detection of Mycoplasma genitalium DNA in males with and without urethritis who were attendees at a sexually transmitted disease clinic. J Clin Microbiol. 2004 Feb;42:683-92

27. Pitt R, Fifer H, Woodford N, et al Detection of markers predictive of macrolide and fluoroquinolone resistance in Mycoplasma genitalium from patients attending sexual health services in England. Sex Transm Infect Published Online First: 17 July 2017. doi: 10.1136/sextrans-2017-053164

28. Couldwell DL, Tagg KA, Jeoffreys NJ, Gilbert G. Failure of moxifloxacin treatment in Mycoplasma genitalium infections due to macrolide and fluoroquinolone resistance. *Int J STD AIDS* 2013; 24: 822-8

29. Bissessor M, Tabrizi SN, Twin J, Abdo H, Fairley CK, Chen MY, Vodstrcil LA, Jensen JS, Hocking JS, Garland SM, Bradshaw CS. Macrolide Resistance and Azithromycin Failure in a Mycoplasma genitalium-Infected Cohort and Response of Azithromycin Failures to Alternative Antibiotic Regimens. *Clin Infect Dis.* 2015;60:1228-36

30. Anderson T, Coughlan E, Werno A. Mycoplasma genitalium Macrolide and Fluoroquinolone Resistance Detection and Clinical Implications in a Selected Cohort in New Zealand. *J Clin Microbiol*. 2017;55:3242-48

W1. Braam JF, van DL, Henquet CJM, van de Bovenkamp JHB, Kusters JG. Multidrug-resistant Mycoplasma genitalium infections in Europe. *Eur J Clin Microbiol Infect Dis.* 2017;36:1565-7.

W2. Ness RB, Soper DE, Holley RL et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the PID Evaluation and Clinical Health (PEACH) randomized trial. *Am. J. Obstet. Gynecol.* 2002;186:929–937

W3. Walker CK, Kahn JG, Washington AE, Peterson HB, Sweet RL: Pelvic inflammatory disease: meta-analysis of antimicrobial regimen efficacy. *J. Infect. Dis*. 1993;168:969–978

W4. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis*. 2005; 41:S144-S157 https://doi.org/10.1086/428055

W5. Read TRH, Fairley CK, Murray GL et al. Outcomes of Resistance-guided Sequential Treatment of Mycoplasma genitalium Infections: A Prospective Evaluation. *Clin Infect Dis* 2018;68:554-560

W6. Public Health England: Table 1: STI diagnoses & rates in England by gender, 2009 – 2018. (https://www.gov.uk/government/statistics/sexually-transmitted-infections-stis-annual-data-tables) (Accessed 18th November 2019)

W7. Dyer C. Doctors warn local authorities about putting sexual health services out to tender. *BMJ* 2014; 348:f7715 doi: https://doi.org/10.1136/bmj.f7715

W8. Written evidence from The King's Fund submitted to the Health & Social Care Committee's

sexual health inquiry
https://www.kingsfund.org.uk/sites/default/files/201906/Sexual%20health%20inquiry_proofed.pdf

W9. Health and Social Care Act 2012.http://www.legislation.gov.uk/ukpga/2012/7/contents/enacted (Accessed 25th November 2019)

W10. Goller JL, De Livera AM, Fairley CK et al. Characteristics of pelvic inflammatory disease where no sexually transmitted infection is identified: a cross-sectional analysis of routinely collected sexual health clinic data. *Sex Transm Infect.* 2017;93:68–70. doi:10.1136/sextrans-2016-052553

W11. Petrina MAB, Cosentino LA, Wiesenfeld HC et al. Susceptibility of endometrial isolates recovered from women with clinical Pelvic Inflammatory Disease or histological endometritis to antimicrobial agents. *Anaerobe* 2019;56:61-65. doi: 10.1016/j.anaerobe.2019.02.005

W12. Horner P, Ingle SM, Garrett F, Blee K, Kong F, Muir P, Moi H. Which azithromycin regimen should be used for treating *Mycoplasma genitalium*? A meta-analysis. *Sex Transm Infect*. 2018;94:14-20. doi: 10.1136/sextrans-2016-053060

W13. Durukan D, Read TRH, Murray G, Doyle M, Chow EPF, Vodstrcil LA, Fairley CK, Aguirre I, Mokany E, Tan LY, Chen MY, Bradshaw CS. Resistance-guided antimicrobial therapy using doxycycline-moxifloxacin and doxycycline-2.5g azithromycin for the treatment of *Mycoplasma genitalium* infection: efficacy and tolerability. *Clin Infect Dis*. 2019 Oct 20. pii: ciz1031. https://doi.org/10.1093/cid/ciz1031 [Epub ahead of print]

Legends for figures:

Figure 1: Randomised and eligible populations in standard of care and intervention arms