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Ads
Neisseria gonorrhoeae Is Evolving into a ‘Superbug’ – what Measures Can Be Implemented to Combat the Emergence of Multidrug and Extensively-drug Resistant Gonorrhoea in Latin America and Globally?

Infections with Neisseria gonorrhoeae remains an important public health concern worldwide. In 2008, the World Health Organization (WHO) estimated the global burden of gonorrhoea among adults to be 106 million cases, which represented a 21% increase since 2005. Most of those cases (64%) were in the WHO Western Pacific Region (42 million cases) and WHO South-East Asia Region (25 million cases), however, 11 (10%) million cases were in the WHO Region of the Americas (including both North America and Latin America)(1). Gonorrhoea may result in pelvic inflammatory disease, ectopic pregnancy, infertility and enhanced transmission of HIV. These complications cause substantial morbidity and economic costs, particularly in those resource-poor regions of the world where gonorrhoea is most prevalent.

Public health control of gonorrhoea requires treatment with appropriate antimicrobials, as well as generalized and targeted prevention efforts, use of reliable diagnostics, effective partner notification processes and quality-assured surveillance activities. Antimicrobial therapy should cure individual cases in order to reduce the risk of complications and prevent further transmission of the infection. However, from the beginning of the antimicrobial era (1930s), N. gonorrhoeae has consistently shown its extraordinary genetic capacity to develop antimicrobial resistance (AMR) to all drugs introduced for treatment of gonorrhoea (2-4). Currently, N. gonorrhoeae has consistently shown its extraordinary genetic capacity to develop antimicrobial resistance (AMR) to all drugs introduced for treatment of gonorrhoea (2-4). In addition, the European Centre for Disease Prevention and Control and the US Centers for Disease Control and Prevention have published regional response plans. Furthermore, dual antimicrobial treatment regimens for uncomplicated anogenital gonorrhoea have been introduced in the USA and Europe. Those dual antimicrobial therapies mainly recommend single-dose combinations of intramuscular ceftriaxone (250-500 mg) together with oral azithromycin (1-2 g).

One key component of the international action/response plans is to enhance the timely and quality-assured surveillance of AMR (preferably using WHO gonococcal control strains) and treatment failures. This is imperative because gonococcal AMR data are lacking in many settings and the true global problem remains unknown. In 2009, the WHO’s Global Gonococcal Antimicrobial Surveillance Programme (GASP) was revitalized, in close liaison with other existing AMR surveillance programmes. The WHO Global GASP network aims to recruit laboratories worldwide to monitor quality-assured gonococcal AMR data (with particular attention to ESCs), to provide support to establish gonococcal culture and AMR testing, to inform public health authorities and treatment guidelines on trends in gonococcal AMR, to optimize early detection of emerging resistance and, finally, to identify and verify treatment failures with ESCs. Worryingly, longitudinal quality-assured gonococcal AMR surveillance programmes remain sporadic, limited or even lacking in large parts of many regions worldwide, including Eastern Europe, Central Asia and Africa as well as Latin America and the Caribbean (LAC). These regions also suffer from a high burden of gonorrhoea, creating the prerequisites for rapid emergence and spread of gonococcal AMR.

In LAC, a strong and quality-assured GASP was established in the 1990s and there have been recent attempts to revitalize this GASP network. The connections and programmes of the GASP-LAC have been maintained in many LAC countries, and, in response to the WHO 2009 call for revitalization, the GASP-LAC regional network has been renewed. Several countries in Latin America have on-going national GASP networks. Gono-
coccocal AMR surveillance efforts, such as the one reported from Brazil in the current issue by Medeiros et al., will help catalyse enhanced regional and national GASP networks that are important not only for Brazil, but also for the entire LAC region. Recent GASP-LAC surveillance established that several countries in the region, including Brazil, still recommend ciprofloxacin for the treatment of gonococcal infections (15). The paper by Medeiros et al., which reports on high percentages of isolates resistant to ciprofloxacin, underscores the importance of GASP surveillance to inform the development and implementation of updated treatment guidelines for gonorrhoea infections. It is also notable that early GASP regional surveillance in Brazil also reported the first emerging resistance to azithromycin, a trend that has continued and is reflected in the Medeiros paper (17). Based on the results reported by Medeiros et al., although the sample size of isolates was low, it appears that ceftriaxone might be the only antimicrobial that can be recommended for national first-line empiric monotherapy of gonorrhoea in Brazil.

Recently, Brazil banned the sale of over-the-counter antibiotics, an essential first step in ensuring the prudent use of antibiotics for treatment. In addition, well-conducted microbiological surveys or, ideally, a sustainable national GASP network, testing substantial numbers of consecutive non-selected gonococci from multiple sites within a country, should provide the evidence base for local and national treatment guidelines. To achieve this, it is essential to strengthen and further develop regional and national capacity to undertake gonococcal culture and AMR testing. This requires substantial political will and funding as well as an investment in laboratory infrastructure and staff training. Brazil may now be ready to undertake this national challenge (Franchini M, personal communication).

Although enhanced surveillance of gonococcal AMR and treatment failures are critical, more holistic views and actions are required to truly combat the emergence and spread of possibly untreatable gonorrhoea nationally and internationally. Substantially enhanced and broad disease control activities (i.e., improved prevention, better diagnostics, effective treatment and surveillance) are needed to reduce the global burden of gonorrhoea combined with the implementation of wider strategies for general antimicrobial control (such as guidelines for antimicrobial use, appropriate selection of therapeutic agents, uninterrupted supplies and quality of generic drugs), sustainable implementation of most components of the action/response plans and an increased awareness among clinicians, microbiologists, epidemiologists and policy-makers in respect of the public health threat of MDR/XDR gonorrhoea. Internationally, there is an urgent need for an enhanced focus on reducing gonorrhoea burden in high-risk frequently transmitting populations (such as CSWs and MSM) as well as appropriate diagnosis and treatment of pharyngeal gonorrhoea, which is harder to eradicate and is an asymptomatic reservoir for gonorrhoea and emergence of AMR.

In conclusion, essential public health actions are required to retain gonorrhoea as a treatable infection including enhanced awareness; implementing action/response plans for potentially untreatable gonorrhoea infections nationally and globally; enhancing surveillance of gonococcal antimicrobial resistance, treatment failures and antimicrobial use/misuse; and improving both prevention and early diagnosis and treatment of gonorrhoea in index cases and their sexual contacts. Unfortunately, all these actions are likely only to mitigate the spread of MDR and XDR N. gonorrhoeae in the short-term. It thus remains imperative to develop novel treatment strategies, new antimicrobial agents (or other compounds) and ideally a vaccine for effective treatment and prevention of gonorrhoea in the longer term.

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REFERENCES
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**Note of the Editors**

From this issue, 25 (1), 2013, we will publish the Brazilian Journal of STD, online edition, ISSN: 2177-8264, all in English.
In the printed version, ISSN: 0103-4065, we will continue to publish in the original language of submission of articles (Portuguese, Spanish, English).
Thus, we are working to expand our indexes, in order to increase the visibility of our authors and our articles.
We would like to ask the readers and contributors to disseminate this initiative.

Sincerely,

*Mauro Romero Leal Passos  
Angelica Espinosa Miranda  
José Eleutério Junior  
Mariangela Silveira  
Paulo César Giraldo  
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Epidemiological Analysis of Congenital Syphilis in the State of Ceará, Brazil

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Abstract

Introduction: Congenital syphilis is a systemic infectious disease of chronic evolution caused by the Treponema pallidum bacterium dissemination to the fetus through the placenta of infected pregnant women untreated or treated improperly, occurring at any stage of pregnancy or clinical stage of the disease. Objective: epidemiological analysis of congenital syphilis in the State of Ceará from 2007 to 2010. Methods: documentary study conducted in March, 2013, through the database available at the Center for Information and Analysis in Health which keep the information about the National System of Notifiable Diseases records. There were 1,577 notifications of congenital syphilis cases. Results: the following results were observed: 71.78% (n = 1,132) of women who had their children diagnosed with congenital syphilis attended to prenatal consultation; 46.16% (n = 728) had a diagnosis of syphilis identified only during delivery/curettage; about 69.5% (n = 1,096) of pregnant women partners did not undergo any treatment for congenital syphilis. It was noted that over 90% of children were diagnosed with congenital syphilis until the sixth day of birth, and the most prevalent final classification was recent syphilis with 83.83% (n = 1,322) of cases. The most common clinical evolution for children had a favorable outcome, as more than 75% of them underwent treatment and remained alive during the studied period. Conclusion: the thorough analysis of congenital syphilis cases and the factors involved in the process are of fundamental importance to support the actions to prevent and control the disease.

Keywords: syphilis, congenital syphilis, health surveillance, STD, prenatal.

Introduction

Congenital syphilis is a systemic infectious disease of chronic evolution subject to acute outbreaks and latency periods when left untreated. It is caused by the dissemination of Treponema pallidum bacterium to the fetus by placental route through the untreated or improperly treated infected mother, and may occur at any phase of gestation or clinical stage of the disease.

Although syphilis is a disease of easy diagnosis and effective treatment of pregnant women, its mother-to-child transmission is still considered a public health problem due to the high frequency of serious effects on the pregnancy and on the child, such as miscarriage, stillbirth, or perinatal death, with a chance of transmission subject to acute outbreaks and latency periods when left untreated. It is caused by the dissemination of Treponema pallidum bacterium to the fetus by placental route through the untreated or improperly treated infected mother, and may occur at any phase of gestation or clinical stage of the disease.

Although syphilis is a disease of easy diagnosis and effective treatment of pregnant women, its mother-to-child transmission is still considered a public health problem due to the high frequency of serious effects on the pregnancy and on the child, such as miscarriage, stillbirth, or perinatal death(2), with a chance of transmission from 70 to 100% in the primary and secondary stages of the disease, and of 30% in the late stages of maternal infection(3).

Therefore, in order to facilitate the epidemiological surveillance of congenital syphilis, the disease was included in the notifiable illnesses list since 1986. In addition, the Ministry of Health set up a goal to be accomplished: the improvement in the quality of prenatal care and timely diagnosis and treatment of gestational syphilis cases in order to prevent the vertical transmission of the disease(3).

Despite all efforts for the prevention of congenital syphilis and its control, 16,911 cases of the disease were reported in Brazilian States between 2007 and 2009, showing that the incidence remains high(4). In the State of Ceará between 2001 and 2006 1,203 cases of congenital syphilis were reported, and a growing increase in the course of this period has occurred(5).

It is recommended that all pregnant women carry out the syphilis test at the beginning of pregnancy, being the serologic tests the main way to establish the diagnosis. Among them, there are non-treponemal tests such as VDRL, in which the result is described qualitatively in “reagent” and “not” reagent, and quantitatively by means of titrations, for example 1:2 and 1:32, and treponemal tests such as TPHA, FTA-Abs and ELISA, which are specific tests used to confirm the infection(6).

However, the elimination of congenital syphilis as a public health problem requires the reduction of its incidence through an organized and quality prenatal care, and its emergence is considered an event that exposes the limitations of health services, especially in the basic attention(7).

It is known that the congenital syphilis can be controlled through appropriate diagnosis and treatment of pregnant women during prenatal follow-up. Thus, educational strategies should be developed on prenatal care and childbirth to ensure the promotion and prevention of health and appropriate diagnoses and treatment(7), i.e., a humanized and capable prenatal care and childbirth aiming at the health and well-being of both the mother and the baby.

Prenatal examination is a right of every pregnant woman and a duty of health professionals, including nurses, who should do so in their best way in order to reduce the syphilis vertical transmission, also including sexual partners of positive VDRL women to prevent their reinfection.

The importance of epidemiological identification of congenital syphilis is then verified, and both maternal and neonatal characteristics noted as well, so that health professionals could be able to perform interventions that prioritize not only the early identification but also the treatment of syphilis in pregnant women.
OBJECTIVE

Epidemiological analysis of congenital syphilis in the State of Ceará, verifying the prenatal care for pregnant women who had their children diagnosed with congenital syphilis, as well as treatment for syphilis by these pregnant women partners, the diagnosis period of syphilis in pregnant women and the age group, the classification of syphilis and the clinical evolution of children with congenital syphilis from 2007 to 2010.

METHODS

This is a transverse type and documentary study with a quantitative approach held in the city of Fortaleza, State of Ceará, in the Center for Information and Analysis in Health (NUIAS) of the Health Office of Ceará (SESA-CE).

NUIAS is the SESA’s area responsible for storage and processing of information from the National System of Notifiable Diseases (SINAN). The study population was composed of all notified cases of congenital syphilis in SINAN from 2007 to 2010, consisting of 1,577 cases. Data were collected in March, 2013, from the State database available in the NUIAS SESA-CE, which contains the information compiled from SINAN’s records.

The variables investigated in this study are the following: pregnant women prenatal care; period of syphilis diagnosis in pregnant women, treatment for syphilis by pregnant woman partner, age group of syphilis diagnosis in children, final classification of disease and clinical evolution.

Data obtained were organized and presented in graphs and charts and analysed according to the absolute and relative frequencies.

The research project was submitted to the Research Ethics Committee of the Federal University of Ceará, and approved under protocol no. 139/10. All ethical and legal aspects of the resolution 196/96 of the National Health Council-CNS on research involving human subjects were fulfilled.

RESULTS

In the historical series evaluation it was observed that between 2007 and 2010, 1,577 cases of congenital syphilis were notified in the State of Ceará. The analysis of Figure 1 showed that most women who had their children diagnosed with congenital syphilis attended to some prenatal consultation during the gestational period, equal to 71.78% (n = 1,132) of cases. However, there was still a considerable percentage of women who did not attend to any prenatal consultation, i.e. 28.22% (376) of cases.

When a percentage analysis of each year under study was carried out, it was noted that there was no regularity in the frequency of these prenatal pregnant women consultations. In 2007 and 2008 there was an increase of the percentage of these prenatal visits, 73.92% and 79.36%, respectively. In 2009 this percentage dropped to 66.93%, and in 2010 reached 70.64% of pregnant women with children diagnosed with congenital syphilis who attended to prenatal care.

Other identified results are related to the period of syphilis diagnosis in pregnant women, and it was verified that 46.16% (n = 728) of women had the diagnosis of syphilis identified only during childbirth or curettage, whereas 41.34% (n = 652) were diagnosed on prenatal care according to Figure 2.

In the course of each year, an increase in the percentage of cases of syphilis diagnosis was observed during the childbirth/curettage in women who had children with congenital syphilis in 2009 and 2010 when compared to previous years. While in 2007 and 2008 the percentage of diagnoses of the disease during childbirth/curettage were around 40%, in 2009 and 2010 the percentage surpassed 50% of cases, ahead of what would be the appropriate moment of the prenatal diagnosis of syphilis in pregnant women.

Regarding the treatment for syphilis by the pregnant women partner, a disturbing data was noted: about 69.5% (1,096) of women’s partners did not carry out the treatment, according to Figure 3.

Evaluating each year’s percentage, it was noted that the rates of treatment for syphilis by the partner remained below 25%. It should also be noted that these data obtained lower numbers, equal to 13.76% (n = 70) of cases in 2010.

Table 1 analysis evidenced that most children was diagnosed with congenital syphilis until the sixth day of birth, surpassing 90% of cases during all years evaluated in this research. The final ranking of the most prevalent syphilis strain was the recent syphilis, equivalent to 83.83% (1,322) of cases. In addition, the most common clinical evolution presented a favorable outcome, in which more than 75% of children during each year of the study received treatment and remained alive.

It is worth mentioning the considerable number of subentries identified in the following variables: final classification and clinical evolution. In the first variable, the ignored cases represented 23.49% (n = 74) of cases in 2008. Concerning the clinical evolution variable, the number of subentries remained above 10% throughout the analysed period under review, especially in 2010, when 21.56% (n = 47) of ignored cases were identified.

DISCUSSION

This study identified that although most women who had their children diagnosed with congenital syphilis received prenatal care, a considerable number of them did not have any prenatal consultation or these data were registered as an ignored information. Given this fact, the quality of prenatal consultations is questioned, as even for those who attended to consultations it is observed that neither treatment nor interventions occurred properly, considering the amount of cases of syphilis vertical transmission.

Due to the above mentioned, it appears that rates related to prenatal care percentage remained high. However, they are still below the Ministry of Health recommendations, which advocates that antenatal coverage must be performed properly, with quality, covering 100% of pregnant women. The main purpose of prenatal care is to attend woman since early pregnancy in a qualified and humanized way, adopting a cozy procedure and timely interventions. The prenatal care should ensure the early assistance to pregnant woman (up to 120 days of gestation), with at least six prenatal consultations and the provision of basic laboratory tests, especially VDRL.

According to data from the National System of Notifiable Diseases (SINAN) of the National Program for STD and AIDS of the Ministry of Health, only 75% of nearly three million women who conceive annually in Brazil carry out prenatal care. Only 50% of these are tested for VDRL at the beginning of prenatal period and...
only 23% repeat this test in the third quarter of pregnancy, as recommended by Brazilian standards\textsuperscript{(9)}.

Study of 46 recent mothers who had a history of syphilis or positive VDRL assisted in a maternity ward in the State of Pará, pointed out that only 55.6% of VDRL tested pregnant women received prenatal care and only 13.9% repeated the test in the third quarter. The study also showed that only 53.8% of mothers who had a diagnosis of syphilis during prenatal period received appropriate treatment, data that also denounces the low quality of the prenatal care. Incomplete or even incorrect prenatal care, either by late beginning or nonattendance at consultations, impedes the implementation of a routine for the diagnosis of syphilis and its early intervention, and can explain many cases of congenital syphilis\textsuperscript{(9)}.

It also became evident in a study conducted with 16,158 parturients that despite the availability of cheap and efficient prophylactic resources for the reduction of mother-to-child transmission, 75.1% of pregnant women showed at least one syphilis test result during the hospitalization for childbirth, but only 16.9% presented the results of two tests; 11.8% had prenatal card, but had no result of syphilis. Moreover, even among women who have six or more prenatal consultations, the coverage of two tests for syphilis in pregnancy is low, only 26.2%, and 2.6% of women were completely excluded since syphilis

\textbf{Figure 1} – Number of newborns diagnosed with congenital syphilis according to prenatal care by pregnant women – Ceará, 2013.

\textbf{Figure 2} – Number of newborns diagnosed with congenital syphilis according to period of syphilis diagnosis in pregnant women – Ceará, 2013.
testing did not occur during prenatal care or childbirth. Therefore, it is necessary to point out that the absence of detection of syphilis during the prenatal period means a lost opportunity for intervention in infected pregnant women, limiting the possibilities for reducing the incidence of cases of congenital syphilis(11).

It was observed that between 2007 and 2010 most syphilis diagnoses was held at time of delivery or curettage, the phase woman should have had the proper prenatal care, should have made at least two VDRL tests and should have received the diagnosis, together with the proper treatment for her and her partner as well, thus avoiding the exorbitant increase of congenital syphilis cases.

More than 95% of childbirths in Brazil occur in a hospital environment. If the health network is not able to detect and treat syphilis in pregnant women, there is one more opportunity to dis-

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**Figure 3** – Number of newborns diagnosed with congenital syphilis according to treatment of syphilis by partners of pregnant women – Ceará, 2013.

**Table 1** – Number of newborns diagnosed with congenital syphilis according to children age group, final classification and clinical evolution of syphilis in newborns – Ceará, 2013.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 6 days</td>
<td>402</td>
<td>294</td>
<td>608</td>
<td>214</td>
<td>96.17</td>
<td>93.33</td>
<td>97.12</td>
<td>98.16</td>
</tr>
<tr>
<td>7 to 27 days</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>1.91</td>
<td>2.54</td>
<td>0.96</td>
<td>1.38</td>
</tr>
<tr>
<td>28 days to 365 days</td>
<td>6</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>1.44</td>
<td>3.81</td>
<td>1.44</td>
<td>0.46</td>
</tr>
<tr>
<td>1 year or more</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0.48</td>
<td>0.32</td>
<td>0.48</td>
<td>0</td>
</tr>
</tbody>
</table>

**Final classification**

<table>
<thead>
<tr>
<th>Classification</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent syphilis</td>
<td>361</td>
<td>227</td>
<td>509</td>
<td>175</td>
<td>86.36</td>
<td>72.06</td>
<td>81.31</td>
<td>80.28</td>
</tr>
<tr>
<td>Late syphilis</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0.24</td>
<td>1.27</td>
<td>0.96</td>
<td>0</td>
</tr>
<tr>
<td>Miscarriage by syphilis</td>
<td>4</td>
<td>10</td>
<td>49</td>
<td>23</td>
<td>0.96</td>
<td>3.18</td>
<td>7.83</td>
<td>10.55</td>
</tr>
<tr>
<td>Ignored</td>
<td>52</td>
<td>74</td>
<td>62</td>
<td>20</td>
<td>12.44</td>
<td>23.49</td>
<td>9.9</td>
<td>9.17</td>
</tr>
</tbody>
</table>

**Clinical evolution**

<table>
<thead>
<tr>
<th>Classification</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>325</td>
<td>269</td>
<td>488</td>
<td>165</td>
<td>77.75</td>
<td>85.39</td>
<td>77.95</td>
<td>75.68</td>
</tr>
<tr>
<td>Death by syphilis</td>
<td>38</td>
<td>9</td>
<td>9</td>
<td>4</td>
<td>9.09</td>
<td>2.86</td>
<td>1.44</td>
<td>1.83</td>
</tr>
<tr>
<td>Death – another aggravation</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2.15</td>
<td>1.27</td>
<td>0.48</td>
<td>0.92</td>
</tr>
<tr>
<td>Ignored</td>
<td>46</td>
<td>33</td>
<td>126</td>
<td>47</td>
<td>11.01</td>
<td>10.48</td>
<td>20.13</td>
<td>21.56</td>
</tr>
</tbody>
</table>

| Total                     | 418  | 315  | 626  | 218  |      |      |      |      |

*Note: The data includes only the cases diagnosed during prenatal care.*

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*DST* - *J bras Doenças Sex Transm* 2013;25(1):7-12
cover it during delivery. And the most important at this stage is
to verify the vertical transmission of syphilis and treat infected
newborns to prevent the manifestation of the disease or reduce
its consequences(12).

Some reference maternity wards of the city of Fortaleza offer
VDRL test during childbirth, according to Projeto Nasce, but there
is a need for its expansion to ensure the supply of VDRL to all par-
turients and provide a maternal-fetal health adequate to the whole
State of Ceará.

In a study developed in Rio de Janeiro with the purpose of eval-
uating the effectiveness of campaigns for the elimination of con-
genital syphilis, it was observed that prenatal care for over 80% of
the cases of congenital syphilis mothers does not ensure early diag-
nosis of pregnant women nor the proper treatment, which would
prevent cases of congenital syphilis(13).

As for treatment for syphilis by partners of pregnant women
who had their children diagnosed with congenital syphilis, our
study noted that most of them did not carry out the treatment for
syphilis, consisting in a means of reinfection by pregnant women.
Thus, although pregnant women receive prenatal care properly
and follow the treatment for syphilis effectively, they will still be
susceptible to reinfection by partners who did not perform the tre-
ment for syphilis, contributing to the elevation of the rates of
congenital syphilis.

It should be emphasized the importance of notification at SI-
NAN as one of the ways for the congenital syphilis control, becaus-
se when collecting, transmitting and disseminating data on repor-
table diseases, SINAN becomes a relevant instrument to support
health planning, setting priorities for action, besides allowing the
evaluation of their impact(1).

Thus, it is evident the negligence of health services for the tre-
ment of syphilis of pregnant women partners, which should be a
priority, considering the risk of vertical transmission of the dis-
ease. Health professionals’ unpreparedness is manifested both by
the high number of cases in which there was no treatment of the
partner and the high amount of treatments ignored, because it is
the professional’s duty to ensure the active search of partners, to
advise and to treat properly.

According to a research, one criterion to define the cases of
congenital syphilis is the untreated partners, including cases where
there was inadequate treatment for pregnant women and also tho-
se who were not treated in accordance with the current treatment
guidelines, or when the father is unknown or there is no documenta-
tion of his treatment(14).

A research conducted in 2007 in the State of Ceará supports the
data found in this study, confirming the high number of untreated
partners and ignored treatments, in addition to the existing problem
of underreporting of cases through SINAN(5).

It was observed that the age group concentrating the largest
number of diagnoses of congenital syphilis is the first days of the
neonate life. In accordance with the data of the documentary study,
a research conducted in the city of Natal, State of Rio Grande do
Norte, in order to trace the epidemiological profile of congenital
syphilis identified that in most cases (90%) the disease was diag-
nosed in the first two days of life of the newborn, while only 9.1%
of them were diagnosed between two and 28 days of life, and only
0.9% after 28 days of life(15).

As for the final classification of congenital syphilis, it was iden-
tified a prevalence of syphilis considered recent throughout the
period of this study. Confirming this data, a research developed in
the city of Carapicuíba, State of São Paulo, observed that 94.0% of
reported cases had the final classification as suspected congeni-
tal syphilis (31 cases), 3.0% of congenital syphilis confirmed (one
case) and 3.0% dropped (one case). Of cases classified as congeni-
tal syphilis 100% were diagnosed as recent type(16).

Regarding the clinical development of children identified with
congenital syphilis, this study observed the prevalence of favorable
outcomes. In a study published in Portugal, similar results have
been observed, indicating that most newborns, 361 (77%), complet-
ed treatment with procaine or crystallized penicillin. Thirty-one
(6%) were treated with benzathine penicillin. Finally, 75 NB (16%)
did not adhere to any therapy, because the latter had less infectious
risk. Thus, in the above mentioned cases NB had conditions to sur-
vive, grow and develop healthy(17).

CONCLUSION

Congenital syphilis is still considered an important public
health problem, although it is a disease of easy diagnosis and
completely avoidable when treatment of pregnant women and her
partner is performed properly. However, the occurrence rates of
this aggravation remain high, constituting therefore a determin-
ing factor in the rise of maternal and perinatal morbidity and
mortality indicators.

We then emphasize the importance of a thorough analysis of
congenital syphilis cases, as well as of factors involved in the
process of occurrence of the disease vertical transmission, such
as prenatal care and testing recommended by the Ministry of He-
alth, the early diagnosis in infected pregnant women and the de-
velopment of their immediate treatment, because the implemen-
tation of these measures ensures the prevention and control of
congenital syphilis.

In addition, it appears that mothers of children who caught con-
genital syphilis are at risk due to the lack of development of actions
that prevent the occurrence of this disease, making them vulnera-
bles to contract sexually transmitted diseases. It was also noted
that there was a deficiency in healthcare in all cases, contributing to
the incidence of CS.

Consequently the development of similar studies in other re-
ions of the country becomes relevant, in order to analyse and
evaluate the real situation of information and practices of health
professionals in the prevention of vertical transmission of syphilis,
as well as monitoring the effectiveness of educational programs
and training of these professionals.

Conflict of interest

There is no conflict of interest to declare.

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COMPARISON BETWEEN TWO METHODS FOR MOLECULAR CHARACTERIZATION OF HUMAN PAPILLOMAVIRUS

Ludmila Entiauspe1,3,5, Emily Nunes2,5, Tiago Collares3,5, Mariângela Freitas da Silveira4, Fabiana Seixas1,3,5

ABSTRACT

Introduction: a sensitive method of detection for Human Papillomavirus (HPV) is important to facilitate the early treatment of cervical cancer precursors. Objective: to analyze the spectrum of HPV infection and compare the sensibility of DNA HPV detection using polymerase chain reaction (PCR) and nested PCR (nPCR) methods in a group of 251 women of Pelotas-RS. Methods: genomic DNA was extracted from the collected samples and was submitted to PCR methods with the primers MY09/11 and nPCR with the pair of primers MY09/MY11 and GP5+/6+. The results were applied to the softwares EpInfo v.3.5.18 and STATA v.11.8 for analyzes. Results: the prevalence of HPV infection was 6.8% with the use of primers MY09/11. When associated with primers GP5/6, this result increased to 29.9% (p < 0.001). Conclusion: the increase founded in HPV DNA detection from 6.8 to 29.9% suggests that the technique of nPCR MY09/11 followed by GP5/6 is the most sensitive method to detect HPV DNA from cervical specimens.

Keywords: HPV, molecular diagnostics, nested PCR

INTRODUCTION

Estimates show that about 291 million women worldwide are infected with human papilloma virus (HPV)1,2. According with the Brazilian Ministry of Health, Brazil is one of the world leaders in the incidence of HPV, with 137,000 new cases of infection each year2. With the introduction of biomolecular techniques, it was possible to confirm that the cervical cancer (CC) development is closely associated with the HPV, showing the significance of the HPV infection for the dysplasia development and the transformation of normal cervical cells into cancerous3,4. This type of cancer is the responsible for the death of 31.400 women in Latin America, 11.000 only in Brazil5,6 each year. Even though HPV infection can be detected by preventive examinations for CC (Pap test), or pathological (by colposcopic directed cervical biopsy), this is often not possible. However, the presence of HPV can be confirmed with high accuracy, by identifying the viral genome present in cervical lesions7.

There are currently several techniques for the molecular diagnosis of HPV, ranging from a conventional Polymerase Chain Reaction (PCR) methods complex, such as real-time PCR, hybrid capture (HC) and microarray8,9. The PCR technique is still considered the “gold standard” for HPV diagnosis, as the DNA-target is selectively amplified. However, this characteristic makes the method susceptible to contamination by exogenous or amplified nucleic material from another sample10. A variation of this technique called nested-PCR (nPCR) with MY09/11 and GP5+/6+ primer sets, is a high sensitive specific method for HPV DNA detection11, with both targeting the L1 conserved region of the viral genome, allowing the detection of a broad range of HPV types12.

The widely used MY09/11 consensus primers set is synthesized with several degenerated nucleotides in each primer and is thus a mixture of 25 primers, targets a 450bp conserved sequence in the HPV L1 gene, and is therefore able to amplify a broad spectrum of HPV types13. The GP5 and GP6 primer set consists of a fixed nucleotide sequence for each primer and detects a wide range of HPV types by using a lowered annealing temperature during PCR, and targets a 140bp sequence of HPV L1 gene, located inside the sequence recognized by the MY primers10.

OBJECTIVE

Considering that HPV infection is an integral part of CC development, the viral genome detection can be used as a surveillance strategy, to identify HPV infected women and to monitor the progression of cervical lesions, as it is a disease of high mortality that can be prevented7. Based on these data, this study aimed to analyze the spectrum of HPV infection and compare the sensibility of DNA HPV detection using polymerase chain reaction (PCR) and nested PCR (nPCR) methods in a group of 251 women of Pelotas-RS.

METHODS

Study population

This is a cross-sectional study. From July to October 2010, 251 women seeking gynecologic care at the clinic of the Faculty of Medicine – Federal University of Pelotas (UFPel) were sequentially selected. The study was approved by the Ethics Committee of the Faculty of Medicine – Federal University of Pelotas in June 2009, and informed consent was obtained from all participants. All procedures were carried out in accordance with the guidelines of the Helsinki Declaration.

Statistical analyses

Chi-square (χ²) test was used to evaluate the HPV presence by PCR and nPCR detection techniques. The analysis was performed using SPSS 16.0 software (SPSS, Chicago, IL). Significancy was considered if the P value was bellow 0.05.

Sample collection and processing

Cervical samples were collected from each patient with a cytobrush, and placed into 1.5 mL Eppendorf tubes containing 300
mL of Cell Lysis Solution (Puregene™ DNA Extraction Kit, Gentra Systems Minneapolis, MN). The tubes were submitted to digestion using 1.5 µL of Proteinase K (10 mg/mL, New England Biolabs, MA), and incubated overnight at room temperature. The genomic material (DNA) was extracted, according to manufacturer specifications. As a control for extracted DNA quality, the human TP53 gene PCR was performed, using the primers previously described(14). PCR were performed in a final reaction volume of 12 µL, and was carried out with one cycle 94°C for 3 min, followed by 40 cycles at 94°C for 30 sec, 57°C for 30, 72°C for 30 sec and a final extension for 3 min at 72°C (24).

**HPV detection by polymerase chain reaction (PCR) method**

We used the MY09/11 external primers (Table 1), previously described by Manos et al.(15). The MY90/11 PCR reaction was performed in a final volume of 25 µL, and the conditions were as follows: 40 cycles of denaturation (1 min at 95°C), annealing (1 min at 55°C), and extension (1 min at 72°C)(16,17). Cervix carcinoma cell line HeLa was used as positive control, and amplification mix without DNA as negative control.

**HPV detection by the nested polymerase chain reaction (nPCR) method**

HPV detection was carried out using nested-PCR (nPCR) technique, which is performed in two rounds: the first using MY09/11 primers, described previously. The second used GP5/6 internal primers (Table 1), which amplify the 140 pb fragment(18). The conditions were 40 cycles of denaturation (30 sec at 94°C), annealing (30 sec at 45°C), and extension (30 sec at 72°C) (7). Both PCR reactions were preheated for 9 min at 95°C, and a final extension for 5 min at 72°C. All PCR products were visualized on a 2.0% agarose gel with GelRed™ (Biotium Inc., CA)(19).

**RESULTS**

All 251 samples were amplified for the TP53 gene, checking DNA quality for HPV detection by PCR and nPCR methods. The HPV-DNA analysis by PCR MY09/11 was observed in 17 samples, whereas nPCR technique found HPV positivity in more 58 samples (24.8%) shown in Table 2, increasing up to 4 times the detection of viral DNA (p < 0.001). The comparative test showed 100% sensitivity in conventional PCR, and a specificity of 75.2% when compared to nPCR (Table 3).

**DISCUSSION**

There are several comparative studies of different methods for HPV-DNA detection. Husnjak et al.(17), also with cervical samples, using conventional PCR with primers MY09/11 compared with nPCR, observed 38.8% of increase in the rate of positivity for HPV DNA by nPCR method, showing that it is more effective in HPV detection. Evander et al.(20) reported 5.9% of HPV-DNA detection by the MY09/11 PCR technique. When the nPCR with MY09/11 and GP5/6 was performed, the rate of HPV detection increased to 20.3%, suggesting that GP5/6 primers may result in increased amplification efficiency for not contain any degenerate bases, and for cover a small region compared with MY09/11 primers. However, in a similar study, the authors do not find significant difference: the HPV-DNA detection with MY09/11 primers was 45.2%, and 42.8% for GP5+/6+ primers(21)(Qu et al., 1997).

According to Demathe et al.(21), the variations of HPV-DNA detection suggest a potential difference in the ability to amplify fragments of different sizes and specific HPV types, in accordance with the methods of DNA detection used, and also the types of material (smears, frozen material, paraffin or formalin embedded), anatomical location, population issues and the design of primers. The authors evaluated samples from lip squamous cell carcinoma, and observed that the use of nPCR increased by up to 6 times the rate of HPV DNA detection, when compared to MY09/11 PCR.

This study aimed to compare the detection rate of HPV-DNA by PCR method through MY09/MY11 oligonucleotides and nPCR through MY09/MY11 oligonucleotides in the first stage and GP5+/GP6+ in the second stage. This results suggests nPCR technique for HPV-DNA detection is as an alternative to early identification of women at high risk for CC development, showing that the nPCR MY09/11 followed by GP5/6 technique is the most sensitive method to detect HPV DNA from cervical specimens. Moreover, it emphasizes the importance of molecular diagnostic methods as a complementary tool to conventional preventive screenings.

---

**Table 1 – General primers sequences for HPV DNA detection**

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequences* (5'-3')</th>
<th>Size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MY11</td>
<td>GCMCAAGGGWCATAAYATGG</td>
<td>~ 450(17)</td>
</tr>
<tr>
<td>MY09</td>
<td>CGTCMARRGGAAWACTGATC</td>
<td></td>
</tr>
<tr>
<td>GP5</td>
<td>TTGTGTTACTGTGGTAGATAC</td>
<td>~ 140(19)</td>
</tr>
<tr>
<td>GP6</td>
<td>GAAAAATAAACCTGAAATCA</td>
<td></td>
</tr>
</tbody>
</table>

* M = A+C; R = A+G; W = A+T; Y = C+T.

**Table 2 – Comparison between PCR MY09/11 and nPCR MY09/11 and GP5/6 methods**

<table>
<thead>
<tr>
<th></th>
<th>PCR MY09/11</th>
<th>nPCR MY09/11</th>
<th>nPCR GP5/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (%)</td>
<td>58 (24.8)</td>
<td>100.0%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>75.2%</td>
<td>0%</td>
<td>75.2%</td>
</tr>
<tr>
<td>Total (%)</td>
<td>234 (100.00)</td>
<td>275 (100.00)</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

**Table 3 – Sensitivity and specificity of MY09/11 PCR compared with nPCR**

<table>
<thead>
<tr>
<th></th>
<th>nPCR Negative</th>
<th>nPCR Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (%)</td>
<td>0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>75.2%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Total (%)</td>
<td>176</td>
<td>75</td>
</tr>
</tbody>
</table>

**Qui-square (χ²): p < 0.001.**
CONCLUSION
The increase in HPV DNA detection from 6.8 to 29.9% suggests that the technique of nPCR MY09/11 followed by GPS/6 is the most sensitive method to detect HPV DNA from cervical specimens.

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Conflict of interest
The authors declared no conflict of interest

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INTRODUCTION
Throughout its evolution, the epidemiological profile of the infection by HIV/AIDS underwent deep transformations, marked by processes of heterossexualization, feminization, impoverishment and internalization. Despite the current tendency towards stabilization, the epidemic continues to be a public health problem in Brazil and in the world as well(1).

According to data from the Epidemiological Bulletin published in 2011, a total of 608,230 cases of Aids have been notified in the country from 1980 to June 2011. Throughout these years, there was also a decrease in the infection rate between genders. In 1985, for every 26 cases among men there was 1 case between women. In 2010, this rate became 1.7 man for each case in women. The Southeast region continues to focus the largest number of cases in the country, and the State of Minas Gerais, in the Southeast region, held the third place in notifications in 2010, representing 16.6% of the total cases in the region(2). Aids expansion in the small and medium cities, as Montes Claros and other cities in the North region of Minas Gerais reflects the general trend of the epidemic internalization, as shown in the country from the 1990’s(1,3).

HIV/Aids collected data in the last 30 years in Brazil and in the world as well, pointed at a complex and unstable dynamic with significant regional differences and determinants related to individual, social, cultural and political factors, whose interaction results in a bigger or lesser vulnerability of the individual in contracting the HIV virus during his life(4-7).

In this context, the “behavior” factor plays an important role in the virus transmission chain(8). However, it must be considered that this factor is strongly influenced by others, such as access to education, health and prevention tools, such as condom. In addition, power inequalities still existing in the construction of masculine and feminine genders continue to stand out as an important risk practice operator in the epidemic HIV/Aids scenario(9).

In general terms, male and female vulnerabilities are built from a differentiated socialization for both men and women, still traditional for gender relations and to the development of sexuality that despite encouraging men, in a way, make not only women vulnerable, but men too(10).

Due to gender differences, already considered natural in social and sexual behavior of general population and of its relation to a greater vulnerability to HIV infection(9), studies comparing male and female behaviors are fundamental to a better understanding of the difference between these behaviors’ patterns, as well as to assess and adopt health prevention and care measures that take into consideration genders issues(4-6).

Thus this study’s objective is to identify social and behavioural differences related to the HIV infection risk, as well as the infection prevalence and the rate among genders in users that sought anti-HIV testing in the Testing and Counseling Center (CTA) of the city of Montes Claros, Minas Gerais.
METHODS

This is a retrospective cross-sectional study with a quantitative approach, in which medical records of 1,409 users who sought the Testing and Counseling Center in STD/Aids (CTA) were analyzed in the city of Montes Claros, Minas Gerais, for HIV testing, from December 2006 to March 2009. Pregnant women, due to their specific indication for examination in prenatal service and users under 13 years old, due to their possible diagnosis association with vertical transmission, have had their medical records excluded from the study.

Secondary data source were obtained from the Testing and Counseling Centers Information System (SI-CTA) forms, filled in during the individual counselling and available on the users’ records served by the service.

The variables selected for the study were the following: social and demographic (age, sex, marital status and schooling), behavioral risk related to HIV infection (type of risk exposure to HIV, use of legal and/or illegal drugs during past year, number of sexual partners in the past year and use of condoms with fixed and casual partners during past year) and serologic variable (positive anti-HIV test result).

Data analysis

Data were organized by Microsoft Excel® 2007 spreadsheets and analyzed by the Statistical Package for Social Sciences (SPSS) 15.0, being considered a significance level of 5% (p < 0.05). Descriptive analysis was made of the data, showing the absolute and relative frequencies. To verify if the distribution of several categorical variables was similar between genders, univariate inferential statistic was used through the Chi-square test ($\chi^2$) of Pearson and Fisher exact. The prevalence of HIV infection was determined by the percentage of seropositive users for the anti-HIV test in relation to the total users of the group concerned. The gender ratio was calculated from the division between the absolute value number of positive results in individuals of one gender by the absolute value number of positive results of the opposite gender.

Ethical aspects

The study met the guidelines and standards determined by resolution 466/2012 of the National Health Council (CNS) which regulates the research conduct involving humans. It was approved by the ethics and research committees of UNIMONTES (opinion n° 763/07) and of UNIFESP (opinion n° 1368/08).

RESULTS

The study’s sample was composed of 1,409 records of users of the service, composed of 716 (50.8%) men and 693 (49.2%) women. The average age found in men was 30.5 years (DP ± 11.5) and 29.5 years (DP ± 10.3) in women.

Twenty-eight people among this population and period were infected with HIV, with the prevalence of infection of 2% and the rate of genders of 1:1, i.e., for each infected man, a woman was also diagnosed.

Table 1 shows that men and women had similar schooling, predominantly those who had completed 8 to 11 years of study. It was observed that the marital status and drug abuse variables were significantly associated to gender, showing that there is a higher percentage of singles and people who used drugs (in general), including marijuana, alcohol, snorted cocaine and crack among male users.

Regarding the type of HIV exposure, men and women exposed themselves mainly and similarly through sexual intercourse without protection. Other possible, although more rare forms of exposure to injury, such as blood/hemoderivatives and transfusion accidents with biological material, were also identified and occurred more significantly among women (Table 2).

Table 1 – Distribution of social and demographic variables and use of legal/illegal drugs during last year among CTA users according to gender, in Montes Claros, MG, 2007-2009.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/concubine</td>
<td>206 (29.1)</td>
<td>289 (42.2)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Single</td>
<td>462 (65.3)</td>
<td>344 (50.2)</td>
<td></td>
</tr>
<tr>
<td>Divorced/widower</td>
<td>39 (5.5)</td>
<td>52 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Schooling (years of study)</td>
<td></td>
<td></td>
<td>0.304*</td>
</tr>
<tr>
<td>None</td>
<td>10 (1.5)</td>
<td>10 (1.5)</td>
<td></td>
</tr>
<tr>
<td>From 1 to 3</td>
<td>35 (1.5)</td>
<td>39 (5.8)</td>
<td></td>
</tr>
<tr>
<td>From 4 to 7</td>
<td>181 (26.3)</td>
<td>210 (31.3)</td>
<td></td>
</tr>
<tr>
<td>From 8 to 11</td>
<td>356 (51.8)</td>
<td>319 (47.5)</td>
<td></td>
</tr>
<tr>
<td>12 and more</td>
<td>105 (15.3)</td>
<td>94 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Used legal and/or illegal drugs</td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>No</td>
<td>189 (26.5)</td>
<td>307 (44.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>524 (73.5)</td>
<td>383 (55.5)</td>
<td></td>
</tr>
<tr>
<td>Used alcohol</td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>No</td>
<td>212 (29.6)</td>
<td>318 (45.9)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>504 (70.4)</td>
<td>375 (54.1)</td>
<td></td>
</tr>
<tr>
<td>Used marijuana</td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>No</td>
<td>609 (85.1)</td>
<td>660 (95.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107 (14.9)</td>
<td>33 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Used snorted cocaine</td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>No</td>
<td>642 (89.7)</td>
<td>677 (97.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74 (10.3)</td>
<td>16 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Used injectable cocaine</td>
<td></td>
<td></td>
<td>0.968*</td>
</tr>
<tr>
<td>No</td>
<td>713 (99.6)</td>
<td>690 (99.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>03 (0.4)</td>
<td>03 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Used crack</td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>No</td>
<td>665 (92.9)</td>
<td>685 (98.8)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51 (7.1)</td>
<td>08 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Used heroine</td>
<td></td>
<td></td>
<td>0.508*</td>
</tr>
<tr>
<td>No</td>
<td>715 (99.9)</td>
<td>693 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>01 (0.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Chi-square test ($\chi^2$).
* Fisher exact test.
p < 0.05 results were considered significant.
Men were more sexually active last year and had a greater number of sexual partners but, on the other hand, used more condoms during intercourse than women, which is a significant difference when it is about fixed partnership (Table 2).

**DISCUSSION**

This study was based on secondary data and therefore is subject to limitations which may interfere in a greater or lesser degree to the results presented. It is worthy to mention the non-representativeness of the studied population compared to general population. Users of CTA, besides constituting a constrained demand, tend to riskier behaviors. The occurrence of a “socially acceptable” response is also predictable when it comes to issues related to sexuality.

Despite its limitations, the results showed the vulnerability of the population studied in relation to the risk of HIV transmission/infection and allowed to note a greater prevalence of the virus in relation to the one estimated for the general population of the country(21). In addition, it was possible to verify that, although women declare greater predominance of intercourse with fixed and exclusive partners and less involvement with drugs, they were infected in the same proportion as men, pointing to the trend of feminization of the epidemic in the region.

In the period delimited for the study, single men were the ones who most sought the CTA to perform the anti-HIV test. This draws attention to the fact that, historically, women have a better perception concerning health care. However, this may not apply to services such as the ones of the Testing and Counseling Center (CTA), once their search involves, in most cases, the perception of STD risk. The fact of being man and single is most frequently associated with certain risk behaviour(6,10) and possibly to a greater perception of these risks also, which may justify the greater presence of single men in the CTA of Montes Claros.

Users of both genders with more than seven years of study represented more than 50% of the total. This suggests that the CTA of Montes Claros, as well as others(8,11,12), has predominantly served a population more favored from a social and cultural point of view, possibly more educated, but not necessarily more cautious and careful, as the results of this and other research conducted in Brazil have shown(9,11,12).

Some authors(13-15) have suggested that education seems to have lost its prominence as an indirect indicator to characterize the differences concerning the practices of risk against HIV, since regardless of educational level and income, population has currently a considerable degree of basic information about the forms of the virus transmission, information that is not always translated towards the adoption of safer practices.

Regarding the use of drugs, other studies have also found an association between males and higher consumption of drugs, as well as lower frequencies of risk behaviors among women(7,10).

In that context, the intoxication caused by drugs, including alcohol, favours the decreased ability to discern the risks associated with HIV infection, which complicates the negotiation and, consequently, the use of condoms, thereby facilitating the spread of HIV and other STDs(16-18). Men engage more often in risky sexual behavior while drunk, tending to practice sex without condom, both with fixed partners as with casual partners, including with sex professionals(1).

The sexual via, like the national reality, is the main way of exposure of women and men to HIV virus(1). As for the sexual behavior, although the National Survey on Sexual Behavior and Practices, published in 2008, pointed to a declining trend of differences of behaviors and sexual practices between men and women, signaling to a process of change in the country(19), significant differences of these behaviors between genders are still observed in CTA of Montes Claros.

### Table 2 – Distribution of exposure forms to HIV and behavior and sexual practices during last year among CTA users according to gender, Montes Claros, MG, 2007-2009.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprotected sexual intercourse (in life)</td>
<td></td>
<td></td>
<td>0.173</td>
</tr>
<tr>
<td>No</td>
<td>50</td>
<td>7.0</td>
<td>62</td>
</tr>
<tr>
<td>Yes</td>
<td>666</td>
<td>93.0</td>
<td>631</td>
</tr>
<tr>
<td>Blood transfusion/hemoderivatives</td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>No</td>
<td>710</td>
<td>99.2</td>
<td>675</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>0.8</td>
<td>18</td>
</tr>
<tr>
<td>Syringes/needles sharing</td>
<td></td>
<td></td>
<td>0.246</td>
</tr>
<tr>
<td>No</td>
<td>711</td>
<td>99.3</td>
<td>691</td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>7.2</td>
<td>5</td>
</tr>
<tr>
<td>Occupational (exposure to biological material)</td>
<td></td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td>No</td>
<td>713</td>
<td>99.6</td>
<td>682</td>
</tr>
<tr>
<td>Yes</td>
<td>03</td>
<td>0.4</td>
<td>11</td>
</tr>
<tr>
<td>Had sexual partner last year?</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>No</td>
<td>35</td>
<td>4.9</td>
<td>60</td>
</tr>
<tr>
<td>Yes</td>
<td>680</td>
<td>95.1</td>
<td>633</td>
</tr>
<tr>
<td>Number of sexual partners last year</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>None</td>
<td>35</td>
<td>4.9</td>
<td>60</td>
</tr>
<tr>
<td>1 partner</td>
<td>226</td>
<td>31.7</td>
<td>451</td>
</tr>
<tr>
<td>2 partners</td>
<td>153</td>
<td>21.5</td>
<td>95</td>
</tr>
<tr>
<td>3 or more partners</td>
<td>298</td>
<td>41.9</td>
<td>86</td>
</tr>
<tr>
<td>Condom use with partner last year</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Used every time</td>
<td>109</td>
<td>20.1</td>
<td>73</td>
</tr>
<tr>
<td>Did not use</td>
<td>233</td>
<td>43.0</td>
<td>287</td>
</tr>
<tr>
<td>Used less than half of the times</td>
<td>112</td>
<td>20.7</td>
<td>135</td>
</tr>
<tr>
<td>Used more than half of the times</td>
<td>88</td>
<td>16.2</td>
<td>95</td>
</tr>
<tr>
<td>Condom use with casual partner last year</td>
<td></td>
<td></td>
<td>0.312</td>
</tr>
<tr>
<td>Used every time</td>
<td>207</td>
<td>44.4</td>
<td>57</td>
</tr>
<tr>
<td>Did not use</td>
<td>85</td>
<td>18.2</td>
<td>33</td>
</tr>
<tr>
<td>Used less than half of the times</td>
<td>47</td>
<td>10.1</td>
<td>21</td>
</tr>
<tr>
<td>Used more than half of the times</td>
<td>127</td>
<td>27.3</td>
<td>39</td>
</tr>
</tbody>
</table>

* Chi-square test ($\chi^2$).  
  p < 0.05 results were considered significant.
Men are more sexually active and had a higher number of sexual partners than women, but on the other hand reported more frequent use of condoms. Although men were more protected from a sexual point of view, this has not occurred in more than 50% in both genders, showing that the use of condoms in these intercourses, fixed or casual, are still below the expected. In reproductive and sexual life, the use of male condom, although meeting the dual function of protection, both of unwanted pregnancy and STDs, still finds explicit or veiled resistances described mainly in stable relationships between men and women.

Probably the shortest adherence to a consistent use of condoms in stable relationships also observed in this study is justified by the concept embodied by the society that vulnerability is greater in situations of non-marital intercourse, especially when the other person involved is not “yet” known in such a way that it can be considered reliable. In this perspective, “meeting and/or relying” on a partner becomes a risk factor of difficult intervention, which increases the vulnerability of people to HIV. Thus, many people are contaminated for trusting stable or casual partners, although the campaigns emphasize the practice of safe sex as a protection factor against HIV.

Besides the confidence in existing stable relationships supposedly fidelity, other factors also contribute to the unprotected sex, especially among women, such as the low bargaining power between them and their partners, lower vulnerability self-perception, as well as prejudice against the use of condoms, especially regarding the sensitivity and the discomfort caused during sexual intercourse.

Perhaps the most important amongst these factors is the lower self-perception of the risk, especially in heterosexual, caused by beliefs and cultural habits that harm the individual risk assessment.

A study of Ferreira showed an increase in the proportion of Brazilians who declared not present risk regarding Aids, in relation to a survey conducted earlier. It has been shown that the self-perception of risk is smaller in women, especially among those who have stable relationships, which may explain the low adherence to condom. In this way, ads and campaigns divulging the adoption of safe practices solely through the use of condoms have little success among women with regular partner, probably because they consider themselves protected by this kind of relationship, where manifestations of love and affection don’t match the requirement of condom use.

Similarly, suggesting monogamy as a means of HIV prevention, especially for the male audience, doesn’t seem to be a compelling strategy, since the infidelity is something adopted in the construction of men’s sexuality. Alternatively, authors have suggested strengthening the need for the association of preventive measures, at least to extramarital or casual affairs, as well as encourage couples living in fixed partnership to have access to testing and to communicate about the results, defining the use of condom in a context considered as “shared prevention, and not assumed”. Regarding the use of protection in casual intercourses, a national study showed an increased condom use among those who have had only casual partners last year, from 63.5% in 1998 to 78.6% in 2005. Men and singles from 16 to 24 years were the most protected, especially in casual intercourses. In this study, although it was not found significant differences between genders regarding the use of condom in casual relationships, women are also less protected in these circumstances.

Similar to fixed intercourses, the reasons that usually justify this practice are grounded in cultural bases involving power relationship and affection between the genders, as the male immediacy and the female submission and difficulty in the negotiation of “standardization” of behaviors. Although the use of condom is the method proven to be safer to avoid HIV transmission, the prevention speech cannot be crystallized, as even having this knowledge, people don’t always use it in practice, even in situations recognized as most risky.

**CONCLUSION**

The results of this study confirm the higher prevalence of HIV in users of the Testing and Counseling Centers in relation to the estimated prevalence for the general population of Brazil. They show that although women have engaged less frequently in risky behaviors, their proportion of infection was the same of men’s, probably due to unprotected sex.

This no condom use practice evidenced mainly among women involves feelings that cross gender relations, such as submission and trust by interfering in the risk perception and in the possibility of rational adoption of protective behaviours against the virus, which contributes to the feminization of the epidemic.

Due to what was presented, we reiterate the idea that prevention programs to succeed must consider the social, economic and cultural components that structure the inequalities between men and women and that are able to settle a distinct epidemic profile for the genders.

**Conflict of interests**

Authors declared there was no conflict of interests.

**Acknowledgement**

To Thiago Luis de Andrade Barbosa, for the critical review of the manuscript, especially on the methodological aspects.

**REFERENCES**

INCIDENCE OF CONGENITAL SYPHILIS IN A METROPOLITAN REGION OF RIO DE JANEIRO STATE: SOCIAL INEQUALITIES

Sandra C Fonseca¹, Leticia M Oliveira², Natalia MR Almeida², Katia S Silva³, Pauline Lorena Kale⁴

ABSTRACT
Introduction: congenital syphilis remains a public health matter, with no perspective of reaching governmental reduction goals. There are few studies about social inequalities and its relation with this disease in Brazil. Objective: describe occurrence of congenital syphilis in a reference hospital in a Metropolitan Region of Rio de Janeiro State, according to socioeconomic and clinical-laboratorial variables as well. Methods: cross-sectional study, based on interviews, review of medical records and prenatal cards. Population: all women admitted to a maternity ward during a trimester in 2011. Maternal variables: age, schooling, skin color, income, prenatal visits. Fetus/neonate variables: birth weight, gestational age, clinical and laboratory outcomes. Incidence of congenital syphilis (Brazilian Ministry of Health criteria) was calculated for all live births and for each social and economical variable. Results: there were 666 eligible women, comprehending 576 deliveries – 558 live births and 18 stillbirths. We identified 22 CS cases: 18 live births, three fetal deaths and 1 abortion. One of the neonates died in the third day of life. The incidence of CS was of 39.4/1,000 live births. Socioeconomic variables – low education, low income and black skin – were related to a greater incidence. Only 13 out of 22 cases were identified in prenatal care. Conclusion: our results pointed to social inequalities in the congenital syphilis incidence. As prenatal care is also related to socioeconomic variables, investments in quality of maternal assistance should be directed to more vulnerable women.

Keywords: congenital syphilis; incidence; perinatal mortality; prenatal care; social inequalities.

INTRODUCTION
Congenital syphilis (CS) is the infectious disease that results from the vertical *Treponema pallidum* transmission of the non-treated or inadequately treated infected mother, to her child⁴⁵. CS is an important cause of perinatal morbidity and mortality, leading to negative outcomes, such as spontaneous abortion, natimortality, neonatal mortality, low weight and prematurity, according to the stage of infection in the woman and the moment of the mother-to-child transmission. Most newborn cases are asymptomatic; when symptomatic, cases can present low birth weight, prematurity, fetal hydropsy, vesicular-bullous rash on palms and plants, hepatosplenomegaly and sepsis⁴⁵.

Syphilis during pregnancy contributes to 650,000 fetal and neonatal deaths per year in developing countries⁴⁶. Based on these data, World Health Organization (WHO), in 2009, released an initiative aiming at the improvement of maternal and newborn health by decreasing the number of cases of congenital syphilis for at least 80% in five years⁴⁶.

Additionally, Pan American Health Organization (PAHO) has developed, also in 2009, the “Regional Initiative for the Elimination of mother-to-child transmission of HIV and congenital syphilis in the Latin America and Caribbean”, which was approved in 2010 by the member States of PAHO with the purpose of reducing the incidence of CS to less than or equal to 0.5 per thousand live births by 2015⁴⁶.

In Brazil, despite advances in the diagnosis and effective treatment of the disease, the vertical transmission rates remain very high. Between January 1998 and June 2012, 80,041 cases of congenital syphilis in children under 1 year of age were notified. The Southeast region recorded 45.9% of these cases. The incidence rate of congenital syphilis, in 2011, was of 3.3 cases per 1,000 live births, while in the Southeast, the value was a little higher – 3.8 per 1,000 live births. The State of Rio de Janeiro was prominent⁵, with the highest rate of 2011 (9.8 per 1,000 live births).

According to SINAN (Information System for Reportable Diseases), most CS cases occur in Rio de Janeiro State capital, followed by Baixada Fluminense and two cities of the Metropolitan Region II: Niterói and São Gonçalo⁶. The objective of the present study is to describe the occurrence of the disease in a reference maternity ward located in the Metropolitan Region II in the State of Rio de Janeiro. The social and the demographic profiles, and the assistance to recent mothers, as well as clinical and laboratory characteristics of fetuses and neonates were taken into consideration.

METHODS
A cross-sectional study was performed with interview, medical records review and prenatal cards of all mothers and their newborn babies in the State Hospital Azevedo Lima (HEAL) maternity, from September to November, 2011. Located in the city of Niterói, Rio de Janeiro State, this is a reference hospital of the Unified Health System (SUS - Sistema Único de Saúde) for the Metropolitan Region II, including the cities of Itaboraí, Maricá, Niterói, Rio Bonito, São Gonçalo, Silva Jardim and Tanguá with an estimated population around 1,957,936 in 2011 according to DATASUS⁷.

This study is a subproject of the “Maternal and perinatal morbidity-mortality in the cities of Rio de Janeiro and Niterói: the role of race, schooling, and social level in the access to health services” accomplished in a partnership between the Community Health Institute (ISC-UFF), Collective Health Studies Institute (IESC-UFRJ), Fernandes Figueira Institute (IFF-FIOCRUZ), and Public Health School (FSP-USP). The FSP original project, named “Mother-child Binomial Study: a necessity commanded to meet the needs of the millennium development”, was adapted to the State of Rio de Janeiro reality.

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In order to attend to the multiple outcomes of the research, the sample size was based on the livebirth number at the maternities included in the study, foreseen the collecting data for a period of three months, according to a similar WHO study.

A congenital syphilis case definition of the National STD and Aids Program of the Health Ministry was adopted as follows: every child, or abortion, or stillbirth of mother with clinical evidence for syphilis serology and/or with non-treponemal reagent for syphilis with any titration, in the absence of confirmatory test held at treponemal prenatal care or at delivery time or curettage, which had not been treated or had received inadequate treatment.”

Total and specific perinatal mortality rates were calculated for CS per thousand births, and also the incidence rates of total congenital syphilis: new congenital syphilis cases, including miscarriages, stillbirths and live births divided by the total number of live births in the quarter in question, multiplied by 1,000(5) – and according to socioeconomic characteristics (skin color, average income per capita and schooling). Despite the cross-sectional feature of the study, the calculation of CS incidence is recommended because it considers all possible outcomes during pregnancy.

The maternal characteristics assessed for the study population in general, and in particular the cases of CS were: age (19 years, 20-34 years, ≥ 35 years); schooling (low < 8 years of study, and high ≥ 8 years of study); skin color, as declared by woman; per capita family income; number of prenatal visits and adequacy of prenatal care. The criterion of adequacy considered the following number of visits: for women with 37 or more weeks, seven visits or more, for those between 32 and 36 weeks, five visits; between 28 and 31 weeks, four visits; between 22 and 27 weeks, three visits; and at least two visits for women with less than 22 weeks. The month of the beginning of prenatal care was also taken into consideration, and considered adequate if the first consultation occurred until 16 weeks of pregnancy. For CD cases, non-treponemal tests – VDRL – during prenatal care and of last menstruation and/or ultrasonography of the first quarter.

The research project was approved by the Research Ethics Committee of IESC-UFRJ (approval n° 35/2011). Informed consent was requested to all eligible pregnant women or to their respective responsible when they were under 18 years of age.

### RESULTS

A total of 666 women were eligible for the study, of whom there were 576 births, 52 miscarriages, and 12 ectopic pregnancies. Only four refused to participate in the study.

Of the total births, 558 were live births (four twins) and 18 fetal deaths. Perinatal mortality in the period studied was of 50 per 1,000 births.

The user population of HEAL showed unfavorable socioeconomic conditions, with a high percentage of adolescents (30%) and women with incomplete elementary school (35%). The average per capita income was of R$ 300.00. About prenatal care, less than half reported having done seven or more visits (Table 1).

A total of 22 cases of CS was verified, of whom 18 livebirths, three stillbirths, and one miscarriage. Thirteen cases of women resident in the city of Niterói, seven from São Gonçalo, one from Maricá, and one from Itaboraí. The incidence found in CS was of 39.4 per 1,000 live births for the quarter reviewed. Congenital syphilis was responsible for four of the 29 deaths during the perinatal period with a CS perinatal mortality rate of 6.9 per 1,000 births, being the fetal component of 5.2 per 1,000 births.

Through the analysis of the 22 women whose fetuses or newborn babies (NB) had a diagnosis of CS, it was observed an age between 15 and 33 years, with an average of 20.5 years and a percentage of adolescent mothers of 40.9%.

### Table 1 – Characteristics of recent mothers and subgroup of women with outcome of congenital syphilis (CS) admitted in the State Hospital Azevedo Lima (HEAL) maternity ward, Niterói, Rio de Janeiro, September to November, 2011

<table>
<thead>
<tr>
<th>Variable</th>
<th>HEAL* women N = 553</th>
<th>CS Subgroup N = 22</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 19 years</td>
<td>29.8</td>
<td>40.9</td>
<td>0.268</td>
</tr>
<tr>
<td>20-34</td>
<td>62.4</td>
<td>59.1</td>
<td></td>
</tr>
<tr>
<td>≥ 35 years</td>
<td>7.8</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td><strong>Color (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>27.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>24.7</td>
<td>40.9</td>
<td></td>
</tr>
<tr>
<td>Mulatto</td>
<td>46.5</td>
<td>54.6</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1.3</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td><strong>Schooling (%)</strong></td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>&lt; 4 years</td>
<td>2.7</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>4-7 years</td>
<td>30.4</td>
<td>72.7</td>
<td></td>
</tr>
<tr>
<td>8-11 years</td>
<td>63.6</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>12 years or more</td>
<td>3.1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Per capita income (R$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>R$ 401.00</td>
<td>R$ 245.00</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prenatal visits (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3 visits</td>
<td>16.2</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>4-6 visits</td>
<td>36.7</td>
<td>39.9</td>
<td></td>
</tr>
<tr>
<td>7 or more</td>
<td>47.1</td>
<td>36.3</td>
<td></td>
</tr>
</tbody>
</table>

*Total of women whose children have not had congenital syphilis.
In relation to socioeconomic characteristics, the percentage of incomplete elementary education was of 81.8%, and the average per capita income was of R$ 250.00; 21 of them reported family income less than one minimum wage at the time (Table 1). Twenty-one (95.4%) declared to be black or mulatto, and one was of Asian origin. There were no cases among white women nor in those with more than 11 years of education. Table 1 shows the differences between the subgroup of women with CS and the total of recent mothers (live births and deaths) without syphilis studied in the maternity ward of HEAL.

The 22 women had at least one prenatal visit. However, according to the parameters used to assess the adequacy of prenatal, 59.1% received an inadequate prenatal. Only 13 (59.1%) of 22 mothers with syphilis were identified in prenatal care; seven cases (31.8%) of syphilis were diagnosed only at time of delivery, and two (9.1%) cases were not aware of information about laboratory tests performed during the prenatal period. The VDRL collected at the maternity ward ranged from 1:1 (a patient HIV+) to 1:256 (Table 2).

Regarding live births with CS, three of them weighed less than 2,500 g and five had less than 37 weeks. Two babies were small considering the gestational age, one term newborn and one pre-term newborn, which evolved into death. Serum VDRL was positive in 16 cases (88.9%), and there were four cases (22.2%) of neurosyphilis. The neonates VDRL ranged from 1:1 to 1:256 (Table 2).

Blood evaluation tests showed anemia in five newborn (27.8%) and thrombocytopenia in four (22.2%). Two neonates showed hepatic alterations: one of them with hepatic hyperbilirubinemia, and the other one with hepatomegaly. One newborn presented a serious blood dyscrasia, leukopenia, sepsis, kidney failure, and pancytopenia, evolving into death. His mother had five prenatal visits and was identified 1:8 VDRL. She did not receive treatment, as this serology was erroneously considered a “serological scar”. On admission, the patient presented an upward titration (1:16) and the final outcome was the newborn death.

The incidence of congenital syphilis was significantly higher in black women with low schooling and low income (Table 3).

**DISCUSSION**

Since the 90’s, WHO and other health organizations have been striving to control the congenital syphilis in the world. In Brazil, transmission rates remain very high and it seems unlikely to achieve the goal of global elimination of the disease\(^ (24)\). In our study, it was identified an incidence rate (39.4%) much higher than the target set to us and higher than in other national studies\(^ (14-16,19,22,23)\) with the same CS criteria\(^ (20)\). It is worth noting that there were diverse methodology studies, with primary data, as well as data from SINAN, population and hospitals.

From 2002 to 2004, a study performed in HEAL\(^ (13)\) presented an incidence of 21.9%; however, after 10 years it was observed an incidence of congenital syphilis almost twice greater.

We have observed a high percentage of adolescent mothers, data presenting similarity in the same hospital between 2002 and 2004\(^ (13)\). Some studies have found links between adolescence and occurrence of congenital syphilis\(^ (16,19)\); however Lima et al. (2013) did not demonstrate this association in the city of Belo Horizonte, State of Minas Gerais.

The user population of the HEAL maternity has unfavorable socioeconomic conditions, and we have observed that the subgroup of women whose fetuses had CS proved even a greater disadvantage, particularly in relation to income, race and education, and these data were confirmed in other national studies\(^ (14-16,19,22,23)\).

Another factor probably related to the disease is the race issue, yet little studied in our country\(^ (16,18,19)\). In our research, the incidence rate of congenital syphilis in black women was very high, 62.5%, and there were no cases, in that period, among white women. The black population is socially more vulnerable, which may in part explain this association.

The twenty-two women with an outcome of CS had at least one prenatal visit, however, more than 60% had insufficient amount of visits. However, the number of visits is not the only factor contributing to the perpetuation of congenital syphilis; the quality of prenatal care offered by the health services regarding the timely diagnosis and treatment of the disease must also be examined. We have identified a considerable portion of the population studied (36.3%) that even performing appropriate prenatal visits failed to prevent the unwanted outcome. This proves the quality deficiency of prenatal care, which has been one of the main factors for the high rates of congenital syphilis, confirmed in many national studies\(^ (15-20)\).

In general neonates infected by *Treponema* are asymptomatic at birth, a result observed in our study. Nevertheless, complications such as prematurity, low birth weight, liver and hematological changes are expected in these newborn babies\(^ (25-27)\). Prematurity and low birth weight due to congenital syphilis are causes that raise the risk of perinatal mortality\(^ (25)\). Even in the presence of negative VDRL, as noted in two newborn babies, the thorough investigation of congenital syphilis should be performed, since this finding is not unusual\(^ (25)\).

The perinatal mortality rate for congenital syphilis found in our study was greater than the one observed in the city of Rio de Janeiro\(^ (23)\) in 2002 (0.89%), the same occurring with the fetal mortality for syphilis\(^ (26)\), which was twice the mortality found in the same city in 2004 (2.55%). These studies also used primary data and were not based on SINAN. The negative impact of the disease on fetal viability justifies the intensification of preventive measures of syphilis vertical transmission.

As a limitation of our study, we point out the small number of cases and the short period of time (a quarter). This was due to the
Table 3 – Syphilis incidence due to socioeconomic variables – color of skin, income and schooling, State Hospital Azevedo Lima (HEAL) maternity ward, Niterói, Rio de Janeiro, September to November, 2011

<table>
<thead>
<tr>
<th>Socioeconomic variables</th>
<th>Incidence rate (by 1,000 live births)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Color of skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>62.5</td>
<td>0.012a</td>
</tr>
<tr>
<td>Mulatto</td>
<td>45.0</td>
<td></td>
</tr>
<tr>
<td><strong>Per capita income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; R$ 200.00</td>
<td>67.0</td>
<td>0.035b</td>
</tr>
<tr>
<td>R$ 200 to 749.00</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>≥ R$ 750.00</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td><strong>Schooling</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 8 years</td>
<td>90.5</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>≥ 8 years</td>
<td>10.8</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square.
* Chi-square with linear trend.

methodology of the original research, based on the outcomes of neonatal morbidity. However, a strong point was the daily collection data, using various sources: interview, prenatal card, medical records and lab tests. In studies using the Information System for Reportable Diseases (SINAN) as a source, although there is the advantage of being able to cover longer periods, there is a risk of underreporting and poor quality of data\(^{27,28}\).

CONCLUSION

Despite the simple, effective and affordable technology for diagnosis and treatment, congenital syphilis remains high in Rio de Janeiro women users of SUS, its higher incidence being emphasized among those with social vulnerability features.

Our results showed socioeconomic factors – low income, low education and black/mulatto race – as predictors of the occurrence of congenital syphilis, which may reflect inequalities in self-care, access and continuity of health services. We believe that a differentiated attention to these most vulnerable groups would be an important strategy to be considered for the disease control guidelines.

It should also be noted that the risk of congenital syphilis is directly related to the health service provided. The lack or precariousness of prenatal care is a risk factor for vertical transmission of syphilis. Despite protocols are clear as to the appropriate diagnostic and treatment guidelines on pregnancy, it seems this is not being fully followed by health professionals. The bankruptcy of prenatal care, either due to the difficulty of access of users, or by the caregiver inadequacy or assistance processes, is therefore the critical point for the elimination of congenital syphilis\(^{29-30}\).

We can’t generalize our data, as this is a study in just one health unit, but it suggests that a better care quality of pregnant women, combined with the reduction of social inequalities, would have an impact on the incidence of congenital syphilis. As mentioned by Saraceni et al. (2007), “it is in that portion of the population, using the public service, where the syphilis hides and multiplies”\(^{28}\).

Syphilis is not a disease of the past, and we should remind health professionals, especially in the mother-child area, of the importance of congenital syphilis among vertical transmitted diseases.

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Conflict of interest

There is no interest conflict to be declared.

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HIV PREGNANT WOMEN WITH MORE THAN ONE PREGNANCY AND THE USE OF ANTIRETROVIRAL DURING PRE-NATAL CARE AND CHILDBIRTH

Dai Chengyao1 & Lucia Yi Nichiata2

ABSTRACT

Introduction: the increasing numbers of women infected by HIV resulted in the risk of a vertical transmission of the virus, and prevention has been conducted by means of prophylaxis and antiretroviral (ARV) interventions. Although medication in Brazil has been available since 1996, only 69% of HIV positive pregnant women used ARV methods properly during pre-natal care. Objective: to describe the socio-demographic and reproductive health profile of women who had more than one HIV positive pregnancy and identify the use of antiretroviral during pre-natal care and childbirth. Methods: we accessed 2,106 registers of HIV pregnant women at the SINAN, residing in São Paulo, from January 2007 to March 2011, and we selected 284 notifications of women with more than one pregnancy. Dependent variable: use of ARV; independent variables: age, race/color, education, occupation, pre-natal care, type of delivery, use of ARV in childbirth, pregnancy outcome, use of ARV prophylaxis in children. We conducted a Pearson Chi-square test, considering a confidence interval (CI) p < 0.05. Results: of the 284 pregnant women, 254 were HIV positive in their second childbirth and 30 in their third. The women were predominantly young, white, had a high school degree, and were housewives and workers in industries and services. 84.9% of them had pre-natal care, and of these, 82.6% used ARV during their term. During childbirth 77.3% received intravenous AZT. Over the course of the first 24 hours after birth, 91.5% of the infants received prophylaxis treatment. There was a significant statistical relation between the use of ARV during pre-natal care. Conclusion: the study revealed that, although these women were HIV positive in their second or third pregnancy, there is a lower percentage of HAART use than what is shown in present publications. Keywords: anti-retroviral agents, pregnancy, HIV, pre-natal care, prevention & control

INTRODUCTION

The heterosexual transmission of HIV resulted in a larger number of infected women, and consequently, the vertical transmission of HIV became an important issue for collective health policies(1-3).

It has been demonstrated that, during pregnancy, the risk of infecting the child, when there is no prophylaxis intervention, is estimated at 25 to 30%. During childbirth the risk increases to 65 to 70%, and during the lactating period the rate is of 7 to 39%(4).

With the introduction of the ACTG protocol 076, in 1996, and in 2001 of Highly Active Antiretroviral Therapy (HAART) for pregnant women, it has been possible to reduce this rate to less than 1%(5). It is estimated that in Brazil, following the recommendation for vertical transmission prophylaxis, with the use of HAART, the risk of HIV infection for infants is 3%(6).

The country’s prophylaxis recommendations, for preventing the vertical transmission of HIV, are as follows: provide anti-HIV testing, with pre and post-test counseling for all pregnant women in pre-natal care services; testing should be voluntary and confidential; administer Zidovudine (AZT) oral medication in HIV positive pregnant women, starting on the 14th week of pregnancy, intravenous AZT during labor and childbirth, un-til the umbilical cord is clamped and oral AZT for the infant over the course of 6 weeks, according to the 076 Protocol of the ACTG. Preferably the delivery method should be a c-section, to avoid contact of the baby with the virus, but vaginal delivery is recommended when the viral load test is less than 1,000 copies/mL or undetectable and the gestational age is over 34 weeks. Pregnant or postpartum women are advised to replace breast-feeding with artificial milk and other foods, according to the child’s age, as long as it does not hinder the infant’s proper growth and development(7).

In Brazil there has been a progressive increase in the number of women diagnosed prior to their pregnancy, consequently the percentage of HIV positive pregnant women with antiretroviral (ARV) treatment during pre-natal care has increased(8).

However, despite of all the investments made by public policies in the country to expand the access of HIV positive pregnant women to HAART, there is still a significant percentage of women who have not received the medication, either during their pregnancy or during childbirth.

In a study conducted by Nichiata(9), it was possible to identify women who had more than one pregnancy, and were aware of the HIV positive diagnosis, where more than one child from the same mother was born with HIV. The study questioned if women in these conditions used ARV prophylaxis.

OBJECTIVE

To describe the demographic and reproductive health profile of women who had more than one HIV positive pregnancy and identify the use of antiretroviral during pre-natal care and childbirth.
METHODS

It is an exploratory, descriptive, cross-sectional and quantitative study, using a secondary database.

Data collection was made by means of the Sistema de Informação de Agravos de Notificação (SINAN), where we accessed the registrations of HIV positive pregnant women in the city of São Paulo, over the course of January 2007 and March 2011. Of a total of 2,106 registrations in the original database, we elaborated a specific spreadsheet containing the total of HIV positive pregnant women who had more than one pregnancy, and we identified 284 registrations.

Dependent variables were: the use of ARV interventions during pre-natal care, during delivery and by the child. Independent variables were: age, race/color, education, pre-natal care, and evolution of the pregnancy.

The results underwent a Pearson Chi-square test, in order to verify the connection between the study’s variables, with a confidence interval of 95%, or in other words, there is a 5% acceptable probability of error for the connection, p < 0.05. Over the course of the test, for the use of ARV interventions during delivery and evolution of the delivery, we used as criteria the factor of women who had their pregnancy outcome during the notification period of the SINAN.

The research was approved by the Comitê de Ética em Pesquisa da Secretária Municipal da Saúde (Ethics Research Committee of the Municipal Secretariat of Health) of the city of São Paulo, with the protocol nº 255.0.162.000-10.

RESULTS

Of the 284 pregnant women identified as being HIV positive, 254 (89.4%) were in their second pregnancy and 30 (10.6%) were in their third pregnancy. They were mainly young, white, had a high school degree, and were housewives and workers in industries and services.

Their age ranged from 20 to 39 years old (87.0%), 13 were teenagers, with ages ranging from 17 to 19, and one of them was HIV positive and was in her third pregnancy. (Table 1).

The majority of women, 136 (47.9%) had 8 or more years of education. As for their jobs¹⁰, they were mainly classified as “undefined” (48.2%), and this category includes housewives, unemployed and students (Table 1).

The majority of women 241 (84.9%) had pre-natal care. And 107 of them (37.7%) were in the first quarter of their pregnancy when they started pre-natal care (Table 2).

Of the 241 women who had pre-natal care, 30 (12.4%) did not use ARV treatment during this period. Of the women that gave birth, (216), 41 (19%) of them did not receive prophylactic ARV treatment during pre-natal care. The majority of the women, 119 (55.0%) gave birth with a c-section (Table 2).

The use of ARV during pre-natal care was associated to the pregnant women’s education (p < 0.05), and it showed that the women that used ARV during pre-natal care were, for the most part, the ones with 5 to 8 years of education (Table 3).

<table>
<thead>
<tr>
<th>Socio-demographic variables</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 19 years old</td>
<td>13</td>
<td>4.6</td>
</tr>
<tr>
<td>20-29</td>
<td>122</td>
<td>43.0</td>
</tr>
<tr>
<td>30-39</td>
<td>125</td>
<td>44.0</td>
</tr>
<tr>
<td>40-49</td>
<td>23</td>
<td>8.0</td>
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<tr>
<td>No information</td>
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<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Race/Color</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>123</td>
<td>43.3</td>
</tr>
<tr>
<td>Black</td>
<td>50</td>
<td>17.6</td>
</tr>
<tr>
<td>Yellow</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>Brown</td>
<td>91</td>
<td>32.0</td>
</tr>
<tr>
<td>Indian</td>
<td>2</td>
<td>0.7</td>
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<tr>
<td>No information</td>
<td>14</td>
<td>4.8</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td>1-3 years</td>
<td>13</td>
<td>4.6</td>
</tr>
<tr>
<td>4-7 years</td>
<td>100</td>
<td>35.2</td>
</tr>
<tr>
<td>8 or more years</td>
<td>136</td>
<td>47.9</td>
</tr>
<tr>
<td>No information</td>
<td>31</td>
<td>10.0</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Occupation (CBO, 2002)**¹⁰

<table>
<thead>
<tr>
<th>Occupation</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public servants. managers in public organizations or private companies. managers</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Sciences and arts</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Mid level technicians</td>
<td>17</td>
<td>6.0</td>
</tr>
<tr>
<td>Management services</td>
<td>15</td>
<td>5.3</td>
</tr>
<tr>
<td>Services. sales and supermarkets</td>
<td>38</td>
<td>13.4</td>
</tr>
<tr>
<td>Goods production and industry workers</td>
<td>7</td>
<td>2.5</td>
</tr>
<tr>
<td>Other occupations. undefined – unemployed. students. housewives. others</td>
<td>137</td>
<td>48.2</td>
</tr>
<tr>
<td>No information</td>
<td>66</td>
<td>23.2</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Data from March 2011.

Source: SINAN.
Pregnancy Characteristics | N  | %
--- | --- | ---
Pregnancy stage when pre-natal care began
1st trimester | 107  | 37.7
2nd trimester | 89   | 31.3
3rd trimester | 62   | 21.8
Sem informação  | 26   | 9.2
Total           | 284  | 100.00
Pre-natal care
Yes            | 241  | 84.9
No              | 14   | 4.9
No information  | 29   | 10.2
Total           | 284  | 100.00
ARV use during pre-natal care (N = 241)
Yes            | 199  | 82.6
No              | 30   | 12.4
No information  | 12   | 5.0
Total           | 241  | 100.00
ARV use during delivery** (N = 216)
Yes            | 167  | 77.3
No              | 41   | 19.0
No information  | 8    | 3.7
Total           | 216  | 100.00
Type of delivery (N = 216)
Vaginal         | 86   | 39.8
Elective c-section | 102 | 47.2
Urgent c-section  | 17   | 7.9
No information  | 11   | 5.1
Total           | 216  | 100.00
Evolution of the pregnancy (N = 216)
Live birth      | 200  | 92.6
Stillborn       | 4    | 1.8
Abortion        | 12   | 5.6
Total           | 216  | 100.00
Start of prophylaxis in the child (N = 200)
First 24 h of birth | 183  | 91.5
After 24 h of birth | 3    | 1.5
None            | 10   | 5.0
No information  | 4    | 2.0
Total           | 200  | 100.00

* Data from March 2011.
** The cases considered were the ones that resulted in delivery.

Table 3 – Number and percentage, according to the use of ARV during pre-natal care and education, from 2007 to 2011*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Use of ARV</th>
<th>Non use of ARV</th>
<th>Value of p**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>75.0</td>
<td>1</td>
</tr>
<tr>
<td>1 to 4 years</td>
<td>114</td>
<td>83.8</td>
<td>22</td>
</tr>
<tr>
<td>5 to 8 years</td>
<td>69</td>
<td>95.8</td>
<td>03</td>
</tr>
</tbody>
</table>

* Data from March 2011.
** Cases with no information were excluded.
Source: SINAN.

As for the use of ARV during delivery there was a significant connection between the variables: pre-natal care, type and evolution of the delivery (p < 0.05). The use of ARV during delivery was higher among women who attended pre-natal care and opted for a c-section (Table 4).

Table 4 – Number and percentage, according to the use of ARV during delivery, type and evolution of the delivery with pre-natal care, form 2007 to 2011*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Use of ARV</th>
<th>Non use of ARV</th>
<th>Value of p**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Pre-natal care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>162</td>
<td>84.4</td>
<td>30</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>18.2</td>
<td>9</td>
</tr>
<tr>
<td>Type of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>55</td>
<td>67.1</td>
<td>27</td>
</tr>
<tr>
<td>Elective c-section</td>
<td>96</td>
<td>98.0</td>
<td>2</td>
</tr>
<tr>
<td>Urgent c-section</td>
<td>12</td>
<td>80.0</td>
<td>32</td>
</tr>
<tr>
<td>Evolution of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>162</td>
<td>84.4</td>
<td>30</td>
</tr>
<tr>
<td>Stillborn</td>
<td>1</td>
<td>50.0</td>
<td>1</td>
</tr>
<tr>
<td>Abortion</td>
<td>2</td>
<td>16.7</td>
<td>10</td>
</tr>
</tbody>
</table>

* Data from March 2011.
** Cases with no information were excluded.
Source: SINAN.

DEBATE

It is known that pre-natal care during the pregnancy is a crucial factor for the health of the mother and the child, especially for HIV positive pregnant women, and that the sooner it begins it increases the chances of intervening in the transmission of the virus from mother to child.

The women in the study were notified as pregnant and HIV positive for the second and third time and had, therefore, knowledge about their condition since their first pregnancy.
Although the majority of women in the study had pre-natal care, we expected a higher percentage of antiretroviral use during pre-natal care and during delivery, given that they knew about their HIV positive condition. According to reports from HIV positive women who had seronegative children, we found that they were encouraged to seek assistance during their pregnancy\(^{13}\).

The study found a percentage of approximately 85% compliance with pre-natal care, lower than what is found in Brazil\(^{12,13}\) and in the world, with a variation of 90 to 100%\(^{14,15}\). As for compliance with pre-natal care and childbirth ARV treatment, 82.6% and 77.3% pregnant women had prophylaxis treatment, respectively.

In a study conducted in Porto Alegre, without taking into account the number of pregnancies, a higher percentage was found of women who had pre-natal care (97.7%), with the use of ARV for 86.6% of them and a 92.8% use of prophylaxis during delivery. At the same time there were a percentage of women who were previously diagnosed as HIV positive who didn’t use ARV during their pregnancy\(^{16}\).

There are doubts about why women who are seropositive, and know about their condition and about the risk of vertical transmission, do not have pre-natal care or use ARV during their second and third pregnancies.

In this instance, the determinant factor to be considered is the quality of pre-natal care. According to reports from seropositive women, the challenges they face for this kind of health service are numerous: too much bureaucracy for pre-natal care, high turn-around of professionals, lack of educational practices and laboratory resources within the health units, lack of communication and clarity by the professionals\(^{17,18}\). Even though Brazil has 97.1% coverage of pre-natal care for pregnant women in general, only 26.5% of pre-natal care is considered adequate, according to the PHPN (Programa de Humanização do Pré-natal e Nascimento) parameters\(^{19}\).

Being HIV positive makes it even more difficult to access treatment, given the complexity of HAART, side effects, forgetfulness, and the incompatibility between the treatment and the routines of life and self-esteem\(^{20}\).

Prevention during the intra-delivery period is another crucial factor in reducing vertical transmission of the virus, given the increased risk of transmission during this period. In the study, 19.0% of women did not have prophylaxis during delivery. National studies showed variations between 10 and 23%\(^{21,22}\), and a lower value when the women knew about their condition during the pregnancy\(^{22,23}\). Analyzing the quality of pre-natal assistance and the deliveries in public maternities provided for pregnant women, we identified a reality that is far from what is recommended by the Ministry of Health, showing how fragile the Programa Brasileiro de Redução da TV do HIV (Brazilian Program to Reduce the Transmission of HIV), regarding its organization, management and health service assessment\(^{24}\).

There were a higher percentage of women who had a normal delivery (39.80%) than in other studies (20.5% to 27.3%)\(^{13,25}\). The definition of normal delivery is based on the results of the maternal viral load (less than 1.000 copies/mL), conducted after the 34th week of pregnancy, and in association with an obstetric evaluation\(^{26}\). It is possible that women who had more than one pregnancy are in this condition, ensuring a safe vaginal delivery. There was a connection between the use of ARV during delivery and pre-natal care and a c-section delivery. We expected that, knowing about their HIV positive condition, there would be a greater probability that these women would seek pre-natal care, use HAART prophylaxis and opt for a c-section, in order to prevent the vertical transmission of HIV.

Of the 200 live born, 5% did not receive prophylaxis during the first 24 hours after birth. A higher value than what has been found in some studies (2.1 to 2.2%)\(^{25,26}\).

In this study, despite the norms and measures to prevent the vertical transmission of HIV, a part of the country’s health policy, with a clear definition of the commitment to these actions by health organizations, the institutionalization process of these recommendations in practice is limited.

Missed opportunities to perform preventive interventions, in pre-natal care, during delivery or for the newborn, show the vulnerability of women and children in the program to HIV, regarding the prevention of vertical transmission.

One of the study’s limitations was the incorrect filling of reports, the inconsistence of some data and incomplete information that were important for the analysis. Our suggestion is that the database can be improved by adding information related to the reasons why women do not attend pre-natal care and do not go through HAART intervention.

**CONCLUSION**

The study showed that, although they were notified as second or third pregnancies with a previous HIV+ diagnosis since their first pregnancy, there weren’t a higher percentage of pregnant women in the program than what other studies showed. It is necessary to verify the reasons for the non-adherence to prophylactic treatment and the type of health care provided to these women, since they are HIV positive since their first pregnancy, particularly as to the quality and accountability of these services.

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Antimicrobial Resistance in Neisseria gonorrhoeae Isolates from Ribeirão Preto, São Paulo, Brazil

Marta Inês C Medeiros¹, Jaqueline O Silva¹, Ana Maria M Carneiro², Silvia Helena C Reche³, Luiz Sérgio D’ Oliveira Rocha⁴, Paulo da Silva⁵

ABSTRACT

Introduction: gonorrhea is sexually transmitted, with a high incidence worldwide. Occurrence of resistance and difficulties in treatment is often reported. Penicillin is not used anymore, and quinolones or cephalosporins are the remaining therapeutic options. However, there are resistance reports to these drugs as well. Objective: to evaluate the occurrence of resistance to penicillin, tetracycline, ofloxacin, ciprofloxacin, azithromycin and ceftriaxone in Neisseria gonorrhoeae (gonococcus). Methods: ninety-three endocervical and urethral secretion samples, suspected of gonorrhea, were cultured from September 2008 to May 2012. Samples were collected at the STD/AIDS Reference Center and processed at Instituto Adolfo Lutz in Ribeirão Preto, SP, Brazil. Antimicrobial susceptibility tests were performed by the E-test (Oxoid). Beta-lactamase was determined by the cefinase disk method (BD BBL). The susceptibility study included a gonococcus isolated from a case of conjunctivitis. Results: gonococcus was isolated in 41.9% (35) of the cases in the study. Male patients were predominant in 92.3% of samples, with ages ranging from 14 to 62 years, and the conjunctivitis isolate was recuperated from a 1 month old patient. Isolates were resistant to penicillin (44.4%); tetracycline (55.5%); ofloxacin (36.1%) and ciprofloxacin (36.1%). All isolates were susceptible to ceftriaxone, and 80.6% were susceptible to azithromycin. The beta-lactamase test was positive for 31.0% of isolates. Conclusion: in vitro results showed that tetracycline was less effective, and ceftriaxone the most effective antibiotic against gonococcus. The resistance to different drugs limits the options of gonococcus effective treatment.

Keywords: Neisseria gonorrhoeae, resistance, antimicrobials, gonorrhea, STD

INTRODUCTION

Gonorrhea, which etiologic agent is the bacterium Neisseria gonorrhoeae (gonococcus), is one of the oldest sexually transmitted diseases (STD), with worldwide high incidence. Transmission occurs by direct contact with secretions of infected mucosal surface, and the incubation period can range from 1 to 10 days⁴. The most common clinical manifestations of the infection are urethritis and cervicitis, although it can affect the anal mucosa, oropharynx, conjunctiva, among others⁵.

About 30 to 80% women and 5 to 85% men can remain asymptomatic carriers of gonococcus, making it difficult to break the transmission chain of the disease. Therefore, along with the assessment of sexual partners and health education, the detection of carriers are among the main control strategies of gonorrhea⁶. In Brazil, the absence of a notification system of STD cases makes information scarce. In 2003, the Ministry of Health National STD/Aids Program estimated the occurrence of 1.5 million cases of gonorrhea⁷.

The high demand for medical care, the cost of treatment and the socioeconomic impact of STDs represent an economic loss of 17%, mostly in developing countries⁸.

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Gonorrhea, as well as any other STD, can work as a gateway to the HIV and other microorganisms. According to Wasserheit⁹ and Cohen⁹, STDs increase the risk of acquiring HIV infection from three to five times.

Direct bacterioscopy of secretions stained by Gram and culture are the traditional methods used for diagnosis of gonococcal infections⁹. Bacterioscopy has 90% sensitivity and 98% specificity in the detection of purulent gonococcal infections, although this sensitivity becomes reduced in asymptomatic patients. In this context, culture is an indispensable method for the diagnosis, allowing the isolation of gonococcus and the subsequent determination of antimicrobial sensitivity profile⁹.

Molecular techniques have been made available through commercial kits for the diagnosis of gonococcus, using nucleic acid amplification tests, which show high sensitivity and specificity. Gonococcus intolerance in the transportation of the sample and the rapidity of the result are advantages of these techniques on the culture⁹.

The gonococcus is a highly fastidious bacterium, which success in isolation and identification depends on the adequate collection and transportation of the sample, in addition to the quality of inputs used and trained personnel⁹. Few laboratories carry out this methodology routinely due to the specificity concerning the cultivation of gonococcus. The difficulty in the infection diagnosis, coupled with inadequate use of antimicrobials, promotes the development of resistance to available drugs, which is the biggest obstacle to the control of the disease, by limiting the therapeutic options for effective treatment. When not carried out correctly, especially in women, treatment can cause serious sequelae, such as infertility, miscarriage and ectopic pregnancy⁹.

The production of enzymes, the acquisition of plasmids, and genetic mutations are among the various resistance mechanisms of antimicrobial gonococcus⁹. The β-lactamase enzyme gives the gonococcus the ability to inactivate β-lactam antibiotics. The isolates of gonococcus should be investigated concerning the pro-
duction of this enzyme, which can be detected by iodometric and acidimetric methods, and also through chromogenic cephalosporin (nitrocefin)\(^{(11)}\).

Due to the acquisition of resistance to antimicrobials, the treatment of gonococcus has evolved through time. The sulfonamide was the first indication for the treatment of gonorrhea, and subsequently penicillin followed by tetracycline. The fluoroquinolones (ciprofloxacin, ofloxacin and levofloxacin) were introduced more recently, but there are already reports of emergence of resistance to this class of antibiotics in many countries\(^{(12)}\).

Because the constant changes of antimicrobial sensitivity profile of the gonococcus, the monitoring of circulating strains is essential to detect the emergence and spread of drug-resistant strains, helping the institution of effective measures in the control of gonococcal infections\(^{(13)}\).

For the treatment of urethritis, specialized clinics in the city of Ribeirão Preto, use penicillin, azithromycin, ciprofloxacin and ceftriaxone. However, clinicians have noted some cases of treatment failure with the use of such antibiotics.

**OBJECTIVE**

Evaluate the occurrence of isolates of gonococcus and its in vitro susceptibility to antibiotics: penicillin, tetracycline, ofloxacin, ciprofloxacin and ceftriaxone, and determine its production of β-lactamase.

**METHODS**

This is a retrospective study of 93 patients of both genders, clinically suspected urethritis and/or gonococcal cervicitis, which appeared spontaneously in STD/AIDS Reference Center in the city of Ribeirão Preto, São Paulo State, Brazil, from September 2008 to May 2012. These patients signed an informed consent, agreeing to participate in the study, which was reviewed and approved by the opinion of CONEP number 5.071/2008.

A gonococcus isolate was included in the evaluation of antimicrobial susceptibility, in a culture recovered eye secretion of a newborn from a hospital in the city of Ribeirão Preto, which was sent to the Instituto Adolfo Lutz-RP (IAL-RP) for identification.

The culture method for the isolation and identification of Neisseria gonorrhoeae were according to the Brazilian Ministry of Health Manual recommendations\(^{(14)}\). The urethral secretion or endocervical swabs were collected from the patients and immediately spread in Thayer-Martin (selective) and chocolate agar (non-selective) culture media, and incubated in 5-10% of CO\(_2\) atmosphere. Part of secretion was collected with bacteriological loop for direct bacterioscopy. Samples were forwarded to the IAL-RP, where plates were incubated at 35-37°C for at least 48 hours, and then observed the growth of colonies suspected of gonococcus. The phenotypic identification has taken into consideration the colony morphology, the cell morphology (Gram-negative diplococci), the oxidase proof (positive), and the carbohydrates utilization in the Cystine Tryptic Agar - CTA medium: dextrose (positive), lactose (negative), sucrose (negative) and maltose (negative)\(^{(15)}\).

Direct bacterioscopy were realized by Gram stain and observed in immersion (1,000 x), in common optical microscope for the presence of Gram-negative intracellular diplococcal characteristic of gonococcus.

Antimicrobial sensitivity was evaluated by Minimum Inhibitory Concentration (MIC), using the episolometric test or E-test (Oxoid). The interpretation of results and reference values used for penicillin, tetracycline, ciprofloxacin, ofloxacin and ceftriaxone was based on the recommendations of the Clinical Laboratory Standards International (CLSI, 2009)\(^{(16)}\). For azithromycin the values considered were described in literature\(^{(17,18)}\). The Neisseria gonorrhoeae ATCC 49226 strain reference was used for the quality control of culture media and the CIM, as recommended by CLSI\(^{(16)}\).

The research of β-lactamase enzyme was determined by the cefinase disk method (Becton Dickinson), described by Swenson et al.\(^{(19)}\). In contact with cefinase disk β-lactamase enzymes producing strains break the β-lactam ring and produce a red color pigment.

The following control strains were used: Staphylococcus aureus (ATCC 29213): positive, and S. aureus (ATCC 25923): negative.

**RESULTS**

Of the 93 suspected cases of gonorrhea, 52 were men and 41 women, ranging from 14 to 62 years of age. Among the suspected cases 43% (n = 40) were diagnosed as positive for gonorrhea, and in two of them there was no growth in culture, and the diagnosis was made only by bacterioscopy. In three cases it was not possible to carry out the sensitivity test, due to the loss of viability of strains for the achievement of the MIC.

Among the suspected cases of gonorrhea 90% (n = 31) were male. The predominant age group (55%) was 21 to 30 years. The 14 to 20 years age group was the second most incident among the 40 patients with suspicion of gonorrhea, 15% (n = 6) were already in use of antibiotics and 17.5% (n = 7) showed some sort of associated pathology (Table 2).

**DISCUSSION**

In developing countries, STDs are among the five major diseases for which medical attention is sought\(^{(10,20)}\). STDs' control has been a concern for health authorities, mainly due to their increase in the young and adolescents\(^{(21,22)}\). In this study, it was observed that the 14 to 20 years age group was the second most incident among cases of gonorrhea.

Blocking of the transmission chain is among the main ways of control and prevention of STDs, as well as the appropriate treatment of infections and the proper management of partners\(^{(23)}\). Gonorrhea’s control is hampered by the large number of asym-
Table 2 – Associated pathologies and previous use of antibiotics in 40 suspected cases of gonorrhea

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated pathologies</td>
<td></td>
</tr>
<tr>
<td>HPV/condyloma</td>
<td>5% (n = 2)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>5% (n = 2)</td>
</tr>
<tr>
<td>HCV</td>
<td>2.5% (n = 1)</td>
</tr>
<tr>
<td>Ulcerated lesion</td>
<td>5% (n = 2)</td>
</tr>
<tr>
<td>Previous antibiotic therapy</td>
<td></td>
</tr>
<tr>
<td>Benzetacil</td>
<td>5% (n = 2)</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>5% (n = 2)</td>
</tr>
<tr>
<td>Azitromycin</td>
<td>2.5% (n = 1)</td>
</tr>
<tr>
<td>Ciprofloxacin + benzetacil</td>
<td>2.5% (n = 1)</td>
</tr>
</tbody>
</table>

HPV: human papillomavirus, HCV: hepatitis C virus.

Figure 1 – Distribution of 40 gonorrhea cases by age group.
coccus resistance to quinolone antibiotics occurs probably due to the use of inadequate dosage, in addition to the widespread use of these antibiotics for other infections(38).

The gonococcus isolates of this study were different from those studied in the city of Manaus. The results found in both locations were, respectively, related to the production of beta-lactamase enzyme (34.4% and 14.5%), resistance to penicillin (44.4% and 21.8%) and ciprofloxacin (36.1% and no fully resistant strain)(39).

Barreto et al. (2004), in Rio de Janeiro, alert to the use of penicillin, tetracycline and azithromycin in the treatment of gonorrhoea because found that 8.7% of gonococcal strains were beta-lactamase producing, to penicillin, 76.5% had intermediary resistance, 20.0% with reduced susceptibility to azithromycin and only 33.9% were fully sensitive to tetracycline(40).

For azithromycin, appropriate results in vitro have been recommended by Mehaffey et al.(27), considering the MIC with ≤ 2 μg/mL breakpoint. In this study it was observed that sensitivity decreased 19.4% to this antibiotic, following the recommendations of Dillon et al.(13), who have established the MIC with breakpoint = 0.25 to 1 μg/mL. Studies of Ferreira et al.(34) in 2004, found a resistance of 21.9%.

Azithromycin has been employed in the treatment of gonorrhoea as well as in the standardized treatment urethritis and cervicitis of uncertain cause or chlamydial infection. However, for treatment of chlamydial infection is recommended regimen azithromycin 1 g orally in a single dose, inadequate in cases of gonococcus infection, which may be favoring the emergence of resistance(34).

Due to the resistance of Neisseria gonorrhoeae to penicillin, tetracycline and quinolones (ofloxacin and ciprofloxacin) found in the present study, is not advised the use of these antimicrobials as first choice drugs for the treatment of gonorrhea. The CDC(13) and the World Health Organization(23) not recommend use of drugs whose strains exceed 5% resistance.

Acknowledgements

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Conflict of interest

Authors declared there is no conflict of interest.

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Antimicrobial Resistance in Neisseria gonorrhoeae Isolates from Ribeirão Preto, São Paulo, Brazil


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VULVOVAGINITIS AND THE TREATMENT OF ASYMPTOMATIC PARTNERS: A SYSTEMATIC REVIEW AND METAANALYSIS

Paulo César Giraldo¹, Hugo Marcus Rodrigues², Amanda G Melo², Rose Luce do Amaral³, Mauro Romero L Passos⁴, José Eleutério Junior⁴, Ana Katherine Gonçalves⁶

ABSTRACT

INTRODUCTION

Vulvovaginitis (VV) is a common complaint and one of the most frequent reasons patients seek gynecologistsⁱ. Annually, approximately 10 million consultations are attributed to symptoms and signs of vaginal discharge².

Despite VV being a very relevant condition to women due to the high personal and financial costs ensued, it is often minimized by women and the medical community. This repeatedly results in incorrect diagnosis and treatment by both women and doctors⁴, resulting in exaggerated use of antibiotics and antifungals.

The main causes of VV are well established: bacterial vaginosis (BV), vaginal candidiasis (VVC) and trichomoniasis (VT). However, several questions are debatable, such as best drug to be used, treatment regimen and most appropriate route of administration. Since VT has been confirmed as a sexually transmitted disease (STD), the treatment of an asymptomatic partner is uncontested⁴⁻⁵.

Some studies suggest that treatment of sexual partners of women with BV could reduce recurrence rates from 5% to 20%. However, data evaluating the efficacy of this practice is controversial⁶⁻⁸. In with BV, could reduce recurrence rates from 5% to 20%.

INTRODUCTION: treating sexual partners of women with vaginal candidiasis and bacterial vaginosis is an issue in debate. Despite the present recommendations of the international guidelines to not treat the asymptomatic sexual partners, this is a frequent practice between gynecologists. OBJECTIVE: evaluate the influence of treating asymptomatic sexual partner of women with recurrent vulvovaginitis. METHODS: databases searched: PubMed, Embase, Scielo and CINAHAL. Selection criteria: randomized clinical trials published from 1982 to 2012 were included. Studies involving pregnant women were excluded. Methodological quality was assessed using the Jadad scale. Data collection and analysis: Review Manager 5.1 was used for statistical analysis. Results: eight randomized clinical trials were included based on the chosen criteria: 1,088 women were enrolled. For bacterial vaginosis, the RR for cure was 1.00 (95%CI: 0.95–1.05) (p = 0.13), and for recurrence 0.84 (95%CI: 0.62–1.14) (p = 0.34). Vaginal candidiasis had a RR of 1.03 (95%CI: 0.94–1.14) (p = 0.48) for cure, and 1.02 (95%CI: 0.77–1.33) p = 0.91) for recurrence. Conclusion: treatment of asymptomatic sexual partners of women with vaginal candidiasis or bacterial vaginosis does not affect the cure or recurrence rates and may increase the risk of side effects and unnecessary financial costs.

Keywords: vulvovaginitis, bacterial vaginosis, candidiasis, partner, treatment

METHODS

OBJECTIVE

This study proposes to systematically evaluate the influence of asymptomatic partner treatment in the cure and recurrence of VV.

Inclusion criteria

Randomized controlled trials published in the last 30 years to assess the effectiveness of partner treatment in the cure and recurrence of VV.
Exclusion criteria

Women under 16 years of age, HIV+, pregnant, asymptomatic, and sex workers were excluded. These groups represent populations at increased or decreased risk for STDs, wherein the prevalence of disease differs from the general population. This could interfere with the sensitivity and/or specificity of the analysis in this review.

Search and selection of literature

Eligible studies were identified by searching the following databases: PubMed, Embase, Scielo, CINAHL, and Google Scholar. The studies were identified by a literature search of databases following medical subject heading terms and/or text words (Mesh Terms): (Treatment) AND (Vulvovaginitis) OR (Candidiasis) OR (Moniliasis) OR (Vaginitis, Monilia) OR (Vaginosis) OR (Vaginitis) OR (Trichomonas) AND (Partners) AND (randomized controlled trial) OR (clinical trial) OR (follow-up) OR (prospective) NOT (Pregnant Woman).

The bibliographies of the identified publications were reviewed for additional pertinent studies. No language restrictions were applied.

Two researchers (AKG and HMR) searched for articles published up to May 2012. After searching the databases, 513 potentially relevant papers were identified, 102 of which were excluded after review of titles. Next the abstracts of the 411 remaining titles were read, removing a further 313 titles. Of the 98 remaining articles, 8 were duplicated among the databases, which left 90 articles to be methodologically adequate when they obtained a score of 3 or more points by the Jadad scale(21). the Jadad scale considered studies to be high methodological quality and remained in the systematic review (Figure 1).

Data extraction

Several characteristics of the original articles were extracted and included in the systematic review. The data included the last name of the first author, the year of publication, country, number of subjects, type of VV studied as well as type of intervention and results.

Analysis

Statistical analysis was done using Review Manager (RevMan) 5.1 to provide a group analysis of the results of the selected clinical trials. The pooled analysis was obtained by analyzing the combined results of the chosen studies using the random effect model, and then testing for heterogeneity using the Chi-square test. The homogeneity of the selected studies was realized.

RESULTS

Bacterial vaginosis

Four randomized controlled trials were selected: Verjorop (1988)(10) conducted a major randomized double blind clinical trial with 117 women using 500 mg of metronidazole 2 x day for 7 days. Half of the partners were randomly treated with the same treatment regimen or a placebo. Cure and recurrence rates were similar among women with treated partners (cure: 51/54 and recurrence: 13/54) or placebo partners (cure: 44/53 and recurrence: 14/53) (Table 1).

Moi et al. (1989)(4) in another double-blind randomized controlled trial with 241 women who were treated with 2 g of metronidazole, and repeated 2 days later. The partners were randomly treated with the same dose of metronidazole. Cure and recurrence rates were similar among women with treated partners (cure: 115/119 and recurrence: 19/112) or placebo partners (cure: 111/113 and recurrence: 14/106) (Table 1).

Vutyavanich et al. (1993)(11) conducted a randomized clinical trial of 250 Thai women treated with 2 g of tinidazole and a partner randomly treated to placebo or tinidazole. Cure and recurrence rates were similar among women with treated partners (cure: 111/122 and recurrence: 43/117) or placebo partners (cure: 113/119 and recurrence: 33/126) (Table 1).

Colli et al. (1997)(12) carried out a randomized double-blind study with 131 Italian women who were treated with 2% clindamycin cream in the form of vaginal cream for 7 days. The partners were randomly treated with oral clindamycin or a placebo. Cure and recurrence rates were similar among women with treated partners (cure: 66/69 and recurrence: 5/38) or placebo partners (cure: 65/69 and recurrence: 9/32) (Table 1).

The total RR for cure and recurrence were similar among women whose partners were treated or not for BV: cure RR 1.00 (95% CI: 0.95-1.05) (p = 0.13) Recurrence RR 0.84 (95% CI: 0.62-1.14) (p = 0.34) (Figure 2).

Vaginal candidiasis

Bishop et al. (1986)(22) conducted a double blind randomized clinical trial in Belgium with 117 women treated with 200 mg of ketoconazole 2 x daily for 3 days whose partners were randomly treated with ketoconazole or placebo. Cure and recurrence rates were similar among women with treated partners (cure: 48/57 and recurrence: 13/48) or placebo partners (cure: 53/60 and recurrence: 19/53) (Table 1).

Figure 1 – Study selection cure.
Calderón-Marquez (1987)\textsuperscript{(23)} carried out a randomized double-blind study which included 44 women who used 50 mg itraconazole 2 x day for 5 days and their randomly treated partners. Cure and recurrence rates were similar among women with treated partners (cure: 17/20 and recurrence: 0/16) or placebo partners (cure: 15/19 and recurrence: 2/15) (Table 1).

Fong et al. (1992)\textsuperscript{(24)} conducted a randomized clinical trial with 54 Canadian women who received 400 mg of ketoconazole for 7 days. The partner received 200 mg of ketoconazole for 5 days, or a placebo. Cure rates and recurrence were similar among women with treated partners (cure: 26/28 and recurrence: 8/26) or placebo partners (cure: 15/19 and recurrence: 9/26) (Table 1).

Shihadeh et al. (2000)\textsuperscript{(25)} carried out a randomized clinical trial in Jordan with 144 women who received 400 mg of ketoconazole for 7 days. Half the partners received 400 mg ketoconazole for 7 days. Cure and recurrence rates were similar among women with treated partners (cure: 57/72 and recurrence: 35/57) or placebo partners (cure: 53/72 and recurrence: 28/53) (Table 1).

The total RR for cure and recurrence was similar among women whose partners were treated or not for VVC: cure RR 1.03 (95% CI: 0.94-1.14) (p = 0.48), recurrence RR 1.02 (95% CI: 0.77-1.33) (Figure 3).

### Vaginal trichomoniasis

Interestingly, in the last 30 years no trials have been performed evaluating the indication of treatment of partners of women with VT. The only randomized clinical trial was conducted over 30 years ago; it was not possible to include it in this study. In 1981 Lyng & Christensen\textsuperscript{(26)} conducted a randomized clinical trial with 118 women, which found that the persistence of the infection was significantly higher in the group which had no partner treatment (14/59) compared to the group which did (3/59) (RR: 0.21, 95% CI: 0.06-0.71). This difference persisted in the subgroup who resumed sex with untreated partners. More recently, in a study testing the efficacy of intravaginal nonoxynol 9 for VT, Antonelli et al. (2000)\textsuperscript{(27)} observed that women whose partners were treated with metronidazole showed better cure rates compared those whose partners went untreated. This study cannot be considered for this meta-analysis since the randomization, tracking was not described.

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### Table 1 – Characteristics of selected randomized clinical trials for BV and VVC

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Subjects</th>
<th>Randomized Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verjtorp (1988)</td>
<td>Denmark</td>
<td>107 non-pregnant women with BV</td>
<td>Women: 500 mg of metronidazol 2 x day/7 days Partners: 50% = same treatment, 50% = placebo</td>
<td>Treated cure: 51/54 Recurrence: 13/54</td>
</tr>
<tr>
<td>Moi (1989)</td>
<td>Denmark</td>
<td>241 non-pregnant women with BV</td>
<td>Women: 2 g of metronidazol 2 x day Partners: same treatment randomized</td>
<td>Treated cure: 115/119 Recurrence: 19/112</td>
</tr>
<tr>
<td>Vutyavanich (1993)</td>
<td>Thailand</td>
<td>250 non-pregnant women with BV</td>
<td>Women: 2 g of tinidazol Partners: randomized tinidazol or placebo</td>
<td>Treated cure: 111/122 Recurrence: 43/117</td>
</tr>
<tr>
<td>Colli (1997)</td>
<td>Italy</td>
<td>131 non-pregnant women with BV</td>
<td>Women: clindamycin 2% vaginal cream/ 7 days Partners: randomized oral clindamycin or placebo</td>
<td>Treated cure: 66/69 Recurrence: 5/38</td>
</tr>
<tr>
<td>Bishop (1986)</td>
<td>Belgium</td>
<td>117 non-pregnant women with VVC</td>
<td>Women: 200 mg 2 x day ketoconazole for 3 days Partners: randomized ketoconazole or placebo</td>
<td>Treated cure: 17/20 Recurrence: 0/16</td>
</tr>
<tr>
<td>Calderon-Marquez (1987)</td>
<td>Mexico</td>
<td>44 non-pregnant women with VVC</td>
<td>Women: 200 mg 2 x day ketoconazole for 3 days Partners: randomized ketoconazole or placebo</td>
<td>Treated cure: 17/20 Recurrence: 0/16</td>
</tr>
<tr>
<td>Fong (1992)</td>
<td>Canada</td>
<td>54 non-pregnant women with VVC</td>
<td>Women: 400 mg 2 x day ketoconazole for 7 days Partners: randomized 200 mg ketoconazole for 5 days</td>
<td>Treated cure: 26/28 Recurrence: 8/26</td>
</tr>
<tr>
<td>Shihadeh et al. (2000)</td>
<td>Jordan</td>
<td>144 non-pregnant women with VVC</td>
<td>Women: 400 mg 2 x day ketoconazole for 7 days Partners: half received randomized ketoconazole</td>
<td>Treated cure: 26/28 Recurrence: 8/26</td>
</tr>
</tbody>
</table>
DISCUSSION

The medical literature and most researchers suggest that sexual partners of women with VV should not be treated (27). However, some national health programs, including Brazilian health services, treat VV erroneously as a STD and leave treatment to the discretion of gynecologists. Unfortunately this results in over treatment which increases costs and causes unnecessary physical side effects. There are also serious social and emotional implications which cause conflict within the couple due to having transmitted a STD. Very few studies consider the latter or more importantly, the microbial resistance resulting from this practice.

Proponents of partner treatment argue that this practice could reduce recurrences in women as well as new transmissions. However our findings do not confirm these VT assertions. VT seems to be the only infectious VV wherein treating the partner increases the chances of cure and reduces recurrence. This being said, the only study that confirms this hypothesis, by Lyng & Christensen (26), was conducted in 1981. Besides this, it is accepted that VT is a protozoan and cannot be found in the vaginal cavity under normal conditions and is not part of the vaginal flora. It follows that VT must be treated in both parties.

We believe that the ban on placebo use in clinical trials in recent years has impeded randomized trials (28). Since VT is considered a STD the consequence of prescribing a placebo instead of the treatment is not ethically accepted. In vivo studies in animal models are a solution, even though they are difficult to perform. Even so, it is fundamental to encourage both studies in vitro and in animal models, which are already well known for VVC, but not yet established for BV.

Contrary to VT, BV and VVC are caused by microorganisms part of the normal microflora composition which sometimes assume the role of pathogens.

The pooled analysis suggested a slightly lowered risk of recurrence was from the group of women with partners treated for BV-RR 0.84 (95% CI: 0.62-1.14), however no statistically significant values were found for cure rates. There was no difference between the group of men who received a placebo and those who were treated-RR: 1.00 (95% CI: 0.95–1.05).

The pooled analysis of studies on VVC suggests that the evidence pointing to asymptomatic partner treatment is much weaker than for VB. The total RR for cure was 1.03 (95% CI: 0.94-1.14), and for recurrence 1.02 (95% CI: 0.77-1.33).
Therefore, it is evident from these results that partner treatment does not significantly influence the outcome of cure and/or recurrence rates of BV and VVC.

This evidence can help the General Practitioner to treat patients and their partners more adequately, thus avoiding the side effects of overtreatment.

Conflict of interest
No conflict of interest to declare.

REFERENCES
VIROLOGICAL AND EPIDEMIOLOGICAL ASPECTS OF ANAL CARCINOMA: CURRENT AND FUTURE CHALLENGES

Elisabete Dobao¹ & Silvia Maria B Cavalcanti²

ABSTRACT
Human papillomavirus infection, a sexually transmitted disease studied mainly in women due to its link to uterine cervical carcinoma, has become a health problem in men also, mainly by the significant increase of the prevalence and incidence of anal intraepithelial neoplasia and anal carcinoma in specific groups, such as men who have sex with men, HIV-seropositive and immunocompromised. The anal carcinoma, as cervical cancer, is associated with high-risk oncogenic HPV in 90% of cases, with HPV 16 as the predominant, followed by HPV 18. This fact occurs in a moment when there are no management protocols for HPV infection in the anal area, either preventive, diagnostic or therapeutic, and without an unique specialty that embraces the problem of HPV anogenital infection in men as does the gynecology for women, causing a dispersion of expertise. Added to this, there are still many doubts in the medical and general population about prophylactic vaccination for HPV in boys, and the absence of its distribution in a public health scale in most countries that still wait for statistical calculations to justify its use.

Keywords: HPV, anal carcinoma, HIV, STD, intraepithelial neoplasia

INTRODUCTION
The infection by the human papillomavirus (HPV) results of one of the most commonly transmitted diseases (STDs) at present time. In recent years, the male infection has increasingly become a research object(1) after the awareness that sexual transmission is the main way of dissemination to women and that men also take the consequences of anogenital HPV infection in the form of anogenital warts (AGW), penile intraepithelial neoplasia (PIN) and anal intraepithelial neoplasia (AIN) and carcinoma invader, added to the development of prophylactic vaccination for both genders.

Although benign, AGWs take on the psycho-social stigma character, often leading to depression and loss of quality of life, with a high social cost(2).

Penile carcinoma often occurs in men in their 60’s, with incidence ranging from 0.3 to 4.2/100,000, depending upon socioeconomic differences and religious conditions, reason why this pathology studies have low priority(3). However, anal carcinoma, which until recently were thought to arise as a result of chronic inflammatory intestine disease, has today on HPV infection its primary etiologic agent, being the high-risk types associated with approximately 90 cases of anal squamous cell carcinoma, and most of these associated with HPV 16, followed by HPV 18(4,5). Its incidence has been increasing in the general population around 2% per year(2), however, in some specific groups, such as men who have sex with men (MSM), HIV-seropositive men for the human immunodeficiency virus (HIV) and immunosuppressed, rates are more alarming – a recent study in San Diego shows the incidence of 224 per 100,000 individuals/year(6). To better understand this figure, we should mention that the incidence of UCC before the introduction of routine Pap smear examination was around 37/100,000 individuals/year(7).

Sorting through cytology, similar to Pap smear, has been progressed for anal carcinoma, however there is still no consensus on the reliability of the method(8). Physical examination with biopsy and histopathologic study is still considered a good option, although the visualization of sub-clinical lesions (anial intraepithelial neoplasias) most time is only possible with a set up view by a high resolution videocapsuloscope(9), a kind of examination not yet well known by other experts than Gynecologists(10).

The tests for the detection of viral nucleic acid have high sensitivity and specificity – like the polymerase chain reaction (PCR) and the capture of the hybrid (not available in all health services, mainly in public health) – and require knowledge about the viral behavior and the pathology in question, so that the interpretation of the results have a practical significance and not be just another inconvenience, with a waste of time and money.

ANAL INFECTION BY HPV
Transmission and epidemiology
HPV transmission occurs by direct contact of two surfaces, i.e., through the skin or mucous membrane microtrauma, exposing the epithelial basal layer. The main route of transmission is the sexual contact without the exclusive need for penetration, followed by episodes in which microtraumas may also occur. As the HPV are quite resistant to heat and drying, it is still possible a reduced transmission via contaminated fomite(11). HPV transmission does not occur through blood, since it doesn’t make viremia, or through ejaculation, except in the presence of urethral injury by HPV. Although it has already been detected in sperm, it has not been possible to prove its infectious potential in this circumstance(12). The potential transmission of HPV through seminal fluid raises the question of what might be possible for the transmission of HPV via sperm donation(13).

There is still no accurate HPV acquisition and elimination rates data, nor the incidence and duration of infection nor the production of antibodies in response to HPV infection in man. In Giuliano et al. study(12), the prevalence among men and women in the same age group would be between 52.8% and 53.8%, respectively. Also Giuliano et al.(11) in a recent prospective study, with heterosexual men aged between 18 and 44 years, points to the probability of 0.29% HPV infection per year.

According to Burd(10) and Frisch et al.(12), following are the main factors predisposing individuals to a greater risk of infection: pri-

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arily sexual activity at an early age, poor hygienic conditions, history of other STDs and multiple partners. It is estimated that the use of condom can prevent from 70% to 80% of transmissions and its effectiveness is not greater because condom does not cover all the anogenital area and it is very rarely used throughout time. Male circumcision is associated with a reduced risk of penile HPV infection, and a reduced risk of UCC on latest partners is observed on men with a history of multiple sexual partners.

According to Joseph et al., the incidence of anal carcinoma has been growing in the United States population, contrasting with the incidence of UCC, which has declined over the past 40 years. Among the risk factors for anal carcinoma are the history of AGW and the large number of partners, reflecting exposure to HPV and its various types, respectively. It is not surprising, therefore, that men who have history of receptive anal sex with men have a major risk for anal carcinoma. Before the epidemic of the Acquired Immunodeficiency Syndrome (Aids), in 1982, the incidence of anal carcinoma among MSM was estimated between 12.5 and 36.9/100,000 individuals/year, values almost as high as the incidence of UCC in the female general population before the introduction of cytology screening. But in a database study related to anal carcinoma and Aids, the relative risk of developing anal carcinoma among HIV-seropositive MSM was 37 times greater than in the general population. Comparing with the prevalence of uterine cervical infection by HPV, which decreases after the age of 30 years, the rate of anal HPV infection in MSM HIV-seronegative remains high (50% to 60%) and it is constant throughout life. This fact may be a reflection of the differences between the biology of the anal canal and uterine cervix, and probably the acquisition of new types of HPV may occur from a greater number of new sexual partners over time among MSM compared with women.

Prevalence studies have been made by some groups. After anal swabs analysis, more than 96% of MSM HIV-seropositives showed HPV DNA and this index drops to 60% in MSM HIV-seronegatives. Of HIV-seropositives patients, 81% had anal intraepithelial lesion, 52% of which of high-grade. In Bochum’s cross-sectional study, in Germany, 59.3% of the MSM HIV-seropositives presented intraepithelial lesions, 31.2% of which of high-grade.

Although anti-retroviral therapy (HAART) has decreased the mortality and the incidence of opportunistic infections in patients, studies show none or only a modest effect on the anal carcinoma, and point out that men and women with Aids have an increased risk of developing invasive anal carcinoma.

The site of infection

There is a similarity between the uterine cervical and the anal epithelium: the epithelial transformation area. In the cervix, this is the HPV’s target, where occurs the transition between two types of epithelium, the ectocervix squamous and the endocervical columnar. In the anus, this transition occurs when the anal squamous epithelium meets the rectum glandular epithelium. In these regions of active metaplasia there is a replacement of the glandular epithelium by the squamous. The metaplastic immature squamous epithelium is at greater danger of high-risk HPV infection, probably by the easiness of the virus to reach the basal cell bed.

The high-risk HPVs, particularly HPV 16, are etiologically associated with virtually all cervical carcinomas, and types 16 and 18, alone or in association, are present in 78% of all anal carcinomas. HPV 16 is present in 65% to 75% of anal carcinoma samples analyzed, followed by HPV 18. The populations considered high-risk for anal carcinoma are HIV-seropositive women and men, MSM, women with uterine cervical or vulvar carcinoma history and immunosuppressed. Anal cytology, like the annual or biannual Pap smear, is being studied as an alternative for the prevention of anal carcinoma in high-risk groups.

Chin-Hong et al. demonstrated that anal HPV infection in MSM may probably be associated with HIV acquisition. The mechanisms are not yet clear, however an important factor would be that the HPV-induced lesions are often brittle and susceptible to breakage of mucosal integrity during intercourse, with blood loss.

Anal carcinoma screening aims to identify and treat high-grade AIN and invasive squamous carcinoma. Following the cervical model, anal cytology can be used to detect precursor lesions, and in case of detection of atypical cells, be followed by a high-resolution videoanuscopy with directed biopsy. However, most clinicians and cytopathologists still have little experience of collecting and reading anal specimens respectively. Anal cytology should cover the entire anal canal, including mainly the transformation zone. The cells sample should be collected through a long swab of synthetic fiber, in circular motion, inserted into the anal canal and taken up after the dentate line and the distal rectal wall, always with firm pressure to touch all the anal wall. Conventional smears may be used, but the liquid-based preparation increases the efficiency of the sample, reducing fecal contamination and desiccation by air, which cause common artifacts in this type of examination.

Data published by the College of American Pathologists (CAP), in its annual disclosure of 2009, indicate that the categorization of anal HSIL cytology specimens is still problematic. In a recent study, only 61% of the blades showing anal HSIL were recognized by the specialists and compared with cervical cytology more than 85% of HSIL blades were correctly classified. It is worth mentioning that for the anal cytology reading, cytomorphology of gynecological lesions associated with HPV is used, and the employed terminology is that of Bethesda’s.

A retrospective Australian study examined the presence of AIN in all excised condylomatous lesions of most of HIV-seronegatives male patients during a period of 9 years in a clinic. HSIL lesions were present in the anal canal in 44% of 27 HIV-seropositive men (of these, 26 MSM), and 18% of 88 HIV-seronegative men (half supposedly heterosexual). The authors concluded that most HIV-seropositive men with untreated anal warts can develop anal carcinoma, a view that seems alarmist, but completely supported by epidemiological data available. This study clearly underlines the importance of anal warts treatment.
HIV infection in HIV-seropositive men

The prevalence of HPV infection with higher viral load and the presence of multiple types are greater in HIV-seropositive patients, resulting in a higher incidence of pathological conditions of worse prognosis. These patients also have lower resolution rate of latent infections by HPV or increased reactivation, with higher risk for all kinds of low and high intraepithelial neoplasia grades and carcinomas(30).

HIV-associated immunosuppression seems to play an important role in the pathogenesis of HPV in HIV-seropositive men, as the organic defense against HPV infection requires a competent cellular immunity, which is reduced during HIV infection(31). Other interaction mechanisms between HIV and HPV have been postulated, such as: the increased expression of cytokines (e.g., interleukin-6) known to modulate the expression of HPV genes that would allow its reactivation in keratinocytes when there is a latent infection; the increase of growth factors; the effect of HIV-1 Tat protein, which would intensify the E6 and E7 expression(32), and the activity of lymphocytes CD4+ T, also in E6 and E7, similar to that observed in other immunosuppressive conditions, leading to a decreased ability to detain HPV, which consequently will have its replication increased, keeping intact its epithelial proliferation(33,34). Low CD4+ T-lymphocyte count is associated with a statistically significant risk to increased incidence of invasive carcinoma, by infection with HPV among HIV-seropositive women and men(31).

Although there are no well-controlled studies demonstrating the latent infections reactivation, this seems to occur when immunocompetent patients move to conditions of immunosuppression, occurring during the use of steroids for long periods or in chronic diseases. It was observed that in celibate HIV-seropositive women, the count of lymphocytes CD4+ T was strongly associated with the detection of new types of HPV, presumably by reactivation of latent infection previously acquired(33). Herdman et al.(34) postulate the hypothesis that, during the latent HPV infection phase, some infected cells can contain both the integrated viral form and the episomal. However the factors of this possible reactivation are mostly unknown.

According to Meys et al.(35), inflammatory syndrome of immune reconstruction (ISIR) could also be seen as a cause of the persistence of HPV infection in HIV-seropositive individuals due to the change in the modulation of the cutaneous inflammatory response from the introduction of anti-retroviral therapy (HAART), when the improvement of cellular immunity occurs, producing reactions similar to those reverse reactions for leprosy, through mechanisms still misunderstood.

Several studies in recent years have shown that the incidence of induced carcinomas in HIV-seropositive population by infection with HPV has not diminished, despite the institution of HAART since 1996. The first indicator was the observation that the development of cervical and anal carcinoma is not directly related to the development of AIDS, unlike other malignant diseases associated with HIV, such as Kaposi’s sarcoma and non-Hodgkin’s lymphoma(3,16). In recent analysis, anal carcinoma is the only one which incidence is increasing among HIV-seropositive individuals in the United States of America (USA), from 19/100.000 individuals/year in the pre-HAART era to 78.2/100.000 individuals/year from 2000 to 2003(36), and 224/100.000 in a cohort study in San Diego(37).

Corroborating these findings, it was observed that the anal HPV infection and its consequent lesions have also high prevalence in HIV-seropositive women, observed by a cross-sectional prospective study with 167 women in the USA, where the prevalence of HPV infection was shown to be similar in the anus (38%) and uterine cervix (33%)(37). According to De Vuyst et al.(38), most cross-sectional studies shows that prevalence of HPV in the uterine cervix is higher in HIV-seropositive patients than in seronegatives, even after the elimination of bias factors, such as age and sexual behavior.

Treatment of anal lesion associated with HPV

Smaller lesions and perianal warts are usually easier to treat than larger lesions or anal canal. For the anal region, the common and well known therapies, such as the use of trichloroacetic acid 70%, electrocauterization, imiquimod or podophyllotoxin gel can be used for all injuries smaller than 1 cm² at the base. Larger lesions, especially in HIV-seropositive men have a higher rate of recurrence feature and evolution with high-grade lesions, and a study is usually necessary with an additional biopsy so the type of injury can be known(39).

All patients with perianal lesions and obligatorily HIV-seropositive immunosuppressed patients should always be referred for an evaluation by the coloproctologist. If injuries to anal canal are detected, they must be treated by this expert(39). Due to the local anatomical challenges, as the presence of hemorrhoids and crypts, it can be much more difficult to treat AIN, compared to CIN. As occurs in the cervical disease, the histology, the size of the lesion and its location are the determining factors that influence the type of treatment to be chosen. The AIN I, which probably does not advance directly to the invasive carcinoma, aims to reduce the risk of progression or increase of the injury in its early treatment, which would prevent the use of topical agents and would require a wider resection with greater morbidity.

Recent guidelines have been published for the treatment of AIN in the presence of HIV co-infection, which can always be treated in any grade. And in all patients, AIN II and III should be treated for prevention of invasive carcinoma(40). In 2007, the New York State Department of Public Health AIDS Institute recommended the digital anorectal touch and cytological examination during first appointment of HIV-seropositive MSM, and also of any patients with a history of AGW and in women with abnormal histopathological result in cervix and vulva too. Most early stage anal invaders carcinomas are easily palpable to the touch, even when asymptomatic, and are marked by the presence of hardening or thickening in the anal canal. Despite the low cost and the unnecessary technology, digital anal touch is unfortunately underused. Suspicion and search for anal carcinoma must be adopted by professionals as part of the routine clinical care in MSM and in people with AGW(40).

The self-examination without prior guidance can lead to an excessive fear due to patient’s non-acquaintance of prominences that can be part of his/her anatomy, as pilcomas and hemorrhoids. Therefore, first examination should be performed by a doctor, so that a parameter can be established by them both. Those who are unable or reluctant to self-examination should delegate the task to their doctors routinely. Proctoscopy, although desirable, is not strictly necessary, unless a nodule is detected(41).
Prophylactic vaccination

Sexual abstinence, mutual long-term fidelity and use of condoms were the only possible actions in the primary prevention of anogenital HPV infections until recently. Currently, the more effective weapon in primary prevention of HPV infection is the vaccination aimed at viral types most frequently responsible for anogenital lesions. Today there are two safe and effective vaccines for infections and diseases caused by HPV types contained in the products. Both of these use vectors that express the L1 gene of the virus, used successfully to generate VLP, that induce high titers of specific antibodies(33).

The quadrivalent vaccine approved by ANVISA (Brazilian Health Surveillance Agency) has four VLPs: 6, 11, 16 and 18 – viral types associated with AGW and carcinomas. In Brazil, it is released for use in women and men from 9 to 26 years of age(10).

The vaccine induced protection mechanism seems to be mediated mainly, if not entirely, by high concentrations of neutralizing antibodies (or ten times higher than the concentrations after natural infection). Prophylactic vaccination with L1 VLP has shown to be very effective in the prevention of primary infection, latent infection and associated diseases. However, serum concentrations of antibodies necessary to grant protection against this infection are unknown, therefore the period of protection given by vaccines continues to be indeterminate(33). In the Australian study to evaluate the quadrivalent vaccine, from a randomized double-blind trial with 1,781 males and females aged 9-15 years, 99.5% or more patients had high rate of antibodies in the serum in the seventh month after applying the third dose, a rate also above the natural infection(42).

So far the effectiveness of prophylactic vaccination against HPV infection in men is still unknown and results from various studies are expected to occur in a near future(33). Farley et al. study in Australia, in 2009(43), observed a sharp reduction of AGW among women in the target age group in the year following the implementation of a national programme of vaccination against HPV, a decrease that clearly differed from previous trends in clinical diagnostics. Another subgroup which showed a modest decrease of AGW presented by this same study was the heterosexual men group, and remarkably there was no difference in the AGW diagnosis in the studied period between gay men or women outside the age range eligible for free vaccination. The quadrivalent vaccine has also shown efficacy against infection in heterosexual men and MSM between 16 and 26 years of age. In a randomized trial with 4,065 people, the quadrivalent vaccine efficacy against AGW was of 89.4%. Further analysis of effectiveness of the vaccine in MSM (n = 602; age: 16-26 years) confirms the benefits of HPV vaccination in reducing the burden of anogenital HPV infection and incidence of AGW (79.0%). However, the most anticipated data are about the impact both of the vaccine on AIN and the inclusion of male in vaccination programs.

The potential impact of vaccination programs is estimated via mathematical modeling. This model predicts that a vaccination programme for children of 12 years of age, male and female, would prevent 90 cases of UCC until 2055, compared with 71 cases with the vaccination programme solely aimed at girls up to 15 years of age(33). No model predicted the impact of a vaccination programme for all about the rates of penile carcinoma, anal, male and female, or of any impact on oropharyngeal carcinoma.

It is obvious thinking that the incorporation of men in a routine vaccination against HPV will probably reduce the burden of the disease not only in men, but also in women, and would help eliminate the stigma that focuses on the disease in women. However, considering public health, we recognize that the cost-benefit analysis is necessary to determine the effectiveness of these programs for the general population. Such analyses shall be fundamental in guiding the conception, acceptance and implementation of those programmes in clinical practice(42).

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CASE REPORT

A 38 years old male patient, infected by human immunodeficiency virus (HIV) for six years and six months, without adhering to antiretroviral therapy since diagnosis, he presented the main complaint as “the presence of a wound on his penis” for 30 days. Initially it was diagnosed as “candidiasis” in a service, and was treated with ketoconazole 200 mg/day and nystatin 100.000 IU (units per gram) cream for 10 days without clinical improvement.

Then in another service it was requested VDRL(1) (Venereal Disease Research Laboratory) and FTA-Abs (fluorescent treponemal antibody absorption) with negative results, diagnosed with HSV (Herpes simplex virus) infection he used acyclovir 200 mg, 5 x/day, PO, for 7 days, with no difference to the same lesion. In another appointment with a dermatologist, after anamnesis the patient stated that he did not have an exclusive steady partner, he had a sporadic use of condoms and his last sexual intercourse had occurred 20 days before the onset of the lesion. His CD4 (CD4 lymphocytes) count was 250 mm³ and HIV viral load 90,000 copies/mm³ and he was under use of Highly Active Antiretroviral Therapy (tenofovir, lamivudine and efavirenz).

Clinical examination showed a lesion in the glans of the penis involving the urethral meatus, with raised edges, well defined, measuring about 3.0 cm in diameter and clean background, odorless, with right inguinal lymphadenopathy, suggestive of “syphilitic hard chancre” (Figure 1 – A and B). VDRL titling was conducted with 1/8 and value of 1/16 after 10 days. Benzathine penicillin was prescribed and the patient refused the treatment. However, the patient was seen by another professional who prescribed after diagnosis doxycycline 100 mg po 12/12 h for 14 days (2), which was followed showing complete regression of the lesion in 3 weeks. Even without making use of penicillin and azithromycin, he performed control of cure with no treponemal serology quantitative test for 3 in 3 months during the first year and then was discharged (3).

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