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Adverse Adolescent Reproductive Health Outcomes After Pelvic Inflammatory Disease

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Abstract

Objective—To compare longitudinal adolescent and adult reproductive outcomes after pelvic inflammatory disease (PID).

Design—Secondary analysis of longitudinal data from the Pelvic Inflammatory Disease Evaluation and Clinical Health study.

Setting—A large multicenter randomized clinical trial assessing PID treatment strategies in the United States.

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Participants—Eight hundred thirty-one female patients aged 14 to 38 years with a diagnosis of PID.

Main Exposure—Adverse longitudinal outcomes were compared in adolescents (≤19 years) and adults (>19 years).

Outcome Measures—Primary outcome measures included recurrent sexually transmitted infection at 30 days, recurrent PID, chronic abdominal pain, infertility, pregnancy, and times to recurrent PID and pregnancy. Cox proportional hazards modeling was used to examine the effect of young age on times to pregnancy and recurrent PID.

Results—Adolescents were more likely than adults to have positive results of sexually transmitted infection testing at baseline and at 30 days. There were no significant group differences in chronic abdominal pain, infertility, and recurrent PID at 35 or 84 months, but adolescents were more likely to have a pregnancy at both time points. Adjusted hazard ratios (95% confidence intervals) also demonstrated that adolescents had shorter times to pregnancy (1.48 [1.18–1.87]) and recurrent pelvic inflammatory disease (1.54 [1.03–2.30]).

Conclusion—Adolescents may require a different approach to clinical care and follow-up after PID to prevent recurrent sexually transmitted infections, recurrent PID, and unwanted pregnancies.

The Centers for Disease Control and Prevention (CDC) estimates that more than 1 million women are affected with pelvic inflammatory disease (PID) each year in the United States.[1] Adolescent girls are at risk for developing PID because of behavioral risk factors such as sexual concurrency[2,3] and biological risk factors such as cervical ectopy that increase their risk of sexually transmitted infections (STIs).[4] Adolescents are also at risk for the development of subsequent STIs after an initial episode of PID,[5] and it is well established that recurrent STIs and/or PID increase the risk of associated reproductive health sequelae such as tubal infertility, ectopic pregnancy, and chronic abdominal pain.[6] Optimal PID management requires that the affected patient engage in an effective but complicated regimen of self-treatment during a 14-day period. According to the treatment recommendations from the CDC, affected patients need twice-daily dosing with antibiotics to treat infection, to avoid reexposure to STIs during the treatment period, to assist in secondary prevention through partner notification and treatment, and to arrange for appropriate follow-up assessments. Research, however, has consistently demonstrated that adolescents and adult women with PID often have difficulty adhering to these recommendations.[7–10] Given the risks to future fertility among women just entering their reproductive years, previous sexually transmitted disease treatment guidelines from the CDC have suggested that adolescents with PID should be considered separately in treatment recommendations. In the past, hospitalization was used to provide additional clinical care support to adolescents with PID. Although outpatient treatment was initially controversial,[11] hospitalization for PID is now usually reserved for those with severe manifestations of disease given the availability of effective oral antibiotic regimens. As a first step in determining the current need for more structured management of mild-to-moderate disease among adolescents in the outpatient setting, we compared longitudinal behavioral correlates and reproductive health outcomes between adolescents and adults with PID.

METHODS

PATIENTS AND SETTING

We conducted a secondary analysis of data from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) study, a large multicenter randomized clinical trial assessing PID treatment strategies. Although the methods used in this seminal trial have been well described in the literature,[12,13] they will be briefly reviewed herein. Patients aged 14 to 38 years with mild to moderate PID based on predetermined diagnostic criteria were enrolled at diagnosis at one of the 8 centers participating in the trial. The 3 required diagnostic criteria included (1) pelvic discomfort for fewer than 30 days, (2) pelvic organ tenderness on bimanual examination, and (3) leukorrhea, mucopurulent cervicitis, and/or known positive laboratory findings for *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection. Patients were excluded if they were identified as being at risk for acute morbidity in the outpatient setting (eg, pregnancy, inability to tolerate an outpatient regimen, tubo-ovarian abscess, or a potential surgical abdomen); if they had pelvic pain for more than 30 days, allergy to study drugs, antibiotic treatment within 7 days of recruitment, delivery or a gynecologic surgical procedure (including abortion) within the past 30 days, or a previous hysterectomy or salpingectomy; and if they were homeless.

Using these criteria, 1515 patients were eligible for participation in the study; of these, 651 (43.0%) refused participation, and, among the remaining 864 who consented to participate, 831 were randomly assigned to inpatient or outpatient antibiotic therapy (Figure 1). Refusal rates were similar to those of other studies that compared treatment strategies,[14] and patients who refused to participate did not differ significantly by race, age, or clinical status. Perceived hardship for a potential hospitalization was noted as the primary reason for refusal.[13] Parental consent was obtained for minors who participated in the trial.

Inpatient therapy included 48 hours of intravenous antibiotics on an inpatient unit with subsequent outpatient therapy with an oral antibiotic. Outpatient therapy included treatment with an oral antibiotic. All patients were advised to rest, notify partners of treatment, and abstain from sexual intercourse until both partners completed a course of treatment.

MEASURES

All participants completed a 20-minute baseline interview with reevaluation at 5 and 30 days from the time of enrollment and then a telephone interview every 3 to 4 months for 84 months. Data collected at the baseline interview included demographic information, reproductive health history, lifestyle habits, and details of the current clinical illness. Patients also underwent a gynecologic examination with collection of biological specimens to test for *N gonorrhoeae* by culture and *C trachomatis* by polymerase chain reaction (Roche Medical Laboratories, Burlington, North Carolina) and an endometrial biopsy for detection of infection and determination of histology consistent with endometritis.

The primary outcomes of interest were recurrent STI at 30 days and recurrent PID, chronic pelvic pain, infertility, and pregnancy at 35 and 84 months. Each of the primary outcome variables was measured as yes or no and dichotomously coded (1 or 0). Time to pregnancy and recurrent PID were also measured. Recurrent PID was self-reported and verified

whenever medical records were available. As previously reported, confirmation of recurrent PID by self-reports and medical record reviews was similar.[13] Infertility was defined when a sexually active patient with at least 12 months of follow-up did not report conception (a positive urine or blood test finding or a clinician's diagnosis of pregnancy) despite rare or no use of contraceptive methods. Ectopic pregnancy was based on self-report, verified whenever possible by medical record review. Medical records were available for 45.0% of the cohort. Patients were considered to have chronic pelvic pain if pelvic pain was reported during at least 2 consecutive follow-up visits, thereby suggesting a minimum duration of pelvic pain of 6 months. Specific measures used in this analysis included demographic data, baseline reproductive health histories (ie, pregnancy history, PID history, evidence of endometritis at baseline, and level of distress if unable to have a child), sexual risk behavior (new sexual partners, number of partners in the past 4 weeks, contraceptive use in the past 4 weeks, condom use by partner in the past 4 weeks, consistent condom use, and occasional condom use), adherence data (days between enrollment and follow-up, pill counts, intercourse during treatment window, and partner treatment), short-term treatment outcomes (STI [infection with *N gonorrhoeae* and/or *C trachomatis*] at 30 days after PID treatment and condom use at 30 days), and long-term treatment outcomes (recurrent PID and/or pregnancy at 35 and 84 months).

Other variables used to assess baseline differences between the age groups included age and race, health care access, insurance status, and regular access to health care (yes or no). Other baseline reproductive health history variables included ever having been pregnant (yes or no), live birth (yes or no), ectopic or tubal pregnancies (yes or no), miscarriages (yes or no), abortions (yes or no), cervical and/or endometrial *N gonorrhoeae*/C *trachomatis* infection at baseline (yes or no), baseline endometritis (yes or no), history of PID (yes or no), level of distress if the participant could not have a child (a 10-item scale recoded into 3 categories [0–3, 4–6, and 7–10]), mean days to follow-up, adherence to medication via pill counts (yes or no), sex during the treatment window (yes or no), and partner treatment after diagnosis (yes or no).

DATA ANALYSIS

Summary statistics by adolescents and adults were generated for each of the descriptive and primary outcome variables using commercially available software (SAS, version 9.2; SAS Institute, Inc, Cary, North Carolina). Adolescents were defined as participants aged 19 years or younger and adults were defined as participants older than 19. The parent study did not find differences between inpatient and outpatient treatment groups. However, before making comparisons across age groups, we conducted stratified within-group (adolescent and adult) analyses (not shown) to examine whether there were differences by intervention status (inpatient vs outpatient therapy) from the parent study.[14] Baseline variables were then compared by age group strata. In all bivariate analyses, χ^2 and unpaired *t* tests were used to evaluate differences for proportions and continuous variables, respectively. Times to recurrent PID and pregnancy were examined using Cox proportional hazards modeling adjusted for possible confounders, including history of pregnancy, history of PID, level of distress if the participant could not have additional children, consistent condom use, and treatment group.

The original data collection was approved by the University of Pittsburgh institutional review board and each associated trial site. This analysis was approved by The Johns Hopkins University School of Medicine institutional review board.

RESULTS

SELECTED DEMOGRAPHICS

Adolescents represented 25.1% of the final sample size (Table 1). The mean (SD) ages for the adolescent and adult groups were 17.9 (1.1) and 25.3 (4.7) years, respectively. Except for the age differences, patients were demographically similar. Most were of African American descent, were of low-income status as measured by insurance status (uninsured/public insurance), and reported regular access to health care. As previously reported, there were no significant differences between the inpatient and outpatient trial groups.[13,15] Within age groups, adolescents and adults were also demographically similar regardless of randomization assignment.

REPRODUCTIVE HEALTH HISTORY AND RISK BEHAVIORS

Adolescents were less likely to have a history of pregnancy, live birth, abortion, or previous PID but were more likely to report higher levels of distress if unable to have a child. There were no significant differences in the numbers of new sexual partners or of partners in the past 4 weeks or contraceptive use in the past 4 weeks between the adolescents and adults. However, adolescents were more likely to report condom use by male partners within the past 4 weeks and to be engaging in consistent (10 of 10 times) condom use.

BASELINE AND LONGITUDINAL REPRODUCTIVE HEALTH OUTCOMES

There were no differences in the mean days to follow-up, adherence to medication via pill counts, sexual intercourse during the treatment window, or partner treatment after diagnosis (Table 2). However, adolescents were significantly more likely than adults to have evidence of endometritis and positive results of STI testing (*N gonorrhoeae*/*C trachomatis* infection) at baseline (63.2% vs 40.8%) (Table 1) and at 30 days (20.0% vs 5.2%) (Table 2).

As previously reported,[15] at 35 months, 31.8% of participants had chronic abdominal pain, 18.2% were categorized as infertile, 41.8% became pregnant, and 14.5% experienced recurrent PID. At 84 months, 42.7% of participants reported chronic abdominal pain, 18.6% were categorized as infertile, 57.2% became pregnant, and 21.3% had recurrent PID. There were no significant group differences in chronic abdominal pain, infertility, and recurrent PID at either time point, but adolescents were more likely to have a pregnancy at both time points (Table 3).

Graphical displays of the survival distribution against the times to pregnancy (Figure 2) and recurrent PID (Figure 3) show clear deviation between the 2 groups of study participants over time. Adjusted hazards models controlling for history of pregnancy, history of PID, level of distress if infertile, consistent condom use, and treatment group demonstrate that adolescents had shorter times to recurrent PID (hazard ratio, 1.54 [95% confidence interval,

1.03–2.30]; *P* = .03) and pregnancy (1.48 [1.18–1.87]; *P* <.001) compared with adult women (Table 4).

Two post hoc power analyses were conducted. The post hoc analysis for time to recurrent PID suggested 70% power for bivariate analyses, declining to 43% for the multivariable analysis with 5 confounders to detect a true hazard ratio of about 1.30. The post hoc analysis for time to recurrent pregnancy suggested greater than 80% power for bivariate and multivariate analyses to detect a true hazard ratio of about 1.60.

COMMENT

This study supports previous research by Weström and colleagues[6] demonstrating that women experience significant reproductive health sequelae after a PID diagnosis.

During the 84-month study, 42.7% of patients in this US sample experienced chronic abdominal pain, 18.6% experienced infertility, and 21.3% had recurrent PID. Although adolescents reported more consistent condom use than adults at baseline and at follow-up, they were more likely to be infected with an STI at baseline and at 30 days and to have a shorter time to development of PID, further risking preservation of their reproductive function.

Although more than half the patients experienced a pregnancy, the rates of infertility among this mostly minority, low-income population of women were significant, particularly because these data derive from patients with the least severe symptoms (mild to moderate disease). The STI findings in adolescent girls appear counterintuitive given the reports of consistent condom use. These findings may reflect the highly contextual and evolving nature of condom use based on relationship status.[16,17] Recent studies have suggested that reports of unprotected vs protected sexual intercourse do not correlate well with the presence of semen biomarkers in adult women.[18] The social desirability bias that is likely driving this observation may be even greater when adolescents are questioned about sexual practices compared with adult women. Adult women are also more likely to be married or in a stable relationship, which may explain lower rates of condom use and STIs. Ultimately, these observations likely reflect the epidemiology of STIs among adolescents and young adults and the increased likelihood of encountering a partner with an STI over time.[19] This analysis does not examine partner factors, but examination of relationship concurrency, disclosure, and partner treatment after each STI would be important factors to consider in future work.

Although adverse outcomes were similar by treatment arm in the entire cohort,[15,20] our main goal was to determine whether, by comparing adolescent-specific outcomes with those of the adults, additional follow-up recommendations should be made to optimize outpatient care for adolescents facing a PID diagnosis. These data suggest that adolescents may be more likely to experience a pregnancy, have recurrent STIs, and have a shorter time to development of recurrent PID than adult women. The pregnancy finding is not surprising because previous studies have suggested that girls who perceive an impairment of their fertility are less likely to use contraception,[21] that few adolescents diagnosed as having PID in observational trials are using contraception,[10] and that adolescents often believe that prevention of infertility is beyond their control.[22] These data, combined with our earlier

work demonstrating the disparities in health care delivery for PID in pediatric ambulatory settings, the difficulty with adherence faced by many adolescents,[8,10] and recurrent rates of STIs and PID after a diagnosis of PID,[5] suggest that health service delivery should be expanded for prevention of recurrent STIs, PID, and teen pregnancy through risk reduction interventions.

The findings from this study must be considered in light of several general limitations. The sample primarily consisted of low-income African American women and may not be generalizable to other patients in other settings. However, research in this population is important given the documented racial/ethnic health disparities associated with STIs, PID,[23] and infertility in the United States.[23–26] There is limited variability of the adolescent cohort because this sample primarily consists of older adolescents and young adults as indicated by the mean (SD) age of the adolescent sample. Younger adolescents and/or adolescents who refused to participate because they were seeking confidential services may have differed systematically from participants in ways that could have resulted in more negative PID outcomes. The adolescents in this sample were, however, clearly different in behavior and outcome than the adult sample; thus, the stratification and findings from this work are still important. Although the study findings suggest high adherence to medication regimens, the measure of adherence for most patients in the study was limited to pill counts performed at clinic visits. Thus, differences in adherence between adolescents and adults may exist, but we are unable to determine them based on available data. Given that this was a randomized controlled trial, it is possible that the participants in the study were dissimilar to patients in reality settings. As an example, previous studies have demonstrated very low contraceptive use rates among adolescents with PID,[10,27] but more than 70% of the participants in both groups reported using some form of contraception. This might suggest a slightly lower risk profile for women in this sample. However, the PEACH study represents the most comprehensive longitudinal data with US women affected by PID and has provided excellent efficacy data on outpatient treatment under the best possible conditions and should be used as a template for translational work that establishes the effectiveness of outpatient treatment approaches among the high-risk populations often affected by PID.

The CDC has been clear in that health care providers working with adolescents diagnosed as having PID should engage in careful, developmentally appropriate, and non-judgmental discussions aimed at reduction of high-risk behaviors in adolescents.[28] The findings from this research suggest that, although adolescent-specific PID management needs to include more aggressive risk reduction interventions to prevent subsequent STIs, PID, and teen pregnancy after a PID diagnosis, a reduction in PID-associated chronic abdominal pain and infertility among all women is also needed.

Acknowledgments

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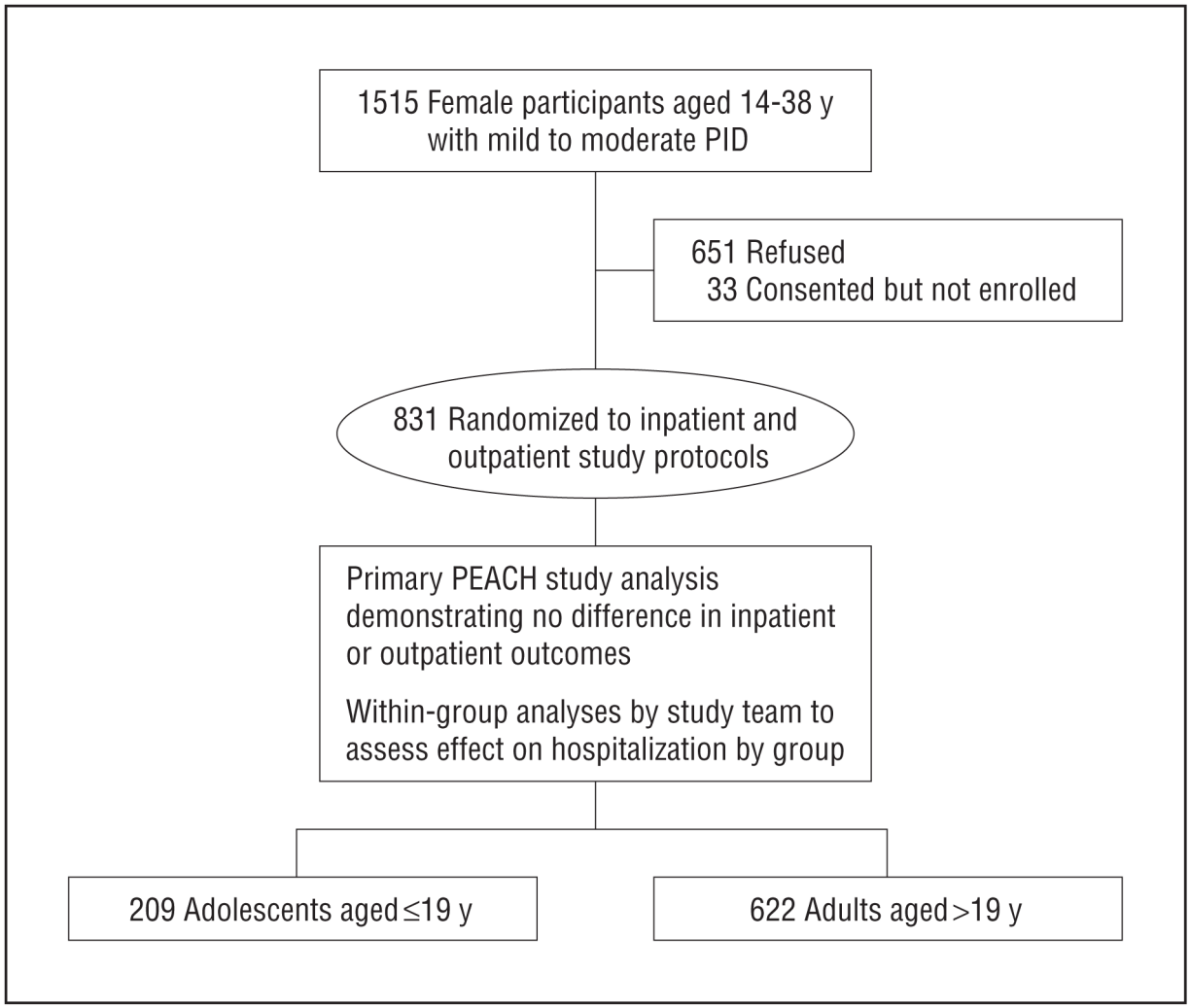

Figure 1.
Approach to analysis in the context of the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) study design. PID indicates pelvic inflammatory disease.

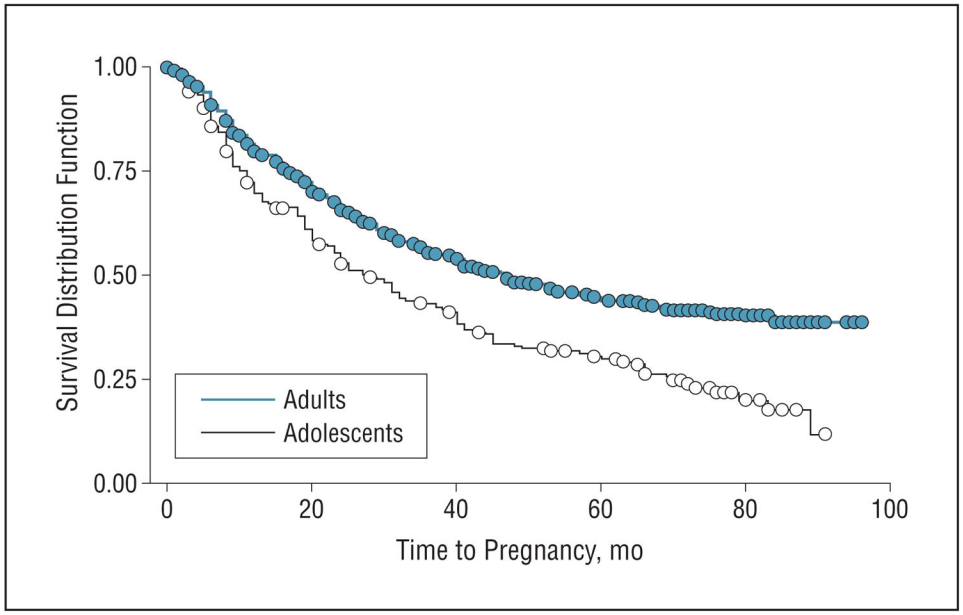

Figure 2.

Survival curves depicting time to pregnancy by age group status (adults >19 years and adolescents ≤19 years). Circles indicate censored individuals.

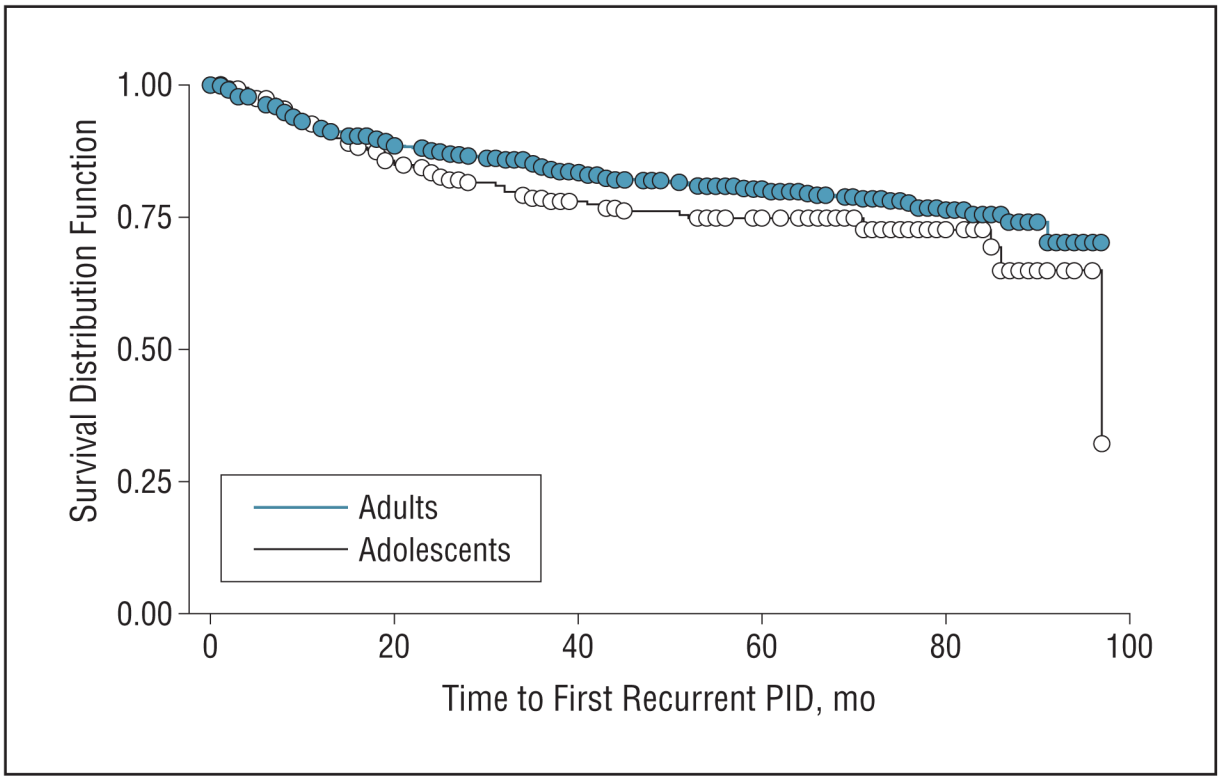

Figure 3.
Survival curve depicting time to recurrent pelvic inflammatory disease (PID) by age group status (adults >19 years and adolescents ≤19 years). Circles indicate censored individuals.

Table 1

Selected Baseline Demographics, Reproductive Health History/Status, and Reported Risk Behaviors by Group Status[a]

Characteristic	Adolescents (n=209)	Adults (n=622)	*P* Value
Demographics			
Age, mean (SD), y	17.9 (1.1)	25.3 (4.7)	<.001
Race			
African American	158 (75.6)	463 (74.4)	.54
White	32 (15.3)	101 (16.2)	
Hispanic	10 (4.8)	41 (6.6)	
Native American/Alaskan native/Asian	9 (4.3)	17 (2.7)	
Health care access and insurance status			
Health care insurance	101 (54.9)	292 (51.0)	.35
Regular access to health care	124 (67.4)	415 (72.4)	.19
Insurance status			
Uninsured	83 (45.1)	281 (49.0)	.44
Private insurance	33 (17.9)	82 (14.3)	
Public insurance	68 (37.0)	210 (36.6)	
Reproductive health history/status			
Ever been pregnant	109/209 (52.2)	516/618 (83.5)	<.001
Live births	83/209 (39.7)	453/618 (73.3)	<.001
Ectopic pregnancies	3/209 (1.4)	36/617 (5.8)	.01
Miscarriages	34/209 (16.3)	164/618 (26.5)	.003
Abortions	29/209 (13.9)	172/618 (27.8)	<.001
Positive cervical and/or endometrial *Neisseria gonorrhoeae*/*Chlamydia trachomatis*	110/174 (63.2)	195/477 (40.8)	<.001
Evidence of endometritis	92/164 (56.1)	219/490 (44.7)	.01
History of pelvic inflammatory disease	52/207 (25.1)	199/615 (32.4)	.051
Level of distress if you could not have a child			
0–3	16 (15.5)	93 (32.3)	.004
4–6	13 (12.6)	35 (12.2)	
7–10	74 (71.8)	160 (55.6)	
Sexual risk behavior			
New sexual partner	26 (12.4)	52 (8.4)	.08
No. of sexual partners in past 4 wk, mean (SD)	1.3 (3.9)	1.0 (1.2)	.33
Any contraceptive use in past 4 wk	131/175 (74.9)	377/528 (71.4)	.38
Any condom use by male partner in past 4 wk	112/176 (63.6)	259/528 (49.1)	<.001
Consistent condom use (10 of 10 sexual encounters)	34/176 (19.3)	59/528 (11.2)	.006

[a]Unless otherwise indicated, data are expressed as number (percentage) of participants. Percentages have been rounded and may not total 100. Adolescents are aged 19 years or younger; adults, older than 19 years.

Table 2

Patient Adherence and Short-term Outcomes by Group Status[a]

Adherence Measure	Adolescents (n=209)	Adults (n=622)	*P* Value
Time from enrollment to first follow-up, mean (SD), d	6.2 (3.5)	6.2 (3.3)	.87
Pills (2 tablets/14 visits)			
Total No. of pills taken, mean (SD)	27.6 (1.7)	27.5 (2.5)	
Median	28.0	28.0	.25
Adherence, %			
Mean (SD)	98.7 (6.1)	98.2 (8.9)	
Median	100.0	100.0	.25
Sex during treatment window	28/184 (15.2)	84/571 (14.7)	.85
Partner treatment after PID diagnosis	42/140 (29.8)	137/469 (29.2)	.88
Cervical and/or endometrial *Neisseria gonorrhoeae*/*Chlamydia trachomatis* at 30 d after treatment	19/95 (20.0)	13/250 (5.2)	<.001
Self-report of patient/partner STI since diagnosis	60/144 (41.7)	175/442 (39.6)	.66
Condom use at 30 d	123/138 (89.1)	281/387 (72.6)	<.001

Abbreviations: PID, pelvic inflammatory disease; STI, sexually transmitted infection.

[a]Unless otherwise indicated, data are expressed as number (percentage) of participants. Adolescents are aged 19 years or younger; adults, older than 19 years.

Table 3

Adverse Reproductive Health Outcomes After PID at 35 and 84 Months and Time to Pregnancy and Recurrent PID[a]

Outcomes	Adolescents	Adults	*P* Value
At 35 mo			
Chronic pelvic pain	58/192 (30.2)	180/557 (32.3)	.55
Infertility	34/193 (17.6)	104/567 (18.3)	.82
Pregnancy	109/207 (52.7)	229/601 (38.1)	.003
Recurrent PID	36/207 (17.4)	81/601 (13.5)	.17
At 84 mo			
Chronic pelvic pain	82/204 (40.2)	259/595 (43.5)	.41
Infertility	36/207 (17.4)	116/610 (19)	.60
Pregnancy	149/207 (72.0)	321/610 (52.6)	<.001
Recurrent PID	50/199 (25.1)	118/590 (20.3)	.13
Time to event, mean (SD), mo			
Pregnancy	33.0 (26.6)	39.8 (28.9)	.003
Recurrent PID	50.4 (29.4)	52.0 (29.3)	.52

Abbreviation: PID, pelvic inflammatory disease.

[a] Unless otherwise indicated, data are expressed as number (percentage) of participants. Adolescents are aged 19 years or younger; adults, older than 19 years.

Table 4

Effect of Adolescent Age on Time to Pregnancy and Recurrent PID

	HR (95% CI)		
	Unadjusted	**Adjusted[a]**	***P* Value**
Time to recurrent PID	1.28 (0.92–1.79)	1.54 (1.03–2.30)	.03
Time to pregnancy	1.59 (1.31–1.93)	1.48 (1.18–1.87)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; PID, pelvic inflammatory disease.

[a]Adjusted for history of pregnancy, history of PID, level of distress if the participant could not have additional children, consistent condom use, and treatment group.