Mini Review

CLINICAL INVESTIGATION

Clostridium difficile infection in obstetrics and gynecology patients

Abstract

The incidence of nosocomial infections or, in other words, healthcare-associated infections, is bigger in developing countries. World Health Organisation (WHO) estimates that as much as 15% of all hospitalized patients will contract an infection related to medical procedures.

Nosocomial pathogens are represented by viruses, bacteria, fungal and parasites. The pathway of contamination is different and these could be represented by environmental sources, healthcare staff or other infected patients.

Over the past decades, *Clostridium difficile* infection became more and more frequent in hospitalized patients. Unfortunately, not all the cases are reported and some of the patients are diagnosed with time after discharge, in other medical services.

Gynecologic surgery, as well as obstetric patients already, have numerous risk factors for infection. The addition of *Clostridium difficile* infection in these patients could be catastrophal. Thus, the reported rising incidence of *Clostridium difficile* infection in gynecological and obstetric patients should be alarming and unacceptable since the pathogen is transmitted from one infected patient to another through unproperly cleaned medical staff hands.

Although the main risk factor for *Clostridium difficile* infection is the use of broad-spectrum antibiotics, the treatment is also antibiotic. Thus, the overuse of prophylactic antibiotherapy in patients undergoing gynecologic surgery should not be recommended.s.

Keywords: infection • *Clostridium difficile* • gynecologic surgery

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Introduction

Numerous recent reports in the literature emphasise the increasing incidence as well as the severity of *Clostridium difficile* infection over the past decades. Moreover, the number of pregnant women diagnosed with *Clostridium difficile* infection was rising over the past years and this was associated with a significant increase in maternal morbidity and mortality [1].

Among other risk factors, the extensive use of antibiotics is strongly associated with this morbidity.

Short literature review

Decades ago, *Clostridium difficile* infection was very rare and only a few cases documented. In a report published by James et al., only 18 cases of *Clostridium difficile* infection were documented among 74120 admissions in obstetric and gynecology units of two tertiary level hospitals [2]. A more recent retrospective cohort study, published in 2017, included 2757 cases complicated by *Clostridium difficile* infection of all the 12592178 obstetrical patients [1].

According to a recent study over a 3-year period published by *Clostridium difficile* Meda et al., in January 2019 in UK, *Clostridium difficile* the rate of *Clostridium difficile* infection documented in pregnant as well as postpartum women increased from 0.41 to 0.93 per 1,000 deliveries [3].

Yet, more and more studies seem to suggest the same idea: that the *Clostridium difficile* infection in peripartum women may be an underreported problem outside North America [3-7].

The pathological mechanism is not very complicated. The overuse of broad-spectrum antibiotics will eventually disrupt the normal bowel flora and thus, the colonic *Clostridium difficile* will freely multiply and will subsequently produce its exotoxins [8].

Toxins A and B, encoded by TcdA and TcdB, are the main primary mediators produced by *Clostridium difficile*. Both toxins are structurally large molecules in which four polypeptide domains could be identified: N-terminal glucosyltransferase, cysteine protease, central translocation domain and C-terminal receptor-binding domain [9].

The first step in the pathogenic pathway is represented by the adhesion of TcdA and TcdB to the cell-surface carbohydrates through the C-terminal receptor domain followed by entry into the cell by receptor-mediated endocytosis [9,10].

Once entered into the intestinal cell, both toxins will act as glucosyltransferases which will activate the enterocytes Rho GTP-ases. The final effect of these reactions will be the disorganization of the colonocytes` cytoskeleton and disruption of cellular junctions which could eventually lead to cellular death [11-13].

Although *Clostridium difficile* is the most common cause of diarrhea in hospitalized patients [14], there is actually a wide spectrum of clinical manifestations associated with this infection. The signs and symptoms could range from a totally asymptomatic patient to a fulminant disease with toxic megacolon. It is clear that this diversity in clinical manifestations is related to host and pathogen interaction [15]. It is about the ability of the immune system to produce a certain amount of serum IgG antitoxin A [16,17]. Other patient risk factors or comorbidities could play an important role as well.

There are some well-documented risk factors associated with *Clostridium difficile* infection and these include age over 65, female gender, chronic bowel inflammatory diseases, malnutrition, obesity, immunodeficiency syndromes, prolonged hospital admissions, use of antibiotics or other medications such as histamine-2 blockers, the surgery itself [15].

Patients undergoing gynecologic surgery have at least 3 of the well-known risk factors. In gynecologic surgery, prophylactic antibiotics are intended to prevent surgical site infections in procedures that expose the abdominal cavity to the polymicrobial flora of the vagina [18]. However, antibiotic prophylaxis is considered to be overused [19].

In pregnant women, additional risk factors could be identified. Besides cesarean or perineal wound infections, multiple gestations, pregnancy in young women or over the age of 35 and smoking, comorbidities such as pneumonia or pyelonephritis during pregnancy are predisposing factors.

Young pregnant women are increasingly recognized as being susceptible to this infection, even if they have traditionally been considered low-risk patients for the *Clostridium difficile* infection [20].

Unger et al reported in their case-control study that Caesarean section, previous hospitalization

during pregnancy and significant underlying illness were statistically significant ($p<0.001$) [20].

Among these risk factors, numerous meta-analysis from the literature emphasize once more the relationship between antibiotic exposure and *Clostridium difficile* infection. This could have a major impact since almost 50% of women are receiving antibiotics during a hospital delivery and up to 30% of cesarean delivery cases are receiving prophylactic antibiotherapy in the USA [8,21,22]. Yet, the numbers are surely greater in other countries, including Romania.

A study including 2671 pregnant women revealed two risk factors for the *Clostridium difficile* infection in this category of patients: cesarean section delivery and the use of antibiotics, especially ampicillin/gentamicin/clindamycin [8].

A recent American study concluded that, in most of the cases, prophylactic antibiotherapy is not indicated [23]. Thus, careful analysis of risks and benefits of antibiotic therapy on every pregnant woman and selection of patients who will truly benefit from this therapy is mandatory. This is even more sustained by the fact that *Clostridium difficile* infection in pregnancy is associated with an increase in maternal death rates [24].

Large scale, multicenter studies that focus on the *Clostridium difficile* infected patients undergoing gynecologic surgery are lacking. In this context, there are many questions that need answers. One of the questions is about the surgical procedure. Are different procedures associated with different rates of *Clostridium difficile* infection and, if so, which procedure is associated with the highest risk [25].

It is clear now that the use of broad-spectrum antibiotics predisposes women to *Clostridium difficile* infection. But not all the patients who are exposed to *Clostridium difficile* and receive antimicrobials will develop the infection.

Antibiotics most commonly associated with *Clostridium difficile* infection are penicillins, clindamycin, and cephalosporins [26].

Repeated doses of antibiotics are strongly associated with *Clostridium difficile* infection. In order of higher to a lower risk of *Clostridium difficile* infection, the antibiotics are second and third-generation cephalosporins, amoxicillin or ampicillin with clavulanic acid, antipseudomonal penicillins, clindamycin, quinolones, aminoglycosides, ampicillin, and penicillin [27].

The Infectious Diseases Society of America (IDSA) recommends restriction of fluoroquinolones, clindamycin, and cephalosporins [28].

For mild to moderate *Clostridium difficile* infections the recommended treatment is with oral Metronidazole. In severe or recurrent infections, Vancomycin is the treatment of choice.

Conclusion

It is very clear that the incidence of *Clostridium difficile* infection is rising in all surgical patients. It is our responsibility to limit as much as possible the risk of infection.

The antibiotic exposure is the main risk factor for the *Clostridium difficile* infection, so the overuse of prophylactic antibiotherapy is not recommended.

Executive summary

The incidence of nosocomial infections or, in other words, healthcare-associated infections, is bigger in developing countries. World Health Organisation (WHO) estimates that as much as 15% of all hospitalized patients will contract an infection related to medical procedures.

Nosocomial pathogens are represented by viruses, bacteria, fungal and parasites. The pathway of contamination is different and these could be represented by environmental sources, healthcare staff or other infected patients.

Over the past decades, *Clostridium difficile* infection became more and more frequent in hospitalized patients. Unfortunately, not all the cases are reported and some of the patients are diagnosed with time after discharge, in other medical services.

Gynecologic surgery, as well as obstetric patients already, have numerous risk factors for infection. The addition of *Clostridium difficile* infection in these patients could be catastrophic. Thus, the reported rising incidence of *Clostridium difficile* infection in gynecological and obstetric patients should be alarming and unacceptable since the pathogen is transmitted from one infected patient to another through unproperly cleaned medical staff hands.

Although the main risk factor for *Clostridium difficile* infection is the use of broad-spectrum antibiotics, the treatment is also antibiotic. Thus, the overuse of prophylactic antibiotherapy in patients undergoing gynecologic surgery should not be recommended.

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