Doctoral thesis

-abstract-

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2013
Microbiological study of antepartum and postpartum vaginal flora. Clinical and laboratory research and therapeutical particularities.

Keywords: *S. aureus, E. coli*, bacterial vaginosi, pregnant women, postpartum women.

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LITERATURE

High prevalence of gynecological infections worldwide requires that every patient with gynecological symptoms should be carefully investigated.

Genital infections with *Escherichia coli* or *Staphylococcus aureus* are more common in nasal carriers of *S. aureus* or occur in case of prolonged or repeated hospitalizations of patients with multiple risk factors.

In obstetrical or gynecological infectious pathology, *Escherichia coli* can function as a monoetiological pathogen causing urinary infections or chorioamnionitis or can be isolated in polymicrobial infections (e.g. septic abortion, postpartum endometritis or wound infection). Both monoetiological and polymicrobial infections can cause septicemia.

Coagulase-positive staphylococci, important constituents of the microbiological flora of the skin, may play an important role in wound infection. Their ability to replicate in aerobic and anaerobic conditions and their ability to synthesize bacteriocins and bacteriocin-like substances increases the recognition of this organism as a cause of wound infections, although the anaerobes which are concurrently involved often escape recognition. *Staphylococcus aureus* functions as a copathogen in the progressive gangrene of soft tissues.¹

*Staphylococcus aureus* is the most prevalent vaginal pathogen and remains one of the germs the most involved in infection, an incidence which is steadily increasing. The colonization of the vaginal mucous membrane with this germ can predispose to toxicoseptic shock.²

NORMAL VAGINAL FLORA

Normal flora of the lower female genital tract is complex but very little known in detail. Normal vaginal flora contains a wide range of bacteria but it mainly consists of lactobacilli (90-95%) and other bacterial species found in extremely small percentages.

Most women present at vaginal level a single dominant species and they are colonized by a single species of lactobacilli. *Lactobacillus crispatus* and *Lactobacillus jensenii* are the most commonly found in Caucasians. Lactobacilli maintain the normal vaginal ecosystem, inhibiting the growth, adhesion and expansion of potential pathogens.³

Normal microbial flora of the vagina is an important factor in the antiinfectious defense of this ecosystem.

The resident flora include those micro-organisms well adapted to the conditions of the vaginal ecosystem, fairly constant in its component species and characteristic to it, and it is found inside the vagina from puberty until menopause.
The composition of the resident flora is represented by those microorganisms phyllogenetically selected and adapted to the conditions offered by epithelium lining of the vaginal mucous.

Quite often there are established symbiotic relationships between the host and her resident flora. Due to the ideal adaptations to the development on the vaginal mucous membrane, the resident flora prevent the populating of vagina with other more aggressive species. Thus, its main action is antipatogenic.\textsuperscript{8, 4}

Floating flora is represented by those bacterial species unadapted or less adapted to the vaginal ecosystem, so it comes to species with temporary variable persistence. Under normal health conditions, these micro-organisms are efficiently countered, their presence on the surface of the epithelium of the vaginal mucous being nonmanifest.\textsuperscript{5}

Normal vaginal flora is dynamic, presenting numerous fluctuations throughout a woman's life, under the influence of hormones, sexual activity and associated diseases.\textsuperscript{5}

Numerous studies have been carried out on the vaginal flora of pregnant women and it has been demonstrated that it is represented by Gram positive cocci, Gram positive bacilli and Gram negative bacilli.\textsuperscript{6}

\textbf{OWN CONTRIBUTIONS}

\textbf{Purpose of the study}

Genital infections during perinatal period are a relatively common cause of morbidity, occurring in approximately one third of pregnant women. Late presentation to the doctor increases the risk of maternal-infant morbidity on the one hand and of premature birth on the other hand.

Inappropriate use of antibiotics has resulted in the occurrence of attenuated clinical forms of genital infections which chronicized, infections with germs with multiresistance to usual antibiotics.

The aim of our study is to analyze the clinical and paraclinical and therapeutic peculiarities in genital infections occurring in antepartum and postpartum, caused by \textit{Staphylococcus aureus} and \textit{Escherichia coli}, by microbiological study of the vaginal flora, in order to better understand the patterns of colonization and to prevent infection by the two germs during the peripartum. In addition, the study will also focus on optimizing and improving the treatment of genital infections caused by the two germs.

\textbf{OBJECTIVES of the RESEARCH}

The research objectives are:
Microbiological study of vaginal flora in antepartum and postpartum genital infections;
- Study of sensitivity to antibiotics and chemotherapeutic agents of *S. aureus* isolated in genital infections occurring perinatally;
- Study of sensitivity to antibiotics and chemotherapeutic agents of *E. coli* isolated in genital infections occurred antepartum and/postpartum;
- Evaluation of clinical-paraclinical and therapeutic peculiarities for *S. aureus* and *E. coli*.

**Design of the study**

**RESULTS and DISCUSSION**

From the 686 samples taken from pregnant and postpartum women during the period 1 January 2007 - 31 December 2010, along with the strains of *S. aureus* (153 cases) and *E. coli* (190 cases), we isolated and identified strains of *Streptococcus* gr. B, *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Pseudomonas aeruginosa*, *Proteus* spp., anaerobic germs, *Enterococcus* and *Candida* spp., met with a much lower frequency (Figure 1).
Figure 1. Graphical representation of bacterial strains isolated from vaginal secretions and lochia.

Distribution of cases in pregnant and postpartum women

The 343 cases of genital infections with S. aureus and E. coli were classified as follows: 172 (50.15%) of cases in pregnant women in the third trimester and 171 (49.85%) cases in postpartum women within the first 3 days postpartum. The average age across the entire study group was 30.28 ± 7.68 years, and within the 20-35 years group occurred the most cases of genital infections (229 patients, 66.76%).

Table 1. Complications of genital infections with S. aureus in pregnant women in third quarter.

<table>
<thead>
<tr>
<th>Total of patients (N = 66)</th>
<th>Week 28-32</th>
<th>Week 32-36</th>
<th>Over 36 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># / % of patients</td>
<td>3 / 4.55%</td>
<td>7 / 10.61%</td>
<td>5 / 7.58%</td>
</tr>
<tr>
<td><strong>Leucorrhea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># / % of patients</td>
<td>21 / 31.82%</td>
<td>7 / 10.61%</td>
<td>15 / 22.73%</td>
</tr>
<tr>
<td><strong>UTI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># / % of patients</td>
<td>8 / 12.12%</td>
<td>12 / 18.18%</td>
<td>6 / 9.09%</td>
</tr>
</tbody>
</table>

UTI = Urinary Tract Infection
Table 2. Complications of genital infections with E. coli in pregnant women in third quarter.

<table>
<thead>
<tr>
<th>Total patients</th>
<th>Week 28-32</th>
<th>Week 32-36</th>
<th>Over 36 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>9 / 8,49%</td>
<td>13 / 12,26%</td>
<td>11 / 10,38%</td>
</tr>
<tr>
<td>Leucorrhrea</td>
<td>18 / 16,98%</td>
<td>23 / 21,70%</td>
<td>17 / 16,04%</td>
</tr>
<tr>
<td>UTI</td>
<td>9 / 8,49%</td>
<td>17 / 16,04%</td>
<td>11 / 10,38%</td>
</tr>
</tbody>
</table>

UTI = Urinary Tract Infection

Table 3. Complications of genital infections with S. aureus in postpartum women.

<table>
<thead>
<tr>
<th>Total patients (N= 87)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>15 / 17,24%</td>
<td>7 / 8,05%</td>
<td>19 / 21,84%</td>
</tr>
<tr>
<td>MAL</td>
<td>9 / 10,34%</td>
<td>16 / 18,39%</td>
<td>11 / 12,64%</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1 / 1,15%</td>
<td>2 / 2,30%</td>
<td>1 / 1,15%</td>
</tr>
</tbody>
</table>

MAL= modification of appearance of lochia.

Table 4. Complications of genital infections with E. coli in postpartum women.

<table>
<thead>
<tr>
<th>Total patients (N=84)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>9 / 10,71%</td>
<td>4 / 4,76%</td>
<td>13 / 15,48%</td>
</tr>
<tr>
<td>MAL</td>
<td>17 / 20,24%</td>
<td>10 / 11,9%</td>
<td>15 / 17,86%</td>
</tr>
<tr>
<td>Dysuria</td>
<td>14 / 16,67%</td>
<td>8 / 9,52%</td>
<td>19 / 22,62%</td>
</tr>
</tbody>
</table>

MAL= modification of appearance of lochia.
Analysis of sensitivity to antibiotics and chemotherapy agents of *S. aureus* and *E. coli*

**Sensitivity to antibiotics and chemotherapeutic agents of *S. aureus* isolated from pregnant women with infections (subgroup A1).**

![Graphical representation of sensitivity to antibiotics and chemotherapeutic agents of *S. aureus* strains isolated from pregnant women with a history of staphylococcal infections.](image)

Figure 2. Graphical representation of sensitivity to antibiotics and chemotherapeutic agents of *S. aureus* strains isolated from pregnant women with a history of staphylococcal infections.

The sensitivity of *S. aureus* strains to penicillin was low, namely: only one single strain (3.7%) was sensitive to penicillin G, 10 strains (37.03%) to ampicillin-sulbactam and 3 strains (11.11%) to oxacillin. The sensitivity to macrolides, namely to clarithromycin, was of 48.14% (12 strains), somehow greater than to aminoglycosides-gentamycin 55.55% (15 strains). A low sensitivity has been recorded to clindamycin – 18.51% (5 strains). A high sensitivity was obtained to cephalosporins: Cefuroxime sodium 70.37% (18 strains) and Ceftriaxone 66.66% (18 strains). Yet the highest sensitivity was obtained to ciprofloxacin 74.07% (20 strains). A significant sensitivity (59.25%) was also obtained to trimethoprim-sulfamethoxazole (16 strains) (Figure 2).

**Sensitivity to antibiotics and chemotherapeutic agents of *S. aureus* isolated from pregnant women without history of staphylococcal infections (subgroup A2)**

On patients of A2 subgroup we found levels of sensitivity to antibiotics of the isolates strains higher than on patients of A1 subgroup, namely: sensitivity to penicillin G 7.69% (3 strains), to ampicillin-sulbactam 41.02% (16 strains) and to oxacillin 15.38% (6 strains). The sensitivity to macrolides, namely to clarithromycin, was of 56.41% (2 strains), to aminoglycosides-gentamicin 61.53% (24 strains). A low sensitivity was recorded to clindamycin - 23.07% (9 strains).
A high sensitivity was obtained to cephalosporins: Cefuroxime sodium 71.79% (28 strains) and Ceftriaxone 69.23% (27 strains).

Comparing subgroup A1 and subgroup A2, we found that on pregnant women without a history of diagnosed staphylococcal infections (subgroup A2) there was a significantly higher sensitivity of *S. aureus* to the full range of antibacterial agents tested. Therefore, we may suggest that on carriers of *S. aureus*, either diagnosed or asymptomatic, the sensitivity to antibiotics of the germ is reduced compared to non-carriers.

Our observations are consistent with those of other researchers. Asymptomatic colonization with *S. aureus* is common; recent studies suggest that about 30% of the U.S. population carry *S. aureus* in the anterior nostril and that 1-2% of the population carries MRSA in the nostrils. These people colonized with *S. aureus* present a higher risk of subsequent infections than those uncolonized. Most infections are caused by the same strain of *S. aureus* that previously colonized the person.

In response to these findings, greater attention was given to detect *S. aureus* (especially MRSA) on carriers, along with their subsequent decolonization as a potential method for preventing infections with *S. aureus*. Although the nose is the most common situs in carriers of *S. aureus*, the bacteria can also colonize the throat, skin and gastrointestinal tract.

**Sensitivity to antibiotics and chemotherapeutic agents of *E. coli* isolated from pregnant women with a history of *E. coli* infections (subgroup B1) - Figure 3.**

**Sensitivity to antibiotics and chemotherapeutic agents of *E. coli* isolated from pregnant women without a history of *E. coli* infections (subgroup B2).**

In case of the B2 subgroup, the sensitivity to antibiotics of strains of *E. coli* was as follows: sensitivity to ampicillin 12.85% (9 strains), to ampicillin-sulbactam 75.71% (53 strains), to gentamicin 78.57% (55 strains), the cefuroxime sodium 74.28% (52 strains), to cefoperazone 62.85% (44 strains), cefotaxime 54.28% (38 isolates), cefoxitin 64.28% (45 strains) and to imipenem 92.85% (65 strains). The sensitivity to trimethoprim-sulfamethoxazole was 81.42% (52 strains).

Comparing the sensitivity to antibiotics of subgroups B1 and B2, we found that there is a marked similarity, which shows that previous infection with *E. coli* did not increase the resistance to antibiotics of the bacteria, as observed for *S. aureus*, regarding bacterial vaginosis.

Our observations are consistent with data from other studies. The rates of resistance to antibiotics of *E. coli* seen in France were significantly smaller than those seen in all the other countries that participated in the ARESC study, for most of the nine antibiotics studied (the
most usually prescribed for cystitis). In France, the prescription of antibiotics, assayed as daily dose per 1000 inhabitants, is the largest in Europe.\textsuperscript{11}

Figure 3. Graphical representation of sensitivity to antibiotics and chemotherapeutic agents of \textit{E. coli} strains isolated from pregnant women with a history of \textit{E. coli} infections.

This powerful exposure to antibiotics does not appear to affect the rate of resistance to antibiotics in cystitis. An appropriate use of antibiotics and, especially, a reasoned prescribing of fluoroquinolones, in accordance with the recommendations, are probably the explanation for the results of the above mentioned study.\textsuperscript{12}

\textbf{Sensitivity to antibiotics and chemotherapeutic agents of \textit{S. aureus} isolated from postpartum women with a history of staphylococcal infections (subgroup C1)}

The strains of \textit{S. aureus} isolated from the patients of this subgroup presented the following sensitivity to antibiotics: to penicillin G 6.45\% (2 strains), to ampicillin-sulbactam 35.48\% (11 strains), and to oxacilin 12.9\% (4 strains).

The sensitivity to macrolides, namely to clarithromycin, was of 45.16\% (14 strains), to aminoglycosides-gentamicin 51.61\% (16 strains). A low sensitivity has been recorded to clindamycin – 19.15\% (6 strains). A high sensitivity was obtained to cephalosporins: Cefuroxime sodium 67.74\% (21 strains) and Ceftriaxone 61.29\% (19 strains).

The highest sensitivity was obtained to ciprofloxacin 70.96\% (22 strains). A sensitivity of 54.83\% was also obtained to trimethoprim-sulfamethoxazole (27 strains).
Sensitivity to antibiotics and chemotherapeutic agents of S. aureus isolated from postpartum women without a history of staphylococcal infections (subgroup C2).

Figure 4. Graphical representation of sensitivity to antibiotics and chemotherapeutic agents of S. aureus strains isolated from postpartum women without a history of staphylococcal infections.

As in the case of pregnant women, we found out that the strains isolated from symptomatic carriers of S. aureus postpartum women (those who had a history of diagnosed infections) are significantly more resistant to the antibiotics tested than the strains isolated from the postpartum women without a history of staphylococcal infections. Comparing C2 subgroup with A2 subgroup (pregnant women without a history of staphylococcal infections), we found out a slightly increased sensitivity to antibiotics of strains of S. aureus isolated from postpartum women, without reaching the significance threshold.

Sensitivity to antibiotics and chemotherapeutic agents of E. coli isolated from postpartum women with a history of E. coli infections (subgroup D1)

The strains of E. coli isolated from the patients in D subgroup presented the following sensitivity to ampicillin 8% (4 strains), to ampicillin-sulbactam to 66% (33 strains) to gentamicin 70% (35 strains), 74% Cefuroxime sodium (37 strains), cefoperazone 56% (28 strains), cefotaxime 46% (23 strains), Cefoxitin 64% (32 strains). To imipenem, the sensitivity was in 92% (46 strains), to ciprofloxacin 72% (36 strains) and to trimethoprim-sulfamethoxazole in 74% (37 strains).

Comparing the sensitivity to the antibiotics tested in subgroup D1 (postpartum women with a history of E. coli infection) to subgroup B1 (pregnant women with a history of E. coli infection), we found out a higher resistance of the E. coli strains isolated from postpartum women.
Sensitivity to antibiotics and chemotherapeutic agents of E. coli isolated from postpartum women without a history of E. coli infections (subgroup D2)

![Graphical representation of sensitivity to antibiotics and chemotherapeutic agents of E. coli strains isolated from postpartum women without a history of E. coli infections.](image)

**Figure 5.** Graphical representation of sensitivity to antibiotics and chemotherapeutic agents of E. coli strains isolated from postpartum women without a history of E. coli infections.

In terms of sensitivity to the tested antibiotics of E. coli isolated from patients without a history of E. coli infection, we found out that there was a slight decrease, not statistically insignificant, of the sensitivity to antibiotics of strains isolated from postpartum women compared to those isolated from pregnant women.

Our observations are consistent with data from other studies. The rates of resistance to antibiotics of E. coli seen in France were significantly smaller than those seen in all the other countries that participated in the ARESC study, for most of the nine antibiotics studied (the most usually prescribed for cystitis). In France, the prescription of antibiotics, assayed as daily dose per 1000 inhabitants, is the largest in Europa.\(^\text{13}\)

This powerful exposure to antibiotics does not appear to affect the rate of resistance to antibiotics in cystitis. This fact could be explained by the compliance of French doctors who prescribe medicine with the recommendations of AFSSAPS (the French Agency for the Safety of Health Products). The appropriate use of antibiotics and, especially, a reasoned prescribing of fluoroquinolones, in accordance with the recommendations, are probably the explanation for the results of the above mentioned study.\(^\text{14}\)

The relentless progress of bacterial resistance to drugs compels us to reconsider the first-intent therapy for some infections.
GENERAL CONCLUSIONS

1. Pregnancy is characterized by a state of relative immunosuppression that tolerates fetal antigens, a necessary condition for fetal survival. There is a high probability that the pregnant woman is contaminated with germs present in various sources of infection, as well as the severity of the pathology caused by them.

2. Among the causes of perinatal mortality, the infectious pathology has 20 to 65.6%, and more than a third of deaths in childbirth and children who died in the early neonatal period are due to an infectious cause.

3. Bacterial vaginosis is one of the most common vaginal disorders. It results from a profound imbalance of the vaginal ecosystem, whose mechanisms yet remain unknown, although recent progress has been made in understanding them.

4. The presence of bacterial vaginosis was found to be a risk factor for adverse obstetrical outcomes such as preterm labor and preterm birth, premature rupture of membranes, miscarriage, chorioamnionitis, postpartum infections such as endometritis and post-caesarean wound infection.

5. In our study, the most common bacterial strains isolated in genital infections in pregnant and postpartum women were the gram-positive cocci (S. aureus, Streptococcus gr. B, Enterococcus spp.) and in higher proportion of gram-negative bacilli (E. coli, Citrobacter spp., Klebsiella spp., Proteus spp., Pseudomonas aeruginosa, Enterobacter spp.)

6. We noticed that the high prevalence of gynecological infections requires that pregnant and postpartum women be thoroughly investigated. Since the culture provides identification of the causative pathogens, it must invariably be done.

7. Significant complications seen on pregnant women in the third quarter with genital infections with S. aureus were represented by leucorrhea (65.15% of cases) and urinary tract infection (39.39% of cases) and in pregnant women with genital infections with E. coli there were recorded leucorrhea (54.72% of cases) and urinary tract infection (34.91% of cases).

8. In this study, we noticed a significant correlation between the existence of a previous infectious episode with the isolated strain and the incidence of genital infection, both for S. aureus and E. coli.

9. The anatomical and physiological particularities of the pregnant woman’s body ranks the genital infection among the serious infections. Septic complications significantly increase in births through caesarean section and therefore administration of antibiotics is necessary during surgery.
10. In order to evade the action of antibiotics, bacteria have the capacity to modulate the expression of resistance genes, thus ensuring a rapid evolution with a minimum energy cost, even in the presence of antimicrobial agents. Its resistance manifests at both individual and population (even global) level, resulting in increased morbidity, mortality, cost/patient and generally a very large list of problems.

11. In our study, the *S. aureus* strains isolated from pregnant women who were colonized in history showed a significantly increased resistance to the tested antibiotics and chemotherapeutic agents, compared with the strains isolated from pregnant women without a history of *S. aureus* infection. Therefore, we may suggest that on carriers of *S. aureus*, either diagnosed or asymptomatic, the sensitivity to antibiotics of the germ is reduced compared to non-carriers.

12. The *S. aureus* strains isolated from postpartum women with a history of staphylococcal infections showed a significantly increased resistance to the antibiotics tested, compared with the strains isolated from postpartum women without a history of staphylococcal infections.

13. The sensitivity of *S. aureus* to the antibiotics tested was lower in isolates from postpartum women compared with isolates from pregnant women, in case of subgroups with a history of staphylococcal infections.

14. In terms of the high overall level of methicillin-resistance of *S. aureus*, also highlighted in our study, the use of oxacillin in first-intention treatment of staphylococcal infections severe potential becomes inopportune (more than 85% of strains were resistant to oxacillin). In our study, the highest sensitivity of *S. aureus* was recorded to ciprofloxacin, followed by cefuroxime and ceftriaxone.

15. It is noteworthy that, in our study, the resistance of the *S. aureus* strains to antibiotics and chemotherapeutic agents tested was significantly increased compared with *E. coli* in all cases.

16. The *E. coli* strains isolated from pregnant and postpartum women showed the highest sensitivity to Imipenem, followed by Sulfamethoxazole/Trimethoprim and Ciprofloxacin without significant differences between the groups and subgroups studied.

17. In case of multidrug-resistant strains of *S. aureus*, sulfamethoxazole/trimethoprim, whose clinical effectiveness is not fully proven, but recommended by treatment guidelines, may be a therapeutic option given the high sensitivity when tested in vitro, fact also observed in the strains analyzed in our study, where 60.17% of all strains studied were susceptible.
18. Although clindamycin has increased antistaphylococcal activity, the high percentage of resistance observed in the tested strains (78.07%) limits the usefulness of clindamycin in the treatment of genital infections caused by *S. aureus*.

19. Aminoglycosides must be used in combined therapy, as their use as sole antimicrobial agent predisposes to emergence of resistance.

20. In order to limit the sometimes devastating consequences of infections with antibiotic-resistant germs, we emphasize the importance of a closer cooperation in teams (epidemiologists, microbiologists, clinicians, pharmacists) for the establishment of a way of monitoring and control of these infections, which are a current and future matter of the health system.

21. Medical institutions should carry out screening for MRSA on women during obstetric admission, if they come from communities with a high incidence of MRSA colonization or if they had hospitalizations in the last 12 months. A culture from the anterior nostril should be mandatory, as nostrils are the most frequently colonized site.
SELECTIVE BIBLIOGRAPHY


