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Prevalence and Significance of Vaginal Group B Streptococcus Colonization in Pregnant Women from Osijek, Croatia

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ABSTRACT

The aim of the study was to determine the prevalence of vaginal group B streptococcus (GBS) colonization in pregnant women from Osijek area, the possible effect of GBS colonization on pregnancy outcome and neonatal complications and the role of intrapartum prophylaxis in this context. This retrospective case-control study took place at the Department of Gynecology and Obstetrics, Osijek University Hospital Center from December 2003 to June 2006. A total of 118 pregnant women was enrolled in study and divided into two groups: 59 women in 35th–37th week of gestation, free from risk factors for infection (control group); and 59 women in 25th–41st week of gestation with risk factors for infection. Low vaginal swab for GBS isolation and identification on selective and enriched medium was obtained from each woman. GBS colonization was recorded in 29 (24.6%) women: 12 (20.3%) control and 17 (28.8%) women at risk of infection, yielding a statistically non-significant difference ($\chi^2=1.480489; p<0.48$). Early neonatal infection was observed in six (20.7%) neonates born to 29 mothers with GBS colonization, pointing to a correlation between vaginal GBS colonization and early neonatal infection ($\chi^2=88.68; p<0.001$); however, gestational age and pregnancy outcome were not influenced by GBS colonization. In eight (36.4%) newborns, early neonatal infection developed in spite of intrapartum administration of antibiotics; three of these children were born to GBS positive mothers, and perinatal GBS infection was demonstrated in one (0.84%) child. Study results revealed a relatively high rate of GBS colonization in the population of pregnant women in Croatia, occasionally leading to early neonatal infection. Large studies are needed to develop national strategy for the prevention of GBS infection in Croatia.

Key words: group B streptococcus (GBS), pregnancy, neonatal infection, early neonatal group B streptococcal septicemia (ENGBSS), prevention

Introduction

The prevalence of genital system colonization with beta-hemolytic serogroup B streptococcus (group B streptococcus, GBS) is estimated to 5–40% of healthy women, varying among different populations. Vaginal or rectal GBS colonization, found in 10–30% of pregnant women, can cause puerperal sepsis, vaginitis, urinary infections in otherwise normal individuals, skin infections and endocarditis.

In the 1990s, guidelines for the prevention of neonatal GBS infection were developed in most western European countries and the USA, which have resulted in a significant reduction in the incidence of these infections in these countries. In spite of this favorable tendency, GBS remains the major cause of neonatal morbidity and mortality of infectious etiology in the western world.
In newborns, the disease develops as early-onset neonatal infection within the first 7 days of birth or as the late-onset form that develops at 7 or more days of birth. Neonatal infection manifests with sepsis, pneumonia and meningitis, however, soft tissue and bone infection may also occur. 1,4,5 The mean rate of GBS transmission to newborns is 60% (40–70%). Early-onset neonatal infection is recorded in 1–3% of children born to mothers with GBS colonization. 1 The newborn’s passage through the infected birth canal may result in GBS induced early neonatal septicemia, with a mortality rate of 20–30%. 6 Early-onset neonatal disease caused by GBS accounts for 80% of all GBS infections in childhood and is associated with severe neurologic sequelae in 5% of cases. 7

Late-onset neonatal disease results from horizontal transmission, with a prevalence of 1.3–1.6/1000 newborns. 1 The pathogenesis of this form of GBS caused disease is less known. In some cases, it develops upon microorganism acquisition during the newborn’s passage through the birth canal. 1

The risk factors that can lead to the development of early neonatal group B streptococcal sepsicaemia (ENGBSS) are well defined. Besides maternal vaginal swab positive for GBS, the following factors can result in an increased incidence of early-onset neonatal infection: amniotic sac rupture for more than 18 hours, premature delivery (<37 weeks), amniotic sac rupture before 37th week of gestation, body temperature at delivery of 38 °C or more, GBS in urine during pregnancy, and neonate born with ENGSS. 8,9 Although vaccination of pregnant women against GBS in urine during pregnancy, and neonate born with GBS colonization is an additional risk factor for premature delivery, untimely amniotic sac rupture, positive urinary culture and development of early-onset neonatal infection of the newborn; and to determine correlation of GBS positive urinary culture and vaginal GBS colonization.

Materials and Methods

The study included 118 pregnant women from the Osijek area, east Croatia, followed-up at the Department of Gynecology and Obstetrics, Osijek University Hospital Center; between December 2003 and June 2006. Study women were divided into two groups: control group consisting of 59 pregnant women at 35th to 37th week of gestation, free from risk factors for GBS infection, examined and followed-up at Outpatient Obstetric Clinic, Department of Gynecology and Obstetrics, Osijek University Hospital Center; vaginal swab was obtained on routine follow-up examination; and study group consisting of 59 pregnant women at 23th to 41th week of gestation, with risk factors for GBS infection (premature delivery, untimely amniotic sac rupture, body temperature >38 °C, signs of intra-amniotic infection, urinary culture positive for GBS, hospitalized at Division of Pregnancy Pathology, Department of Gynecology and Obstetrics, Osijek University Hospital Center; vaginal swab was obtained on hospital admission.

The two groups of pregnant women were analyzed according to age, number of deliveries, level of education, marital status, gestational age, newborn sex, type of delivery, number of fetal/neonatal deaths, birth weight, Apgar score, and early neonatal period of their infants. The prevalence of vaginal GBS colonization was determined in both study groups. The early neonatal period was monitored and newborns with clinical signs of perinatal infection were analyzed. The diagnosis of perinatal infection was based on clinical picture, laboratory test findings and microbiology of blood culture, urinary culture, gastric aspirate and tip of tube. In neonates with perinatal infection, comparison with the maternal gestational vaginal swab microbiology findings, GBS positive in particular, and with/without intrapartum antibiotic prophylaxis was performed.
Urinary culture was done in all women exhibiting signs of urinary tract infection. The sample for vaginal colonization testing was obtained without the use of speculum, i.e. the swab was obtained through introitus by wiping the inferior vaginal wall and anus\textsuperscript{11,12}. Isolation and identification of the grown bacteria were performed at laboratory of microbiology, according to Centers for Disease Control and Prevention (CDC) recommendations\textsuperscript{11,12}. All samples were incubated in aerobic conditions at a temperature of 37°C in selective and enriched Todd-Hewitt buillon with the addition of gentamicin (8 mg/L) and nalidixic acid (15 mg/L). Then, sample subcultivation on solid nutritive medium (streptococcus selective agar, Biolife, Italy; Todd-Hewitt broth, Biolife, Italy) was performed. Gram-positive catalase-negative cocci with a narrow β hemolysis zone were tested by the method of latex agglutination, a standard microbiology method for identification of group B streptococci (Prolex TM, latex agglutination system, Streptococcal Grouping Latex kit for identification of groups A, B, C, D, F or G streptococci; Pro-lab Diagnostics, Canada).

Prior to enrolment in the study, each woman was thoroughly informed on the objectives and purpose of the study, and gave her informed consent for inclusion. The study was approved by the Osijek School of Medicine Ethics Committee, and all procedures used in the study were performed in line with ethical standards, recommendations of the Osijek School of Medicine Ethics Committee and Helsinki Declaration provisions.

Statistical analysis of the data obtained was performed by use of the specialized Statistica 6.0, StatSoft Inc. software, processed by the methods of descriptive statistics and compared by use of \( \chi^2 \)-test and Spearman correlation coefficient.

**Results**

The group of pregnant women free from risk factors after 35\textsuperscript{th} week of gestation (control group) and the group of women with the presence of risk factors (premature delivery with or without untimely amniotic sac rupture, premature amniotic sac rupture for >18 hours, elevated body temperature, signs of intra-amniotic infection, positive urinary culture, and delivery of a newborn with ENGBSS in history) were statistically significantly comparable according to all epidemiological variables (age, sequence of deliveries, level of education, marital status, type of delivery, and newborn age and Apgar score). Analysis according to gestational age revealed a high statistically significant between-group difference in gestational age and newborn birth weight. The rate of premature delivery (below 37\textsuperscript{th} week of gestation) was 5.1\% in the control group versus 61.0\% in the group at risk (\( \chi^2=30.26; p<0.001 \)). The newborn birth weight of ≤ 2500 g was recorded in 5.1\% and 42.4\% of control group and risk group women, respectively (\( \chi^2=19.37; p<0.001 \)).

Microbiology of low vaginal swab revealed GBS colonization in a total of 29 (24.6\%) women, including 12 (20.3\%) control group women and 17 (28.8\%) risk group women (\( \chi^2=1.48; p<0.48 \)), yielding no statistically significant between-group difference (Table 1).

Early neonatal period in children born to mothers with GBS colonization is illustrated in Table 2. Signs of early-onset neonatal infection were observed in six (20.7\%) newborns of 29 GBS colonized mothers. Spearman correlation coefficient (\( r_s=0.99 \)) indicated very high mathematical correlation between vaginal GBS colonization and early neonatal infection irrespective of the causative agent identified.

Clinical and laboratory signs of early-onset perinatal infection were found in 22 (18.6\%) newborns (Table 1), i.e. five (8.5\%) newborns from the control group and 17 (28.8\%) newborns from the risk group (\( \chi^2=88.68; p<0.001 \)). These results pointed to a high, statistically significant between-group difference in the presence of risk factors, while at the same time suggesting the presence of risk factors to be independent of vaginal colonization. This in turn implied that bacterial colonization had no effect on gestational age and pregnancy outcome.

Eight (36.4\%) of 22 newborns with the signs of early-onset neonatal infection including four children born to GBS positive mothers had received intrapartum antibiotic prophylaxis. The causative agent was isolated in three (75.0\%) and GBS infection was demonstrated in one (0.84\%) of these four newborns (Table 3).

Positive urinary culture was found in 26 (50.0\%) of 52 women exhibiting symptoms of urinary tract infection (Table 4). GBS was isolated in 12 (23.1\%) women exhibiting symptoms of urinary tract infection irrespective of the causative agent identified.

The correlation of GBS positive urinary culture and vaginal GBS colonization is shown in Table 5. Vaginal GBS colonization in pregnancy is shown in Table 6. The presence of risk factors was associated with a statistically significant increase in the rate of vaginal colonization.

**TABLE 1**

<table>
<thead>
<tr>
<th>Vaginal GBS colonization</th>
<th>Control group (%)</th>
<th>Risk group (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) positive</td>
<td>12 (20.3)</td>
<td>17 (28.8)</td>
<td>29 (24.6)</td>
</tr>
<tr>
<td>(-) negative</td>
<td>47 (79.7)</td>
<td>42 (71.2)</td>
<td>89 (75.4)</td>
</tr>
<tr>
<td>Total</td>
<td>59 (100.0)</td>
<td>59 (100.0)</td>
<td>118 (100.0)</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Control group (%)</th>
<th>Risk group (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>1 (8.3)</td>
<td>5 (29.4)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td>Normal finding</td>
<td>11 (91.7)</td>
<td>10 (58.8)</td>
<td>21 (72.3)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (100.0)</td>
<td>17 (100.0)</td>
<td>29 (100.0)</td>
</tr>
</tbody>
</table>
tion was present in 12 women with GBS positive urinary culture, pointing to their high correlation (rs=0.99) whereby the likelihood of vaginal colonization considerably increased with positive urinary culture.

Discussion and Conclusion

Although being normal commensal and part of the complex microflora of the gastrointestinal and genitourinary tract, *Streptococcus agalactiae* (GBS) is a major cause of severe neonatal infections. Some 10% to 35% of pregnant and non-pregnant women are (mostly asymptomatic) GBS carriers. The increasing utilization of antibiotics as the only prophylaxis currently available, especially in cases of penicillin hypersensitivity, is a matter of growing concern about the increasing bacterial resistance, thus questioning the efficacy of intrapartum prophylaxis. In addition, it remains obscure why GBS causes colonization in some pregnant women and leads to infection in others; colonization density, virulence variability among GBS clones and infection sensitivity of the host play a role in the development of infection.

In Croatia, there are no data or systematic monitoring of the prevalence of neonatal disease irrespective of the causative agent, including the prevalence of neonatal infection caused by GBS. There is no consensus on the monitoring of pregnant and non-pregnant women with GBS colonization either.

On comparison of the group of pregnant women with risk factors with control group, the rate of women with GBS colonization was not statistically significantly higher in the former. However, the risk of early-onset neonatal infection was statistically significantly increased by the presence of GBS colonization in the group of women with risk factors, but had no impact on the term (presence of risk factors in the antenatal period) and outcome.
of delivery. Our study results suggested that vaginal GBS colonization significantly increased the likelihood of early neonatal disease in the newborn irrespective of the causative agent, since more than 20% of children born to mothers with GBS colonization developed this neonatal disease.

Furthermore, the use of intrapartum antibiotic prophylaxis (either with or without bacterial colonization) was found to fail to prevent the onset of early neonatal disease with certainty, since over one-third (36.4%) of children developed the disease in spite of prophylaxis. Despite prophylaxis, at least one causative agent, including GBS in one child, was demonstrated in three of four (75.0%) children born to GBS positive mothers. These findings have opened an array of other issues in the field. Namely, due to the lack of rapid tests such as PCR, including antibiotic sensitivity of the causative agents, in daily routine, intrapartum antibiotic prophylaxis is generally administrated on the basis of individual assessment and experience, *ex iuvantibus*. In our study, results of swab testing were not known during labor, in the group at risk in particular, because rapid tests were not available and intrapartum prophylaxis was not used, not even in women with verified bacterial colonization. On the other hand, the prophylaxis administered without the antibiotic sensitivity report (of GBS and other agents) was, conceivably, only partially efficient. In addition, the possible development of resistance, hypersensitivity reaction to antibiotic therapy and GBS substitution by another causative agent(s), gram-negative in particular, should always be considered.

Correlation was also found between GBS positive urinary culture and vaginal GBS colonization, whereby the former increased the likelihood of the latter; accordingly, GBS positive urinary culture should be considered as an indication for prompt therapy introduction, as suggested by most literature reports\(^{19}\). A meta-analysis of the prevalence of vaginal GBS colonization in 24,093 women from 13 European countries, reported in 2008, found it to range from 6.5 to 36.0%, but exceeding 20.0% in one-third of the studies included\(^3\). The same report describes regional variations in the prevalence of vaginal GBS colonization among particular regions of Europe, i.e. 19.7–29.3% in eastern Europe, 11.0–21.0% in western Europe, 24.3–36.0% in northern Europe, Scandinavia in particular, and 6.5–32.0% in southern Europe\(^5\). Data obtained in our study on vaginal GBS colonization recorded in 24.6% of study women are comparable with these data, yet indicating the rate of GBS colonization in Croatian women to exceed the rate recorded in western European countries.

Our study as the first of the kind in Croatia suffered from some limitations. Verified additional and independent risk factors such as diabetes\(^{20}\), increased body mass index\(^{21}\), intensity of sexual activities and number of partners\(^{22,23}\), increased number of examinations and of intravaginal and intruterine manipulations in general\(^{24}\) were not taken in consideration and should be involved in future studies.

CDC has issued recommendations for the prophylaxis of GBS infection\(^{11,12,25}\). Based on these recommendations and epidemiological studies, national strategies for the prevention of GBS infections, aimed at identification of pregnant women at a high risk of neonatal GBS infection in their newborns, have been developed in a number of countries, e.g., Canada, UK, Ireland, Australia, etc.\(^{23,26,27}\). In Croatia, data on the prevalence of GBS colonization and early neonatal infection, GBS induced in particular, should first be collected at the national and regional level to start considering development of the procedure algorithm for GBS colonization. This would certainly require large-scale and comprehensive studies. In addition, in the era characterized by the need of the most cost-effective and at the same time highly efficient and efficacious health care, the question arises whether it is reasonable to perform any preventive actions if the incidence of ENGBSS is lower than 0.6 per 1000 live births\(^{11,12}\).

Anyhow, respective studies should be continued and extended in Croatia. The announced introduction of a GBS vaccine to be administered to pregnant women\(^{1,10}\) while also protecting the newborns is perceived as a definitive solution, although the issues of indications, route and timing of administration remain open. Maternal immunization against GBS appears to settle at long-term the problem of prevention of neonatal sepsis, premature delivery and growth retardation in children\(^{28,29}\). GBS type Ia, Ib and III capsular polysaccharides appear to be efficient in the induction of type-specific antibodies in healthy vaccinated pregnant women\(^{28}\). Antibodies to GBS surface protein also contribute to the protection from neonatal infection\(^{28}\). The GBS type Ia, II, III and V vaccine is expected to provide protection from more than 90% of infections, suggesting that the program of GBS vaccination should take in consideration geographical variations as well as monitoring of the prevalence GBS serotypes as major guidelines to identify the components of a polyvalent GBS vaccine\(^7\). Along with the development of polyvalent GBS vaccine, the question arises of vaccination timing, since vaccination in pregnancy is certainly controversial. Therefore, vaccination could potentially be performed in women of reproductive age before pregnancy, could be offered to adolescents, or even included in regular pediatric immunization\(^{28}\).

In conclusion, GBS colonization of pregnant women in Croatia is a complex problem because of its potential severe sequels for both the mother and the child on the one hand, and for the need of savings in health care in general while ensuring the most efficient health care for this vulnerable population group on the other hand. Therefore, it is necessary for both clinicians and public health professionals to be involved in solving the issue because definitive conclusions on the development of the national program of prevention of GBS infections and on the type of health care measures to be included in such a program under current conditions can only be made upon large-scale and comprehensive epidemiological studies.
Cijel istraživanja bio je utvrđeno učestalost kolonizacije rodnice streptokokom grupe B (GBS) trudnica grada Osijeka. Istražiti ima li utvrđena kolonizacija i kakav utjecaj na ishod trudnoće te na nastanak komplikacija kod rođene djece, te uzet je donji vaginalni obrisak radi izolacije i identifikacije GBS na selektivnoj i obogaćenoj podlozi. Kolonizacija GBS-om značajna pojava u populaciji trudnica, koja u određenog broja trudnica može rezultirati razvojem rane neonatalne infekcije, što govori o korelaciji kolonizacije rodnice GBS-om i rane neonatalne infekcije (rs=0.99).

UČESTALOST I ZNAČAJ KOLONIZACIJE RODNICE STREPTOKOKOM GRUPE B TRUDNICA S RIZIČNIH ~IMBENICA ZA INFEC~NJU U ~ESTALOST I ZNA~AJ KOLONIZACIJE RODNICE GBS-OM, RIZIČnih ~IMBENICA I RANE INFEC~NJU

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SAŽETAK

Cijel istraživanja bio je utvrđeno učestalost kolonizacije rodnice streptokokom grupe B (GBS) trudnica grada Osijeka. Istražiti ima li utvrđena kolonizacija i kakav utjecaj na ishod trudnoće te na nastanak komplikacija kod rođene djece, te kakav je kod toga uloga i značaj intrapartalne profilakse. Među trudnicama s područja grada Osijeka praćen je donji vaginalni obrisak radi izolacije i identifikacije GBS na selektivnoj i obogaćenoj podlozi. Kolonizacija GBS-om značajna pojava u populaciji trudnica, koja u određenog broja trudnica može rezultirati razvojem rane neonatalne infekcije, što govori o korelaciji kolonizacije rodnice GBS-om i rane neonatalne infekcije (rs=0.99).