Gas gangrene in pregnancy, parturition, and abortions requiring urological and surgical intervention: aetiology, pathogenesis, risk factors, and some current practices

Monday Komene Sapira 1, * and Emmeh Sweiyi Fiddo 2

1 Department of Surgery, University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria.
2 Department of Obstetrics and Gynecology, University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria.

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Abstract

Introduction: Gas gangrene in pregnancy, perinatal periods, or after an abortion has a poor prognosis. This study aims to present risk factors for the disease as reported worldwide and to discuss current concepts of its aetiology, pathogenesis.

Materials and Methods: Using search terms, a bibliographical search was done in PubMed/ Medline and PubMed Central databases for publications on gas gangrene in pregnancy, abortions, and delivery published within the study period. Risk factors for the disease were identified by studying each of the reports. Results were presented with a discussion of the aetiology of the disease.

Results: Eighty-one (81) studies reporting on 67 patients and aetiology of the disease were studied. The most common causes of the disease were clostridia which infected 63 (94.03%) of the patients. Identified risk factors were abortions, prolonged labor, prolonged obstructed labor, standard spontaneous vaginal delivery, Cesarean sections, episiotomy, amniocentesis, cordocentesis, ruptured uterus with fetal death, perforated appendix, pelvic tumors, trauma, foreign bodies in living tissues, accumulation of hematoma and devitalized tissues in pelvic tissues. Lethal effects of the pathogens were reported to be mediated by exotoxins produced by clostridia.

Conclusion and Recommendations: Common risk factors are standard diagnostic and therapeutic procedures in pregnancy and its outcome. Local policies need to be developed for the extended use of antibiotics in normal labor and when carrying out procedures in pregnancy, delivery, and abortions. Attractive points in the aetiology for the prevention of the disease are (i) prevention of attachment of clostridia to tissue cells and (ii) pre-pregnancy immunization of women of childbearing age.

Keywords: Gas gangrene in pregnancy; Delivery and abortions; Aetiology; Pathogenesis; Risk factors

1 Introduction

Gas gangrene affecting any part of the body may rapidly develop fatal complications. When it occurs in pregnancy, it may result in fetal and maternal deaths. Available treatment methods, especially for advanced cases, are sometimes very invasive and leave patients with wide-ranging functional deficiencies and outcomes that might have unacceptable cosmetic results. Reports in the literature indicate that worldwide, the disease has high morbidity and high mortality [1]. In its early stages, the disease may simulate common febrile conditions and other illnesses [2]. An adequate understanding of its risk factors, diagnostic features, and aetiology is, therefore, necessary for early diagnosis, informed, aggressive treatment, and good prognosis.

* Corresponding author: Sapira Monday Komene; Email: monday.koesi@gmail.com

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This study aims to present the risk factors for gas gangrene in pregnancy, its outcome, and the current aetiopathogenesis of the disease. We shall also critically appraise some standard diagnostic and therapeutic procedures in urological and surgical practice, as well as obstetrics and gynecology. How they may affect the risk of developing the disease shall be examined.

2 Material and Methods

This study was carried out at the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria. Using search terms, a bibliographical search was done in the Pub Med/Medline, and Pub Med Central computerized databases for articles on gas gangrene in pregnancy, delivery, and abortions (GGPDA) published during the 56 years from January 1966 to June 2022. Keywords used were “Gas gangrene in pregnancy,” “Gas gangrene in abortions,” “Risk factors for gas gangrene after childbirth,” Aetiopathogenesis of gas gangrene in pregnancy,” “Risk factors for gas gangrene in abortions,” and “Risk factors for gas gangrene in pregnancy and delivery.” Relevant references to these articles were also searched for complete articles. Other relevant texts not in the databases above were consulted and cited. In each case, the authors’ information and patient data were studied to record the origin of the publications.

Scope of the Study

Publications on GGPDA affecting any part of the maternal or fetal tissues and publications on the lesion from the first day of the last menstrual period to the 42nd day post-partum were included. These included articles on incomplete, therapeutic, and criminally induced abortions. All reported prenatal, intrapartum, and post-partum interventions or procedures were studied. GGPDA complicating therapeutic procedures, spontaneous vaginal delivery (SVD), and assisted vaginal delivery and abortions were studied.

3 Results

The bibliographical search revealed 81 articles that satisfied the primary inclusion criteria of the study. These were studied. Of these case reports were sixty-seven (67). Fourteen (14) reports were either review articles, case series, or discussions of the aetiopathogenesis of the lesion. Due to the heterogeneous nature of the reports, a meta-analysis of the reports could not be done. Instead, data considered to be relevant to the objectives of the study were extracted, collated, and presented.

One hundred patients were reported to have had gas gangrene in pregnancy. Sixty-seven patients had specific bacteriological diagnoses. Sixty-three of these (94.03%) infections were due to clostridia. Further details are presented as cluster charts (Figures 1 and 2).

![Figure 1](image)

**Figure 1** Pathogenic causes of gas gangrene in pregnancy, delivery and abortions.
Figure 2 The percentage of other pathogens compared with clostridia as causes of gas gangrene in pregnancy, delivery, and abortions

Table 1 Risk factors for gas gangrene in pregnancy delivery and abortions with references.

<table>
<thead>
<tr>
<th>Author(s)/ Journal/Year of Publication</th>
<th>No of Patients</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirkpatrick CJ et al Arch Gynecol 1982 [12]</td>
<td>1</td>
<td>Normal labor, spontaneous vaginal delivery (SVD)</td>
</tr>
<tr>
<td>(ii) Milchev N et al Akush Ginekol (Sofia) 1990 [16]</td>
<td>1</td>
<td>Criminal abortion</td>
</tr>
<tr>
<td>(iv) Barret JP et al Obstet Gynecol 2002 May [18]</td>
<td>1</td>
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### Discussion

#### 4.1 This is part of a series of studies by the authors on gas gangrene in pregnancy and its outcome.

Advances in medical sciences and technology have probably improved the management and outcome of infective diseases. Generally worldwide such advances, including appropriate use of antimicrobials, good nutrition and improved levels of hygiene, might have also reduced the incidence and prevalence of infections. However, in many communities and countries, infections still contribute substantially to fetal and maternal deaths, infant morbidity and mortality, poor outcomes of pregnancies, and complications of abortions [30]. Reports in the literature observed in this study indicate the potentially lethal nature of gas gangrene in pregnancy and its outcome [1, 31]. The success of prevention of the disease and its current treatment methods depends on adequate understanding of its aetiopathogenesis. Knowledge of the risk factors of the disease outlined in this study (Table 1) will facilitate its early diagnosis, prevention and treatment.

Sixty-three of 67 patients (94.03%) that reported a specific pathogenic diagnosis of gas in pregnancy or its outcome in this study had infections with clostridia. This means that if clostridia could be controlled, gas gangrene in pregnancy could be virtually eradicated. These species of clostridia, which are obligatory anaerobes, Gram-positive, exotoxin-producing bacilli with sub-terminal spores, have been isolated from cervical flora of 10% to 17% of healthy women in different and independent studies [32, 33]. Clostridium perfringens species were isolated from 47% of patients reported in this index study (Figures 1 and 2). In different earlier studies reported in the literature, clostridia were also detected as usual residents of intestinal and vaginal cavities of 25% of healthy women [23]; and vaginal flora of 3% to 10% of normal women [34]. Clostridium perfringens was found to be the most commonly isolated clostridium in necrotizing fasciitis [35, 36]. Our observations in this study are in agreement with these observations.

Clostridium septicum, Clostridium sordellii, and group A streptococcal species (Figure 1) were reported in association with the spontaneous occurrence of gas gangrene, rapid clinical deterioration of the disease, and poor prognosis [1, 31, 37]. This shows the high levels of virulence possessed by these clostridia. Specific diagnosis of these pathogens should elicit prompt, aggressive, and dedicated treatment for patient survival. It is unclear from available and consulted records whether Toxoplasma gondii (Figure 1) reported in the literature can cause gas gangrene as a single pathogen. It was, however, reported to have caused the disease in synergism with Clostridium perfringens [38]. The clinical significance is that both organisms should be eradicated during therapy with appropriate treatment methods and antimicrobials.
4.2 Classification of Risk Factors

For ease of clinical application, risk factors for gas gangrene in pregnancy and its outcome listed in Table 1 are reclassified as follows:

Procedures that cause a breach of pelvic, abdominal or fetal, and maternal tissue barriers, iatrogenic and, or traumatic lesions that cause accumulation of tissue fluids and debris, including hematoma and devitalized tissues in the pelvic cavity. These form ready substrates for anaerobiosis and the activities of clostridia [39]. Others include procedures associated with direct inoculation of infective aerobic organisms, pathogenic clostridia, or other gas-forming organisms into fetal and maternal tissues during prenatal diagnostic and therapeutic procedures, parturition, and abortions. Examples are episiotomy, cordocentesis and amniocentesis (Table 1).

There may be spontaneous occurrence of infections with clostridia in the absence of trauma or obvious portal of entry of infectious agents, e.g. site of cutaneous lacerations, perineal infections, or infestations. As suggested by Monneuse O et al [40], when the anterior abdominal wall is the primary site of spontaneous clostridium infection, a primary gastrointestinal etiology needs to be searched for. This means that treating anterior abdominal wall gas gangrene alone may not be enough. The primary gastrointestinal cause of the gangrene coexisting with pregnancy should be investigated, and if the diagnosis is confirmed, the disease should be treated. Clinically it will usually be necessary to weigh the benefits of such additional treatments against the risk to the pregnancy and maternal health. Existing malignant or benign pelvic tumors (e.g. uterine fibroids and choriocarcinoma) and appropriate but invasive treatment methods have been well-documented as risk factors for the disease (Table 1). A combination of the above risk factors, local and, or generalized immune deficiency may also predispose particular patients to this disease.

4.3 Aetiopathogenesis

A patient with clostridium infection may present with only local wound contamination, cellulitis without myonecrosis, necrotizing fasciitis, or an advanced form of the disease in which there may be rapidly progressing myonecrosis, intravascular hemolysis, anemia, jaundice with shock syndrome [41].

4.4 Stages of Spread of Clostridia Infections

In a study, the disease was staged as follows: - [42].

- "Stage 1: infection is confined to the dead fetal tissue, and gas begins to form.
- Stage II: Infection spreads to the endometrium without causing systemic maternal symptoms.
- Stage III: The myometrium is damaged, and the infection spreads to the adjacent muscle tissues with the formation of gas formation. This stage may also spread to the peritoneal cavity.
- Stage IV: Infection is established in the maternal tissues. There is the release of exotoxins that may cause rapid hemolysis; infection may involve the liver, kidneys, and other viscera."

This staging is a valuable guide for clinical decision-making in choosing life-saving therapeutic methods and supportive treatment. It applies to an infection that spreads from the fetus as the primary site of infection. However, considering the fetus and the maternal uterus as the center of initial infection (as in this classification), the spread of infection in this scenario is centrifugal, occurring from the fetal tissues to the maternal uterus and then to the peripheral maternal tissues. Clostridium infections and myonecrosis may also spread centripetally from a peripheral maternal extra-uterine source to the maternal uterus and the fetal tissues. An example of the centripetal spread of clostridia infection and advancing myonecrosis was described by Sapira MK et al [43]. In that report, in a mother aged 35 years at mid-trimester of gestation, the infection spread from the maternal right hypochondrium toward the pelvis. At the point when the mother had severe life-threatening complications, the fetus and the maternal uterus had no echogenic features of abnormality. This was confirmed intraoperatively. Both the mother and the fetus survived after aggressive treatment. The baby was delivered well at term. Both methods of spread seem to have some differences that may, depending on the stage of the disease at intervention, impact the choice of treatment, organs to be affected, post-treatment health-related quality of life, and survival. This will require another study. However, an early stage of the disease that starts from maternal tissues will correspond to stage IV of the above grading, no matter how slight.

Certain features of gas gangrene in pregnancy and its outcome appear to contribute appreciably to the poor prognosis of the disease. These include (i) simulation of common illnesses at the early stages of infection (ii) rapidity of the pathogenic process, which in a typical case, may terminate the life of a mother and the baby within less than 16 hours of the first symptom [1, 12] (iii) production of powerful exotoxins by causative clostridia that mediate most of the lethal effects on tissues, organs, and the systemic circulation [44] (iv) the short incubation period of the pathogens and the
short course of the disease from first symptom to patients’ death. The rapidity of the pathogenic process appears to be tied up with the short incubation period of the disease and the high level of virulence of the pathogens. The pathogens spread to the site of primary infection, get attached to the tissue cells, and invade the tissues [29]. Different aspects of the activities of these pathogens seem to facilitate the rapid infective course of the disease. These include the attachment of clostridia to tissue cells, how the organisms overwhelm the host’s immunity, and the production and mechanisms of actions of their toxins.

4.5 Attachment of the Organisms to Tissue cells
The attachment of Clostridium perfringens to target cells has been attributed to the production of fibronectin by the pathogen [45]. In this same Japanese study 2 genes that encode for fibronectin-binding proteins (fibronectin-binding protein-A (fbpB) and fibronectin-binding protein-B (fbpB) were identified in three different strains of Clostridium perfringens isolated from three patients who had gas gangrene. They opined that these binding proteins enhanced the binding properties of the organisms to tissue fibronectin. Fibronectins are members of a group of proteins of the extracellular matrix (ECM) and are involved in a variety of functions, including “cell attachment, phagocytosis, wound healing, blood clotting, and organization of extracellular matrix” [46]. Apart from fibronectin, sialidases have also been found to be produced by Clostridium perfringens to facilitate its attachment to target cells [47].

4.6 Exotoxins Produced by Clostridia and their Effects on Tissues
Infections due to clostridia and synergistic oxygen-depleting activities of aerobic bacteria occur at the sites of primary, advancing, and metastatic infections. However, clostridium-induced myonecrosis and systemic complications, including intravascular hemolysis, jaundice, toxemia, toxic shock syndrome, and multiple organ failure, are mediated by toxins produced by the invading clostridia [29].

Exotoxins produced by Clostridium perfringens are classified as major and minor [48]. Of the major toxins (alpha, beta, epsilon and iota toxins), it is the alpha toxin that is involved in clostridium myonecrosis in humans [44, 49]. The alpha toxin has phospholipase C activity and hydrolyzes the bond between phosphoric acid and glycerol molecule in the phosphoglycerate moiety of cell membranes [50]. Activities of Clostridium perfringens beta and epsilon toxins cause the formation of abnormal pores in cell membranes while the iota toxin acts to destroy the actin components which act as support for the cells [48, 51]. Clostridium septicum also produces different types of exotoxins (alpha, beta, gamma, and delta toxins), the alpha of which causes cell lysis and abnormal cell membrane vacuolation. This is similar to the effects of the alpha toxin of Clostridium perfringens [52, 53].

4.7 Effects of toxins of clostridia on the distribution of ions in affected tissues
Cell membrane abnormal vacuole formation, cell lysis, and cell membrane pore-forming activities of the epsilon and beta and alpha toxins alter membrane permeability of the tissue cells to ions and cause an abnormal and pathological redistribution of ions between the intracellular and the extracellular compartments of the affected tissues [54, 55]. In normal cells, potassium ions are predominately intracellular while sodium and chloride ions are predominantly extracellular [56]. These changes in membrane permeability result in cellular dysfunction, lysis of cell membranes, and cellular death.

Apart from effects on cell membranes, Flores-Diaz M et al [57] observed that alpha exotoxin also has a variety of other tissue effects, which include “increasing platelet aggregation and microvascular permeability, decreasing cardiac contractility as well as alteration of intracellular signal transduction mechanisms in platelets, neutrophil polymorphs and cells of endothelia.” It is unclear whether these mechanisms alone can explain the severity of myonecrosis and the rapidity of the pathologic process. There was a report that, at the initial stages of the pathologic process, neutrophils and mononuclear phagocytes are rapidly depleted [58]. Neutrophils are known for their phagocytic activities in acute inflammatory responses [59].

The reduction of capillary perfusion, microvascular thrombosis, and the resultant tissue ischemia independently reported by Flores-Diaz et al and Hickey MJ et al [57, 60] were considered by them the most important mechanisms involved in myonecrosis caused by clostridia, irrespective of the species of clostridia involved.

The different areas relating to the activities of clostridia that stand out for further studies and hypothesis development in the prevention of gas gangrene in pregnancy include (i) Preventing and controlling aerobic and anaerobic infections of surgical procedures in pregnancy, (ii) Prevention or inhibition of attachment of clostridia to target tissue cells, and (iii) Prevention or inhibition of the effects of the toxins on the tissues. For the third purpose, while animal vaccines and antitoxins were produced and are in use, it is not to our knowledge that human vaccines are in clinical use [61, 62].
4.8 Some common standard procedures and risk of infection by clostridia

Table 1 shows the various risk factors reported in different studies worldwide. Apart from neoplastic diseases, iatrogenic and accidental trauma constitute substantial parts of the risks for developing the disease. Certain time-honored practices may need to be reviewed to achieve the best results in preventing gas gangrene in pregnancy and its outcome. The procedures that seem particularly associated with bad prognosis in various reports as risk factors for gas gangrene in pregnancy include amniocentesis, Cesarean sections, and abortions.

(i) Amniocentesis: This procedure is often used for the diagnosis of inherited fetal genetic or inherited disorders in addition to other indications [63]. It involves aseptic preparations, observance of precautions, and under sterile conditions advancing a needle with ultrasound guiding via an appropriate site of the anterior abdominal wall to the amniotic sack to aspirate small quantities of amniotic fluid for studies [63]. Basically, in the procedure, the needle breaches fetal and maternal tissue barriers and carries the risk of inoculating clostridia, aerobes, or other pathogens that may cause gas gangrene and other infections in the amniotic sack. There have been numerous reports of post-amniocentesis complications with poor prognosis, which include chorioamnionitis [64]. These include maternal septic shock and multiple organ failure (MOF). In four (4) patients with post-amniocentesis complications, the procedures were done during the mid-trimester of pregnancy (16 to 18 weeks). The first symptoms of gas gangrene were noticed as early as 12–24 hours after the procedure [21, 65, and 66]. This attests to the level of virulence associated with these pathogens. A large-scale global study of complications of amniocentesis may justify its discontinuation as a diagnostic procedure in pregnancy.

(ii) Cesarean sections are frequently performed in clinical scenarios that demand fast delivery of babies for the survival of babies and their mothers or both. In such situations, attention to surgical details may be overlooked. Pelvic accumulation of hematoma and amniotic fluid may occur. However, the immediate intraoperative post-delivery period offers an opportunity for adequate evacuation of pelvic collections.

(iii) Prevention of perineal infections: It is always necessary to prevent perineal and vulvar infections in cases assessed well for spontaneous vaginal delivery (SVD). Such infections may be complicated by clostridium necrotizing fascitis and myonecrosis. Measures that may help minimize the risk of perineal infections include (i) appropriate supervision of labor to prevent varying degrees of perineal tear and vulvar lacerations, (ii) emptying the rectum of fecal matter before the onset of active phases of labor, (iii) avoiding shaving with razors and surgical blades that may cause abrasions, ulcerations, and minor lacerations of the perineum, and the suprapubic/inguinal regions. These regions may be contaminated by fecal matter, and (iv) Prompt control and treatment of comorbidities, e.g. diabetes mellitus, should not be overlooked.

The residence of these anaerobes in the intestinal tracts and vaginal cavities of humans suggests that, given appropriate combinations of adverse or confounding factors, deep-seated wounds of the vulva, perineum, buttocks, lower anterior abdominal wall, and thighs may easily be contaminated by effluents from these cavities and may be infected by clostridia[67, 68, 69]. It also suggests that if maternal and fetal tissue barriers are breached, ascending bacterial pathogens may spread retrogradely to infect fetal tissues and the maternal uterus. This was the opinion of Rzanek- Glowacka et al [70] when they concluded that “in the presence of maternal bacterial vaginosis, premature rupture of fetal membranes (PROM) was the important factor in intrauterine neonatal infections.” For the purpose of preventing infections, the washing of the perineum, inter-gluteal cleft, and groins thoroughly with soap and water as part of a full bath should be preferred to shaving before the onset of active phases of labor. This requires an appropriate local study.

4.9 Abortions

An abortion of pregnancy is done either by (i) administration of a drug or drugs to cause uterine contractions and expulsion of products of conception or (iii) dilatation of cervical canal to accommodate cannulas of various sizes and removal products of conception by suction pressure. By whichever method an abortion is performed, there is (i) injury to the endometrium, the cervix, and even the myometrium, (ii) bleeding and hematoma formation in the uterine cavity, (iii) risk of transmission of pathogens either from contaminated instruments or inoculation of hitherto innocuous resident vaginal or cervical flora to the injured endometrium. The risk of post-abortion sepsis is increased by the presence of uterine fibroids and uterine instrumentation [71, 72, and 73]. Decker and Hall [74] had earlier emphasized the risks of infections borne by accumulated tissue fragments and damage to the endometrial tissues during abortions.

Another critical aspect of post-abortion sepsis is the ease of spread of endometrial infections, including endometrial necrotizing fascitis. During the procedure of abortion, there may be direct passage of contaminated microscopic tissue fragments and infected blood into the uterine microvasculature to cause systemic infection. Accumulated tissue...
fragments, hematoma, residual products of conception, and septic materials usually elicit powerful uterine contractions to expel them. These contractions may spread septic uterine contents through the fallopian tubes to the peritoneal cavity to cause perforinitis [75]. There may also be lymphatic and direct spread of uterine infections.

4.10 Severe accidental pelvic and retroperitoneal trauma

Severe pelvic trauma, as may occur with multiple pelvic fractures and pelvic soft tissue injuries, is usually associated with severe hemorrhage and accumulation of tissue debris with hematoma. A similar situation may occur in moderate-to-severe or severe renal trauma at the renal retroperitoneum. In both cases, associated urinary tract laceration or rupture may result in extravasation of urine into the extra-peritoneal spaces along with hematoma. Shock with cardiovascular instability is the common indication for immediate exploration, control of hemorrhage, and further resuscitation. However, in some cases, pelvic fasciae or prerenal fascia effectively controls bleeding by providing a tamponade effect. In such patients, there may be cardiovascular stability, while others may be in shock due to excessive and continuous bleeding. The immediate evacuation of accumulated hematoma in patients with cardiovascular stability, in the absence of other indications, is usually controversial. Opponents of immediate evacuation of the hematoma advise that such may give rise to very torrential and exsanguinating hemorrhage, which may overwhelm the capacity for blood replacement.

When the decision is not for immediate evacuation, the hematoma may provide substrates for aerobic infections, and anaerobic infection by clostridia. The argument may be that such lesions are not common in pregnancy. However, with the increasing use of firearms in civilian populations, wars, and natural disasters, including earthquakes, these lesions may be more common. In these cases, programmed use of antibiotics based on local experience, insertion of appropriate drains to decompress the space with fluid collection, and selective embolization of any bleeding vessel may be salutary.

5 Conclusion and Recommendations

Apart from accidental trauma, tumors (benign and malignant), foreign body in tissues, common risk factors of gas gangrene in pregnancy, parturition, and abortions are mostly open standard diagnostic and therapeutic procedures in pregnancy and its outcome, including abortions. These include normal spontaneous vaginal childbirth. The common underlying principles, from different reports, include the accumulation of hematoma and devitalized tissue debris in living tissues, low tissue oxygen tension, and breaches of perineal skin, epithelial coverings, and protective fetal and maternal tissue barriers. Clostridia are the most common causes of the disease. However, the disease would probably not have been as lethal as it is without the tissue and systemic activities of their powerful exotoxins. Local policies need to be developed for extended use of antibiotics in normal labor and when carrying out procedures in pregnancy, delivery, and abortions. Attractive points in the aetiopathogenesis for the development of hypothesis and further studies aimed at prevention and treatment of the disease are (i) prevention of attachment of clostridia to tissue cells, (ii) prevention of infection by aerobes, (iii) pre-pregnancy immunization of women of childbearing age, and (iii) attention to surgical details to minimize accumulation of devitalized tissues, blood, urine, pus and other fluids in pelvic, perineal and retroperitoneal spaces during surgery.

Sometimes such accumulations may become inevitable as may occur in excessive hemorrhage due to severe accidental retroperitoneal and pelvic trauma. In some of such instances, the tamponade effects of retroperitoneal and pelvic fasciae limit excessive hemorrhage and maintain cardiovascular stability. In such cases, a local extended antibiotics policy, use of open drains, wound exposure as well as selective embolization of large bleeding vessels may be salutary.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest.
Statement of informed consent

Informed consent was obtained from all individual participants included in this study. No direct humans or animals were involved in the study.

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