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MODERN ANTIBIOTIC THERAPY REGIMENS IN CHORIOAMNIONITIS: EFFICACY AND PERINATAL OUTCOMES

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Abstract: Background: Chorioamnionitis (intra-amniotic infection) is a serious complication of pregnancy associated with significant maternal and neonatal morbidity. The optimal antibiotic regimen to mitigate these risks, particularly in the context of increasing antimicrobial resistance in the Fergana Valley, remains a subject of debate. This study compares the efficacy of a standard dual-therapy regimen versus an enhanced triple-therapy regimen. Methods: A prospective randomized controlled trial was conducted involving 150 pregnant women diagnosed with clinical chorioamnionitis. Participants were divided into two groups: Group A (n=75) received the standard regimen (Ampicillin + Gentamicin), while Group B (n=75) received an enhanced regimen (Ampicillin + Gentamicin + Clindamycin). Outcomes measured included time to defervescence, incidence of postpartum endometritis, and neonatal early-onset sepsis. Results: Group B demonstrated a significantly lower rate of postpartum endometritis (4.0% vs. 13.3%, $p < 0.05$) and wound infections following cesarean section compared to Group A. Time to maternal defervescence was shorter in Group B (3.5 ± 1.2 hours) vs Group A (5.8 ± 1.5 hours). Neonatal outcomes were comparable, but the triple-therapy group showed a trend towards reduced NICU admissions for suspected sepsis. Conclusion: The addition of an anaerobic agent (Clindamycin) to the standard Ampicillin/Gentamicin regimen provides superior maternal coverage, significantly reducing postpartum infectious complications, especially in women undergoing cesarean delivery.
Keywords: Chorioamnionitis, intra-amniotic infection, antibiotic therapy, Ampicillin, Gentamicin, Clindamycin, neonatal sepsis.

XORIOAMNIONITDA ANTIBIOTIK TERAPIYANING ZAMONAVIY SXEMALARI: SAMARADORLIK VA PERINATAL NATIJALAR

Annotatsiya: Kirish: Xorioamnionit (intra-amniotik infeksiya) ona va chaqaloq kasallanishining jiddiy oshishiga olib keluvchi homiladorlik asoratidir. Farg‘ona vodiysida mikroorganizmlarning antibiotiklarga chidamliligi oshib borayotgan sharoitda ushbu xavflarni kamaytirish uchun optimal antibiotik sxemasini tanlash munozarali bo‘lib qolmoqda. Ushbu tadqiqot standart ikki komponentli terapiya va kuchaytirilgan uch komponentli terapiya sxemalarining samaradorligini taqqoslaydi. Usullar: Klinik xorioamnionit tashxisi qo‘yilgan 150 nafar homilador ayol ishtirokida prospektiv randomizatsiyalangan nazoratli tadqiqot o‘tkazildi. Ishtirokchilar ikki guruhga bo‘lindi: A guruhi (n=75) standart sxema (Ampitsillin + Gentamitsin) oldi, B guruhi (n=75) esa kuchaytirilgan sxema (Ampitsillin + Gentamitsin + Klindamitsin) qabul qildi. Isitmaning tushish vaqti, tug‘ruqdan keyingi endometrit va chaqaloqlarda erta sepsis uchrash darajasi baholandi. Natijalar: B guruhida A guruhiga nisbatan tug‘ruqdan keyingi endometrit

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(4,0% ga 13,3%, p < 0.05) va kesar kesishdan keyingi jarohat infeksiyalari sezilarli darajada kam kuzatildi. Onada tana haroratining normallashish vaqti B guruhida qisqaroq bo‘ldi (3,5 ± 1,2 soat va 5,8 ± 1,5 soat). Neonatal natijalar o‘xshash bo‘ldi, ammo uch komponentli terapiya guruhida sepsis gumoni bilan reanimatsiyaga yotqizishlar kamayish tendensiyasiga ega bo‘ldi. Xulosa: Standart Ampitsillin/Gentamitsin sxemasiga anaerob agent (Klindamitsin) qo‘shilishi onani yaxshiroq himoya qiladi va ayniqsa kesar kesish orqali tug‘ruqlarda tug‘ruqdan keyingi infeksion asoratlarni sezilarli darajada kamaytiradi.
Kalit so‘zlar: Xorioamnionit, intra-amniotik infeksiya, antibiotik terapiya, Ampitsillin, Gentamitsin, Klindamitsin, neonatal sepsis.

СОВРЕМЕННЫЕ СХЕМЫ АНТИБИОТИКОТЕРАПИИ ПРИ ХОРИОАМНИОНИТЕ: ЭФФЕКТИВНОСТЬ И ПЕРИНАТАЛЬНЫЕ ИСХОДЫ

Аннотация: Введение: Хориоамнионит (интраамниотическая инфекция) является серьезным осложнением беременности, связанным со значительной материнской и неонатальной заболеваемостью. Оптимальная схема антибиотикотерапии для снижения этих рисков, особенно в условиях растущей устойчивости к противомикробным препаратам в Ферганской долине, остается предметом дискуссий. В данном исследовании сравнивается эффективность стандартной двухкомпонентной терапии и усиленной трехкомпонентной схемы. Методы: Было проведено проспективное рандомизированное контролируемое исследование с участием 150 беременных женщин с диагнозом клинический хориоамнионит. Участницы были разделены на две группы: группа А (n=75) получала стандартную схему (Ампициллин + Гентамицин), а группа Б (n=75) получала усиленную схему (Ампициллин + Гентамицин + Клиндамицин). Оценивались время до нормализации температуры, частота послеродового эндометрита и ранний неонатальный сепсис. Результаты: В группе Б наблюдалась значительно более низкая частота послеродового эндометрита (4,0% против 13,3%, p < 0.05) и раневых инфекций после кесарева сечения по сравнению с группой А. Время до нормализации температуры у матери было короче в группе Б (3,5 ± 1,2 часа) против группы А (5,8 ± 1,5 часа). Неонатальные исходы были сопоставимы, но в группе тройной терапии наблюдалась тенденция к снижению поступления в ОРИТ с подозрением на сепсис. Заключение: Добавление анаэробного агента (Клиндамицина) к стандартной схеме Ампициллин/Гентамицин обеспечивает лучшую защиту матери, значительно снижая послеродовые инфекционные осложнения, особенно у женщин, перенесших кесарево сечение.
Ключевые слова: Хориоамнионит, интраамниотическая инфекция, антибиотикотерапия, Ампициллин, Гентамицин, Клиндамицин, неонатальный сепсис.

INTRODUCTION

Chorioamnionitis, recently reclassified by major international bodies as Intrauterine Inflammation or Infection or both (Triple I), represents one of the most critical obstetric emergencies. It is defined as an acute inflammation of the membranes (chorion and amnion) and the placenta, typically resulting from an ascending polymicrobial bacterial infection from the lower genital tract. This condition complicates approximately 1-4% of all pregnancies at term

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but is seen in up to 40-70% of preterm births, particularly in cases of Premature Rupture of Membranes (PROM). In the Andijan region, where managing PROM remains a frequent clinical challenge, chorioamnionitis is a leading driver of maternal admissions to intensive care units and neonatal morbidity.

The clinical significance of chorioamnionitis cannot be overstated. For the mother, it transforms a physiological process (labor) into a pathological state of sepsis. The infected uterus becomes atonic, dramatically increasing the risk of postpartum hemorrhage (PPH), which is the leading cause of maternal mortality in Uzbekistan. Furthermore, if a Cesarean section becomes necessary—which is often the case due to dysfunctional labor associated with infection—the risk of surgical site infection, pelvic abscess, and sepsis skyrockets compared to non-infected surgeries.

For the fetus, the implications are equally dire. The fetus is exposed to a "cytokine storm" within the amniotic fluid. This Fetal Inflammatory Response Syndrome (FIRS) is mechanistically linked to white matter injury in the brain (periventricular leukomalacia), leading to long-term neurodevelopmental disabilities such as Cerebral Palsy. Additionally, early-onset neonatal sepsis and pneumonia are direct consequences of aspirating infected amniotic fluid.

Historically, the standard of care for intrapartum antibiotic prophylaxis has been the dual combination of Ampicillin (to cover Gram-positive organisms like *Group B Streptococcus* and *Listeria*) and Gentamicin (to cover Gram-negative organisms like *E. coli* and *Klebsiella*). While this regimen is effective for many aerobic pathogens, it leaves a significant "coverage gap." The vaginal microbiome is rich in anaerobic organisms (e.g., *Bacteroides*, *Prevotella*, *Gardnerella*, *Ureaplasma*) which are resistant to aminoglycosides and penicillins. In the context of a Cesarean section, these anaerobes thrive in devitalized tissue, driving severe postpartum infections. With the rising global rates of antimicrobial resistance and the high C-section rates in high-risk pregnancies, this study posits that the traditional dual regimen is no longer sufficient. We aim to evaluate whether "modernizing" the protocol by adding a potent anti-anaerobic agent (Clindamycin) improves maternal and neonatal clinical outcomes in our local setting.

LITERATURE REVIEW

Changing Etiology and the "Polymicrobial Biofilm" Chorioamnionitis is rarely a monomicrobial infection. Recent advanced microbiological studies using 16S rRNA gene sequencing have revealed that the amniotic fluid in chorioamnionitis often contains complex communities of bacteria, including fastidious anaerobes that are missed by standard culture techniques. *Ureaplasma urealyticum* and *Mycoplasma hominis* are isolated in nearly 50% of cases and are intrinsically resistant to beta-lactams (Ampicillin). Furthermore, bacteria often form biofilms on the amniotic membranes, making them up to 1000 times more resistant to antibiotics than planktonic bacteria. This biological reality necessitates antibiotic regimens with high tissue penetration and intracellular activity.

Current Guidelines and Contradictions There is a lack of global consensus on the optimal regimen.

WHO (2015): Recommends Ampicillin and Gentamicin as first-line but acknowledges the need for anaerobic coverage during C-sections.

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ACOG (Committee Opinion 712): Recommends Ampicillin + Gentamicin for vaginal delivery, but explicitly adds Clindamycin or Metronidazole for women undergoing Cesarean delivery to reduce endometritis.
Local Practice: In many hospitals in the Fergana Valley, the addition of the third agent is often delayed until *after* the surgery or reserved for severe sepsis, rather than being used as standard intrapartum prophylaxis. This delay potentially allows the seeding of surgical wounds with anaerobes.
Pharmacokinetics in Pregnancy: Why Standard Dosing Fails Pregnancy induces profound physiological changes that alter drug metabolism: increased plasma volume (dilution), increased renal blood flow (rapid elimination), and altered protein binding. *Roberts et al.* emphasize that standard non-pregnant doses of antibiotics are often sub-therapeutic in laboring women. For example, Gentamicin dosing must be weight-based (5 mg/kg) and given daily to maximize the "concentration-dependent killing" effect while minimizing toxicity. Fixed doses (e.g., 80mg) are largely ineffective in obstetrics.
The Role of Clindamycin Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit. Unlike Ampicillin, which relies on cell wall destruction (often releasing endotoxins), Clindamycin inhibits the production of bacterial toxins (e.g., from *Staph. aureus* or *Streptococcus*). This "anti-toxin" effect may be crucial in blunting the inflammatory response (FIRS). Additionally, it has excellent anaerobic coverage against *Bacteroides fragilis*, the primary culprit in pelvic abscesses. Comparing Clindamycin vs. Metronidazole, Clindamycin offers the added benefit of covering Gram-positive cocci (including some MRSA strains), which is valuable for incision site prophylaxis.

MATERIALS AND METHODS

Study Design A prospective randomized controlled trial was conducted at the Andijan Regional Perinatal Center (2023-2024).
Participants 150 pregnant women (>24 weeks gestation) diagnosed with clinical chorioamnionitis were enrolled. Diagnostic Criteria (Gibbs Criteria) -Maternal fever (>38°C) PLUS at least two of: maternal tachycardia (>100 bpm), fetal tachycardia (>160 bpm), uterine tenderness, foul-smelling amniotic fluid, or maternal leukocytosis (>15,000/mm³). Exclusion Criteria - Allergy to penicillins/aminoglycosides, pre-existing sepsis from non-uterine source.
Interventions Patients were randomized upon diagnosis: Group A (Standard Dual Therapy, n=75) - IV Ampicillin 2 g q6h. IV Gentamicin 5 mg/kg q24h. Group B (Enhanced Triple Therapy, n=75) - IV Ampicillin 2 g q6h. IV Gentamicin 5 mg/kg q24h. IV Clindamycin 900 mg q8h (or Metronidazole 500mg q8h if Clindamycin unavailable).
Note: Therapy continued until 24 hours afebrile postpartum.
Maternal: Time to defervescence (fever resolution), postpartum endometritis, wound infection, postpartum hemorrhage (PPH).
Neonatal: APGAR scores, NICU admission, proven early-onset sepsis (positive blood culture).
Statistical Analysis - Data were analyzed using SPSS v26. Significance was set at $p < 0.05$.

RESULTS

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Demographics and Mode of Delivery Both groups were similar in age and gestational age. The rate of Cesarean section was high in both groups (approx. 45%), typical for chorioamnionitis cases due to dysfunctional labor.
Maternal Outcomes Group B showed superior infection control.

Table 1: Maternal Infectious Morbidity

Outcome	Group A (Dual)	Group B (Triple)	P-value
Time to Defervescence (hours)	5.8 ± 1.5	3.5 ± 1.2	<0.01
Postpartum Endometritis	13.3% (10/75)	4.0% (3/75)	<0.05
Wound Infection (in C-section cases)	18.2%	5.8%	<0.05
Postpartum Hemorrhage	12.0%	8.0%	0.42

The addition of Clindamycin reduced the risk of endometritis by nearly 70%.
Neonatal Outcomes Neonatal outcomes were largely driven by gestational age, but trends favored Group B. NICU Admission: 32% in Group A vs 28% in Group B. Culture-Proven Sepsis: 8% in Group A vs 5.3% in Group B (difference not statistically significant). Pneumonia: Incidence was similar, suggesting that transplacental passage of Ampicillin/Gentamicin is the primary factor for fetal protection, and anaerobic coverage mainly benefits the mother.

DISCUSSION

This study validates the shift towards broader coverage for chorioamnionitis in the Andijan region. The standard Ampicillin+Gentamicin regimen leaves a gap in coverage against anaerobes (*Bacteroides*, *Prevotella*), which are abundant in the amniotic fluid of women with prolonged rupture of membranes.
Maternal Safety: The significant reduction in endometritis and wound infections in Group B confirms that anaerobic bacteria play a major role in postpartum complications. This is particularly crucial given the high C-section rate in this population; the surgical incision provides an entry point for skin flora and anaerobes.
Fever Resolution: The faster lysis of fever in Group B suggests a more rapid reduction in bacterial load and cytokine release. This "cooling" effect is vital, as maternal fever is an independent risk factor for neonatal brain injury (cerebral palsy).
Choice of Agent: While some protocols suggest Metronidazole, we preferred Clindamycin (where available) due to its better tissue penetration and coverage of Gram-positive cocci, though Metronidazole remains a cost-effective alternative.

CONCLUSION

The era of "one size fits all" dual antibiotic therapy for chorioamnionitis must evolve to meet the challenges of modern obstetrics, particularly the high rate of surgical deliveries.
Superior Efficacy - The addition of Clindamycin to the standard Ampicillin/Gentamicin regimen creates a robust "Triple Therapy" that significantly reduces maternal infectious morbidity (endometritis and wound infections) without increasing adverse effects.
Surgical Prophylaxis - In the context of Cesarean section, anaerobic coverage is not optional but mandatory. The standard dual regimen fails to protect the surgical site from polymicrobial anaerobic invasion.
Neonatal Benefit - While direct sepsis rates were statistically similar, the rapid reduction in

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maternal fever load in the Triple Therapy group offers potential neuroprotective benefits to the fetus by limiting exposure to hyperthermia and inflammatory cytokines.

RECOMMENDATIONS

Based on the findings of this study and the current global evidence base, we propose the following updates to clinical practice in the Andijan region:

1. Protocol Update:

Triple Therapy as Standard: For all women diagnosed with chorioamnionitis who are undergoing Cesarean Section, the antibiotic protocol must immediately include anaerobic coverage. The recommended regimen is:

Ampicillin 2g IV q6h (OR Cefazolin 2g IV q8h for mild penicillin allergy).

Gentamicin 5mg/kg IV q24h (Single daily dosing is superior to divided doses).

Clindamycin 900mg IV q8h OR Metronidazole 500mg IV q8h.

Vaginal Delivery: For women delivering vaginally, the addition of Clindamycin should be strongly considered if there is prolonged rupture of membranes (>18 hours) or foul-smelling amniotic fluid.

2. Implementation:

"Door-to-Needle" Time: Antibiotics should be initiated *during labor*, as soon as the diagnosis is made. Do not wait until after cord clamping. Intrapartum administration reduces neonatal sepsis and maternal bacteremia.

Duration: Continue antibiotics for at least one dose postpartum. If the patient is afebrile and asymptomatic for 24 hours, antibiotics can be stopped without transitioning to oral therapy.

3. Specific Considerations:

Penicillin Anaphylaxis: For patients with a history of severe penicillin allergy (anaphylaxis), the regimen should be Vancomycin (1g IV q12h) + Gentamicin + Clindamycin.

Fever Management: Use antipyretics (Paracetamol) aggressively alongside antibiotics to lower maternal temperature and protect the fetal brain.

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