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REVIEW ARTICLE

Use of Azithromycin in Pregnancy: More Doubts than Certainties

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Abstract

Macrolides such as azithromycin are commonly prescribed antibiotics during pregnancy. The good oral bioavailability and transplacental transfer of azithromycin make this drug suitable for the treatment of sexually transmitted diseases, toxoplasmosis, and malaria. Moreover, azithromycin is useful both in the management of preterm pre-labor rupture of membranes and in the adjunctive prophylaxis for cesarean delivery. The aim of this comprehensive narrative review is to critically analyze and summarize the available literature on the main aspects of azithromycin use in pregnant women, with a special focus on adverse offspring outcomes associated with prenatal exposure to the drug. References for this review were identified through searches of MEDLINE, PubMed, and EMBASE. Fetal and neonatal outcomes following prenatal azithromycin exposure have been investigated in several studies, yielding conflicting results. Increased risks of spontaneous miscarriage, major congenital malformations, cardiovascular malformations, digestive system malformations, preterm birth, and low birth weight have been reported in some studies but not in others. Currently, there is no conclusive evidence to support that azithromycin use by pregnant women causes adverse outcomes in their offspring. Therefore, this agent should only be used during pregnancy when clinically indicated, if the benefits of treatment are expected to outweigh the potential risks.

Key Points

Macrolides such as azithromycin are commonly prescribed during pregnancy for the treatment of sexually transmitted diseases, toxoplasmosis, malaria, and for the management of some obstetric conditions.

Fetal, neonatal, and infant outcomes following prenatal exposure to azithromycin have been investigated. Increased risks of miscarriage, major malformations, cardiovascular malformations, infantile hypertrophic pyloric stenosis, cerebral palsy, and epilepsy have been reported in some studies, but these findings need to be confirmed.

There is no conclusive evidence to support that azithromycin use by pregnant women causes adverse outcomes in their offspring and more high-quality data are needed on this topic.

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1 Introduction

Macrolides are among the most commonly prescribed antibiotics during pregnancy in the USA and in European countries [1–4]. In particular, azithromycin, a second-generation macrolide, has a better pharmacokinetic profile compared to erythromycin [5], and additional immunomodulatory, anti-inflammatory, and potential antiviral properties [6–9].

Due to its good transplacental transfer (3%) [10], azithromycin is suitable for the treatment of sexually transmitted diseases [11], toxoplasmosis [12], and malaria [13, 14] in pregnant women. In addition, this antibiotic is used in the management of preterm pre-labor rupture of membranes (P-PROM) [15] and in the adjunctive prophylaxis of cesarean delivery [16].

Azithromycin is well tolerated and has a good safety profile. However, warnings regarding a possible risk of QT prolongation have been issued [17, 18].

When considering US Food and Drug Administration (FDA) pregnancy risk categories, clarithromycin belongs to category C. In this category, risk cannot be ruled out: there are no satisfactory studies in pregnant women, but animal studies demonstrated a risk to the fetus; potential benefits of the drug may outweigh the risks [19]. Therefore, clarithromycin use in pregnancy is not recommended unless

clearly needed. Instead, azithromycin belongs to category B. In this case, there is no evidence of risk in humans, and animal studies showed no risk to the fetus [19]. Therefore, based on this categorization, azithromycin appears to be less dangerous than clarithromycin, even though its safety in pregnancy needs to be investigated further.

An increased risk of miscarriage was found among pregnant women treated with azithromycin [20]. Uncertainty exists regarding a possible association between prenatal exposure to this medication and congenital birth defects due to contradictory data [21, 22] or conflicting results [23]. In analyses performed for individual macrolides, no significant association has been found between azithromycin use during the first trimester and any major birth defects compared to penicillins [24, 25]. Other authors hypothesized a possible association with major gastrointestinal and muscular-skeletal malformations and congenital heart defects [8, 26]. In this regard, the UK Teratology Information Advisory Service recommends that "as the number of documented exposures during pregnancy is limited, azithromycin should be avoided during pregnancy, particularly in the first trimester" [8].

In this comprehensive narrative review, the main aspects of azithromycin use in pregnant women will be examined, and a critical analysis of the related literature will be performed, with a special focus on adverse offspring outcomes associated with prenatal exposure to the drug.

2 Pharmacological Features of Azithromycin

Azithromycin, synthesized in the early 1980s, is a semi-synthetic derivative of erythromycin characterized by a 15-membered lactone ring azalide.

2.1 Mechanism of Action/Antimicrobial Spectrum of Activity

Azithromycin, characterized by the same antibacterial mechanism of other macrolides [27] that inhibit bacterial protein synthesis through binding to the 50S ribosomal subunit [28], is bacteriostatic or bactericidal depending on the microorganism. Its antimicrobial spectrum provides an adequate coverage for different microorganisms involved in common respiratory tract and gynecologic infections, including *Chlamydia trachomatis*, *Neisseria gonorrheae, Ureaplasma urealyticum,* and *Mycoplasma genitalium* [29–33]. Moreover, azithromycin reduces in vitro replication of several viruses including rhinovirus, influenza A, enteroviruses, and coronaviruses [9]. Azithromycin spectrum also includes *Toxoplasma gondii* and *Treponema pallidum* [34, 35], involved in fetal/perinatal infections with potential catastrophic complications [36].

Common mechanisms of bacterial resistance to azithromycin include: (a) changes in the target/binding site via methylation of key rRNA nucleotides (the most important mechanism) or mutation of some ribosomal components; (b) decreased intrabacterial accumulation inside the efflux pump activity [37].

Resistance genotypes present a different distribution, varying between and within countries: highest rates are observed in Asia [38] and in some European countries such as France, Italy, Spain, and Belgium [39].

Azithromycin has been shown to have also antiviral, anti-inflammatory, and immunomodulatory effects [6–8] that explain the initial growing interest for its use in the treatment of COVID-19 patients [9] not confirmed by recent clinical studies [40].

2.2 Pharmacokinetics

Azithromycin shows a relatively low oral bioavailability (17–37%), and peak plasma concentrations in adults are observed from 12 to 24 h after oral intake [5]. Plasma concentrations appear to be different between pregnant and nonpregnant women in the first 48 h after the first dose [41]. Umbilical arterial and venous azithromycin concentrations were found to be 20–50% lower than maternal serum concentrations [36].

Plasma protein binding is approximately 30% [42]. Azithromycin is known to have a large volume of distribution (23 L/kg) and a rapid plasma clearance reflecting high tissue concentrations, metabolism, and excretion. Moreover, it is barely metabolized, without formation of active metabolites, and does not induce cytochrome (CYP) enzymes, therefore no clinically significant interactions with p450 enzymes have been reported, unlike with erythromycin [43]. Its extended plasma and intracellular half-life (68 h in plasma and more than 60 h in tissues) allows single-dose administration for acute bacterial infections [5]. The estimated terminal half-life in pregnant women is about 78 h [41].

2.3 Tolerability

Azithromycin is well tolerated and has a better safety profile compared to erythromycin. Approximately 1% of azithromycin users discontinue the antibiotic because of adverse effects, compared to 20% of patients treated with erythromycin [44]. The most common adverse effects, observed in particular with high doses and prolonged treatments, are nausea and vomiting, probably due to the effect of the antibiotic on the motilin receptor present in the upper gastrointestinal tract [45]. Other reported adverse effects include headache, skin rash, and dizziness [44]. In case of long-term azithromycin

treatment, the occurrence of hearing defects is possible, as observed in a small number of patients [46].

Macrolides have a class warning for potential cardiac QT prolongation, but only a few cases have been reported with azithromycin [47], probably because this macrolide, unlike the others, does not interfere with CYP3A4 [48]. However, evidence for increased risk of QT prolongation has been reported in patients susceptible to cardiac effects [49]. In an observational non-randomized study, patients treated with azithromycin enrolled into a Tennessee Medicaid program had an incidence of cardiovascular death 2.88-fold and 2.49-fold higher than those patients receiving no antibiotic or treated with amoxicillin, respectively [50]. As a consequence, the US FDA introduced a "black box" warning concerning the "potential risk of fatal arrhythmias for patients already at risk for cardiovascular events" [17]. A further post-marketing safety surveillance using seven databases in Denmark, Italy, and the Netherlands underlined a suspected association between azithromycin use and acute myocardial infarction [51]. These observational data were criticized and the risk of a cardiovascular event after azithromycin treatment is considered very small [18]. However, in patients with pre-existing congenital or acquired heart diseases this risk is higher and azithromycin use should be considered with care [49].

Safety and tolerability of azithromycin in pregnant women have been investigated by various researchers using different study designs.

A randomized single-blind trial by Kacmar et al. [52] compared adverse effects of azithromycin versus amoxicillin for the treatment of *Chlamydia trachomatis* in pregnancy. Thirty-nine women diagnosed with *C. trachomatis* infection before 33 weeks' gestation were included. Adverse effects were common in both groups (38% overall), but amoxicillin was slightly better tolerated (29.4% vs. 52.6%): 40% of women treated with azithromycin reported moderate to severe gastrointestinal adverse effects compared to 17% in the amoxicillin group ($p = 0.11$). Thirty-eight percent experienced vomiting, 36% nausea, 18% diarrhea, and 15% abdominal pain.

A meta-analysis by Pitsouni et al. [53] examined the use of azithromycin for *Chlamydia trachomatis* infections during pregnancy, comparing this antibiotic with erythromycin (main analysis), erythromycin or amoxicillin (secondary analysis). Eight RCTs comprising 587 pregnant women with documented infection were included. Azithromycin (1 g, single dose orally) was associated with fewer gastrointestinal adverse effects, fewer total adverse effects, and a smaller number of patients who withdrew the therapy compared to erythromycin. The results of the secondary analysis were similar.

In a randomized, phase 3, open-label multicenter study conducted in Sub-Saharan Africa between October 2010 and November 2013, 2891 pregnant women received either azithromycin-chloroquine or sulfadoxine-pyrimethamine for prevention of *Plasmodium falciparum* malaria. Treatment-related adverse effects occurred in a larger proportion of mothers in the azithromycin-chloroquine group than in the sulfadoxine-pyrimethamine group (68.9% vs. 19.8%), mostly vomiting, dizziness, headache, and asthenia [54].

Recently, azithromycin-induced intrahepatic cholestasis in a 30-year-old pregnant woman at 38 weeks' gestation was described. Azithromycin withdrawal, termination of pregnancy by cesarean section, and treatment with silymarin capsules and bifendate led to complete clinical and laboratory recovery within 4 weeks [55].

3 Clinical Use of Azithromycin in Pregnancy

In general, azithromycin may be used in preference to other macrolides for treating some sexually transmitted infections, including chlamydia and gonorrhea.

Important clinical indications for the use of azithromycin in pregnancy are antibiotic prophylaxis for P-PROM, adjunctive prophylaxis for cesarean delivery, and treatment of genital *Chlamydia trachomatis* infection (Table 1).

3.1 Antibiotic Prophylaxis for P-PROM

P-PROM refers to the pre-labor rupture of the amniotic membranes prior to 37+0 weeks gestation. It is the cause of about one-third of preterm births and the single most frequent factor associated with preterm delivery [56]. Prophylactic antibiotics ("latency antibiotics") increase the time from rupture of membranes to delivery ("latency") and decrease maternal and neonatal morbidity. The most common drugs used are beta-lactams and macrolides, either alone or in combination. Currently, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend a regimen consisting of 48 h of intravenous (IV) ampicillin and erythromycin, followed by 5 days of oral amoxicillin and erythromycin. Furthermore, a frequent variation from this regimen is the substitution of azithromycin for erythromycin. Azithromycin is preferred over erythromycin due to its ease of administration, better adverse effect profile, and lower cost [56].

Infection is both a cause and a consequence of P-PROM. Therefore, antibiotic prophylaxis is recommended, although the optimal regimen remains unclear. Mercer et al. [56] conducted a randomized controlled trial to determine whether antibiotic treatment during expectant management of

Table 1 Main clinical indications for the use of azithromycin

Clinical indication	Monotherapy (M)/ combination therapy (CT)	First choice (FC)/ alternative choice (AC)	Azithromycin dosage
Antibiotic prophylaxis for P-PROM	CT (ampicillin + erythromycin)	AC (azithromycin instead of erithromycin)	1 g PO (single dose)
Adjunctive prophylaxis for cesarean delivery	M (cephalosporins)	AC (cephalosporins + azithromycin)	500 mg IV (single dose)
Treatment of skin infection due to *Staphylococcus aureus*, *Streptococcus pyogenes*	CT (cephalosporins + clindamycin)	AC (azithromycin instead of clindamycin)	500 mg PO (once daily)
Prevention and treatment of *Mycobacterium avium* complex disease	CT (ethambutol + clarithromycin + rifamycin)	AC (azithromycin instead of clarithromycin)	1200 mg PO (once weekly)
Prophylactic antibiotic therapy for COPD	M	FC	250 mg PO (once daily)
Treatment of respiratory infection caused by *Chlamydia* and *Mycoplasma* spp.	M	FC (in pregnancy)	500 mg PO (once daily)
Treatment of respiratory infections caused by *Legionella pneumophila*	M	FC	500 mg PO (once daily)
Treatment of respiratory infections caused by *Bordetella pertussis* (whooping cough)	M	FC	500 mg PO on day 1 then 250 mg (once daily)
Treatment of respiratory infections caused by *Moraxella catarrhalis*	M (amoxicillin-clavulanate)	AC (azithromycin instead of amoxicillin)	500 mg PO (once daily)
Treatment of cervicitis and urethritis caused by *Chlamydia trachomatis* and *Mycoplasma hominis*	M	FC	1 g PO (single dose)
Treatment of gonococcal urethritis and cervicitis	CT (cephalosporins + azithromycin)	FC	1 g PO (single dose)
Treatment of pelvic inflammatory disease	CT (cephalosporins + doxycycline)	AC (azithromycin + metronidazole)	500 mg IV once daily for 1–2 days, then 250 mg PO once daily
Treatment of chancroid	M	FC	1 g PO (single dose)
Treatment of granuloma inguinale/Donovanosis	M	FC	1 g PO (once weekly)
Treatment of severe traveler's diarrhea	M	FC	500 mg – 1 g PO (single dose)
Treatment of bacterial enteritis due to *Campylobacter jejuni*	M	FC	500 mg PO (once daily)
Treatment of enteric fever (caused by *Salmonella typhi* and S. *Paratyphi*).	M	FC	500 mg PO (once daily)
Treatment of cholera	M	FC (in pregnancy)	1 g PO (single dose)
Treatment of early Lyme disease	M (amoxicillin-clavulanate)	AC (azithromycin instead of amoxicillin)	500 mg PO (once daily)
Treatment of AIDS with toxoplasmosis encephalitis	CT (pyrimethamine + sulfadiazine + leucovorin)	AC (azithromycin instead of sulfadiazine)	900–1200 mg PO (once daily)
Treatment of lymphadenopathy due to *Bartonella henselae* (cat-scratch disease)	M	FC	500 mg PO on day 1 then 250 mg (once daily)
Prevention of streptococcal/ staphylococcal endocarditis (Penicillin allergy)	M (ampicillin)	AC (azithromycin instead of ampicillin)	500 mg PO (single dose before the procedure)
Treatment of uncomplicated malaria	CT (azithromycin + chloroquine)	AC (sulphadoxine-pyrimethamin + chloroquine)	1 g PO (once daily)

PO oral, *IV* intravenous, *P-PROM* preterm prelabor rupture of membranes, *COPD* chronic obstructive pulmonary disease

P-PROM could reduce infant morbidity. In this trial, a total of 614 pregnant women with P-PROM were treated with the following regimen: IV ampicillin (2 g every 6 h) and erythromycin (250 mg every 6 h) for 48 h, followed by oral amoxicillin (250 mg every 8 h) and erythromycin (333 mg every 8 h) for 5 days.

Azithromycin has an increased pharmacokinetic distribution and slower elimination rate if compared with erythromycin. Other advantages of azithromycin include lower rates of adverse effects, better compliance, reduced drug interactions, and reduced dosing frequency [57].

Recently, a multicenter, prospective observational cohort study by Martingano et al. [58] evaluated if antibiotic regimens including azithromycin versus erythromycin could change pregnancy latency and development of clinical chorioamnionitis in women with P-PROM. In the context of P-PROM, all enrolled women received latency antibiotic treatment with either azithromycin or erythromycin. The azithromycin group had azithromycin 1 g orally once daily and ampicillin 2 g every 6 h IV for 48 h, followed by 5 days of amoxicillin 250 mg every 8 h orally. The erythromycin group had erythromycin 250 mg and ampicillin 2 g every 6 h IV for 48 h, followed by amoxicillin 250 mg and erythromycin 500 mg every 8 h orally for 5 days. This study recruited 310 patients, 142 of whom received the azithromycin regimen and 168 the erythromycin regimen. Patients treated with the azithromycin regimen had significantly better results in overall rates of clinical chorioamnionitis (13.4% vs. 25%; $p = 0.010$), postpartum endometritis (14.8% vs. 31%; $p = 0.001$), and neonatal sepsis (4.9% vs. 14.9%; $p = 0.004$). In crude and adjusted models, a decreased risk for clinical chorioamnionitis, postpartum endometritis, and neonatal sepsis was reported in the azithromycin group. In both models, pregnancy latency was not significantly different between the two groups.

Other authors [59] studied if there were differences in the latency from P-PROM to delivery in women treated with different dosing regimens of azithromycin versus erythromycin. A multicenter, retrospective cohort of singleton pregnancies with confirmed P-PROM between 23^0 and 33^6 gestational weeks was recruited, excluding the patients with a contraindication to expectant management of P-PROM. All patients received ampicillin IV for 2 days followed by amoxicillin orally for 5 days. 453 patients were enrolled. Seventy-eight patients were given azithromycin for 1 day, 191 patients received azithromycin for 5 days, 52 patients were treated with azithromycin for 7 days, and 132 patients received erythromycin. There were no statistical differences in median latency time of azithromycin 1 day (4.9 days, 95% confidence interval (CI) 3.3–6.4), azithromycin 5 days (5.0, 95% CI 3.9–6.1), or azithromycin 7 days (4.9 days, 95% CI 2.8–7.0) in comparison to erythromycin (5.1 days, 95% CI 3.9–6.4), after adjusting for demographic variables ($p = 0.99$). Clinical chorioamnionitis did not differ between groups in the adjusted model. Respiratory distress syndrome was found to be increased in the azithromycin 5-day group versus azithromycin 1 day versus erythromycin (44% vs. 29% and 29%; $p = 0.005$, respectively). Azithromycin could be considered as an alternative to erythromycin in the expectant management of P-PROM whenever erythromycin is unavailable or contraindicated. There seems to be no additional benefit to an extended course of azithromycin beyond the single-day dosing, but conclusive recommendations on dosing strategies should be based on clinical trials. The results of the ongoing superiority trial entitled "Treatment of P-PROM with Erythromycin vs. Azithromycin Trial (TREAT)" (NCT 03060473), which is currently in recruitment phase, will provide additional information on treatment alternatives.

Kole-White et al. [60] investigated pregnancy latency after P-PROM following therapy with oral-only antibiotics compared to therapy with IV antibiotics followed by oral antibiotics. No significant differences in the relative risk (RR) of maternal infection (RR, 0.43; 95% CI, 0.05−3.53) or neonatal infection (RR, 0.43; 95% CI, 0.05−3.52) were found. The authors concluded that the adoption of an oral-only antibiotic regimen for pregnancy latency after P-PROM may be an alternative choice to a standard combined antibiotic regimen.

3.2 Adjunctive Prophylaxis for Cesarean Delivery

Cesarean section (CS) is the most frequent major surgical procedure in the USA, with over 1.2 million carried out annually [61]. Each year, up to 12% of the cesarean deliveries carried out in the USA are complicated by surgical site infection [62], a significant cause of morbidity and mortality [63]. Tita et al. [16] reported that the addition of a single dose of perioperative azithromycin to cephalosporin prophylaxis (azithromycin-based extended-spectrum antibiotic prophylaxis) in patients undergoing unscheduled CS reduced the risk of postoperative infectious morbidities (including wound infections and endometritis) > 50% (6.1% vs. 12%). The efficacy of such prophylaxis was due to coverage for ureaplasma species, which were found to be more commonly associated with infections after CS when compared to anaerobes. Also, there was no significant difference in secondary neonatal composite outcomes (14.3% vs. 13.6%).

3.3 Treatment of Genital *Chlamydia trachomatis* Infection in Pregnancy

Genital *Chlamydia trachomatis* (*C. trachomatis*) infection may result in pregnancy complications including miscarriage, preterm labor, low birthweight, P-PROM, perinatal death, postpartum endometritis, chlamydial conjunctivitis, and *C. trachomatis* pneumonia [64]. A meta-analysis by Cluver et al. [64], including 15 trials (1754 women), investigated the most efficacious and best tolerated therapy for genital chlamydial infection to prevent maternal infection and adverse neonatal outcomes. Azithromycin versus erythromycin (average RR, 1.11; 95% CI, 1.00–1.23; six trials, 374 women; $I^2 = 53\%$; moderate-certainty evidence) had similar efficacy, although the study results appeared to be in favor of azithromycin. The authors documented that treatment with antibacterial drugs achieved microbiological cure from *C. trachomatis* infection during pregnancy, but no difference between evaluated agents (amoxicillin, erythromycin, clindamycin, azithromycin) was found in terms of efficacy (microbiological cure and repeat infection) and complications of pregnancy (P-PROM, preterm birth, and low birthweight). However, azithromycin and clindamycin resulted in fewer adverse effects than erythromycin.

3.4 Treatment of Respiratory Tract Infections in Pregnancy

Although respiratory tract infections usually are not more common in pregnancy, they can result in greater morbidity and mortality secondary to gestational physiologic adaptations. Pregnancy has been identified as a risk factor for complications from respiratory tract infections due to decreased lung capacity, increased heart rate and oxygen consumption, and maternal immune system changes [65].

Most cases of acute bronchitis are caused by rhinovirus, influenza, and adenovirus. Other etiologies include *M. pneumoniae* and *C. pneumoniae*. In addition to the above, other organisms that cause bacterial pneumonia include *S. pneumoniae, H. influenzae, and L. pneumophila.*

Generally, all pregnant women affected by pneumonia are hospitalized for observation and initial therapy. Current guidelines for community-acquired pneumonia (CAP) recommend that patients should be treated for atypical pathogens and pneumococcus.

In pregnant patients with mild CAP, for which outpatient therapy is indicated, an oral macrolide such as azithromycin, which is better tolerated than erythromycin, should be prescribed. In case of risk of drug-resistant streptococcus pneumonia (DRSP), azithromycin should be combined with high-dose amoxicillin, cefpodoxime, or cefuroxime. In hospitalized pregnant women, IV azithromycin should be initially administered if the patient has no risks of DRSP, while IV azithromycin and ceftriaxone or cefotaxime should be given in patients at risk of DRSP. In severe forms of CAP, combination therapy with cefotaxime or ceftriaxone plus azithromycin should be given [66].

A meta-analysis by Laopaiboon et al. [67], by analyzing the results from 15 trials with 2496 participants, compared the effectiveness of azithromycin to amoxicillin/clavulanate in the treatment of acute bronchitis, acute exacerbation of chronic bronchitis, and pneumonia. This study found unclear evidence that azithromycin is superior to amoxicillin/clavulanate in treating acute lower respiratory tract infection. However, in patients with acute bronchitis of suspected bacterial etiology, azithromycin was found to be more effective in lowering the incidence of clinical failure than amoxicillin/clavulanate (RR 0.63; 95% CI 0.45–0.88). Moreover, azithromycin had a non-significantly lower incidence of adverse events as compared to amoxicillin/clavulanate (RR, 0.76; 95% CI, 0.57–1.00).

Pertussis can affect all ages, with potential complications including pneumothorax, fractured ribs, and aspiration pneumonia. In their descriptive analysis of pertussis data collected through the Centers for Disease Control and Prevention's (CDC's) Emerging Infections Program Network/Enhanced Pertussis Surveillance system, Skoff et al. [65] found no differences in incidence, clinical presentation, and severity of pertussis illness between pregnant and nonpregnant women. The majority of pregnant (93.2%) and nonpregnant (95.0%) patients were treated with azithromycin or clarithromycin.

Erythromycin has traditionally been used for treating pertussis, but currently the preferred treatment is azithromycin, which is characterized by a shorter treatment course. The prompt diagnosis and treatment of pertussis infections in pregnant women help to minimize the impact of disease, and prevent transmission to the newborn. Trimethoprim-sulfamethoxazole may be an alternative choice in patients who cannot tolerate macrolides [68].

Azithromycin has been found to improve clinical outcomes in patients with cystic fibrosis (CF) [69], and is recommended for the treatment of CF lung disease. A recently published statement on the management of reproduction and pregnancy in women with chronic airway disease categorizes its use during pregnancy as "probably safe" [70]. Therefore, patients with CF considering pregnancy while on chronic azithromycin therapy should be counselled: the potential risk to the infant of use of azithromycin during pregnancy must be weighed against the potential risk to the mother of lung function decline and/or pulmonary exacerbation [71].

4 Use of Azithromycin in Pregnancy and Adverse Offspring Outcomes

A literature analysis was performed in order to investigate the effects of azithromycin administration during pregnancy on offspring outcomes. References were identified through searches of MEDLINE, PubMed, and EMBASE for articles in English published from 2000 to June 2021, using the key words "macrolides", "azithromycin", "pregnancy", "safety", "fetal/neonatal outcome", "infant/child outcome". No restrictions were placed on article type. Only relevant articles were included.

4.1 Fetal and Neonatal Outcomes

Fetal and neonatal outcomes following prenatal azithromycin exposure have been investigated by several studies, yielding conflicting results (Table 2) [8, 20, 23–26, 54, 72–80]: increased risks of miscarriage, major malformations, and cardiovascular malformations have been reported in some observational studies [20, 54, 76–78, 80], but not in others [23, 73, 75].

Some articles explored the use of azithromycin during pregnancy and the risk of spontaneous abortion or premature birth.

In the aforementioned multicenter study by Kimani et al. [54], 2891 pregnant women received either azithromycin-chloroquine or sulfadoxine-pyrimethamine for prevention of *Plasmodium falciparum* malaria. In total, 378 (26.2%) women in the azithromycin-chloroquine group versus 342 (23.7%) in the sulfadoxine-pyrimethamine group had suboptimal pregnancy outcomes (relative risk not statistically significant): spontaneous abortion, stillbirth, or premature birth. Treatment-related adverse effects, most of which were mild or moderate, were observed in 0.3% of neonates in the azithromycin-chloroquine group and in 0.2% of neonates in the sulfadoxine-pyrimethamine group: low birthweight, anemia, jaundice, and prematurity.

A nested case-control study was conducted within the Quebec Pregnancy Cohort 1998-2009. Among 182,369 pregnancies, 8702 (4.7%) ended with a clinically detected spontaneous abortion (cases) and were compared with 87,020 matched controls. Use of azithromycin during early pregnancy was associated with a RR of 65% for spontaneous abortion (adjusted odds ratio (OR), 1.65; 95% CI, 1.34–2.02; 110 exposed cases), with similar results using penicillins or cephalosporins as comparators [20].

A retrospective case-control study of preterm newborns delivered at $\leq$ 30 weeks of gestational age, admitted to Hallym University Medical Center (Seoul, Korea) from 2012 to 2016, was conducted to evaluate neonatal outcome following maternal azithromycin treatment (500 mg/day for 3 days before delivery) for *Ureaplasma* colonization. During the study period, 161 of 230 preterms admitted to the neonatal intensive care unit (NICU) were born to women with *Ureaplasma* colonization: 51 infants were excluded for different reasons or died, therefore the final number of cases included was 110, which were matched with 55 controls. Despite antenatal azithromycin treatment, the incidence of P-PROM and of moderate/severe bronchopulmonary dysplasia (BPD) was significantly higher in the azithromycin group (54% vs. 29%, $p = 0.003$ and 24% vs. 7%; $p = 0.010$, respectively) [77].

A systematic review and meta-analysis of different observational studies explored a possible association between antibiotic use (comprised macrolides) during pregnancy and spontaneous miscarriage. Twelve studies (eight prospective and four case-control studies), comprising in total 1,084,792 participants and 7015 cases of spontaneous abortion, were included. Percentage of miscarriage was 2.6%. Together with quinolones and tetracyclines, use of macrolides during pregnancy was significantly associated with spontaneous miscarriage [78].

A community-randomized trial of *Trichomonas vaginalis* treatment during pregnancy was performed between 1994 and 1999 in Uganda. Ninety-four pregnant women were treated orally with 1 g azithromycin, 400 mg cefixime, or 2 g metronidazole (intervention arm) and compared with 112 women treated with iron, folate, and multivitamins (control arm). Antibiotic treatment was not associated with improved pregnancy outcome, but, conversely, it was found to be associated with higher risks of low birthweight (18% vs. 7%, treatment in all trimesters), preterm birth (30% vs. 15%, treatment during the first trimester), and infant death (18% vs. 14%) [79].

Past research has mainly focused on neonatal outcome, including the risk of malformations.

In order to determine whether the use of azithromycin, and other macrolides, during the first trimester of pregnancy could be associated with an increased risk of major malformations, a prospective multicenter study was conducted in Israel. In total, 161 pregnant women treated with new macrolides (32 pregnancies exposed to azithromycin) were compared with 953 receiving other antibiotics or non-teratogens: the rate of major malformations was 4.1% in the study group (3.7% for azithromycin) compared to 2.1% and 3%, respectively. The rate of congenital cardiovascular malformations was comparable between the three groups. Instead, pregnancy outcome (spontaneous abortions, stillbirths, elective termination of pregnancy) was significantly different among groups, with higher rates of elective pregnancy termination in the macrolide group (10.2% vs. 2.3% and 2%; $p = 0.0001$). The mean birthweights were overlapped between the groups. Azithromycin did not show an increased risk of

Table 2 Selected studies focusing on adverse fetal/neonatal outcomes following prenatal exposure to macrolides

Author, year [Ref.]	Study design	Study population	Type of macrolide prescribed during pregnancy	Adverse fetal/neonatal outcomes investigated
Sarkar et al. (2006) [23]	Prospective study	123 pregnant women (azithromycin group)	Azithromycin	Major malformations (3.4%; $p = 0.8$). Spontaneous abortion (4.9%; $p = 0.3$). Other endpoints
Bar-Oz et al. (2008) [72]	Prospective multicenter, cohort study	161 pregnant women (macrolide group)	Azithromycin, clarithromycin, roxithromycin	Spontaneous abortion (7.6%; $p = 0.0001$). Major malformations (4.1%; $p = 0.6$). Cardiovascular malformations (1%; $p = 0.8$)
Bar-Oz et al. (2012) [24]	Prospective, multicenter, controlled, observational study	608 pregnant women (exposed to macrolides), and 773 pregnant women (controls)	Azithromycin, clarithromycin, roxithromycin	Major malformations (3.4%; $p = 0.36$). Cardiovascular malformations (1.6%; $p = 0.26$)
Lin et al. (2013) [73]	Case-control study	4,132 infants with CHD and 735 with PS (cases), and 6952 controls	Erythromycin, non-erythromycin macrolides	Cardiovascular malformations (1.1%; OR 0.9, 95% CI 0.6–1.3). Pyloric stenosis (1.6%; OR 1.3, 95% CI 0.6–2.8)
Bérard et al. (2015) [74]	Register-based cohort study	135,859 pregnancies (study cohort) 2286 pregnancies (exposed to macrolides)	Azithromycin, clarithromycin, erythromycin	Major malformations (13.1%; RR 1.38, 95% CI 1.14–1.67). Cardiovascular malformations (2.1%; RR 1.11, 95% CI 0.71–1.75)
Muanda et al. (2017) [20]	Nested case-control study	95,722 pregnancies (study cohort) 1789 (exposed to macrolides)	Azithromycin, clarithromycin, erythromycin, other macrolides	Spontaneous abortion (3%; OR 1.61, 95% CI 1.41–1.85) excluding erythromycin)[a,b]
Muanda et al. (2017) [75]	Population-based cohort study	139,938 pregnancies (study cohort). 15,469 pregnancies (exposed to antibiotics)	Azithromycin, clarithromycin, erythromycin	Major malformations (11.3%; OR 1.08, 95% CI 0.95–1.23). Cardiovascular malformations (2.02%; OR 0.93, 95% CI 0.69–1.25). Digestive system malformations (1.5%; OR 1.46; 95% CI 1.04–2.06)[b]
Damkier et al. (2019) [76]	Population-wide cohort study	932,731 singleton deliveries (study cohort). 82,318 singleton deliveries (exposed to study antibiotics)	Azithromycin, erythromycin, roxithromycin	Major malformations (OR 1.19, 95% CI 1.03–1.38). Cardiovascular malformations (OR 1.29, 95% CI 0.99–1.67)
Kim et al. (2019) [77]	Retrospective case-control study	110 preterm infants ≤ 30 weeks of GA (cases), and 55 preterm infants ≤ 30 weeks of GA (controls)	Azithromycin	P-PROM (54%, p = 0.003).[a] BPD moderate-to-severe (26%, $p = 0.01$)[a]

Table 2 (continued)

Author, year [Ref.]	Study design	Study population	Type of macrolide prescribed during pregnancy	Adverse fetal/neonatal outcomes investigated
Fan et al. (2019) [8]	Systematic review and meta-analysis	10 observational studies and 9 RCTs (228,556 participants)	Azithromycin, clarithromycin, erythromycin, roxithromycin	Spontaneous abortion (OR 1.82, 95% CI 1.57-2.11, $p < 0.001$).[a,b] Major malformations (OR 1.13, 95% CI 0.99–1.29, $p = 0.06$). Gastrointestinal malformations (OR 1.56, 95% CI 1.05–2.32, $p = 0.03$).[a,b] Musculoskeletal malformations (OR 1.18, 95% CI 0.95–1.47, $p = 0.14$).[a] Cerebral palsy and epilepsy (inconsistent association)
Omranipoor et al. (2020) [78]	Systematic review and meta-analysis	8 prospective cohort and 4 population-based case-control studies (1,084,792 participants)	Azithromycin, clarithromycin, erythromycin, roxithromycin	Spontaneous abortion (RR 1.42, 95% CI 1.04–1.93).[a,b]
Mallah et al. (2020) [26]	Systematic review and meta-analysis	17 cohort and 4 case-control studies	Azithromycin, clarithromycin, erythromycin, roxithromycin	Musculoskeletal system malformations (OR 1.06, 95% CI (0.91–1.24).[c] Digestive system malformations (OR 1.13, 95% CI 0.97–1.31).[c] Other malformations
Leke et al. (2021) [80]	Case-control study	145,936 babies with congenital malformations from 15 population-based EUROCAT registries	Azithromycin, clarithromycin, erythromycin, spiramycin	Atrioventricular septal defects (OR 2.98, 95 %CI 1.48–6.01).[a,b] Other congenital malformations[a,b]
Andersson et al. (2021) [25]	Register-based cohort study	1,192,539 live-birth pregnancies (study cohort). 13,019 live birth pregnancies (exposed to macrolides)	Azithromycin, clarithromycin, erythromycin, roxithromycin	Major malformations (RR 0.95, 95% CI 0.84–1.08)

CHD congenital heart defects, *PS* pyloric stenosis, *P-PROM* preterm pre-labor rupture of membranes, *BPD* bronchopulmonary dysplasia

[a]Significant association with prenatal exposure to azithromycin

[b]Significant association with prenatal exposure to macrolides

[c]Weak association with exposure to macrolides in early pregnancy

major malformations strong enough to allow induced abortion after such exposure [72].

In a later study, the same authors evaluated the outcomes of pregnancy in women exposed in the first trimester to the new macrolides including azithromycin, given for upper respiratory or urogenital infections, pneumonia, and *H. pylori* disease, from 2005 to 2008. The prospective, multicenter, observational study involved 608 pregnant women exposed to macrolides (156 to azithromycin) and 773 exposed to non-teratogenic preparations (control group) in Italy, Israel, the Czech Republic, the Netherlands, and Germany. The rate of livebirths was found to be significantly lower in the macrolide-exposed group (86.3% vs. 91.2%; $p = 0.006$), while there were no significant differences between the groups as regards the rates of spontaneous abortions, preterm births, and birthweight. No significant difference in the rate of major congenital malformations (3.4% vs. 2.4%) or in the rate of cardiovascular malformations (1.6% vs. 0.9%) was found. The prevalence of major congenital malformations was 5.2% for azithromycin. No significant difference was also found between the azithromycin and the control groups, although for azithromycin the significance was borderline as regards the proportion of cardiovascular malformations [24].

A possible association between maternal use of macrolides, including azithromycin, and the risk of congenital heart defects (CHD) or pyloric stenosis (PS) has been assessed among women adhering to the Slone Epidemiology Center Birth Defects Study from 1994 to 2008. 4132 infants with CHD and 735 with PS were identified as cases, while 6952 subjects without malformations were considered as controls. No association was found between first trimester maternal use of macrolides (erythromycin, azithromycin, clarithromycin) and the risk of CHD or PS. There was also no association between exposure to macrolides in the second and third trimesters and PS development. Moreover, risks for many specific major congenital malformations have not been identified [73].

Some authors [74] estimated the risk of major congenital malformations after prenatal exposure to macrolides (erythromycin, azithromycin, and clarithromycin) during the first trimester, with a particular focus on cardiac malformations. Taking into account the Quebec Pregnancy Cohort 1998-2008, a register-based cohort study was performed where a group of 2286 pregnant women treated with macrolides was compared with two other groups comprising 9106 pregnancies with exposure to penicillin and a non-exposure category of 124,467 pregnant women. Azithromycin was the most frequently prescribed macrolide (n = 914). No statistically significant association has been demonstrated (RR, 1.19; 95% CI, 0.98–1.44) between azithromycin use and the risk of major congenital malformations and cardiac malformations, in particular atrial septal/ventricular septal defects.

A systematic review and meta-analysis explored the association between macrolide use during pregnancy and adverse fetal/neonatal outcomes [8]. Nineteen studies (ten observational and nine RCTs) comprising 228,556 participants were included. Azithromycin use during pregnancy was significantly associated with an increased risk of major gastrointestinal or musculoskeletal malformations compared to other antibiotics (penicillins or cephalosporins). No evidence of 12 other malformations, stillbirth, or neonatal death has been reported.

A meta-analysis comprising 17 cohort and four case-control studies (six regarding azithromycin) was carried out between 1998 and 2017 in Europe and North America. This meta-analysis assessed the association between prenatal exposure to macrolides and occurrence of congenital malformations by comparing neonates exposed to non-macrolide antibiotics/non-teratogens and neonates unexposed to any medicine before birth. A weak association between macrolides and congenital malformations of any type was observed, with differences between geographical areas. Subgroup analysis showed an association between the exposure to roxithromycin in the first trimester and digestive/musculoskeletal system malformations, while azithromycin was not found to be associated with fetal malformations [26].

A European case-control study investigated the risk of congenital heart defects and other congenital malformations associated with the use of macrolide antibiotics during the first trimester. Data related to 145,936 neonates with a diagnosis of congenital anomalies were obtained from 15 EUROCAT registries of 13 European countries (study period 1995–2012). During the first trimester, 3440 women (2.36%) were exposed to at least one antibiotic. The risk of atrioventricular septal defect and at least one other congenital anomaly increased significantly after exposure to azithromycin (OR, 4.50; 95% CI, 1.30–15.58), but it was not possible to confirm previously reported associations between azithromycin and orofacial clefts [80].

A nationwide, register-based cohort study was performed in Denmark between 1997 and 2016. Among 1,192,539 live-birth pregnancies, 13,019 pregnancies were treated with macrolides and were compared with those in which penicillin was used (51,515) or no antibiotic was given (995,673). Among the pregnancies during which macrolides had been used, 4712 (36.2%) used azithromycin. 457 neonates were born with major birth defects after prenatal exposure to macrolides (first trimester) compared with 481 neonates whose mothers were treated with penicillin. The use of macrolide antibiotics during the first trimester of pregnancy was not associated with an increased risk of major birth defects. No significantly increased risk of major birth defects (12 specific subgroups) was also found for individual macrolides [25].

On 28 June 2021, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) [81] released a report presenting a review of the available safety data for the use of the macrolides erythromycin, clarithromycin, and azithromycin during early pregnancy. The review assessed the quality of the safety evidence relating to three outcomes: major congenital malformations, cardiovascular malformations, and miscarriage. Overall, the quality of available data on the safety of maternal use of erythromycin, clarithromycin, and azithromycin in early pregnancy was found to be low. Moreover, the available evidence was considered to be insufficient to establish the absence of a small increased risk of major malformations or cardiovascular malformations following exposure to azithromycin or clarithromycin.

4.2 Infant and Child Outcomes

The association between use of macrolides in mothers from pregnancy onset until 120 days after birth and infantile hypertrophic pyloric stenosis (IHPS) was assessed through a nationwide register-based cohort study in Denmark between 1996 and 2011 [82]. Among a cohort of 999,378 liveborns during the study period, 30,091 mothers (3%) used macrolides during pregnancy and 21,557 (2.2%) used macrolides from birth until 120 days. 880 infants developed IHPS (0.9 cases per 1000 births). A possible modest association was found between maternal use of macrolides during late pregnancy (from 28 weeks to birth) and IHPS development. The risk of IHPS was found to be increased more than threefold with maternal use of macrolides during the first 2 weeks after birth. The power of the study was unable to document any difference in risk profile according to specific macrolide subtype, but no major differences were apparent across the individual drugs.

In 2019, two separate systematic reviews and meta-analyses evaluated the association of prenatal and postnatal macrolide exposure with subsequent development of IHPS. In the first review, Abdellatif et al. [83] found no significant association between macrolide use during pregnancy and development of IHPS, while the evidence on the effects of prenatal macrolide exposure was not conclusive in the second review [84].

The study by Meeraus et al. [85] evaluated the risk of cerebral palsy or epilepsy in children whose mothers were prescribed antibiotics in pregnancy using a cohort of 195,909 women linked to their live, full-term born, singleton children. In total, 64,623 (33.0%) women were prescribed antibiotics during pregnancy and 1170 (0.60%) children were found to have records indicating cerebral palsy or epilepsy. Adjusted analyses revealed no association between prescribing of any antibiotic and cerebral palsy or epilepsy (adjusted HR, 1.04; 95% CI, 0.91–1.19) in childhood, but macrolides were associated with an increased risk of cerebral palsy or epilepsy (adjusted HR, 1.78; 95% CI, 1.18–2.69) compared with penicillins, though the absolute risk remained low. More recently, similar results were obtained in the study conducted by Fan et al. [8].

Finally, preliminary data suggest that macrolide exposure during pregnancy is associated with an increased risk for childhood asthma.

In a large, population- and register-based study, Metsälä et al. [86] examined the associations between prenatal and post-natal exposure to various antibiotics and the risk of childhood asthma. The study results showed that maternal use of any antibiotics in pregnancy was associated with an increased risk of asthma in the offspring (OR, 1.31; 95% CI, 1.21–1.42). Similar to other maternal-specific antibiotics, macrolides were found to be associated with the risk of childhood asthma (OR, 1.28; 95% CI, 1.07–1.53), although the strongest association was observed for cephalosporins (OR,1.46; 95% CI, 1.30–1.64). According to the authors, the role of effects of antibiotics on the gut microbiota and the development of childhood asthma should be further investigated.

Subsequently, Mulder et al. [87] assessed the association between prenatal antibiotic use and asthma in preschool children. A case-sibling study, in which 1228 children with asthma were compared with 1228 siblings without asthma and a case-control study were conducted. In both analyses, the use of antibiotics in the third trimester of pregnancy was associated with a small increase in the risk of asthma in preschool children (adjusted OR, 1.37; 95% CI, 1.02–1.83 and adjusted OR, 1.40; 95% CI, 1.15–1.47). Moreover, a significant association between exposure to antibiotics in any trimester of pregnancy and the occurrence of asthma in preschool children was found in the case-control analysis only (adjusted OR, 1.46; 95% CI, 1.34–1.59). No significant increases in the associated risk for the development of childhood asthma were found after stratification on the subtypes beta-lactam penicillins, sulphonamides, macrolides, and nitrofurantoin. The findings of this study further support the important role for early-life gut microbiota in the development of childhood asthma.

More recently, to characterise the association between prenatal exposure to antibiotics and childhood asthma, Loewen et al. [88] conducted a population-based cohort study using prescription records, hospitalization records, and physician billing claims from 213,661 mother–child dyads. Prenatal exposure to antibiotics was associated with an increased risk of asthma (adjusted HR, 1.23; 95% CI, 1.20–1.27), with an apparent dose response. When classified by type, most antibiotics were similarly associated with childhood asthma, including macrolides, lincosamides, and streptogramins (adjusted HR, 1.21; 95% CI, 1.15–1.27). Moreover, maternal use of antibiotics during 9 months before pregnancy (adjusted HR, 1.27; 95% CI, 1.24–1.31) and 9

months postpartum (adjusted HR, 1.32; 95% CI, 1.28–1.36) were found to be similarly associated with asthma. The authors concluded that prenatal antibiotic exposure was associated with a dose-dependent increase in childhood asthma risk, but underlined that similar associations were found for maternal antibiotic use before and after pregnancy. The study results suggest that such associations are either not directly causal, or not specific to pregnancy.

5 Concluding Remarks

Macrolides are among the most commonly prescribed antibiotics during pregnancy in the USA and in European countries. These agents cross the placenta, and therefore establishing their fetal safety is essential in ensuring evidence-based safe use during fetal development.

Fetal and neonatal outcomes following prenatal macrolide exposure have been investigated by several heterogeneous studies, yielding conflicting results. Increased risks of spontaneous miscarriage, major congenital malformations, cardiovascular malformations, digestive system malformations, preterm birth, and low birthweight were reported in some observational studies but not in others; moreover, most of these studies were at a serious risk of bias. In addition, there is preliminary evidence that prenatal macrolide exposure is associated with increased risks of infantile hypertrophic pyloric stenosis, cerebral palsy or epilepsy, and childhood asthma, but these findings need to be confirmed by further investigations.

Based on FDA pregnancy risk categories, azithromycin (category B) is less dangerous than clarithromycin (category C), which, therefore, should be used with great caution in pregnant women.

In summary, there remains a great need for high-quality data on adverse offspring outcomes following azithromycin use during pregnancy. These data will be particularly useful for healthcare providers in their decision-making about the treatment of pregnant women with azithromycin, considering that high levels of anxiety among healthcare providers and pregnant women often lead to suboptimal drug therapy even in life-threatening maternal infections.

Therefore, based on available data, we conclude that azithromycin should only be used during pregnancy when clinically indicated if the benefits of treatment are expected to outweigh the potential risks.

Declarations

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Availability of data and materials Not applicable.

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Author contributions RA, LC, CL, and GC designed the study; LC, CL, and FD collected and analyzed data; CL, LC, GC, FD, and RA wrote the manuscript; LC and FD gave technical support and conceptual advice; LC, CL, and RA contributed to manuscript revisions. All authors read and approved the final manuscript.

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