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FEMALE GENITAL TRACT INFECTIONS (JD SOBEL, SECTION EDITOR)

# Out with the Old, In with the New: A Review of the Treatment of Intrapartum Infections

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## Abstract

**Purpose of Review** In 2019, a global meta-analysis demonstrated incidence of 3.9% for chorioamnionitis, 1.6% for endometritis, 1.2% for wound infection, 0.05% for sepsis, and 1.1% for maternal peripartum infection (Woodd et al. in PLOS Med 16(12):e1002984, 2019). Antimicrobial regimens for these infections are based on older microbiology profiles and may not account for changes in antimicrobial susceptibility data or the availability more modern antimicrobial therapies.

**Recent Findings** Recommendations for treatment of puerperal infection have not changed significantly in recent decades, despite the availability of new antimicrobial therapies with improved safety profiles.

**Summary** A consideration should be given to monotherapy or two-drug regimens that have fewer toxicities than older therapeutics and require less monitoring. Obtaining appropriate microbiologic data and antimicrobial susceptibility data is critical to balance broad-spectrum coverage with the threat of antimicrobial resistance.

**Keywords** Chorioamnionitis · Endometritis · Intra-amniotic infections · Antimicrobials

## Introduction

Intraamniotic infections (e.g., chorioamnionitis) (IAIs) are polymicrobial infections of the amniotic fluid, placenta, fetus, fetal membranes, or decidua that can seriously endanger the life of the pregnant person and fetus if not recognized and treated urgently with intrapartum antibiotics and often delivery of the fetus [1–3]. Ascension of microorganisms from the vagina into the previously sterile amniotic cavity is the most likely mechanism of infection, though hematogenous dissemination (e.g., *Listeria*) or iatrogenic introduction after a procedure (amniocentesis, chorionic villus sampling) is also possible [2, 4]. Chorioamnionitis is associated with a 2–3.5 fold increased odds of adverse neonatal outcomes depending on gestational age [5]. IAI also leads to higher odds of adverse maternal outcomes, including 2.3 higher odds of requiring cesarean delivery [6]. In a 2004 multicenter study of IAI, there was an increased risk of

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postpartum hemorrhage, uterine atony, septic pelvic thrombophlebitis, and pelvic abscess, in addition to neonatal outcomes of 5-min Apgar ≤ 3, neonatal sepsis, and seizures [7]. Postpartum endometritis is caused by a similar mechanism of ascension microorganisms from the vagina into upper genital tract but is diagnosed following delivery, often after cesarean section as it is the highest morbidity associated with cesarean delivery [8••, 9].

In 2019, a global meta-analysis of "high-quality" studies demonstrated pooled incidence of 3.9% for chorioamnionitis, 1.6% for endometritis, 1.2% for wound infection, 0.05% for sepsis, and 1.1% for maternal peripartum infection defined as a composite of two or more of the other infection types [1]. There are differences in incidence, particularly for wound infection and postpartum endometritis in patients who had a cesarean delivery versus vaginal delivery, with a 21.2-fold increased risk of endometritis in persons who underwent a trial of labor or 10.3 without the trial of labor, compared to spontaneous vaginal delivery [9].

The American College of Obstetricians and Gynecologists (ACOG) recommended guidelines for diagnosis and treatment in a Committee Opinion "Intrapartum Management of Intraamniotic Infection" in 2017 and reaffirmed in 2022 [2]. The evidence on which these guidelines are based need better informed studies: for example, every conclusion from the 2015 Cochrane review on postpartum endometritis has notation about the "low quality of evidence" for their conclusions and specifically note that the quality of the evidence using GRADE comparing clindamycin with an aminoglycoside to another regimen was "low to very low for therapeutic failure, severe complications, wound infection, and allergic reaction" with unclear risk of bias in most of the studies included [10]. Furthermore, there is a wide variance in clinical approaches to selection of antimicrobial treatment. A 2012 survey of US obstetricians involved in the management of intrapartum and postpartum infections, 212 respondents indicated use of > 25 antimicrobial regimens and a wide range of doses and duration, indicating the dearth of high-quality evidence guiding practice recommendations [11••]. Herein, we review the literature for the modern perspective on appropriate treatment for IAI.

## Microbiology

As IAI is an ascending infection of flora from lower genital tract, particularly the vagina, uterine contractions are presumed to play a role in the ascension of these microorganisms; evidence for this is supported by twin pregnancies where microorganisms are found in the presenting amniotic sac rather than the non-presenting sac [4]. The 2014 Cochrane Review noted that the most commonly isolated organisms were *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Neisseria gonorrhea*, *Trichomonas vaginalis*, *Bacteroides* spp., *Gardnerella vaginalis*, *Escherichia coli*, anaerobic streptococcus, and group B streptococcus (GBS) [12, 13]. Additional studies confirm these organisms with the addition of *Lactobacillus*, with the specific identification of *Streptococcus agalactiae* and *Streptococcus anginosus* group [14–17]. While some of these species remain identified in a more recent (2015–2017) study of endometritis, not all are the same: *E. coli*, *Enterococcus faecalis*, streptococci, *Klebsiella* spp., and *Enterobacter* spp. were the most common organism identified [18••]. This variation in identification of organisms in older studies compared to modern studies has significant implications in antimicrobial therapy.

Some studies rely on placental or amniotic fluid cultures for data. Gram-negative anaerobes were more prevalent in amniotic fluid cultures in low-birth-weight pregnancies with IAI, compared to GBS, *E. coli*, and enterococci [19]. Placentas frequently demonstrate *Ureaplasma urealyticum* (47%) and *Gardnerella vaginalis* (26%), while amniotic fluid demonstrated *Ureaplasma urealyticum* (47%), gram-negative anaerobes (38.4%), *Mycoplasma hominis* (30.4%), *Bacteroides bivius* (29.5%), and *Gardnerella vaginalis* (24.5%) [13]. In an evaluation of mid-gestation (16–26 weeks) fetuses, stillbirths, and placentas that were examined and cultured, microorganisms were recovered in 66% cases. GBS was identified most frequently ($n = 21$, in 13 cases as the sole organism), followed by *E. coli* and *Ureaplasma urealyticum* in mixed infections [15].

However, cultures do not always correlate with the microorganisms identified in the amniotic fluid by 16S rRNA profiles, while > 70% of the organisms on the rRNA gene sequencing revealed a bacterial profile consistent with the vaginal flora (*Sneathia*, *Ureaplasma*, *Prevotella*, *Lactobacillus*, *Escherichia*, *Gardnerella*, *Peptostreptococcus*, *Peptoniphilus*) [4]. It is proposed that vaginal dysbiosis from a dominant *Lactobacillus* flora to a more mixed profile (*Gardnerella*, *Prevotella*, *Prophyromonas*, *Bacteroides*, *Peptostreptococcus*, *Megasphaera*, *Sneathia*) may contribute to development of infection [4].

As expected, considering the pathophysiology, polymicrobial infections are widely documented. In endometritis, Watts et al. noted that 80% of patients had polymicrobial infections and 60% had anaerobes [20]. A small study ($n = 27$) of endometritis demonstrated 5.5 isolates per sample, most commonly *Bacteroides* spp., *Peptostreptococcus*, *Gardnerella vaginalis*, enterococci, facultative gram-negative rods, and *Mycoplasma hominis* [21]. Similarly, a 1986 cohort identified at least one organism in 82% of women with endometritis, with similar microbiology [22]. A 1989 post cesarean delivery endometritis study had 2.3 aerobes plus anaerobes per patient; 11% of patients were also bacteremic, and 45% of those were *Mycoplasma* sp. [23].

There are organisms that should always be presumptively considered as a source of these infections, due to the well-noted polymicrobial nature and high frequency of reported incidence of some particular organisms when cultures are obtained. Of high concern is GBS due to high colonization rates (10–30%) at baseline, and the concern that approximately 50% women who are colonized will transmit the organism to their newborn, through vertical transmission during labor or after the rupture of membranes [24]. Additionally, a 2003 study comparing antibiotics for "acute pelvic infections" including both obstetric and gynecologic infections noted *E. coli* as the single most common pathogen [25]. For chorioamnionitis, *Bacteroides*, *Prevotella*, *E. coli*, anaerobic gram-positive cocci, GBS, and *Ureaplasma urealyticum* are considered the more dominant organisms, for endometritis, GBS, anaerobic gram-positive cocci, aerobic gram-negative bacilli (predominant *E. coli*, *K. pneumoniae*, *Proteus* spp.), and anaerobic gram-negative bacilli (*Bacteroides* spp., *Prevotella*) [18••, 26].

A source of clinical controversy is the discrepant findings of microbiology, lack of targeted antimicrobial to those organisms, and clinical cure. Note that genital mycoplasmas like *Ureaplasma* species and *Mycoplasma hominis* are found in the lower genital tract of > 70% women [27]. The genital mycoplasmas are noted to provoke robust inflammatory reactions affecting the maternal and fetal compartments, and are identified in patients with and without signs of clinical IAI [27]. Virulence factors in the genital mycoplasmas may explain their invasive potential, though not their pathogenesis because other organisms like streptococci have higher pathogenicity [4]. In endometritis and postpartum fevers, studies have shown microbiologic proven involvement of *Gardnerella*, *Ureaplasma*, or *Chlamydia trachomatis*; however, clinical therapy directed at these organisms was not required for clinical cure [20]. However, in persons undergoing non-elective cesarean delivery who received standard of care antimicrobial prophylaxis, adjunctive azithromycin reduced the risk of postoperative infection, presumably targeting those mycoplasms [28]. There is one 1989 study of 67 patients with a 91% success rate that noted all its treatment failures included patients with *Mycoplasma* spp. and *Ureaplasma* spp. [23]. In another situation with *Enterococcus* rather than the genital mycoplasmas, an endometritis cohort which did not receive antimicrobials with enterococcal coverage had similar rates of clinical failure [16]. In a recent study, cultures with *Gardnerella vaginalis*, *Candida albicans*, and coagulase-negative staphylococci were excluded from analyses due to presumed non-pathogenic microorganisms [29]. Therefore, no clear recommendations can be made specifically without further clarity on these issues.

Antimicrobial resistance is an ongoing concern, particularly in infections that are generally diagnosed clinically. In a 2011 review of IAI, there were notes of drug resistance as methicillin-resistant *Staphylococcus aureus* (MRSA), but no vancomycin-resistant *Enterococcus* had been identified [13]. There are reports of very-low-birth-weight infants whose mothers received ampicillin intrapartum being more likely to have ampicillin-resistant *E. coli* [30]. In 2011–2017 study, there was one extended-spectrum β-lactamase (ESBL) producer among 84 patients in Israel [29]. However, a Ukrainian study from 2015 to 2017 noted 22.8% ESBL in their Enterobacteriaceae (now Enterbacterales), and 15.4% MRSA rates, with these antimicrobial resistance rates presenting a significant burden in their healthcare system and raising alarm for the overall trend of increasing antimicrobial resistance [18••]. It is obviously critically important to consider local rates of multi-drug resistance when caring for patients, but also relevant to note that these older studies of microbiologic causes for these infections preceded the significant antimicrobial resistance we have in modern times.

## Antimicrobials

Safety and efficacy data is generally not available for obstetrics from randomized clinical controlled trials, as pregnant women are generally excluded and there are ethical concerns about including them [31••]. Only 10% of medications marketed since the 1980s have sufficient data on risk to the infant. Additionally, physiologic changes like increases in total body water, blood volume, and plasma volume changes all impact the volume of distribution of various antibiotics. Additionally, gastrointestinal motility may impact absorption of oral antibiotics, and antibiotic clearance can vary as renal blood flow changes the serum creatinine and glomerular filtration rate and hepatic enzymes change drug metabolism. All of these physiologic changes in pregnant women make it extraordinarily complex to understand the implications of antimicrobial use in pregnant women [31••]. The beta-lactam antibiotics, including penicillins and cephalosporins, are widely considered safe to use though the changes in plasma volume may impact dose or frequency of dosing. Note that aminoglycosides are considered more harmful to the fetus than beta-lactams, although a short course, where the benefit outweighs risk, is considered acceptable [31••].

Leaning into this lack of safety data, the 2014 Cochrane review on IAI noted that "currently, there is insufficient information to determine the most appropriate antimicrobial regimens for the treatment of intra-amniotic infections" [12]. The 2016 Cochrane Review for treatment of septic abortion also notes the need for high-quality randomized clinical controlled trials to provide evidence; the studies utilized in that review are all > 30 years old [32]. The 2015 Cochrane review on endometritis endorses fewer treatment failures in the clindamycin plus aminoglycoside group compared to those with

cephalosporins or penicillins, but report a low quality of evidence [10]. In one of their analyses of 20 studies, only 6 of those studies still have applicability in the USA in 2023 due to access to those particular antimicrobials included in the analyses. They do also include studies that only utilized penicillin as comparator, which we know would be inferior due to antimicrobial resistance and the understanding of the microbiology of these infections.

Even in 1983, authors wrote that "the newer cephalosporins are also effective as single agent therapy" in reference to using ceftazidime compared to clindamycin and tobramycin in an endometritis cohort, which also had a 9% bacteremia rate; there was no difference in cure rate, side effects, or length of stay [16]. A 1983 study of cefotaxime to gentamicin and clindamycin had 97.5% success rate in the cefotaxime group compared to the gentamicin/clindamycin group at 95% [33]. In 1986, a comparison of cefoxitin to gentamicin/clindamycin in patients with post-cesarean delivery infections saw similar rates of cure and tolerability with no difference in febrile degree hours or length of stay [34].

A 2020 review indicates ceftriaxone, clarithromycin, and metronidazole as an ideal regimen, after clinical trials demonstrated its utility in premature rupture of membranes, partially due to clarithromycin's transplacental passage and coverage of genital mycoplasmas [14]. Note that clarithromycin is recommended for use with caution, while other macrolides such as azithromycin are considered safe in pregnancy [31••]. Also publishing in 2020, ertapenem, piperacillin/tazobactam, and cefotaxime were most consistently active in vitro against organisms identified, namely Enterobacterales [18••].

A 2021 meta-analysis included three trials in an analysis of ampicillin/sulbactam compared to ampicillin with gentamicin and showed no difference in outcomes [35]. A 2015 study of that same regimen showed decreased postpartum morbidity in the ampicillin/sulbactam group, in addition to no difference in the treatment groups [36]. Earlier studies in 1989 (two), 1993, and 1996 compared ampicillin/sulbactam to clindamycin and gentamicin as being equally effective and well tolerated [17, 23, 37, 38]. A comparison of ampicillin/sulbactam to cefotetan in 1989 for gynecologic or obstetric infections found similar outcomes in both groups [39].

There is frequently a lack of antimicrobial susceptibility data, as these are generally clinical diagnosis without microbiologic confirmation. When said data is obtained, as noted above, there can be a successful clinical cure even when resistant or untreated organisms are identified. In a group with polymicrobial endometritis (including enterococci and genital mycoplasmas), a comparison of 96% of these organisms being susceptible to ticarcillin/clavulanate to 86% being susceptible to cefoxitin in vitro, there was no difference in clinical success rates between the two groups [20]. However, empiric antimicrobial coverage was insufficient in 30% of patients for whom microbiologic data was available, and this translated into significantly increased length of stay [29].

Logically, broad-spectrum coverage will be successful. In septic abortion, combinations of ampicillin/gentamicin/metronidazole were "universally efficient" over the multitude of other regimens utilized clinically; however, authors noted that piperacillin/tazobactam as empiric monotherapy covered 93.3% of all isolates [29]. A 2003 randomized double-blind multicenter study compared piperacillin/tazobactam to ertapenem for acute pelvic infections in 412 patients and found similar outcomes and frequency of adverse drug events [25].

*Enterococcus* and *Ureaplasma* can be missed in cephalosporin-based regimens, and *Ureaplasma* needs the specific addition of azithromycin [8••]. None of the ampicillin/gentamicin/clindamycin combination cover genital mycoplasmas; however, this regimen has > 95% success rate in treating maternal infections and as well as reducing neonatal sepsis; therefore, it is unclear if specific genital mycoplasma coverage is needed [27]. Another analysis noted that in comparison of regimens with *B. fragilis* activity to those without, there was still an 80% success rate, "raising questions about the type of woman in which a broad-spectrum regimen is necessary" [10].

Antimicrobial resistance patterns must be considered in the modern era. In anaerobic bacteria, there is widespread resistance to clindamycin in *Bacteroides* spp. (notably *Bacteroides fragilis*) and *Clostridium perfringens*, while metronidazole retains susceptibility in these organisms [39]. Mothers treated with ampicillin intrapartum arean independent risk factor for neonatal ampicillin-resistant *E. coli* early-onset sepsis [40].

## Special Considerations: Cesarean Delivery

According to ACOG, the single most important risk factor for infection in the postpartum period is cesarean delivery. Therefore, the mother should receive appropriate surgical prophylaxis and rapid treatment of recognized infections like IAI [41]. In an attempt to compare different classes of antibiotics given to women to routinely prevent postpartum composite infection during cesarean delivery, there was insufficient evidence and a "gap in knowledge" regarding comparability of first-generation cephalosporins (e.g., cefazolin) to clindamycin or to clindamycin plus an aminoglycoside [42]. Most of the emphasis focused on the impact on infants. During cesarean delivery, patients should receive cefazolin surgical site infection prophylaxis prior to skin incision; prior recommendations included holding antibiotics until after cord clamping are outdated [43].

Notably, this regimen would also include the adjunctive use of pre-incision azithromycin in addition to routine surgical prophylaxis in non-elective cesarean deliveries [28]. The addition of azithromycin over other antimicrobials in the

Tita et al. trial for azithromycin adjunctive to surgical site infection prophylaxis (i.e., cefazolin) was posited to add coverage for ureaplasma, but also, they discuss the potential role for covering broadly in women who are at a higher risk for infection due to the unplanned nature of their cesarean delivery. The cultures in this large randomized clinical controlled trial was most common organisms in wound infections: 2.5% overall had cultures positive for at least one organisms, prevalence of positive cultures at 1.4% in azithromycin group compared to 3.6% in the placebo and the most common organism was gram-negative bacilli, staphylococcal species, and enterococcal species and cultures for ureaplasma and mycoplasmas were not routinely performed [29]. However, this study excludes women undergoing a scheduled cesarean section and those with chorioamnionitis, which limits generalization; the current recommendation is for azithromycin only in those with unplanned or emergency cesareans and not all cesarean deliveries [41].

A thorough antimicrobial allergy history should be obtained. This is critical in women undergoing cesarean delivery, due to a true anaphylactic penicillin allergy driving towards the use of clindamycin or vancomycin [41]. Clindamycin is problematic due to its resistance profile in the modern era. Vancomycin requires a longer infusion time prior to cesarean [41]. Surgical site infections are also overall higher in patients who receive second-line antimicrobial prophylaxis due to penicillin allergy [43]. As always, it is critical that the patient receive the most appropriate antimicrobial regimen for them, and penicillin allergies are frequently inaccurately listed in patient's profiles; up to 95% labeled with penicillin allergies may be able to tolerate this class of medications but are seldom evaluated for accuracy of the allergy [44••].

## Duration

It is worthwhile to note that while older studies withheld antibiotics until after delivery or at the least, after cord clamping due to concerns for the neonates, multiple studies in meta-analysis confirm the logic that earlier antibiotic initiation at the time of recognition of IAI improves maternal, neonatal, and resource-related outcomes when compared to deferring to the post-partum period [35].

The 2014 IAI Cochrane review indicated insufficient evidence to determine whether antibiotics should be continued into the postpartum period [12]. However, a 2003 randomized cohort of patients with IAI to continue antimicrobials until afebrile and asymptomatic for 24 hours compared to receiving the next scheduled dose postpartum determined no difference in treatment failure; this was confirmed in meta-analysis [35, 45]. This was confirmed in a cohort that compared vaginal to cesarean delivery just receiving the postpartum dose, though acknowledged that a subset (15%) of the cesarean deliveries may have benefited from longer courses [46]. This informs the ACOG recommendations around IAI that intrapartum antimicrobial agents administered for suspected or confirmed IAI should not be continued postpartum, unless there is clinical suspicion for endometritis or other clinical features of infection, such as bacteremia or persistent fever postpartum [2]. One dose postpartum should be given to women undergoing cesarean deliveries [2].

The 15% of cesarean deliveries that had clinical failure in the abovementioned cohort were at higher risk for endometritis, which would indicate the need for ongoing treatment for infection. However, one study shows in cesarean delivery after IAI that there was no decreased risk for endometritis if antimicrobials were continued compared to a single preoperative dose [47]. Additionally, if patients are bacteremic, appear septic, or have persistent fever, additional antibiotics and potentially infectious disease consultation may be warranted to help determine why the patients are persistently ill [14]. It is well noted in septic abortion literature that all tissues must be removed to obtain source control and therefore control over the infection, but a short course of antimicrobials is still essential for treatment [47–49].

## Conclusions

There remain significant gaps in knowledge regarding safety of antimicrobial regimens in pregnant or laboring mothers, which leaves insufficient data in clinical trials to modernize clinical practice for these infections. This lack of certainty in evidence likely drives the well-identified significant clinical practice variations in how IAI is treated. Much of the pre-existing data pre-dates modern microbiologic techniques for identifying pathogenic organisms as well as up-to-date antimicrobial susceptibility data. It is likely that monotherapy regimens such as piperacillin/tazobactam, ampicillin/sulbactam, or ertapenem would all provide reliable polymicrobial coverage with favorable side effect profiles and have significantly lower nursing burdens for administration; the local antibiogram must be considered before endorsing too narrow or too broad of an antimicrobial regimen [8••]. Other antimicrobials including second- or third-generation cephalosporins, with or without metronidazole, also likely provide adequate coverage for these infections. Short durations of antimicrobials, while considering the complexity of the individual patient, are sufficient treatment. Allergy histories should be obtained in all patients. Appropriate surgical site prophylaxis should be given prior to incision in cesarean deliveries, preferably guideline-based first-generation

cephalosporins with adjunctive azithromycin in nonelective cesarean delivieries.

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## Compliance with Ethical Standards

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the authors.

**Conflict of Interest** The authors declare no conflict of interests.

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