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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Group B streptococcus in obstetrics: unsolved problems

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Abstract. For several decades, among all possible pathogens of neonatal infections, group B streptococcus has been one of the leading positions. Sepsis, meningitis, and pneumonia are among the most common clinical manifestations of neonatal infection associated with group B streptococcus. In this review, our goal was to analyze the literature demonstrating a worldwide approach to the prevention of vertical transmission of group B streptococcus from mother to child. When writing the review, scientific publications of foreign and domestic authors from the PubMed database were studied. The review considers the drugs of choice for intranatal antibiotic prophylaxis, and their pharmacodynamic, and pharmacokinetic features. The analysis details the problem of the growth of resistance of group B streptococcus to antibacterial drugs. The antimicrobial activity of lactoferrin was noted at a minimum inhibitory concentration of 500 μg/ml. The presented review also reflects the protective and therapeutic effects of oral intake of probiotics containing *Lactobacillus acidophilus*, *Lactobacillus salivarius*, *Lactobacillus rhamnosus GR-1*, and *Lactobacillus reuteri RC-14*. Based on the analysis, it can be concluded that penicillin G and ampicillin have the most pronounced bactericidal effect against group B streptococcus. At the same time, the most common side effects of β-lactam penicillins include an allergic reaction with the possible development of anaphylactic shock. Given this, the antibiotics of the first-line reserve group include cefazolin, clindamycin, and vancomycin. At the same time, it is important to take into account the decrease in the therapeutic concentration of clindamycin with a change in the alpha-1-acid glycoprotein in the blood of the mother and fetus, the nephrotoxic effect of vancomycin and the cross-allergic reaction of cefazolin with antibiotics of the penicillin group. A promising direction in solving the problem of group B streptococcus is the development of new strategies for the prevention of perinatal infection of the fetus and newborn based on a more detailed study of the effects of lactoferrin and probiotics.

Key words: group B streptococcus, neonatal infections, antibiotic sensitivity, antibiotic resistance

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Introduction

Back in the 1970s, group B streptococcus became the leading cause of neonatal morbidity and mortality [1–3] with an intrauterine infection rate of 2–3 cases per 1000 live births [4] and a mortality rate of up to 50 % [3]. Depending on the timing of manifestation, two clinical forms of group B streptococcus (GBS) infection in newborns are distinguished: early (up to 7 days of life) and late (from 7 days to 3 months of life) [4, 5]. Clinical manifestations are more often represented by sepsis, meningitis, and pneumonia, and less often by lymphadenitis, conjunctivitis, and osteomyelitis [6–8].

Pharmacokinetics and pharmacodynamics of intranatal antibiotic prophylaxis

The widespread use of intranatal antibiotic prophylaxis has reduced the rate of early neonatal GBS infection from 1.7 to 0.22 ‰ [9]. At the same time, the resistance of *S. agalactiea* to antibacterial drugs has increased, which is a global problem in the public health system. In European and American countries, for intranatal antibiotic prophylaxis of vertical transmission of GBS from mother to child, penicillin G is recommended as a first-line drug according to the scheme: 5 million units starting dosage, followed by intravenous administration of 2.5 million units every 4 hours until the end of labor [10].

The effectiveness of the bactericidal properties of penicillin G according to the recommended scheme for the prevention of vertical transmission of GBS from mother to child was demonstrated in a clinical study by S. Scasso et al. (2015). Scientists using high-performance liquid chromatography determined the concentration of penicillin G in cord blood and amniotic fluid.

The results obtained made it possible to plot the concentration-time pharmacokinetic curve (Figure 1) [11]. The authors noted that the maximum inhibitory concentration of penicillin G in cord blood and amniotic fluid was reached after 195 minutes, which amounted to 5.6 μg/ml and 5.2 μg/ml, respectively. When comparing the results of rectovaginal cultures of a woman in labor and the concentration of penicillin G, it was found that 2 hours after the start of intravenous antibiotic prophylaxis, penicillin G inhibits the growth of GBS in 53 %, and after 4 hours the bactericidal effect is achieved in 88 % [11].

At the same time, penicillin G is not used as an antibiotic prophylaxis in childbirth in the Russian Federation. According to the clinical guidelines «Singleton birth, spontaneous delivery in the occipital presentation» dated July 6, 2021, women in labor with identified GBS in the urogenital tract are recommended to receive an initial dose of ampicillin 2000 mg intravenously, then 1000 mg every 4 hours until the end of labor [12]. Ampicillin, unlike penicillin G, has a wider spectrum of antimicrobial activity [13]. The effectiveness of the bactericidal properties of ampicillin was proven in a clinical study by A. Berardi et al (2017) [13]. Scientists using high-performance liquid chromatography evaluated the level of ampicillin concentration in umbilical cord blood depending on

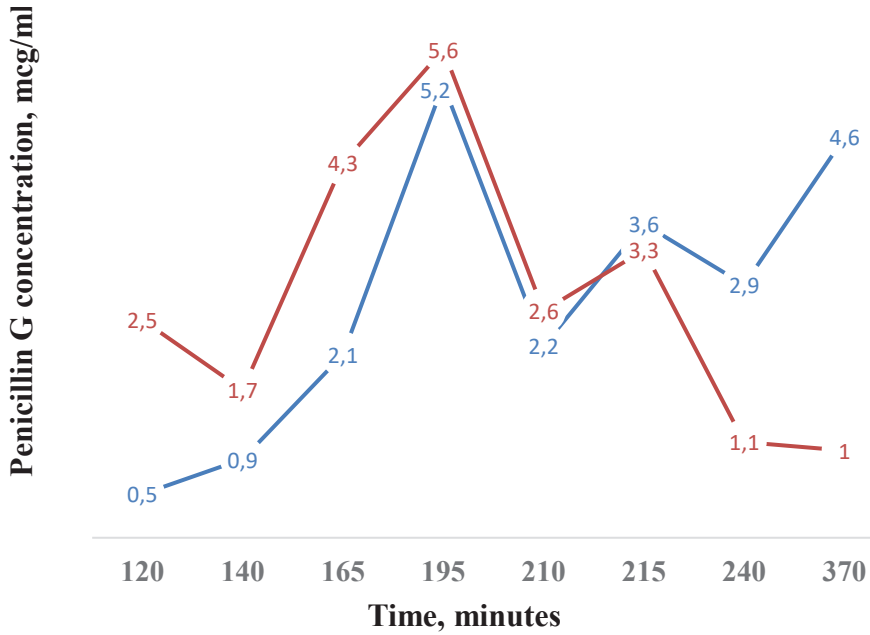

Fig. 1. Pharmacokinetic curve «concentration-time» of penicillin G [11]

the duration of intranatal antibiotic prophylaxis. The achievement of the maximum inhibitory concentration of ampicillin in cord blood was noted 30 minutes after the start of the introduction of the starting dose of ampicillin 2000 mg. It has been proven that the bactericidal effect of the antibiotic persists in the serum of a newborn for 4–5 hours after birth [14]. Penicillin G and ampicillin have high clinical activity and low toxicity [13].

The presence of the β-lactam ring causes a strong bactericidal effect due to disruption of the synthesis of bacterial cell wall components [13]. At the same time, the most common side effects of β-lactam penicillins include an allergic reaction with the possible development of anaphylactic shock [15]. Other manifestations of an allergic reaction are skin peeling, itching, urticaria, rhinitis, conjunctivitis, Quincke's edema, rarely — fever, arthralgia, eosinophilia, erythematous and maculopapular rash, erythema multiforme exudative, Stevens-Johnson syndrome [15]. Because of this, when prescribing an antibiotic during childbirth to prevent vertical transmission of GBS from the mother, the child needs a thorough collection of an allergological history and close monitoring of the woman in labor in the first 30 minutes from the start of administration [13].

Prescribing second-line antibiotics to prevent mother-to-child transmission of GBS during childbirth is based on two principles: information about the presence of an allergic reaction to penicillin G/ampicillin and sensitivity of GBS to clindamycin [10]. First-line reserve group antibiotics include cefazolin, clindamycin, and vancomycin [12]. Dosages and frequency of drug administration are unanimously approved throughout the world and do not cause controversy. At the same time, many issues are the subject of discussion.

Cefazolin belongs to the first generation of cephalosporins [13]. It has been proven that cefazolin with a minimum inhibitory concentration (MIC90) of 0.5 μg/ml inhibits the growth of GBS > 90 % [16]. T. Mitchell et al. (2001) 1–2–4–6 hours before planned operative delivery, cefazolin 1.0 g was administered intravenously once and the concentration of cefazolin in the blood plasma of a pregnant woman, in the amniotic fluid and umbilical cord blood at the time of delivery was determined by high-performance liquid chromatography. It was noted that in all samples the concentration of cefazolin exceeded the MIC90, which amounted to 0.96

μg/ml in the blood plasma of a pregnant woman (95 % CI 0.89–1.0), in umbilical cord blood 0.96 μg/ml (95 % CI 0 .89–1.0) and the amniotic fluid 0.9 μg/ml (0.95 % CI 0.77–1.0) [16]. The presented data emphasize the bacteriostatic properties of cefazolin, manifested in the ability to inhibit the growth of GBS even after 6 hours from the moment of administration of the antibiotic. At the same time, there are conflicting data on the pharmacokinetics of cefazolin during pregnancy. In physiologically developing pregnancy, an increase in glomerular filtration rate is noted.

A. Philipson et al. (1987) noted an increase in the clearance of cefazolin by 57 % during pregnancy compared with non-pregnant patients [17].On the contrary, in a clinical study by J. Popovic et al.(2007), no statistically significant differences were found in the data obtained [18]. At the same time, it was shown that 70–95 % of cefazolin is excreted by the kidneys due to glomerular filtration, and renal clearance is directly proportional to the clearance of cefazolin [13], which corresponds to the data of A. Philipson et al. [17]. Limited data on the pharmacokinetics of cefazolin during pregnancy require a more detailed study.

Clindamycin has a bacteriostatic effect [18]. Antibiotic prophylaxis during childbirth can be prescribed according to the scheme: clindamycin 900 mg every 8 hours until the end of labor [10]. At the same time, C.D. Wear et al. argue that the therapeutic concentration of clindamycin in the blood of the fetus can be achieved only with repeated administration of the antibiotic at least 6 hours before birth [20]. Clindamycin binds primarily to alpha-1-acid glycoprotein [21]. Plasma protein binding is concentration dependent and ranges from 60 to 94 % at therapeutic serum concentrations [13]. Changes in the level of alpha-1-acid glycoprotein in the blood of the mother and fetus alter the pharmacokinetics of clindamycin, which may affect the effectiveness of the bacteriostatic action of antibiotic prophylaxis [21].

With GBS resistance to clindamycin or a high risk of developing an allergic reaction to β-lactam antibiotics, women with GBS are prescribed an antibiotic from the group of cyclic glycopeptides — vancomycin [10]. C.N. Onwuchuruba et al. (2014) determined the concentration of vancomycin in maternal and cord blood at various dosing regimens [22]. With intravenous antibiotic prophylaxis in childbirth according to the scheme vancomycin 1.0 g every 12 hours, the therapeutic concentration of vancomycin is set at 32 % in the blood of the woman in labor and 9 % in the umbilical cord blood. At a dosage of vancomycin 15 mg/kg every 12 hours, the therapeutic concentration was observed at 50 % in the blood of the woman in labor and 33 % in the umbilical cord blood. The dosing regimen of vancomycin 20 mg/kg every 8 hours proved to be the most optimal for the prevention of vertical transmission of GBS from mother to child, and the therapeutic concentration of the antibiotic was achieved in more than 80 % of cases [22].

C.V. Towers et al. in solidarity with the conclusions of C.N. Onwuchuruba et al. and also highlighted the efficacy of the proposed intravenous vancomycin regimen for intranatal antibiotic prophylaxis of GBS. In a clinical study by C.V. Towers et al., indicators of the maximum inhibitory concentration in the blood of a woman in labor and cord blood were established, which amounted to 44.4 μg/ml and 27.4 μg/ml [23]. It was noted that the results obtained were above the minimum inhibitory concentration of vancomycin (>1 μg/ml) for suppressing the growth of GBS, which again emphasizes the effectiveness of vancomycin [23].

Knowledge of the pharmacokinetic characteristics of antibiotics in the mother-placenta-fetus system plays a key role in the dosing schedule and frequency of antibiotic administration to suppress the growth of GBS. However, it is important to monitor the resistance of GBS to the above antibacterial drugs. If in a clinical study by Y. López et al. (2017) noted 100 % sensitivity of GBS to penicillin, ampicillin, and vancomycin [24], but the clinical work of S. Assefa et al. (2018) published the results of GBS resistance to penicillin, ampicillin, and vancomycin, which amounted to 19.5 %, 14.6 %, and 17 %, respectively [25]. A clinical study by M. Ábrók et al. (2019) in the period from 2012–2018. also highlights the growing resistance of GBS to antibacterial drugs. It was noted that the antibiotic resistance of GBS to erythromycin and clindamycin increased from 29.2 % to 39.7 % and from 30.2 % to

38.7 %, respectively [26]. Several of other works also demonstrate the resistance of GBS to macrolides and lincosamides [27, 28], which emphasizes the importance of determining the sensitivity of GBS to antibacterial drugs with the determination of the minimum inhibitory concentration.

Modern methods of prevention of group B streptococcus

Given the growing resistance of GBS to antibacterial drugs, it is necessary to develop new methods for the prevention of GBS in obstetrics. The effectiveness of antiseptic agents for the prevention of vertical transmission of GBS from mother to child was demonstrated in the clinical work of J.J. Hijona et al. (2018) [29]. The day before a «programmed birth», a woman with GBS colonization was vaginally injected with a tablet with the active ingredient dequalinium chloride 10 mg. It was noted that the number of women colonized with GBS on the day of delivery decreased by 57.21 %, which demonstrates the cost-effectiveness of the use in clinical practice [29]. At the same time, chlorhexidine proved to be an ineffective method for the prevention of GBS in pregnant women [30].

Many scientific studies demonstrate that lactoferrin can be used as a prebiotic for the prevention of neonatal GBS infections. Lactoferrin is a globular glycoprotein of the transferrin family [31]. It is produced in high concentrations in breast milk [32, 33]. It has been proven that lactoferrin at a concentration of 500 μg/ml has antimicrobial activity and inhibits the growth of GBS [34]. Lactoferrin supplementation in late pregnancy may be a promising tool to improve pregnancy outcomes and neonatal GBS infections.

L. Hanson (2022) recommends taking oral probiotics as a prevention to reducing the growth of GBS in pregnant women. In a clinical study, pregnant women with GBS colonization from the 28th week of pregnancy took 1 capsule of daily by the mouth of the Floragen3 probiotic. It was noted that in 15.3 % of women at 36 weeks gestation, the GBS carrier status changed from positive to negative [35].

M. Ho et al. (2016) also studied the effectiveness of oral probiotics in pregnancy. Pregnant women with diagnosed GBS colonization at 35–37 weeks of gestation before delivery took 2 probiotic capsules daily before bedtime, containing *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14* strains. At the time of admission to the maternity hospital, 42.9 % of women were diagnosed with a negative recto-vaginal smear for GBS [36].

Y. Liu et al. (2020) also noted a decrease in the colonization of pregnant GBS against the background of oral intake of probiotics containing strains of *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14* [37]. No less interesting data were obtained in a clinical study by V. Martin (2019). Pregnant women with GBS colonization from 26–38 weeks daily took a probiotic containing *Lactobacillus salivarius* by mouth 1 capsule daily. It was established that at 38 weeks of pregnancy, the rectal swab was negative in 72 % of cases, and the vaginal swab was negative in 68 % of cases [38].

Conclusion

To date, intrapartum antibiotic prophylaxis remains the only effective method for preventing mother-to-child transmission of GBS. The rise of antibiotic resistance is a global health problem. A promising direction in solving the problem of GBS is the development of new strategies for the prevention of perinatal infection of the fetus and newborn based on a more detailed study of the effects of lactoferrin and probiotics and the development of new technologies for the treatment of perinatal infections associated with GBS.

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Стрептококк группы В в акушерстве: нерешенные проблемы

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Аннотация. На протяжении нескольких десятилетий среди всех возможных возбудителей неонатальных инфекций стрептококк группы В занимает одну из ведущих позиций. Сепсис, менингит и пневмонию относят к наиболее частым клиническим проявлениям неонатальной инфекции, ассоциированной стрептококком группы В. В рамках данного обзора перед нами стояла цель — провести анализ литературных источников, демонстрирующих всемирный подход к профилактике вертикальной трансмиссии стрептококка группы В от матери ребенку. При написании обзора изучены научные публикации зарубежных и отечественных авторов из базы данных PubMed. В обзоре рассмотрены препараты выбора для проведения интранатальной антибиотикопрофилактики, их фармакодинамические и фармакокинетические особенности. При анализе детализирована проблема роста резистентности стрептококка группы В к антибактериальным препаратам. Отмечена антимикробная активность лактоферрина в минимальной ингибирующей концентрации 500 мкг/мл. Также в представленной работе отражены протективные и терапевтические эффекты перорального приема пробиотиков, содержащих *Lactobacillus acidophilus, Lactobacillus salivarius, Lactobacillus rhamnosus GR-1* и *Lactobacillus reuteri RC-14*. На основании анализа можно сделать вывод, что пенициллин G и ампициллин оказывают наиболее выраженное бактерицидное действие против стрептококка группы В. При этом к наиболее частым побочным эффектам β-лактамных пенициллинов относят аллергическую реакцию с возможным развитием анафилактического шока. Ввиду

этого, к антибиотикам группы резерва первой линии относят: цефазолин, клиндамицин и ванкомицин. Вместе с тем важно учитывать снижение терапевтической концентрации клиндамицина при изменении показателя альфа-1-кислого гликопротеина в крови матери и плода, нефротоксическое действие ванкомицина и перекрестную аллергическую реакцию цефазолина с антибиотиками группы пенициллинов. Перспективным направлением в решении проблемы стрептококка группы В является разработка новых стратегий профилактики перинатального инфицирования плода и новорожденного на основе более детального изучения эффектов лактоферрина и пробиотиков.

Ключевые слова: стрептококк группы В, неонатальные инфекции, антибиотикочувствительность, антибиотикорезистентность

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