

Etiology, frequency and clinical outcomes related to Urinary Tract Infection and Asymptomatic Bacteriuria in pregnant women in a municipality of Southeast Brazil

Etiologia, frequência e desfechos clínicos relacionados à Infecção do Trato Urinário e Bacteriúria

Assintomática em gestantes de um município do Sudeste do Brasil

Etiología, frecuencia y desenlaces clínicos relacionados con Infección de Vías Urinarias y

Bacteriuria Asintomática en gestantes de un municipio del Sudeste de Brasil

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Abstract

Objective: The aim of this study was to investigate cases of Urinary tract infection (UTI) and Asymptomatic bacteriuria (ASB) in pregnant women in a Brazilian city, as well as identify the pathogens causing these diseases and its antimicrobial susceptibility profile. Also, we investigated the antibiotic therapy used in pregnant women to treat UTI and ASB, and the comorbidities which can be related to increased risk of these type of infection. **Methods:** This study was prospective research, descriptive and exploratory, with a qualitative approach, conducted among 35 pregnant women from October 2019 at Basic Health Unit (BHU) in Diadema, São Paulo, Brazil. Patient's data were obtained using specific terms in the search filters from data base of BHU, as well the results of identification of bacterial species isolated from urine culture and the Antimicrobial Susceptibility Testing (AST). **Results:** From 35 study participants, 34.3% had a presumptive diagnosis of ASB and 65.7% had a diagnosis of symptomatic UTI. The predominant bacteria isolated were *Escherichia coli* (n=11) and *Staphylococcus saprophyticus* (n=2). The AST revealed a low rate of resistance to antimicrobials used for the treatment of UTI. The antimicrobial agents most prescribed was cephalexin. Further, 13 pregnant women presented comorbidities. Also, 20% presented premature delivery and 11,4% babies presented neonatal diseases. **Conclusion:** In this study, it was possible to know which bacterial species are commonly isolated from pregnant women urine cultures and evaluate the isolates susceptibility profile, as well as analyze the common antimicrobial therapy prescribed to these women.

Keywords: Urinary tract infections; Asymptomatic bacteriuria; Pregnant women; Antimicrobial resistance; Pregnant health.

Resumo

Objetivo: O objetivo deste estudo foi investigar casos de Infecção do Trato Urinário (ITU) e Bacteriúria Assintomática (BAS) em gestantes de uma cidade brasileira, bem como identificar os patógenos causadores dessa doença e seu perfil de suscetibilidade antimicrobiana. Além disso, investigamos a antibioticoterapia utilizada em gestantes para tratamento de ITU e BSA, e as comorbidades que possam estar relacionadas ao aumento do risco desse tipo de infecção. **Métodos:** Este estudo foi uma pesquisa prospectiva, descritiva e exploratória, com abordagem qualitativa, realizada com 35 gestantes a partir de outubro de 2019 em uma Unidade Básica de Saúde (UBS) de Diadema, São Paulo, Brasil. Os dados dos pacientes foram obtidos por meio de termos específicos nos filtros de busca

do banco de dados da UBS, assim como os resultados da identificação das espécies bacterianas isoladas da urocultura e do Teste de Susceptibilidade Antimicrobiana (AST). Resultados: Dos 35 participantes do estudo, 34,3% possuíam diagnóstico presuntivo de ASB e 65,7% diagnóstico de ITU sintomática. As bactérias predominantes isoladas foram *Escherichia coli* (n=11) e *Staphylococcus saprophyticus* (n=2). O AST revelou uma baixa taxa de resistência aos antimicrobianos utilizados para o tratamento da ITU. O antimicrobiano mais prescrito foi a cefalexina. Além disso, 13 gestantes apresentavam comorbidades. Ainda, 20% apresentaram parto prematuro e 11,4% bebês apresentaram doenças neonatais. Conclusão: Neste estudo foi possível conhecer quais espécies bacterianas são comumente isoladas de uroculturas de gestantes e avaliar o perfil de suscetibilidade dos isolados, bem como analisar a terapia antimicrobiana comum prescrita a essas mulheres.

Palavras-chave: Infecções do trato urinário; Bacteriúria assintomática; Mulheres grávidas; Resistência antimicrobiana; Saúde na gravidez.

Resumen

Objetivo: El objetivo de este estudio fue investigar casos de Infección del Tracto Urinario (ITU) y Bacteriuria Asintomática (BAS) en mujeres embarazadas en una ciudad brasileña, así como identificar los patógenos que causan esta enfermedad y su perfil de susceptibilidad antimicrobiana. Además, investigamos la terapia antibiótica utilizada en mujeres embarazadas para el tratamiento de ITU y BAS, y las comorbidades que pueden estar relacionadas con el mayor riesgo de este tipo de infección. Métodos: Este estudio fue una investigación prospectiva, descriptiva y exploratoria, con enfoque cualitativo, realizada con 35 gestantes a partir de octubre de 2019 en una Unidad Básica de Salud (UBS) en Diadema, São Paulo, Brasil. Los datos de los pacientes se obtuvieron mediante términos específicos en los filtros de búsqueda de la base de datos de la UBS, así como los resultados de la identificación de especies bacterianas aisladas de urocultivos y el Test de Susceptibilidad Antimicrobiana (AST). Resultados: De los 35 participantes del estudio, el 34,3% tenía diagnóstico presuntivo de BAS y el 65,7% tenía diagnóstico de ITU sintomática. Las bacterias predominantes aisladas fueron *Escherichia coli* (n=11) y *Staphylococcus saprophyticus* (n=2). El AST reveló una baja tasa de resistencia a los antimicrobianos utilizados para el tratamiento de la ITU. El antimicrobiano más prescrito fue la cefalexina. Además, 13 gestantes presentaban comorbidades. Aun así, el 20% tuvo un parto prematuro y el 11,4% de los bebés tuvo enfermedades neonatales. Conclusión: En este estudio fue posible conocer qué especies bacterianas son comúnmente aisladas de urocultivos de gestantes y evaluar el perfil de susceptibilidad de los aislados, así como analizar la terapia antimicrobiana común prescrita a estas gestantes.

Palabras clave: Infecciones del tracto urinario; Bacteriuria asintomática; Mujeres embarazadas; Resistencia antimicrobiana; Salud en el embarazo.

1. Introduction

Urinary tract infection (UTI) is the most common bacterial infectious disease that usually affects the lower urinary tract, which is composed by the bladder, ureters and urethra inducing cystitis, ureteritis and urethritis, respectively (Schnarr et al., 2008). Lower UTI is classified as uncomplicated, but if left untreated can also affect the kidneys, causing pyelonephritis and other complications (Kalinderi et al., 2018). UTIs can be also classified according to the presence or absence of symptoms: symptomatic UTIs are characterized by the presence of classic symptoms like malaise, dysuria, increased urinary frequency, low back pain and fever (Dautt-Leyva et al., 2018). On the other hand, asymptomatic UTI, also known as asymptomatic bacteriuria (ASB), can be defined by the presence of bacteria in the urine of asymptomatic patients.

Women are more susceptible to developing UTIs due to their anatomical characteristics, such as the short urethra and its proximity to the anus, which facilitates invasion and colonization of the urethra by bacteria, especially the *Enterobacteriales*, such as *Escherichia coli* (Gyftopoulos et al., 2019). Studies show that more than 50% of women will have at least one episode of UTI during their lifetime (Geerlings, 2016) and that about 11% have UTI annually (Foxman et al., 2000). In pregnant women, due to physiological and anatomical changes that favors the development of UTI (Glaser et al., 2015), this infection ends up being the most frequent within this group and the second most common complication in gestational periods (Amiri et al., 2015; Szweda et al., 2016).

UTIs are closely related to premature birth, risk of abortion and early rupture of amniotic membranes (Byonanuwe et al., 2020). In addition, uncomplicated UTI untreated in pregnant women can lead to the development of pyelonephritis, increasing the risks of bacteremia, followed by sepsis and possible maternal death (Dautt-Leyva et al., 2018). Furthermore, it is often associated with undesirable outcomes (Smaill et al., 2019) such as prematurity that is usually linked to low birth weight

in neonates, for example, factor that may interfere in the survival rate of these neonates (Sousa et al., 2017). A study conducted in Mexico demonstrated that 11.2% of pregnant women with UTI caused by *Escherichia coli*, gave birth to children with low weight, 3.53% reported neonatal death, and 3.53% had an abortion (Dautt-Leyva et al., 2018). Other studies reported the existence of an association between maternal UTIs and congenital diseases in neonates such as left ventricle obstruction, malformation of atrioventricular septa (Cleves et al., 2008), congenital cataract, cleft lip, stenosis, small bowel, duodenum and colon atresia, among others (Howley et al., 2018).

Maternal mortality has been a major concern in Brazil and several strategies to address it have been proposed. The Rede Cegonha Network (RCN) is a strategy launched in 2011 by the Ministry of Health that aims to improve the services offered by the Brazilian Unified Health System (SUS) from family planning to the child development in the first two years of life. Diadema, a city that is part of the metropolitan area of São Paulo, Brazil, has adopted the Family Health Strategy in its Primary Care with the aim of closer monitoring of pregnant women in the municipality, as provided for in the RCN. So, in this scenario the present study was performed, aiming to understand and investigate how the UTIs can be possibly related to undesirable outcomes with the mother and the neonate. Cases of UTI and ASB were investigated, also the comorbidities related to increased risk of this infection, the isolated bacterial antimicrobial susceptibility profile and antibiotic therapy used in pregnant women from Diadema, São Paulo.

2. Methodology

This study was prospective research, descriptive and exploratory with a qualitative approach that was conducted with pregnant women assisted in a Basic Health Unit (BHU) in Diadema, São Paulo, Brazil. In October 2019, pregnant women aged over 18 years in the second or third trimester of pregnancy and with the delivery expected up to January 2020 were selected in this study. The study was approved by the Research Ethics Committee of the Federal University of São Paulo under the number 0544/2019. The authorization to access the patient's data was granted by completing the Informed Consent Form for each pregnant woman.

The inclusion criteria of pregnant women in the study were: (a) pregnant women with a positive presumptive clinical diagnosis and/or suggestive symptomatology for UTIs; (b) pregnant women with a negative clinical diagnosis and/or without suggestive symptoms of UTI but presenting positive urine culture. The exclusion criteria of pregnant women in the study were: (a) pregnant women under 18 years of age and/or with delivery scheduled up to January 2020; (b) pregnant woman without presumptive clinical diagnosis and/or without suggestive symptoms for UTIs; (c) pregnant women without urine culture performed or with negative results for urine culture.

Patient's data were obtained from FormSUS platform and citizen's electronic medical records. Urine culture results were consulted through LISNet. Prospect data analyzed were age, gestational period, number of former pregnancies, comorbidities, description of symptomatology or clinical diagnosis suggestive of UTI and antibiotic therapy. The search for the information necessary for the analysis of the data of the pregnant women was performed using specific terms in the search filters in each of the above-mentioned databases. Also, the identification of bacterial species isolated from urine culture and the Antimicrobial Susceptibility Testing (AST) were performed. A chromogenic agar urine culture (Probac, Brazil) was used for screening followed by 24 hours incubation at 37°C. The colonies grown were identified by automated method Vitek 2® (BioMérieux, Brazil) and their antimicrobial susceptibility profile were determined in the same device. The analysis of the minimum inhibition concentration was performed according to the breakpoints of the Clinical and Laboratory Standards Institute guidelines (CLSI, 2017). The antimicrobial agents tested in this study were amikacin, amoxicillin/clavulanate, ampicillin, cephalothin, cefepime, ceftriaxone, cefuroxime, cefuroxime axetil, ciprofloxacin, clindamycin, ertapenem,

gentamicin, inducible clindamycin resistance, levofloxacin, linezolid, low concentration penicillin, meropenem, nalidixic acid, nitrofurantoin, norfloxacin, oxacillin, piperacillin tazobactam, rifamycin, tigecycline, and trimethoprim/sulfamethoxazole.

3. Results

In October 2019, 238 pregnant women were monitored by family health teams at a HBU in Diadema. Thirty-five pregnant women over 18 years old and with medical records with presumptive information about UTI and/or at least one positive result of prenatal urine culture were included in the study.

In the analysis of the medical records of these 35 pregnant women, urine culture was requested for all and among these patients, 100% (35/35) performed at least one test and 74,3% (26/35) pregnant women performed two or more urine cultures during pregnancy, counting to an average of 2.34 ($\sigma = 1.16$) tests performed per patient.

The diagnosis results showed that 34.3% (12/35) had a presumptive diagnosis of ASB and 65.7% (23/35) had a diagnosis of symptomatic UTI. Furthermore, among the 35 pregnant women, 16 presented positive results for urine culture, 17 obtained negative urine culture result and two results were suggestive of clinical sample contamination during the collection or transport. Moreover, four pregnant women presented two episodes of UTI until the delivery.

The mean age among the 35 pregnant women was 27.7 years old, ranging from 19 to 40. Thirteen were considered primiparous and 22 multiparous; twelve had one previous pregnancy and 10 had two or more previous pregnancies. Furthermore, 13 pregnant women presented comorbidities: type II *Diabetes mellitus* and gestational diabetes were diagnosed in 20% (7/35) and 5,71% (2/35) pregnant women, respectively. Also, three pregnant women (3/35) were diagnosed with hypertension and one of these patients was diagnosed with *Diabetes mellitus* and hypertension (1/35).

Based on laboratory diagnosis, 16 urine cultures were positive and *Enterobacterales* such as *Escherichia coli* (n=11), *Klebsiella pneumoniae* (n=1), *Klebsiella aerogenes* (n=1) and *Proteus mirabilis* (n=1) were isolated. Also, *Staphylococcus saprophyticus* (n=2) were recovered. The AST revealed that all the *Enterobacterales* tested were susceptible to third-generation cephalosporins and carbapenems, also one (*E. coli*) was resistant to ciprofloxacin and three (one *E. coli*, one *K. aerogenes*, one *K. pneumoniae*) showed to be susceptible increasing the exposure to nitrofurantoin. Moreover, three (two *E. coli*, one *K. aerogenes*) were resistant to first generation cephalosporins and two (*E. coli*) were classified as susceptible increasing the exposure. By analyzing the AST of *S. saprophyticus*, both were resistant to penicillin, and one was resistant to oxacillin.

Moreover, the antimicrobial agents most prescribed to these pregnant women diagnosed with UTIs or ASB were cephalixin, followed by fosfomicin/trometamol, nitrofurantoin and amoxicillin/clavulanic acid. The posology prescribed for each antimicrobial agent was: fosfomicin/trometamol 3g single-dose, amoxicillin/clavulanic acid (500mg/125mg) every 12 hours for 10 days, nitrofurantoin 100mg every 6 hours for 10 days, and cephalixin 500mg every 6 hours for 7 days.

Furthermore, as clinical outcome, from these 35 pregnant women, seven (20%) presented premature delivery and four (11,4%) babies presented neonatal diseases.

4. Discussion

In pregnant patients, early screening of UTI and ASB is of paramount importance and shows a predictive overview of the maternal-fetal-infant outcome. The current recommendation is to perform the urine culture at least twice during pregnancy, preferably in the first and third trimesters (Rossi et al., 2020). In the present study, it was observed that urine culture was requested to all the pregnant women, and the majority (74,3%) performed two or more tests, counting to an average of 2.34 ($\sigma = 1.16$) tests per patient, which is accordingly to recommended.

Furthermore, it was observed that 34.3% (12/35) had a presumptive diagnosis of ASB and 62.8% (23/35) had a diagnosis of symptomatic UTI. Azami et al. (2019) reported a rate of 8.7% of ASB in Iranian pregnant women (Azami et al., 2019) and Nteziyaremye et al. (2020) reported in Uganda that 3.75% of the pregnant women were diagnosed with ASB (Nteziyaremye et al., 2020). In the present study, we observed a higher ASB rate, which could be a regional epidemiologic mirror or the data could reflect the need for increasing our sample.

In addition, 17 (17/23) of the pregnant women who were clinically diagnosed with UTI due to symptoms had negative urine cultures. Among many other reasons, a plausible one is the treatment beginning before the urine culture was carried out. This situation could be partially solved by raising awareness about how and when this exam can be performed and about the importance of this procedure during prenatal care. In addition, it is important to highlight the need for a plan to improve the workflow between HBU and clinical analysis laboratory.

Also, concerning pregnant women with comorbidities, the importance of urine culture screening is emphasized, especially for those with *Diabetes mellitus* and gestational diabetes, since they are more likely to develop UTI due to increased glucose in the urine and impaired immune system (Smaill et al., 2019; Belete et al., 2020). Therefore, knowledge about the presence of these comorbidities assists in the therapeutic conduction aiming at satisfactory maternal-fetal-infant outcomes. In this study, seven pregnant women diagnosed with UTI also presented *Diabetes mellitus* and two presented gestational diabetes. From these patients, two reported complications in labor, two reported preterm labor, and one reported baby health complication (cardiac and pulmonary disease).

Furthermore, among the analyzed patients, 20% presented preterm labor. This pregnancy complication is a concern, since it can result in neonatal complications such as impair fetal growth, low birth weight and neonatal death (Kalinderi et al., 2018). In the study conducted by Dautt-Leyva et al. (2018) it was reported that 9.41% of pregnant women with UTI presented preterm labor, a percentage lower than the obtained in the present study.

Regarding the bacterial species obtained in urine cultures in the present study, the most isolated was *E. coli* followed by *S. saprophyticus*. The finding of *E. coli* as the most isolated species is very common, since most studies about UTI usually report the same (Omidifar et al., 2020; Belete et al., 2020). Belete and Saravanan (2020) performed a study in developing countries about UTI during pregnancy, and found mostly Gram-negative strains, being *E. coli* the most isolated microorganism (more than 50% of the cases), followed by *K. pneumoniae* (Belete et al., 2020). Although the present study has showed partially different results, the microorganisms isolated are common as causing UTIs, except for *K. aerogenes* which is rarer.

Among the isolates, it was observed only one *E. coli* isolate resistant to nitrofurantoin, corroborating data from other studies which reported high rates of susceptibility to this antimicrobial agent (Tessema et al., 2020). Besides, two *E. coli* resistant to cephalothin and one resistant to cefuroxime were isolated, first- and second-generation cephalosporins, respectively. In a study conducted by Omidifar et al. (2020), it was observed the *E. coli* as the most common pathogen (78.3%) in cases of UTIs in pregnant women, presenting considerable levels of resistance to cephalosporins (26.1%). In this context, the obtained results should be considered to analyze the main treatment administered to pregnant women with UTI in the BHS studied (cephalexin, a first-generation cephalosporin) as well as help to guide the best treatment option.

Furthermore, all samples of *E. coli* were susceptible to carbapenems and third-generation cephalosporins and only one isolate showed resistance to sulfamethoxazole/trimethoprim. In a similar study, Dautt-Leyva et al. (2018) reported that 60% of *E. coli* isolated samples from pregnant women with UTI were resistant to ampicillin, cephalothin and sulfamethoxazole/trimethoprim, and about 90% showed susceptibility to all carbapenems. These data show that the present study presented similar results, since no resistant isolates to carbapenems and third-generation cephalosporins were found.

Resistance to ampicillin in isolates of *K. aerogenes* and *K. pneumoniae* is expected since these species are intrinsically resistant to this antimicrobial (EUCAST, 2020). However, due to decreased susceptibility to nitrofurantoin, higher care

concerning antibiotic therapy should be taken, since this antimicrobial is one of the most frequently prescribed for pregnant women with UTI at the BHU studied.

Regarding the *S. saprophyticus* isolates, one of them presented resistance to oxacillin, which indicates resistance to most beta-lactams used clinically for the treatment of Gram-positive infections (Leclercq et al., 2013). Furthermore, is important to remember that *S. saprophyticus* is intrinsically resistant to fosfomicin (EUCAST, 2020), thus, is important to prescribe other antimicrobials when detected these bacteria.

The most prescribed treatments in the cases of UTI or ASB of the pregnant women followed in this study were fosfomicin/trometamol, amoxicillin/clavulanic acid, nitrofurantoin, and cephalexin, the latter being the most frequently prescribed. Recently, the Brazilian Society of Infectious Diseases, the Brazilian Federation of Gynecology and Obstetrics Associations, and the Brazilian Society of Clinical Pathology/Laboratory Medicine reported recommendations for the treatment of UTI in women. According to this document, to the pregnant women with cystitis is recommended as the first line of treatment fosfomicin/trometamol 3g single dose or nitrofurantoin 100 mg every six hours for five days. The second line should be cefuroxime 250mg every 12 hours or amoxicillin-clavulanic acid 500mg/125mg every eight hours or 875mg/125mg every 12 hours for seven days (Rossi et al., 2020). Additionally, for pregnant women with ASB are recommended amoxicillin, cephalexin, cefuroxime, fosfomicin and nitrofurantoin. Is important highlight that the use of nitrofurantoin after 37 weeks of gestation is not recommended.

In this context, it is worth mentioning that the use of amoxicillin and other cephalosporins, such as cephalexin, despite being indicated to treat UTI during pregnancy and being the most common antimicrobial prescribed for this purpose at the BHU studied, there are indications of a high chance of therapeutic failure for these antimicrobials, due to the shorter half-life of the compounds (Jancel et al., 2002). Moreover, there is a concern about the adherence to drug therapy by these pregnant women when prescribed cephalexin, since many of them judge as a problem the short interval between the doses. Therefore, it can be noticed that the antimicrobials used as therapy in the municipality of Diadema corroborate with the recommendations, however, it is advisable to prioritize the use of fosfomicin and nitrofurantoin as the first line of treatment.

Our work presents some limitations. First, we worked with a low number of pregnant women. Perhaps, by increasing our sample, we could obtain more accurate data. Although, during our research, we faced the COVID-19 pandemic which harmed our plan in increasing the sample. So, we hope, in the future to conduct more studies which can increase our sample and test the isolates for fosfomicin too.

5. Conclusion

This study aimed to investigate the UTI and ASB cases in pregnant women in a BHU studying the possible relationship between this type of infection and other comorbidities with undesirable clinical outcomes related to the women, the labor and the neonate. It was possible to observe undesirable clinical outcomes as preterm labor, complications during labor and neonate disease among this studied group of pregnant women, being all diagnosed with UTI (symptomatic or asymptomatic). Furthermore, it was possible to understand how this type of infection is treated in this BHU (which reflects all the municipality) as well as which bacterial species are commonly isolated through urine cultures and how is its susceptibility profile.

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