Open Forum Infectious Diseases

REVIEW ARTICLE

Getting With the Times: A Review of Peripartum Infections and Proposed Modernized Treatment Regimens

Zachary Pek,[1] Emily Heil,[2] and Eleanor Wilson[1]

[1]Division of Infectious Diseases, University of Maryland Medical Center, Baltimore, Maryland, USA, and [2]Department of Pharmacy, University of Maryland Medical Center, Baltimore, Maryland, USA

This article provides a review of peripartum infections, including intra-amniotic infection, postpartum endometritis, and postabortal infections. We present a case of postabortal infection to frame the review. The microbiology, pathogenesis, risk factors, diagnosis, and treatment of peripartum infections are reviewed, and a critical appraisal of the literature and available guidelines is provided. There is a focus on discussing optimal antimicrobial therapy for treating these infections.

Keywords. infections in pregnancy review; intraamniotic infection or chorioamnionitis; postpartum endometritis; postabortal infection or septic abortion; antibiotic therapy and stewardship.

CASE REPORT

A 34-year-old woman (gravida 2, para 1) with a history of cesarean section 6 years prior was admitted to the hospital for high fevers and abdominal pain after an outpatient abortion.

One week before admission, the patient was diagnosed with cesarean scar pregnancy at 10 weeks gestation and received uterine artery embolization and intravenous methotrexate 50 mg. On postoperative day 3, there was still fetal cardiac activity, so the patient received a 50-mg injection of saccular methotrexate and 25 mg of methotrexate by mouth. Seven days later, she presented to the emergency department with a 2-day history of worsening fever, lower abdominal pain, and vaginal bleeding. Her temperature was 102.5°F, heart rate 125, and blood pressure 87/45. Examination revealed diffuse abdominal tenderness and exquisite fundal tenderness, and speculum exam revealed cervical bleeding and mild cervical motion tenderness. Complete blood count and chemistries were unremarkable. Blood and urine cultures were negative. Pelvic ultrasound demonstrated a demised embryo with fluid and air in the gestational sac; septic abortion was diagnosed. Intravenous piperacillin-tazobactam and clindamycin were started. There was rapid clinical improvement with normalization of vital signs. Dilation and curettage were performed on hospital day #1, and products of conception were removed. There were no intra-operative cultures. The Infectious Diseases consultants recommended stopping clindamycin and continuing piperacillin-tazobactam for 48 hours postoperation. On hospital day 3, antibiotics were switched to doxycycline and metronidazole by mouth, to complete 10 days total of therapy. The patient was discharged on hospital day 5 and recovered on close outpatient follow-up.

INTRODUCTION

Pregnancy-related mortality remains a serious problem in the United States, with a rate of 17.3 maternal deaths per 100 000 live births in 2017. Infection is the second leading cause of maternal death, responsible for 12.7% of cases [1]. Infectious complications in the peripartum period include antepartum infections (intra-amniotic infection or chorioamnionitis), postpartum infections (postpartum endometritis), and postabortal infections. These diagnoses are made clinically, often without the support of pathologic or microbiologic evidence. Thus, studies of these disorders include heterogenous patient populations, and clinical management relies on empiric antimicrobial therapy and removal of the infectious source either by delivery or curettage of retained products of conception.

This review focuses on the management of peripartum infections, including primarily intra-amniotic infection, early postpartum endometritis, and postabortal infections. The shifting landscape of antimicrobial resistance patterns requires a reevaluation of empiric antimicrobial therapy choices in treating these infections. Particular attention will be paid to postabortal infections, where the shifting legal landscape of abortion rights lends urgency to this discussion. We will also examine the pathogenesis, risk factors, clinical features, and diagnosis of peripartum infections and offer direction for the future.

Received 19 July 2022; editorial decision 30 August 2022; accepted 01 September 2022; published online 5 September 2022

Correspondence: Emily Heil, PharmD, MS, Department of Pharmacy, University of Maryland Medical Center, 20 N. Pine St, N413, Baltimore, MD 21201 (eheil@rx.umaryland.edu).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofac460

MICROBIOLOGIC AND PATHOGENETIC CONCEPTS OF PERIPARTUM INFECTION

Microbiology

Peripartum infections share common microbial pathogens derived from the microbiota of the lower genital tract. However, there are limited high-quality data regarding the specific microbiology of peripartum infections. Most of these data were collected 30+ years ago and were limited by likely contamination of endometrial cultures by the lower genital tract microbiota and unclear pathogenic relevance of certain microorganisms. Generally, peripartum infections are often polymicrobial and are caused by microorganisms found in the endocervix and vagina, including gram-positive bacteria (most importantly group B *Streptococcus*), gram-negative bacteria (*Escherichia coli* and other Enterobacterales), anaerobic bacteria including *Clostridium* spp., and microorganisms responsible for sexually transmitted infection syndromes (including *N. gonorrhoeae*, *C. trachomatis*, and *Mycoplasma/Ureaplasma* spp.) (Table 1) [2–5]. Especially in the case of *C. trachomatis* and *Mycoplasma/Ureaplasma* spp., it is unclear to what degree these organisms have a pathogenic role in peripartum infections [2, 7].

Pathogenesis

Intra-amniotic infection or chorioamnionitis occurs primarily by ascending bacterial invasion from the lower genital tract into the typically sterile amniotic cavity and results in infection of the fetal membranes, amniotic fluid, placenta, and/or decidua (Figure 1). Under normal circumstances, this is largely prevented by the presence of intact fetal membranes and the cervical mucus plug during pregnancy, but these natural barriers are disrupted upon initiation of labor and rupture of membranes, allowing for ascension of bacteria. Rarely, intra-amniotic infection can be caused by hematogenous seeding from maternal bacteremia (in the case of infection with *Listeria monocytogenes*) or after invasive procedures such as amniocentesis [8]. Intraamniotic infection will persist until delivery, but antimicrobial therapy in the intrapartum period significantly reduces the risk of maternal and fetal complications [9].

Postpartum endometritis is an infection of the endometrium and myometrium, and potentially the broad ligament and peritoneal/retroperitoneal space. It most commonly occurs after cesarean section results in contamination of the uterine tissues by infected amniotic fluid [3]. However, neither clinical chorioamnionitis nor cesarean section is a prerequisite to the development of postpartum endometritis, and endometritis can develop in the setting of sterile amniotic fluid, as well as after vaginal delivery [10].

Postabortal infection, sharing a similar pathogenesis to intra-amniotic infection, occurs as a result of ascension of vaginal microorganisms into the uterine cavity, which may occur after spontaneous or induced abortion. This is especially common with unsafe abortions as a result of the lack of sterile procedure, the higher rate of retained products of conception, and operative trauma [3].

Other important peripartum infections not included in this review are cuff cellulitis and abscess, tubo-ovarian abscess, septic pelvic thrombophlebitis, osteomyelitis pubis, clostridial myonecrosis, and Fournier's gangrene. These infections have different microbiologic, pathogenetic, and therapeutic underpinnings than the peripartum infections discussed and would be better considered as a separate topic.

RISK FACTORS

The risk of intra-amniotic infection is directly proportional to the time between rupture of membranes and delivery, increasing with prolonged duration of labor, young/age nulliparity (likely due to longer duration of labor), and preterm premature

Table 1. Microbiology of Peripartum Infections

Microbiology of Peripartum Infections	
Gram-positives	Aerobic: group B *Streptococcus*, coagulase-negative staphylococci, *Enterococcus*, *Listeria monocytogenes*, other *Streptococcus* spp.
	Rarely *Staphylococcus aureus* and group A *Streptococcus*
	Anaerobic: *Clostridium* spp., *Lactobacillus* spp., *Peptostreptococcus* spp.
Gram-negatives	Aerobic: *Escherichia coli* and other Enterobacterales, *Neisseria gonorrhoeae*, *Sneathia*, *Acinetobacter* spp. Rarely *Pseudomonas aeruginosa*
	Anaerobic: *Bacteroides* spp., *Gardnerella vaginalis*, *Prevotella* spp., *Fusobacterium* spp.
Others[a]	*Chlamydia trachomatis*, *Mycoplasma* spp., *Ureaplasma* spp., *Candida* spp.

[a]In rare cases, hematogenous viral infection can involve the placenta and intra-amniotic space including Zika virus, cytomegalovirus, varicella zoster virus, parvovirus B19, rubella, and herpes simplex virus. Similarly, *Plasmodium* spp. can cause placental infection and mimic bacterial chorioamnionitis in the appropriate geographic setting [6].

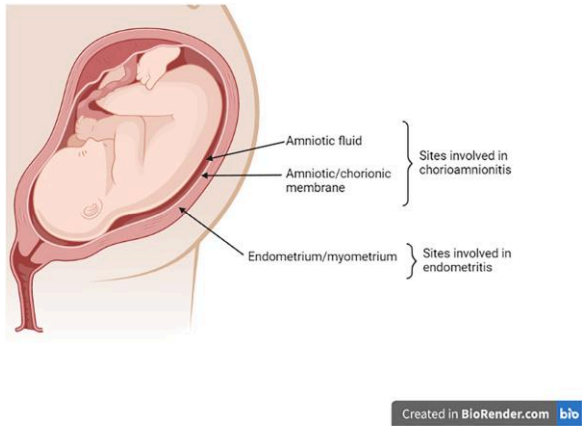

Figure 1. Anatomy of peripartum infections.

rupture of membranes. Preexisting bacterial vaginosis is another recognized risk factor, possibly due to alterations in the vaginal microbiota. Trichomoniasis increases risk of premature rupture of membranes and may thereby increase risk for intra-amniotic infection. However, current Centers for Disease Control and Prevention guidelines do not suggest routine screening for bacterial vaginosis or trichomoniasis in pregnant individuals [11–13]. Epidemiologically, a 2019 meta-analysis of high-quality studies found the incidence of clinical intra-amniotic infection among all pregnancies to be 3.9% [14]. Rates of histologic chorioamnionitis (inflammation without microbiological or clinical signs of infection) are substantially higher, at ~20% for term births and up to 50% for preterm births [15].

The primary risk factor for postpartum endometritis is cesarean section, especially when performed emergently (after onset of labor) and in the presence of concomitant risk factors for intra-amniotic infection [16, 17]. Antibiotic prophylaxis is indicated for all patients undergoing cesarean section to reduce the risk of surgical site infections and postpartum endometritis. Rates vary by study, but a recent Cochrane review showed rates of postpartum endometritis without antibiotic prophylaxis of 27% for patients undergoing emergent cesarean section, compared with 4% for elective cesarean section. With antibiotic prophylaxis, these rates were reduced to 10% and 1.8%, respectively [18]. As above, while cesarean section is the primary risk factor for endometritis, these infections can also occur after vaginal delivery.

Postabortal infection is rare after safe abortion, with most studies showing a rate <5% and many showing a rate <1% [19]. Rates of infection are similar between medical and surgical abortion and between first and second trimester abortion, although the data on infectious complications after second trimester abortion are limited (Table 2) [20]. The primary risk factor for postabortal infection is unsafe abortion, defined as "a procedure for terminating an unintended pregnancy, carried out either by persons lacking the necessary skills or in an environment that does not conform to minimal medical standards, or both" [27]. Legal barriers or limited access to abortion services can increase the rate of unsafe abortion 8-fold [24]. The rate of postabortal infection after unsafe abortion is 20%–30% [24]. Globally in 2000, there were an estimated 67 900 maternal deaths due to unsafe abortion, with a case fatality rate of 0.4% [24]. This case fatality rate in developed countries was 0.1%, ~80-fold higher than for a safe abortion [24].

In the case of spontaneous pregnancy loss, rates of infectious complications may be higher than in induced abortion, possibly as a result of later presentation to medical care, with most studies showing a rate of 1%–3%, with similar rates across treatment approaches of expectant, medical, and surgical management (Table 2) [21, 22].

Table 2. Overview of Abortion Management and Associated Complication Rates

Type of Abortion	Management Options	Rates of Infectious Complications, % [Ref]
Spontaneous[a]	Expectant management	2–3 [21, 22]
	Medical management (most often oral misoprostol and mifepristone)	1–2 [21]
	Surgical management (vacuum aspiration, dilation, and curettage)	2–3 [21, 23]
Induced[b]	Medical management (similar to management of spontaneous abortion) Option for systemic or local methotrexate (low dose)	0.23 [20]
	Surgical management (similar to management of spontaneous abortion)	0.26 [20]
…	Unsafe abortion	20–30 [24]

[a]Spontaneous abortion will refer to pregnancy loss before 20 weeks gestation. Pregnancy loss after 20 weeks gestation is referred to as stillbirth, and there are more limited epidemiologic and treatment studies in this population.

[b]Ninety percent of induced abortions in the United States occur in the first trimester [25]. Data on complications of second trimester abortions are more limited, with 1 study showing a rate of 0.14% of infectious complications (3/2218 women) [26].

CLINICAL FEATURES

Peripartum infections share similar clinical features and are distinguished from one another primarily by the obstetric timeline (Table 3). These infections are suspected upon the presence of fever, with supporting findings including maternal or fetal tachycardia, midline lower abdominal pain or uterine tenderness, and occasional foul-smelling or purulent lochia.

Intra-amniotic infection occurs prenatally and is suspected when fever develops after onset of labor or rupture of membranes. It is usually a self-limited infection that resolves upon delivery, but it may result in maternal complications, including an increased risk of pelvic abscess, wound infection, and maternal bacteremia, and fetal complications, such as fetal death, neonatal sepsis, fetal pneumonia, and other severe complications such as cerebral palsy [28].

Postpartum endometritis occurs postnatally and is suspected when fever develops on the first or second day after cesarean section. Presenting symptoms usually resolve within 24–48 hours of initiation of antibiotic therapy; longer persistence should raise suspicion for an uncontrolled source of infection (retained products of conception, pelvic abscess). In rare cases, infection can result in septic shock or toxic shock syndrome from group A *Streptococcus, Staphylococcus aureus,* or *Clostridium* spp. infection including clostridial myonecrosis [29].

Postabortal infections should be suspected when fever and lower abdominal/pelvic pain develop within 4 days of abortion. Imaging may reveal retained intrauterine fetal material or complications of abortion. Similar to postpartum endometritis, rare cases may be complicated by septic shock, toxic shock syndrome, and Fournier's gangrene [27].

Table 3. Overview of Peripartum Infections

Overview of Peripartum Infections

Infection type	Intra-amniotic infection	Postpartum endometritis	Postabortal infection
Clinical presentation	Fever and maternal or fetal tachycardia, maternal leukocytosis, or purulent cervical discharge Uterine/lower abdominal pain may be present	Fever, uterine/lower abdominal pain and tenderness, purulent uterine drainage Rare cases complicated by septic shock, toxic shock syndrome, pelvic abscess	Fever, pelvic/lower abdominal pain, uterine discharge Rare cases complicated by septic shock, toxic shock syndrome, Fournier's gangrene, pelvic abscess
Obstetric timeline	Antepartum, most commonly after rupture of membranes	Postpartum, within 24–48 h of cesarean section	After abortion, within 96 h
Risk factors	Rupture of membranes, multiple vaginal examinations Prolonged duration of labor, young/age nulliparity, bacterial vaginosis Especially high risk with preterm premature rupture of membranes[a]	Cesarean section, especially when performed emergently (after onset of labor) Presence of intra-amniotic infection or risk factors for the same	Unsafe abortion
Treatment[b]	Piperacillin-tazobactam to be continued until delivery No benefit for continuing antibiotics beyond delivery Alternatives: ertapenem, ceftriaxone plus metronidazole, ampicillin/sulbactam (pending local susceptibilities) Delivery is usually not emergent and can follow typical obstetric indications	Piperacillin-tazobactam to be continued until afebrile ×48 h [c]Alternatives: ertapenem, ceftriaxone plus metronidazole, ampicillin/sulbactam (pending local susceptibilities) If concomitant skin/soft tissue infection is present (eg, with surgical site infection of cesarean section wound), recommend anti-MRSA coverage only in presence of patient risk factors for colonization, presence of necrotizing soft tissue infection, or in cases of septic shock If fever does not resolve in 24–48 h, consider advanced imaging Deliver retained products of conception Prevention: azithromycin ×1 dose perioperatively in nonelective cesarean section	Piperacillin-tazobactam until clinical improvement, then switch to oral antibiotic therapy for 10–14 d Alternatives: ertapenem, ceftriaxone plus metronidazole, ampicillin/sulbactam (pending local susceptibilities) Urgent surgical evacuation of the uterus Prevention: doxycycline 200 mg and metronidazole 500 mg PO ×1 before procedure for patients with: (1) early spontaneous abortion who undergo surgical uterine aspiration and (2) induced surgical abortion at any gestational age

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]Note that preterm premature rupture of membranes is a risk factor for chorioamnionitis but in some cases may itself be caused by chorioamnionitis.

[b]These suggestions are based on the authors' review of the literature and are not reflective of the American College of Obstetricians and Gynecologists' or any other medical society's recommendations.

[c]Routine operative antimicrobial prophylaxis from cesarean section can be discontinued upon initiation of beta-lactam/beta-lactamase inhibitor therapy.

DIAGNOSIS

The diagnosis of peripartum infection is made clinically, and most studies have not shared standardized diagnostic criteria. There is imprecision in these diagnoses (eg, with the overlap in presentation between intra-amniotic infection and epidural-related maternal fever, or between postpartum endometritis and physiologic postoperative fever). Due to the known benefit and relative safety of antibiotic therapy, there should be a low treatment threshold when peripartum infection is suspected.

Intra-amniotic infection, per the American College of Obstetrics and Gynecology (ACOG) guidelines, is "[diagnosed] when the maternal temperature is 38–39°C and one additional clinical risk factor is present…[maternal or fetal tachycardia, maternal white blood cell count (WBC) >15k, foul smelling or purulent cervical discharge]" or when the maternal temperature is >39°C alone [30]. Other tests that are rarely used in clinical practice include amniotic fluid analysis, with a WBC count >50 cells/mm, elevated interleukin-6 level, glucose level <15 mg/dL, or positive gram stain/bacterial culture supporting the diagnosis.

Postpartum endometritis, according to the Centers for Disease Control and Prevention/National Healthcare Safety Network's reporting criteria, is diagnosed when either:

1. the patient has organism(s) identified from endometrial fluid or tissue by a culture- or non-culture-based microbiologic testing method that is performed for the purposes of clinical diagnosis or treatment, for example, not active surveillance culture/testing;

   OR

2. the patient has ≥2 of the following signs or symptoms: fever (>38.0°C), pain or tenderness (uterine or abdominal) with no other recognized cause, or purulent drainage from uterus [31].

Postabortal infections do not have standardized diagnostic criteria, and, similar to other peripartum infections, the presenting symptoms lack specificity. The World Health Organization recommends that any patient who has recently

undergone abortion who presents with abdominal/pelvic pain or vaginal discharge plus fever should be treated with antibiotics for postabortal infection [27]. This recommendation emphasizes the need for a low treatment threshold in these conditions.

It is the opinion of these authors that routine imaging is not necessary for the diagnosis of peripartum infection, but may be useful when patients do not improve after 24–48 hours of appropriate therapy, to evaluate for an uncontrolled infectious focus or to rule out alternate etiologies (ie, appendicitis). In high-resource settings, routine pelvic ultrasound to evaluate for retained products of conception is reasonable when postpartum endometritis or postabortal infection is suspected.

TREATMENT

Source control, as with all infections, represents the most important measure in the management of peripartum infections. Intra-amniotic infection is cured upon delivery of the fetus and placenta, and in postpartum endometritis and postabortal infection, evacuation of any retained products of conception is critical to clinical cure. Antimicrobial therapy is an important addition to source control efforts. Historically, obstetric infections have been treated with a combination of ampicillin, gentamicin, and clindamycin. This empiric regimen is based on *in vitro* culture and susceptibility data from studies in the 1980s and has been shown to be clinically effective [9]. To date, there are very few data allowing for head-to-head comparison of these antibiotics with more modern antibiotic regimens (ie, beta-lactam/beta-lactam inhibitor combinations), and most institutions continue to use traditional 2- or 3-drug combination therapy in the management of peripartum infections.

In intra-amniotic infection, standard management as outlined in a 2017 ACOG Committee Opinion includes initiation of antimicrobial therapy with ampicillin and gentamicin followed by prompt induction or augmentation of labor in the absence of contraindications [30]. Evidence for early initiation of antibiotic therapy is derived from a small randomized controlled trial (n = 45) that showed decreased maternal postpartum hospital days, maternal febrile days, neonatal hospital length of stay, and neonatal pneumonia or sepsis with intrapartum rather than postpartum initiation of antibiotics [9]. Antibiotic therapy is continued through delivery, with a 2014 Cochrane review showing no further benefit of antibiotics when continued after delivery [15]. In this Cochrane review, attention was paid to the choice of specific antimicrobial agent; however, the majority of patients received some combination of ampicillin, gentamicin, and clindamycin, and the number of patients receiving alternative therapy was too low to permit any comparison. A subsequent systematic review in 2021 found that patients treated for intra-amniotic infection with ampicillin/sulbactam compared with ampicillin plus gentamicin had a lower composite end point of endometritis, pneumonia, sepsis, blood transfusion, and ileus [32]. These findings were driven by a 2015 randomized controlled trial comparing ampicillin/sulbactam with ampicillin plus gentamicin for the treatment of intra-amniotic infection, which showed a decreased rate of postpartum infection (including sepsis, endometritis, and pneumonia) in the ampicillin/sulbactam group (0/43 patients vs 4/49 patients; $P = .03$) [33]. Rarely, *Candida* spp. have caused intra-amniotic infection and are associated with high neonatal mortality; however, while the exact epidemiology is unclear, these infections appear to be extremely rare, and we do not recommend empiric antifungal coverage unless they are isolated on culture [34].

For postpartum endometritis, evidence for antimicrobial therapy is summarized in a 2015 Cochrane review, which compiled data from studies mostly conducted in the 1980s and 1990s [35]. Again, there was support for a short duration of antimicrobial therapy, with no further benefit seen after there was clinical improvement and absence of fever for 24–48 hours. In cases where fever persists beyond 24–48 hours after initiation of antimicrobial therapy, we recommend obtaining imaging to evaluate for retained products of conception, pelvic abscess, or any other deep focus of infection. In this 2015 review, there was a comparison between different antimicrobial agents, with the patients who received clindamycin and gentamicin combination therapy experiencing less treatment failure compared with any other regimen. However, this comparator group consisted primarily of penicillin, ampicillin, or early generation cephalosporins plus an aminoglycoside. This comparator group did not have appropriate coverage of penicillin-resistant anaerobes, and a subgroup analysis showed that the improved outcomes in the clindamycin plus gentamicin group were due to appropriate coverage of these anaerobes. This finding is now especially pertinent, as changing patterns of resistance have raised concerns that clindamycin no longer reliably provides coverage of these relevant anaerobes [36, 37]. Of note, a comparison between beta-lactam/beta-lactam inhibitor combination therapy vs any other regimen revealed no difference in rates of treatment failure. Separately, with regards to prevention of infection after nonelective cesarean section, a single dose of azithromycin 500 mg IV given peri-operatively in addition to standard antibiotic prophylaxis was associated with a lower rate of postpartum endometritis (3.8 vs 6.1%) and a lower rate of a composite outcome of endometritis, wound infection, or any other infection [38]. This finding may be attributable to coverage of *Ureaplasma* spp., although these findings have not yet been replicated.

In the prevention of postabortal infections, there are data to support antimicrobial prophylaxis in 2 settings: (1) in patients with early (<22 weeks gestation) spontaneous abortion who undergo surgical uterine aspiration and (2) in patients who undergo first trimester induced surgical abortion. Data supporting the use of prophylactic antibiotics in patients with early

spontaneous abortion are derived from a randomized controlled trial in 2019 that demonstrated that prophylactic doxycycline 400 mg and metronidazole 400 mg given each as a single dose before surgical uterine aspiration reduced the rate of postabortal infection (1.5% vs 2.6%; relative risk [RR], 0.6; 95% CI, 0.37–0.96) [23]. In the case of prophylaxis before induced surgical abortion, a 2012 Cochrane review demonstrated a lower rate of upper genital tract infection (5.8% vs 9.4%; RR, 0.59; 95% CI, 0.46–0.75) when patients were given a dose of prophylactic antibiotics before the procedure [39]. There was significant heterogeneity among antibiotics used in the included studies, which included use of tetracyclines, metronidazole, clindamycin, beta-lactams, and fluroquinolones. Taken together, these findings led to an ACOG recommendation for a single 200-mg dose of doxycycline given preoperatively for both suction curettage of induced abortion at any gestational age and surgical management of early pregnancy loss [40]. We agree with this strategy; however, we recommend adding metronidazole to this regimen, as this was the regimen used in the study by Lissauer and colleagues, which is the strongest evidence in this field at this time.

To date, there are very limited data regarding empiric antimicrobial therapy for postabortal infections. A Cochrane review in 2015 reviewed 3 small randomized controlled trials conducted in the 1960s and 1970s [41]. These trials mostly evaluated antimicrobial agents that are no longer in use, including chloramphenicol, cephalothin, and kanamycin. The results of this review showed that clindamycin alone was superior to penicillin plus chloramphenicol and was likely also superior to cephalothin plus kanamycin, although the generalizability of these findings to current practice is limited. In 2020, a single-center retrospective review from Israel evaluated the adequacy of empiric antibiotic choices in patients with postabortal infection [4]. The investigators collected blood, cervical swab, and uterine product cultures from patients with postabortal infection and compared antimicrobial agents with in vitro microorganism sensitivity data. A combination of ampicillin, gentamicin, and metronidazole was active against 100% of recovered organisms in vitro, with piperacillin-tazobactam covering 93% of organisms in vitro. Piperacillin-tazobactam was active against all but 1 bacterial isolate, an extended-spectrum beta-lactamase-producing Enterobacterales spp. However, in the combination therapy group, coverage of gram-negative organisms relied on gentamicin, which has been shown to be associated with poorer outcomes when used as monotherapy in gram-negative bacteremia compared with beta-lactam antibiotics despite in vitro susceptibility [42]. Of note, clindamycin was replaced with metronidazole in this study, likely due to clindamycin's expected suboptimal anaerobic coverage. Data regarding optimal duration are limited, with common clinical practice including parenteral antimicrobial therapy until clinical improvement is achieved, followed by a 10–14-day oral therapy tail. There are limited data to inform the choice of empiric oral therapy, and in the patient we reported on above, we chose doxycycline/metronidazole based on the common pathogens isolated in pelvic inflammatory disease. After our review of the literature, a more appropriate oral therapy regimen for this condition may be amoxicillin/clavulanate, or levofloxacin plus metronidazole for severely penicillin-allergic patients. If blood or tissue cultures are positive, it is appropriate to give therapy targeted toward the identified pathogen.

A re-evaluation of the traditional regimens used in peripartum infections is needed in light of increasing resistance rates to early-generation beta-lactams among Enterobacterales and to clindamycin among anaerobic pathogens, particularly *Bacteroides* spp. Additionally, there are concerns regarding toxicity and dosing challenges with aminoglycosides, risk for *Clostridium dificile* colitis with clindamycin, and an opportunity to significantly lower the operational burden on nursing and pharmacy services by streamlining current clunky combinations of antibiotics requiring every 6-to-8-hour dosing of multiple agents. Other considerations include selecting antibiotic regimens that are safe in breastfeeding for postpartum patients and regimens that are safe in pregnancy in the event that immediate delivery or induced abortion is delayed due to patient preference, medical considerations, or legal restrictions on abortion procedures. Piperacillin-tazobactam, ertapenem, and ceftriaxone plus metronidazole provide reliable gram-positive, gram-negative, and anaerobic coverage, have a favorable side effect profile, and have a significantly lower nursing burden, particularly once-daily ertapenem. For institutions with high (>80%) local *E. coli* susceptibility, ampicillin/sulbactam is also a reasonable alternative. When indicated, oral stepdown therapy can be accomplished with amoxicillin/clavulanate. Fluoroquinolones are a reasonable option as well for institutions with high local *E. coli* susceptibility and provide an oral option for patients with concomitant bacteremia. While beta-lactam agents are generally considered safe in pregnancy and breastfeeding, safety in pregnancy or breastfeeding of other agents must be considered when relevant as many alternative agents such as quinolones and tetracyclines, while not contraindicated, may carry some risk. One potential gap in coverage with beta-lactam monotherapy is for atypical organisms, specifically *Mycoplasma* and *Ureaplasma* spp. However, it is unclear if mollicutes play a pathogenic role in most of these infections, with multiple studies showing that despite frequent isolation of these organisms from endometrial and occasionally blood cultures, there are no worse clinical outcomes when these organisms are not covered [2, 7]. These organisms have not been covered by traditional regimens of ampicillin, gentamicin, and clindamycin, and we do not feel that coverage is indicated beyond the use of azithromycin for surgical prophylaxis for nonelective cesarean section. Similarly, *Enterococcus* spp. are another gap in coverage if ertapenem or cephalosporin

antibiotics are used; however, these organisms play an unclear role in the pathogenesis of these infections, and the authors believe that empiric coverage of *Enterococcus* is not mandatory. A summary of our recommendations for antimicrobial therapy for peripartum infections can be found in Table 3.

There are important limitations to these recommendations, which do not address cases complicated by septic shock, bacteremia, surgical site infection, clostridial myonecrosis, and Fournier's gangrene, in which setting the relevant guidelines for these conditions should supersede our above recommendations, and Infectious Diseases consultation should be sought if needed [43, 44].

CONCLUSIONS

Peripartum infections remain a common problem facing patients and health care providers. Empiric antimicrobial therapy is based largely on outdated data and habit and must now be reevaluated in the face of growing antimicrobial resistance, new safety information, and available streamlined alternatives. Therapy with a beta-lactam/beta-lactam inhibitor or ertapenem may provide improved antimicrobial coverage, with less risk of antibiotic adverse effects (nephrotoxicity/ototoxicity with aminoglycosides; *Clostridium dificile* colitis with clindamycin) and less burden on nursing and pharmacy services. Further clinical studies evaluating the efficacy of these more modern antibiotics in the management of peripartum infections are needed. Additionally, in the case of postabortal infections, optimal medical therapy is necessary but not sufficient in improving health outcomes. There must be attention to continued advocacy for access to safe abortion as we enter a post-Roe world, a time similar to "the pre-HAART era of AIDS…when needless deaths struck down people in the prime of their lives" [45].

Acknowledgments

Author contributions. All authors contributed directly to writing and editing the manuscript.

Financial support. The authors received no funding or financial support for the production of this manuscript.

Patient consent. We attempted to contact the patient described in the case report for consent; however, we were unable to reach her. We altered the demographics and case description so that the patient is unidentifiable. We obtained approval from the University of Maryland Medical Center Institutional Review Board.

Potential conflicts of interest. The authors: No reported conflicts of interest.

References

1. Centers for Disease Control and Prevention. Pregnancy Mortality Surveillance System. **2022**. Available at: https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm&hash;causes. Accessed May 21, 2022.
2. Watts DH, Eschenbach DA, Kenny GE. Early postpartum endometritis: the role of bacteria, genital mycoplasmas, and *Chlamydia trachomatis*. Orsett Gynecol **1989;** 73:52–60.
3. Beigi RH. Intrapartum, postpartum, and postabortal infections. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; **2020**:1477–81.
4. Fouks Y, Samueloff O, Levin I, Many A, Amit S, Cohen A. Assessing the effectiveness of empiric antimicrobial regimens in cases of septic/infected abortions. Am J Emerg Med **2020;** 38:1123–8.
5. Romero R, Gomez-Lopez N, Winters AD, et al. Evidence that intra-amniotic infections are often the result of an ascending invasion—a molecular microbiological study. J Perinat Med **2019;** 47:915–31.
6. Cappelletti M, Presicce P, Kallapur SG. Immunobiology of acute chorioamnionitis. Front Immunol **2020;** 11:649.
7. McCormack WM, Lee YH, Lin JS, Rankin JS. Genital mycoplasmas in postpartum fever. J Infect Dis **1973;** 127:193–6.
8. Redline RW. Placental inflammation. In: Keeling JW, Khong TY, eds. Fetal and Neonatal Pathology. Springer London; **2007**:90–101.
9. Gibbs RS, Dinsmoor MJ, Newton ER, Ramamurthy RS. A randomized trial of intrapartum versus immediate postpartum treatment of women with intra-amniotic infection. Obstet Gynecol **1988;** 72:823–8.
10. Blanco JD, Gibbs RS, Castaneda YS, Clair P. Correlation of quantitative amniotic fluid cultures with endometritis after cesarean section. Am J Obstet Gynecol **1982;** 143:897–901.
11. Newton ER, Prihoda TJ, Gibbs RS. Logistic regression analysis of risk factors for intra-amniotic infection. Obstet Gynecol **1989;** 73:571–5.
12. Newton ER, Piper J, Peairs W. Bacterial vaginosis and intraamniotic infection. Am J Obstet Gynecol **1997;** 176:672–7.
13. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep **2021;** 70:1–187.
14. Woodd SL, Montoya A, Barreix M, et al. Incidence of maternal peripartum infection: a systematic review and meta-analysis. PLoS Med **2019;** 16:e1002984.
15. Chapman E, Reveiz L, Bonfill Cosp X. Antibiotic regimens for management of intra-amniotic infection. Cochrane Database Syst Rev **2014;** CD010976.
16. Seaward PG, Hannah ME, Myhr TL, et al. International multicentre term prelabor rupture of membranes study: evaluation of predictors of clinical chorioamnionitis and postpartum fever in patients with prelabor rupture of membranes at term. Am J Obstet Gynecol **1997;** 177:1024–9.
17. Burrows LJ, Meyn LA, Weber AM. Maternal morbidity associated with vaginal versus cesarean delivery. Obstet Gynecol **2004;** 103:907–12.
18. Smaill FM, Grivell RM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev **2014;** 2014: CD007482.
19. White K, Carroll E, Grossman D. Complications from first-trimester aspiration abortion: a systematic review of the literature. Contraception **2015;** 92:422–38.
20. Upadhyay UD, Desai S, Zlidar V, et al. Incidence of emergency department visits and complications after abortion. Obstet Gynecol **2015;** 125:175–83.
21. Nielsen S, Hahlin M, Platz-Christensen J. Randomised trial comparing expectant with medical management for first trimester miscarriages. BJOG Int J Obstet Gynaecol **1999;** 106:804–7.
22. Nanda K, Lopez LM, Grimes DA, Peloggia A, Nanda G. Expectant care versus surgical treatment for miscarriage. Cochrane Database Syst Rev **2012;** 2012: CD003518.
23. Lissauer D, Wilson A, Hewitt CA, et al. A randomized trial of prophylactic antibiotics for miscarriage surgery. N Engl J Med **2019;** 380:1012–21.
24. World Health Organization. *Unsafe Abortion: Global and Regional Estimates of the Incidence of Unsafe Abortion and Associated Mortality in 2000*. World Health Organization; **2004**.
25. Kortsmit K, Jatlaoui TC, Mandel MG, et al. Abortion surveillance: United States, 2018. MMWR Surveill Summ **2020;** 69:1–29.
26. Patel A, Talmont E, Morfesis J, et al. Adequacy and safety of buccal misoprostol for cervical preparation prior to termination of second-trimester pregnancy. Contraception **2006;** 73:420–30.
27. World Health Organization. *Safe Abortion: Technical and Policy Guidance for Health Systems*. 2nd ed. World Health Organization; **2012**. Available at: https://apps.who.int/iris/handle/10665/70914. Accessed May 20, 2022.
28. Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol **2010;** 37:339–54.
29. Faro S. Postpartum endometritis. Clin Perinatol **2005;** 32:803–14.
30. Committee opinion No. 712: intrapartum management of intraamniotic infection. Obstet Gynecol **2017;** 712:e95–101.
31. Centers for Disease Control and Prevention. *National Healthcare Safety Network (NHSN) Patient Safety Component Manual*. Centers for Disease Control and Prevention; **2022**. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf. Accessed May 19, 2022.

32. Alrowaily N, D'Souza R, et al. Determining the optimal antibiotic regimen for chorioamnionitis: a systematic review and meta-analysis. Acta Obstet Gynecol Scand **2021;** 100:818–31.
33. Greenberg M, Yeaton-Massey A, Hazard K, et al. 264: comparison of ampicillin/sulbactam versus ampicillin/gentamicin for treatment of intrapartum chorioamnionitis: a randomized controlled trial. Am J Obstet Gynecol **2015;** 212:S145.
34. Qureshi F, Jacques SM, Bendon RW, et al. *Candida funisitis:* a clinicopathologic study of 32 cases. Pediatr Dev Pathol **1998;** 1:118–24.
35. Mackeen AD, Packard RE, Ota E, Speer L. Antibiotic regimens for postpartum endometritis. Cochrane Database Syst Rev **2015;** 2015:CD001067.
36. Hastey CJ, Boyd H, Schuetz AN, et al. Changes in the antibiotic susceptibility of anaerobic bacteria from 2007–2009 to 2010–2012 based on the CLSI methodology. Anaerobe **2016;** 42:27–30.
37. Karlowsky JA, Walkty AJ, Adam HJ, Baxter MR, Hoban DJ, Zhanel GG. Prevalence of antimicrobial resistance among clinical isolates of *Bacteroides fragilis* group in Canada in 2010–2011: cANWARD surveillance study. Antimicrob Agents Chemother **2012;** 56:1247–52.
38. Tita ATN, Szychowski JM, Boggess K, et al. Adjunctive azithromycin prophylaxis for cesarean delivery. N Engl J Med **2016;** 375:1231–41.
39. Low N, Mueller M, Van Vliet HA, Kapp N. Perioperative antibiotics to prevent infection after first-trimester abortion. Cochrane Database Syst Rev **2012;** 2012: CD005217.
40. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG practice bulletin No. 200: early pregnancy loss. Obstet Gynecol **2018;** 132:e197–207.
41. Udoh A, Effa EE, Oduwole O, Okusanya BO, Okafo O. Antibiotics for treating septic abortion. Cochrane Database Syst Rev **2016;** 2016:CD011528.
42. Leibovici L, Paul M, Poznanski O, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteremia: a prospective, observational study. Antimicrob Agents Chemother **1997;** 41:1127–33.
43. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med **2021;** 49:e1063–143.
44. Stevens DL, Bisno AL, Chambers HF, et al. Executive summary: practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis **2014;** 59:147–59.
45. Minkoff H, Gibbs RS. Preparing for a post-Roe world. Am J Obstet Gynecol **2019;** 220:249.e1–3.