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Pyelonephritis in pregnancy. How adequate is empirical treatment?

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ABSTRACT

Objective. To ascertain the adequacy of empirical antimicrobial treatment in pregnant women with acute pyelonephritis.

Material and methods. We have conducted a retrospective observational study of women admitted to the hospital with acute pyelonephritis between May 2004 and April 2011. Patients were included if the results of urine cultures and susceptibility testing to antibiotics were available. Epidemiological, clinical, therapeutic and outcome variables were collected from chart review. We considered inappropriate empirical antimicrobial treatment (IEAT) as the occurrence of microorganism that were not effectively treated at the time when the causative microorganism and its antibiotic susceptibility were known.

Results. Fifty women with appropriate microbiological data from a total of 93 cases of acute pyelonephritis were included in the study. The women's mean age was 26.4 years, and 58% were nulliparous. Pyelonephritis was developed in the 2nd and 3rd trimester in 88% of cases. Previous urinary tract infections were recorded in 34%. *Escherichia coli* was the most frequent microorganism (70%). The proportion of patients who received IEAT was 10%. Amoxicillin-clavulanate and cephalosporines were the most predominant antibiotics used, with a proportion of IEAT of 10.3% and 5.9%, respectively.

Conclusions. Pregnant women with pyelonephritis received IEAT in a small but significant number of cases. Amoxicillin-clavulanate and cephalosporines were adequate in most cases. More studies are needed to define the clinical impact of IEAT on prognosis.

Key words: pyelonephritis, pregnancy, empirical treatment

Pielonefritis en el embarazo. ¿Hasta qué punto es adecuado el tratamiento empírico?

RESUMEN

Objetivo. Valorar la idoneidad del tratamiento antibiótico empírico en la pielonefritis aguda en el embarazo.

Material y método. Estudio observacional retrospectivo de las mujeres embarazadas admitidas en el hospital con pielonefritis aguda entre mayor de 2004 y abril de 2011. Las pacientes fueron incluidas si los resultados de los cultivos de orina y los estudios de resistencias a los antibióticos estaban disponibles. Las variables epidemiológicas, clínicas, terapéuticas y pronósticas fueron recogidas mediante revisión de las historias clínicas. Se consideró que existía un tratamiento antibiótico empírico inadecuado (IEAT) cuando el microorganismo causante de la infección no estaba siendo tratado de manera eficaz en el momento en que se conoció el microorganismo causante de la infección y el estudio de resistencias.

Resultados. De un total de 93 casos de pielonefritis aguda se incluyeron en el estudio 50 mujeres cuyos datos microbiológicos fueron apropiados. La edad media de las mujeres fue de 26,4 años. El 58% de ellas fueron nulíparas. La pielonefritis se presentó en el segundo o tercer trimestre del embarazo en el 88% de los casos. Se documentó infecciones urinarias previas en el 34%. *Escherichia coli* fue el microorganismo más frecuentemente aislado (70%). El 10% de las pacientes recibieron IEAT. Amoxicilina-clavulánico y cefalosporinas fueron los antibióticos usados con mayor frecuencia, con una proporción de IEAT del 10,3 y 5,9% respectivamente.

Conclusiones. Las mujeres embarazadas con pielonefritis aguda recibieron IEAT en un pequeño pero significativo número de casos. Amoxicilina-clavulánico y cefalosporinas fueron antibióticos adecuados en la mayoría de los casos. Se necesitan más estudios para conocer el impacto clínico del IEAT sobre el pronóstico

Palabras clave: pielonefritis, embarazo, tratamiento empírico

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INTRODUCTION

Urinary tract infection (UTI) is the most common bacterial infection in obstetric patients. Asymptomatic bacteriuria carries an increased risk of upper UTI or pyelonephritis in pregnant women, as a consequence of the anatomic and physiologic urinary tract changes in pregnancy, mainly due to the relative obstruction of urine outflow by the gravid uterus and the smooth muscle relaxation caused by progesterone^{1,2}. This risk is about 30% in the absence of antibiotic therapy but it is reduced to less than 5% with the eradication of bacteriuria by adequate treatment^{3,4}.

Acute pyelonephritis is a major complication of pregnancy that may result in significant maternal and fetal morbidity. Most women with acute pyelonephritis should be hospitalized and should receive parenteral antibiotic which is empiric initially. It is widely accepted that the choice of empiric antibiotic therapy should be based on established patterns of antimicrobial susceptibilities in the specific institution. New advances in the pathogenesis of gestational urinary tract infection suggest the presence of gestation-specific virulent strains of *Escherichia coli*⁵. We think that in order to give adequate empirical antimicrobial treatment to pregnant women with pyelonephritis the antimicrobial susceptibility to uropathogens isolated from obstetric patients should be known. As far as we know studies of susceptibility to uropathogens in obstetric women are scarce or they have been done in women with asymptomatic bacteriuria or cystitis^{6,7}.

The goals of this study were to know the adequacy of empirical antimicrobial treatment in acute pyelonephritis in pregnant women admitted to a Department of Obstetrics and Gynaecology in a university hospital, and to gain knowledge about which antibiotics should be used for empiric therapy of gestational pyelonephritis in our setting.

METHODS

We conducted a retrospective review of all pregnant inpatients with pyelonephritis at a single institution between May 2004 and April 2011. The study was conducted at the Department of Obstetrics and Gynaecology of the Hospital Universitario Dr. Peset, a 550-bed academic urban teaching hospital in Valencia, Spain. The study was approved by the Committee on Ethical and Scientific Issues of the Hospital Universitario Dr. Peset. Potential cases were identified using International Classification of Diseases, Ninth Revision, Clinical Modification codes. The code used was 646.6, indicating infections of the genitourinary tract in pregnancy. Acute pyelonephritis was defined as evidence of urinary tract infection via urinalysis (>8-12 white blood cell count, and <2-4 epithelial cells) or urine culture (>100,000 colony forming units) as well as clinical findings of at least 1 of the following: fever (temperature $\geq 38^{\circ}\text{C}$), flank pain, or costovertebral angle tenderness. The pathogen detected in urine samples and its resistance testing were collected by chart review, and every case was checked in the electronic database of the laboratory of microbiology, as well as culture

from blood in patients with an uropathogen isolated in urine. Only cases with an uropathogen isolated in urine were included in the study. Epidemiological, clinical, therapeutic and outcome variables were collected by chart review. Inappropriate empirical antimicrobial treatment (IEAT) was considered as the occurrence of microorganisms in urine that was not effectively treated at the time when the causative microorganism and its antibiotic susceptibility were known, including the absence of antimicrobial agents directed at a specific class of microorganisms and the administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant.

Continuous variables were compared by the t test for normally distributed variables. SPSS 15.0 software was used for data analysis.

RESULTS

During the 83-month observation period, a total of 93 pregnant patients were admitted to the hospital with the diagnosis of acute pyelonephritis. The exclusion of 43 cases, which did not have a microorganism isolated in urine due to antibiotic pre-treatment, resulted in 50 cases included in the study. The clinical and epidemiological characteristics of patients are shown in table 1. Forty-three women (86%) had 2nd and 3rd trimester pyelonephritis. No patient was receiving antimicrobial prophylaxis for urinary infection at the presentation of acute pyelonephritis. Urinary tract ultrasounds were done in 78%, with ectasia of urinary tract or focal signs of pyelonephritis in 82.1% of cases. The median length of stay was 3 days (from 1 to 17 days). Only one patient needed critical care, because of respiratory and renal failure and anemia. There was no mortality. No woman was readmitted for recurrent pyelonephritis during her pregnancy.

Gram-negative pathogens caused the majority of acute pyelonephritis (90%), with *E. coli* being the most common pathogen overall (70%), followed by *Klebsiella pneumoniae* (11%) and *Enterococcus faecalis* (10%). *Proteus mirabilis* was isolated in 2 cases and *Citrobacter amalonaticus*, *Escherichia hermannii* and *Enterobacter cloacae* in 1 case respectively. There was a case of polymicrobial pyelonephritis caused by *E. coli* and *E. faecalis*. Blood cultures were taken in 16% of cases and were positive in 25%. In table 2 is shown the antibiotic resistance patterns of isolated microorganisms.

Empirical antimicrobial treatment was given as monotherapy in 48 cases whereas it was given as combination antibiotic therapy in 2 cases. The empirical antimicrobial antibiotics given to the patients were: amoxicillin-clavulanate (n=29), ceftriaxone (n=10), cefuroxime (n=7), gentamicin (n=2), ampicillin (n=2), fosfomicin (n=1), and erythromycin (n=1). Eleven percent of patients were given IEAT, 3 patients received amoxicillin-clavulanate, 1 ceftriaxone and 1 patient was not given any empirical antibiotic because of a misdiagnosis of renal colic. The microorganisms that caused the cases with IEAT were *E. coli* (n=3, one strain producer of extended-spectrum β -lactamase - ESBL-EC -), *E. faecalis* (n=1) and *E. aerogenes* (n=1). The number (mean \pm SD) of days of intravenous antibiotic therapy

Table 1 Clinical and epidemiological characteristics of pregnant women with acute pyelonephritis.

Characteristics	Patients n (%)
Age, yr	
Mean \pm SD	26.8 \pm 7.3
Range	15-47
Race or ethnic group	
White	43 (86)
Black	2 (4)
Latino	5 (10)
Nulliparous	28 (56)
Trimester of pregnancy	
First	7 (14)
Second	24 (48)
Third	19 (38)
Comorbidities	
Diabetes mellitus	2 (4)
Hypothyroidism	2 (4)
Nephrolithiasis	2 (4)
History of symptomatic UTI	17 (34)
History of symptomatic UTI in this pregnancy	9 (18)
Clinical features	
Fever (temperature \geq 38°C)	38 (76)
Flank pain	40 (80)
Vomiting	7 (14)
Severe sepsis	1 (2)
Laboratory data	
Anemia (hematocrit <30%)	18 (36)
Leukocytosis (WBC >11,000/mm ³)	32 (64)

was 3.14 ± 2.49 , without any difference between the groups of IEAT and adequate empirical antimicrobial treatment.

The length of stay (mean \pm SD) was 4.40 ± 1.51 days and 4.02 ± 2.79 days for both the group of IEAT and the group of adequate empirical antimicrobial treatment ($p=0.769$).

DISCUSSION

The first clinical implication of our findings is that no microorganisms were isolated in urine samples in almost half of acute pyelonephritis cases admitted to the hospital. The importance of empirical treatment is therefore even greater than the presented results, as in 46.2% of the patients this treatment could not be modified with an antibiotic resistance report.

We found that a small (10%) but significant proportion of pregnant women admitted to our hospital with acute pyelonephritis received IEAT. The influence of IEAT on prognosis is well known in studies of severe infections⁸⁻¹⁰. However, a previous study of UTI in pregnancy failed to show a relationship between amoxicillin resistant infections and prognosis⁷. Although we found that the length of stay was slightly higher in patients with IEAT, this difference was not statistically significant, and the small number of patients does not allow us to analyze the influence of IEAT on outcomes.

Surprisingly no patient received antibiotic prophylaxis even though 20% of them had had a previous symptomatic UTI during this pregnancy. This occurred despite the fact that it is recommended to obtain a urine culture as a 'test of cure' and antimicrobial prophylaxis should also be initiated in all patients for the remainder of the pregnancy and should be continued until 4-6 weeks postpartum¹¹. We were unable to identify any association between antibiotic resistance and epidemiological factors in the patients, although again the small number of cases does not allow us to exclude a beta error.

As expected *E. coli* was the most predominant micro-organism (70%). ESBL-EC are emerging pathogens worldwide¹²⁻¹⁴, but in our study there was only one case of ESBL-EC (2.9%), which was inappropriately empirically treated with ceftriaxone. Carbapenems are widely regarded as the drug of choice for treatment of serious ESBL-EC infections, but we do not recommend a carbapenem agent as empirical treatment in acute pyelonephritis in pregnancy in our setting.

Amoxicillin-clavulanate and cephalosporins, the most frequent antibiotics prescribed as empirical treatment, were appropriate in most cases. We want to point out that in this study Gram stain was done in every case and that Gram stain could probably have helped to avoid the inappropriate use of cephalosporins in cases with cocci Gram positive in urine, due to the intrinsic resistance to these drugs of *Enterococcus*. Gentamicin and trimethoprim-sulfamethoxazole were both apparently good choices as empirical treatment according to the antibiotic resistance results, but they are not recommended as first-line agents in pregnancy due to their toxicity. Ampicillin was not used as initial treatment because of the high rate of resistance, which was 49% in this study. Given the rising rates of ampicillin resistance among gram-negative organisms, the use of ampicillin should be limited to patients in whom *Enterococcus* infection is suspected as the pathogen based on previous history. Ampicillin should be accompanied by an aminoglycoside as stated by current guidelines for the treatment of pyelonephritis in non-pregnant women¹⁵. Ampicillin and amoxicillin however are excellent antibiotics for UTI in pregnancy if we can use susceptibility testing to guide treatment. According to the antimicrobial susceptibility test in this study fosfomicin could be a good choice as initial treatment for urinary tract infections but it is not recommended for treatment of pyelonephritis¹⁵. Intravenous fosfomicin should be considered as a last resort option for the treatment of *Enterobacteriaceae* infections¹⁶.

This study has some limitations. First, it was a single-site investigation and our results may not be applicable to other

Table 2 Aetiology and proportion of antibiotic resistance in 50 pregnant women with acute pyelonephritis admitted to the hospital.

Microorganisms	Antibiotic resistance (%)						
	Ampicillin	Amox-Clav ¹	Cefuroxime	Cefotaxime	Gentamicin	TMP-SMX ²	Fosfomycin
<i>Escherichia coli</i> (n=35)	49	14	6	3	3	11	3
Other microorganisms (n=15)	67	20	27	27	27	20	13
TOTAL (n=50)	54	16	12	10	10	14	6

¹Amoxicillin-clavulanate, ²Trimethoprim-sulfamethoxazole. Quinolones are excluded because they are not recommended for pregnant women.

centers or settings. Second, *in vitro* resistance may not adequately predict therapeutic failure because the concentration of most antimicrobial agents used for UTIs is higher in the urine than in serum. Third, the small number of cases does not allow us to analyze the influence of IEAT on the outcome.

In summary, we found that pregnant women with pyelonephritis received IEAT in a small but significant number of cases. Amoxicillin-clavulanate and cephalosporines were adequate initial antibiotics in most cases. The obstetrician should keep in mind the importance of adequate processing of urine samples so as to modify the initial treatment when it is necessary. Other studies are needed to define the clinical impact of IEAT on prognosis in acute pyelonephritis in pregnancy.

REFERENCES

- Gilstrap LC, Ramin SM. Urinary tract infections during pregnancy. *Obstet Gynecol Clin North Am* 2001; 28:581-91.
- Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. *Urol Clin North Am* 2007; 34:35-42.
- Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2007 Apr 18; (2): CD000490.
- Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005; 40:643-54.
- Nowicki B, Sledzinska A, Samet A, Nowick S. Pathogenesis of gestational urinary tract infection: urinary obstruction versus immune adaptation and microbial virulence. *BJOG* 2011; 118:109-12.
- Jamie WE, Edwards RK, Duff P. Antimicrobial susceptibility of Gram-negative uropathogens isolated from obstetric patients. *Infect Dis Obstet Gynecol* 2002; 10:123-26.
- Greer LG, Roberts SW, S. Sheffield JS, Rogers VL, Hill JB, McIntire DD, et al. Ampicillin Resistance and Outcome Differences in Acute Antepartum Pyelonephritis. *Infect Dis Obstet Gynecol* 2008; 2008:891426.
- Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate Antimicrobial Treatment of Infections. A Risk Factor for Hospital Mortality Among Critically Ill Patients. *Chest* 1999; 115: 462-74.
- Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med* 2003; 115: 529-35.
- Ibrahim EH, Sherman G, Wards S, Frase VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patients outcomes in the ICU setting. *Chest* 2000; 118: 146-55.
- Jolley JA, Wing DA. Pyelonephritis in Pregnancy An Update on Treatment Options for Optimal Outcomes. *Drugs* 2010; 70:1643-55.
- Meier S, Weber R, Zbinden R, Ruef C, Hasse B. Extended-spectrum β -lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. *Infection* 2011; 39:333-40.
- Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis* 2008; 8:159-66.
- Zahar JR, Lortholary O, Martin C, Potel G, Plesiat P, Nordmann P. Addressing the challenge of extended-spectrum beta-lactamases. *Curr Opin Investig Drugs* 2009; 10:172-80.
- Gupta K, Hooton TM, Naber K G, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011; 52:103-20.
- Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010; 10:43-50.