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Review Article

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A Review of the Value of Prophylactic Treatment of Maternal Infections Using Azithromycin in Women Undergoing Planned Vaginal Delivery

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Abstract

Aim: Puerperal infections are associated with significant maternal as well as neonatal morbidity and mortality. Puerperal sepsis, which results from infection during pregnancy, childbirth, abortion, or after delivery, is a growing problem in underdeveloped and developing countries. Azithromycin is a broad-spectrum antibiotic and its efficacy as an adjunctive prophylaxis in the cesarean section has been established. This review aims to understand the use of azithromycin prophylaxis in women undergoing planned vaginal delivery, and its place in therapy in resource-constrained settings.

Methods: The articles were sourced from databases like PubMed, Google Scholar, and websites for health agencies, and the literature search was performed methodically. The selected articles focused on puerperal infections, puerperal sepsis, antibiotic prophylaxis, macrolides, azithromycin, and its safety, and efficacy of azithromycin in puerperal infections, particularly puerperal sepsis.

Results: Antibiotics are prescribed in low-resource healthcare settings to overcome the increased risk of puerperal infections as well as the limitations of the healthcare system. Antibiotic prophylaxis involves using broad-spectrum antibiotics to prevent infections. Recent studies have demonstrated the efficacy of a single dose of 2g of azithromycin in reducing maternal sepsis or death in women planning vaginal birth.

Conclusion: Azithromycin could be an important and economical choice for preventing puerperal sepsis in women undergoing planned vaginal delivery.

Keywords: Azithromycin; Antibiotic prophylaxis; Maternal infections; Neonatal infections; Puerperal sepsis; Vaginal delivery

Abbreviations: **A-PLUS:** Azithromycin Prevention in Labour Use Study; **MMR:** Maternal Mortality Ratio; **MRSA:** Methicillin-resistant Staphylococcus aureus; **MHRA:** Medicines and Healthcare Products Regulatory Agency; **SDGs:** Sustainable Development Goals; **UN:** United Nations; **WHO:** World Health Organization

Introduction

Globally, maternal morbidity and mortality are major socioeconomic and healthcare burdens [1]. India is a signatory to the United Nations (UN) SDGs, which set a worldwide maternal mortality ratio (MMR) target of < 70 deaths per 100,000 live births by 2030 [2]. Infections during pregnancy, labor, and the puerperium are linked to significant maternal and neonatal morbidity and mortality [3]. Puerperal infections contribute significantly to this burden, affecting 5%-7% of women [1]. The majority of postpartum infections occur

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after discharge, and in developing countries, numerous cases of puerperal infections go undetected and unreported [4, 5]. Sepsis is the third leading cause of maternal death worldwide [2]. It accounts for one in ten maternal deaths globally; however, data from low- and low-middle-income countries are insufficient [6]. WHO defines puerperal sepsis as "infection of the genital tract occurring at any time between the onset of the rupture of membranes or labor to 42nd day postpartum in which fever and one or more of the following are present: pelvic pain, abnormal vaginal discharge, the abnormal odor of discharge and delay in the rate of reduction of the size of the uterus [7]."

Physiological and immunological changes during pregnancy make pregnant women more susceptible to infections and contribute to a late diagnosis, particularly after birth [8, 9]. Patient-related risk factors include anemia, malnutrition, obesity, immunosuppression, poor hygiene, and diabetes, while obstetric-related risk factors include premature and prolonged membrane rupture, pelvic infection, cesarean section or wound hematoma, amniocentesis or other invasive procedures, and provider interventions such as frequent vaginal examinations, operative vaginal birth, and episiotomy [3, 10-12].

Puerperal sepsis is polymicrobial in origin. *Escherichia coli, Streptococcus pyogenes, Staphylococcus aureus, Streptococcus pneumoniae, Clostridium tetani, Clostridium welchii, Methicillin-resistant S. aureus* (MRSA), Gonococci, or Chlamydia account for the majority of cases [10, 11]. It is characterized by early inflammatory responses and changes in non-immunologic pathways [10].

Infection risk is higher in low-resource healthcare facilities due to poor hygiene, inadequate water and sanitation systems, overcrowding, and a skewed health professional-to-patient ratio. Early identification of microorganisms and selective antibiotic treatment is sometimes limited in such scenarios [3]. Moreover, maternal infection is associated with an increased risk of neonatal sepsis [13].

Antibiotic prophylaxis involves using broad-spectrum antibiotics to prevent infections, and are administered before, during, or after procedures, for a short period, and without any signs of infection [3]. It helps in maintaining therapeutic tissue levels at the time when microbial contamination is most likely to occur [3, 14]. It is one of the approaches for lowering the risk of postpartum infections [12]. In low-resource settings, different antibiotic regimens are frequently prescribed after normal vaginal birth to overcome the limitations of the healthcare system and the increased risk of puerperal infections [3].

Azithromycin is a second-generation macrolide and a broad-spectrum antibiotic. It is effective against several Gram-positive and Gram-negative bacteria [15, 16]. Azithromycin use decreases maternal infection in women having cesarean deliveries and is approved for it [12, 17]. However, its effect on women having planned vaginal deliveries was not established earlier [13]. Recently published clinical studies as well as systematic reviews and meta-analyses have indicated the efficacy of azithromycin prophylaxis in puerperal infections, including sepsis [13, 18-22].

This review will focus on the use of azithromycin prophylaxis in women undergoing planned vaginal delivery, its safety, and its place in therapy in resource-limited settings.

Methods

The articles were sourced from databases like PubMed, Google Scholar, and websites for health agencies, and the literature search was performed methodically. Keywords such as "azithromycin", "macrolides", "puerperal infection", "puerperal sepsis", "maternal sepsis", "antibiotics", "sepsis", "antibiotic prophylaxis", "cesarean", "planned vaginal delivery", "bacterial carriage", "guidelines" and other identical terms were employed during the search process. The final article types included were randomized controlled trials, clinical trials, reviews, systematic reviews, and meta-analyses. The selected articles focused on puerperal infections, puerperal sepsis, antibiotic prophylaxis, macrolides, azithromycin, efficacy and safety of azithromycin in puerperal infections, particularly puerperal sepsis.

Azithromycin prophylaxis in vaginal delivery

The efficacy of a single dose (2 g) of oral azithromycin in preventing maternal infections in women planning a vaginal delivery has been studied primarily in recent years. These studies have also evaluated the effect on neonatal infections [13, 18-22].

Effect of Azithromycin on Bacterial Carriage Mothers and Neonates

In the first proof-of-concept, phase III, a double-blind, placebo-controlled randomized trial, Roca et al investigated the potential of a single dose of oral azithromycin (2g) administered during labor on the bacterial carriage in the mother and the newborn [21, 22]. This study was conducted in Gambia and a total of 829 mothers (azithromycin; N = 414 and placebo; N = 415) and 843 neonates were included. The prevalence of bacterial carriage in the nasopharynx in neonates was lower in the azithromycin group than in the placebo group (28.3% vs. 65.1%, $P < 0.001$). As compared to the placebo group, the prevalence of study bacteria was lower in the nasopharynx (40.0% vs. 9.3%, $P < 0.001$), breast milk (21.9% vs. 9.6%, $P < 0.004$), and vaginal swabs (24.2% vs. 13.2%, $P < 0.001$) in mothers from the azithromycin group. Azithromycin prophylaxis reduced antibiotic prescription by >40% in study women but not in neonates. The findings of this study indicated that oral azithromycin given to women in labor reduced bacterial carriage in mothers and neonates and may reduce the incidence of neonatal sepsis [22].

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Effect of Azithromycin on Maternal and Neonatal Infections

In a follow-up study by Oluwalana C et al, the effect of oral azithromycin (2g) on the occurrence of maternal and neonatal fever and clinical infections was investigated during the 8-week follow-up period. The incidence of maternal infections, mastitis, and fever was significantly lower in the azithromycin group (Figure 1). The overall incidence of infections was also lower among neonates in the azithromycin group and there was a significant difference in the incidence of skin infections as well (Figure 1) [18].

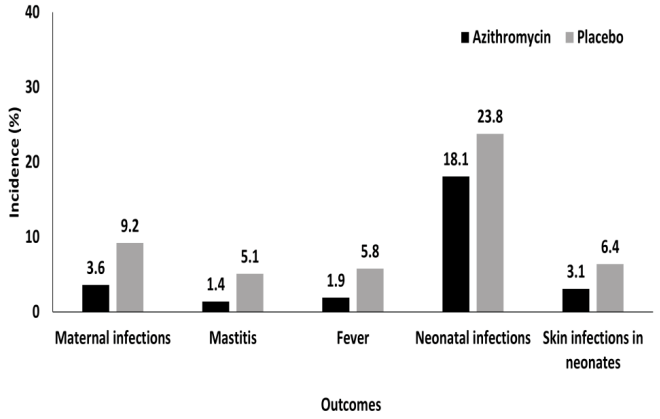

Figure 1: Incidence of maternal infections and neonatal infections with azithromycin and placebo.

In a recent, multi-country, placebo-controlled, randomized trial [Azithromycin Prevention in Labour Use Study (A-PLUS)], Tita et al evaluated the efficacy of a single 2-g oral dose of azithromycin in women planning a vaginal delivery (N = 29, 278). Women who were in labor at 28 weeks gestation or more and admitted for spontaneous or induced vaginal delivery were included. This trial was conducted at eight sites in seven low- or middle-income countries, including Bangladesh, the Democratic Republic of the Congo, Guatemala, India, Kenya, Pakistan, and Zambia [13].

The study participants received either azithromycin (N = 14, 590) or a placebo (N = 14, 688). The groups were well-balanced with respect to labor and delivery characteristics. The participants received necessary care which included procedures and antibiotic use as standard practices needed and followed for vaginal deliveries in addition to study intervention. The use of prophylactic antibiotics during labor or after delivery was similar in both groups. These antibiotics included penicillin, ampicillin or amoxicillin, gentamycin, cephalosporin, metronidazole, clindamycin, erythromycin, azithromycin, and other antibiotics [13].

Treatment adherence in both azithromycin and placebo groups was high (> 98% of cases). The two primary outcomes were a composite of maternal sepsis or death and a composite of stillbirth or neonatal death or sepsis. The incidence of primary composite outcome of maternal sepsis or death was lower in the azithromycin group than in the placebo group with a relative risk of 0.67 ($P < 0.001$). The major difference in maternal primary outcome was majorly due to the reduced incidence of sepsis (relative risk: 0.65; Figure 2). Death due to any cause was 0.1% in both groups. The incidence of secondary outcomes such as endometritis, wound infections, and other infections was lower in women from the azithromycin group compared to the placebo group (Figure 2) [13]. The primary neonatal composite outcome was similar in both groups. In both groups, stillbirth and neonatal death rates within four weeks after birth were 0.4% and 1.5%, respectively [13].

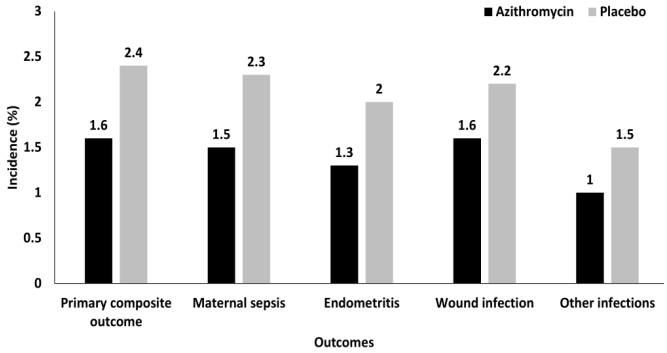

Figure 2: Incidence of the primary composite outcome, maternal sepsis, and some secondary outcomes with azithromycin and placebo.

Azithromycin did not result in a higher incidence of adverse events compared to placebo with a relative risk of 0.93 (7.1% vs. 7.6%). The incidence of gastrointestinal symptoms and other reported side effects was similar in both groups with a relative risk of 1.09 (0.8% vs. 0.8%). No negative safety signals related to cardiac parameters were observed. Following the interim analysis, in which both primary outcomes had been evaluated in almost 70% of patients, the data and safety monitoring committee recommended that the trial be stopped considering the maternal benefits observed [13].

Findings of the A-PLUS trial indicated that intrapartum oral azithromycin reduced the risk of maternal sepsis or mortality in women undergoing planned vaginal delivery, with reduction in sepsis being the main determinant of this outcome. However, azithromycin did not have any impact on the neonatal outcomes [13].

Two recent systematic reviews and meta-analyses have also evaluated the efficacy of azithromycin for prophylaxis [19, 20]. Crosara et al compared the efficacy of a single dose of azithromycin versus placebo in women undergoing planned vaginal delivery at a minimum of 28 weeks of gestation. This study included four randomized controlled trials involving 42, 235 mothers and 42, 492 neonates. The azithromycin

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group was associated with a significantly reduced incidence of all maternal infections (RR: 0.62, P < 0.00001), puerperal sepsis (RR: 0.65, P < 0.00001), and endometritis (RR: 0.65, P < 0.00001). Similarly, the azithromycin group had reduced incidence of mastitis (RR: 0.58, P < 0.001), wound infection (RR: 0.81, P = 0.013), and maternal fever (RR: 0.50, P = 0.018). No significant difference was observed in the neonatal outcomes as well as neonatal infections between the two groups. According to the findings of this study, azithromycin prophylaxis may be an effective measure in preventing puerperal infections but may not have any significant impact on neonatal outcomes [19].

In another similar study, Kuitunen et al evaluated the efficacy of azithromycin versus placebo based on five randomized controlled trials involving 44, 190 mothers and 44, 565 neonates. The azithromycin dose was between 500 mg and 2 g. Major studies reported oral use of azithromycin. Azithromycin was associated with a reduced risk of endometritis (RR: 0.64), chorioamnionitis (RR: 0.50), wound infection (RR: 0.52), and maternal sepsis (RR: 0.66) (Figure 3). However, it was not associated with any significant impact on neonatal outcomes. Thus, intrapartum azithromycin does reduce the risk of maternal postpartum infections and the findings of this study are adaptable to low-income countries [20].

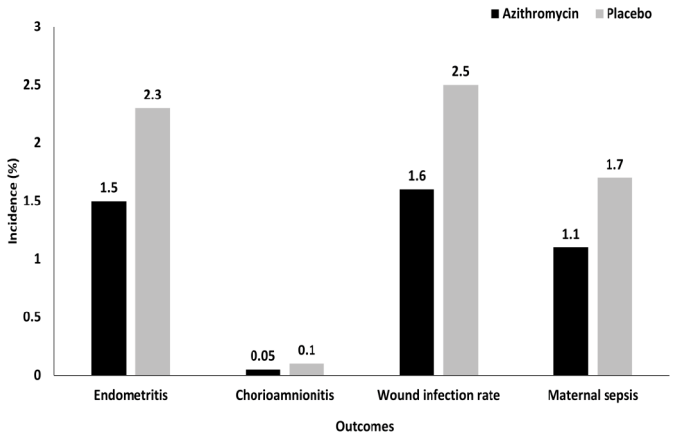

Figure 3: Risk of endometritis, chorioamnionitis, maternal sepsis, and wound infection rates with azithromycin and placebo.

Safety of Azithromycin in Pregnant Women

Azithromycin is a pregnancy category B drug and is considered safe for use in pregnancy and breastfeeding [23, 24]. It is also reported as safe for use in pregnancy by the Medicines and Healthcare Products Regulatory Agency (MHRA) and Medicines and Therapeutics Committee, Government of Australia [25, 26].

Antimicrobial Resistance to Azithromycin

Some potential risks of adding azithromycin to routine vaginal deliveries are increased antimicrobial resistance as well as consequences of alterations to the maternal or neonatal microbiome [13].

In the study conducted by Roca et al., where oral azithromycin was given during labor, the prevalence of azithromycin resistance was greater in bacterial isolates in the azithromycin arm, especially for *S. aureus* [22].

In a follow-up study of the Gambian study, Bojang et al. examined the long-term influence of oral azithromycin 2 g administered in women during labor on the prevalence and antibiotic resistance of *S. pneumoniae* and *S. aureus* in their infants 12 months after treatment. Nasopharyngeal swabs were collected from 461 children. The prevalence of azithromycin-resistant S. pneumoniae (1.8% vs 0.9%) and *S. aureus* (3.1% vs. 2.6%) was similar in azithromycin and placebo arms. Furthermore, there were 427 participants with complete information on resistance during the neonatal period and at 12 months after treatment. The incidence of resistant S. pneumoniae strains was higher after one year of treatment in those harboring resistant strains during the neonatal period (P < 0. 001), while *S. aureus* resistance was not related to the neonatal carriage (P = 0.524). Therefore, azithromycin administration in Gambian women in labor caused transient azithromycin resistance in *S. aureus*, lasting less than 12 months [27].

In another post hoc study, Bojang et al. assessed the impact of intrapartum azithromycin on the frequency of the macrolide-resistance genes, msr(A) and ermC, in the nasopharyngeal samples at different time points of infancy. The study was conducted using 936 samples from 312 children. It was found that the msr(A) and ermC genes were present in both azithromycin and placebo arms at birth (25.2% vs. 25.5%). The prevalence of the msr(A) gene was higher in children in the azithromycin arm at day 28 compared to the placebo (60.7% vs 29.9%) but diminished at 12 months. The ermC gene prevalence was comparable between azithromycin and placebo arms (20% vs. 35%) at day 28, but the difference was no longer significant at 12 months. Although azithromycin increased macrolide-resistance genes within the first month, it was not sustained for one year [28].

These studies indicated that the increase in resistance may be concerning; however, such resistance is unlikely to be sustained as resistance declines in the absence of antibiotic pressure because of the associated fitness cost [22].

Place of Azithromycin in Maternal Infections and Implications in Clinical Practice

In the realm of global healthcare challenges, puerperal infections constitute a significant and frequently avoidable burden. Puerperal sepsis is one of the leading contributors to maternal mortality globally, especially in developing countries [1, 29, 30].

Antenatal care and care during the intrapartum period are

critical in preventing puerperal sepsis [30]. In general, it is presumed that women in developing countries receive some form of antenatal, intrapartum, and postpartum care. However, many women still deliver at home with or without prenatal care [14, 31, 32]. The risk of maternal infections is greater in low-resource settings, and selective antibiotic treatment is limited due to several factors. Thus, postpartum morbidity must be addressed not only from a curative standpoint but also from a preventive standpoint [31].

Puerperal sepsis is caused by several different organisms [10, 11]. Unfortunately, prenatal screening and intrapartum intravenous antibiotic treatment are not viable in low-income countries [15]. Azithromycin has been demonstrated to reduce puerperal infections [13, 18-20, 22, 29] which may be attributed to its extensive antibacterial coverage, including for ureaplasmas and mycoplasmas [15].

Antibiotic prophylaxis has been demonstrated to reduce postoperative puerperal morbidity after cesarean section [12]. WHO also recommends routine antibiotic prophylaxis for women undergoing elective or emergency cesarean section [33]. Furthermore, azithromycin in combination with cefazolin is recommended in cesarean delivery by the Indian Council of Medical Research [17].

In the recent, multi-country, randomized trial (A-PLUS trial) involving women who were in labor and admitted for a vaginal delivery, azithromycin prophylaxis resulted in a 33% risk reduction of maternal sepsis or death than placebo and standard of care. Further, the incidence of adverse events in azithromycin-treated women was similar to those treated with placebo. Out of the eight sites included in this trial, one site was from Bangladesh, one from Pakistan, and two from India. Thus, the findings of this study may be relevant to developing nations [13]. Recently published systematic reviews and meta-analyses have also established the efficacy of intrapartum use of azithromycin in women undergoing planned vaginal delivery [19, 20].

Currently, the majority of these findings can be applied to low-income settings, where the prevalence of maternal infections is higher, and azithromycin's advantages would follow, resulting in reduced incidence of maternal infection and sepsis in low-income countries [20].

Some concerns associated with azithromycin addition to routine vaginal deliveries may be increased antibiotic resistance, effects on the maternal or neonatal microbiome, adverse effects, and cost [13]. No significant associations between a single dose of azithromycin and sustained carriage of resistant organisms or an increase in resistant infections have been reported in available studies [14]. Prophylactic antibiotics must be affordable, accessible, and easy to administer and store. So, a single dose of 2g oral azithromycin may be preferred for prophylaxis [14, 19].

Conclusion

Puerperal sepsis is a life-threatening condition resulting from infection during pregnancy, childbirth, abortion, or after delivery. It is the leading cause of maternal morbidity and mortality in developing countries. The risk of postpartum infection is considered to be higher in low-resource settings due to various factors and prenatal screening as well as intrapartum intravenous antibiotic treatment are not viable. Azithromycin is a broad-spectrum antibiotic and is considered safe for use during pregnancy and breastfeeding. Recent clinical studies as well as systematic reviews and meta-analyses have demonstrated the efficacy of a single dose of 2g of azithromycin in reducing maternal sepsis or death in women planning vaginal birth. Because of its broad-spectrum activity, current evidence on its efficacy in prevention, and safety, as well as affordability, azithromycin may be an important and economical choice for preventing puerperal sepsis in women undergoing planned vaginal delivery.

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Conflict of Interest

Dr. Dinesh Patil, Dr. Heena Bhojwani, and Dr. Onkar C. Swami are full-time employees of Alembic Pharmaceuticals Limited, which actively markets Azithromycin.

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