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Gas gangrene in pregnancy, parturition, and abortions requiring urological and surgical intervention: Patterns, features, and world distribution

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Abstract

Introduction: Gas gangrene in pregnancy and its outcome has a poor prognosis. The aim of this study is to determine the patterns of its occurrence worldwide, and the evolution of its treatment within the last 6 decades.

Materials and methods: The study was done at the University of Port Harcourt Teaching Hospital, Nigeria. Using search terms, a bibliographical search was made in the PubMed/ Medline and PubMed Central computerized databases for articles published on the subject from 01/01/1966 to 31/12/2022. Details of each publication, including the date and location of the study, number and socio-demographic information on affected patient(s), clinical features of the disease, laboratory investigations, types, and outcome of treatments were recorded. Results obtained were collated with simple statistics and presented.

Results: Ninety-five (95) study reports on 153 patients were seen and studied. The disease has global distribution. The number of study reports significantly correlated positively with the number of treated patients. There was no significant increase in the number of study reports, and the number of cases during the study period, P>0.50.

The pattern of treatment was focused on aggressive life-saving surgical excision of all involved tissues. In some cases, these ablative procedures either had fatal complications, or left many patients with loss of vital organs and body parts, with poor functional and cosmetic outcomes.

Conclusion: The dearth of records suggests that, generally worldwide, experience with the disease may be limited. A program of development of conservative treatment of the disease, and pre-pregnancy immunization of women of childbearing age is advocated.

Keywords: Gas gangrene in pregnancy and its outcome; Diagnostic features; Patterns of treatment and outcome; World distribution

1 Introduction

Our previous studies on gas gangrene in pregnancy and its outcome, and information in the literature indicated that the disease could arise from infections originating from fetal tissues, or any part of the maternal extra genital or genital tissue sites [1, 2]. There has also been the notion that the disease occurs mostly in low-income countries with limited resources, and that its early features are non-specific. We considered a pattern study necessary to reasonably characterize this deadly disease. The aim of this study is to determine the patterns of occurrence, and the evolution of

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treatment strategies of the disease worldwide over the past 6 decades of management of affected patients. It is hoped that information from this study will facilitate the formulation of strategies for the prevention and control of the disease.

2 Material and methods

This cross-sectional descriptive study was done at the University of Port Harcourt Teaching Hospital (UPTH), Niger Delta Region of South-Southern Nigeria. Using the Keywords "post-abortion gas gangrene," "gas gangrene in pregnancy," "gas gangrene in the puerperium," "gas gangrene in pregnancy and delivery," a bibliographical search was made in the PubMed/Medline and PubMed central computerized databases. The search was made for articles on gas gangrene in pregnancy, abortions, and the puerperium published from January 1, 1966, to December 31, 2022. In each publication, author information, date and location of the study, study objectives, number and socio-demographic information on affected patient(s), clinical features of the disease, laboratory investigations, types, and outcome of treatments were recorded. A meta-analysis of the data was not done because of the heterogeneous nature of the publications. Types of articles consulted included case reports, case series, original articles, and abstracts of the articles on the subject. Where abstracts were seen, a further search was made for the full texts of the particular articles. Texts on the subject were consulted if they were considered to provide additional information on the subject. Results obtained were collated with simple statistics and presented in prose, tables, and charts. Karl Pearson's Chi Square test, and the Correlation test were used to test for the significance of observations and correlation respectively.

Ethical approval of the study was obtained from the Ethics Committee of UPTH for urological problems in women.

3 Results

Ninety-five (95) studies reporting on one hundred and fifty-three (153) patients with gas gangrene in pregnancy, abortions, and during the puerperium were studied (Figure1). There was a significant positive correlation between the number of study reports and the numbers of patients (correlation coefficient r=0.9213 and p<0.01 >0.001) between 1966 to December 2023. There was no significant increase in the number of study reports, and the number of cases during the study period. There was an average of 1to 2 patients per study report during the period. When the study period was broken into 2 halves, I to 2 patients per study report was recorded for each half of the study period. There was a global distribution of study reports with the greatest number of patients and reports from Europe, followed by the USA (Figure2). One hundred and twenty-two patients had the primary site of infection that gave rise to gas gangrene at the maternal uterus. Reports had supposed the primary site of infection was the fetus but diagnosis of these that case was postmortem

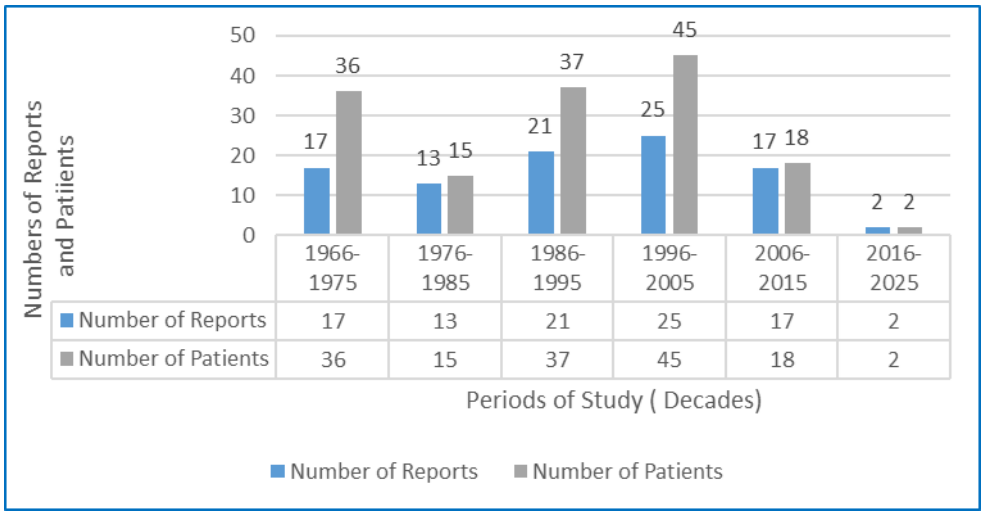

Figure 1 Distribution of study reports, and the number of patients treated during the study period.

Majority (73, 48%) of infections and gas gangrene occurred after abortions. No case of gas gangrene was recorded the first trimester of pregnancy.

Surgery remained the mainstay of treatment during the study period. The trend was to resort to very invasive and ablative surgery to excise all involved tissues and organs. Common recorded surgical procedures included total

abdominal hysterectomy and pelvic disarticulation (amputation) in cases involving the thigh Intrauterine and fetal deaths puerperal mortality of infants and maternal deaths were recorded. A meta-analysis of findings could not be done because of the heterogeneous nature of the reports.

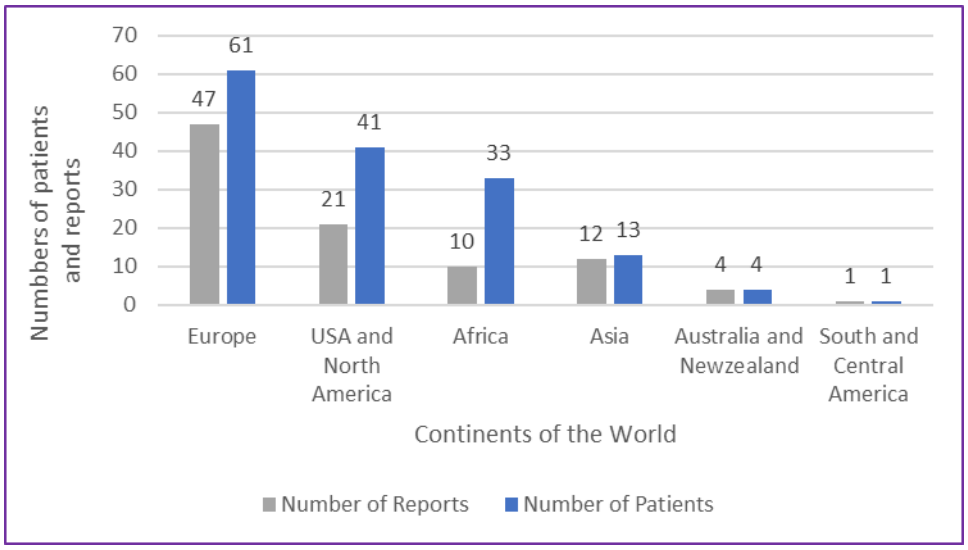

Figure 1 World Distribution of study reports and patients treated during the study period

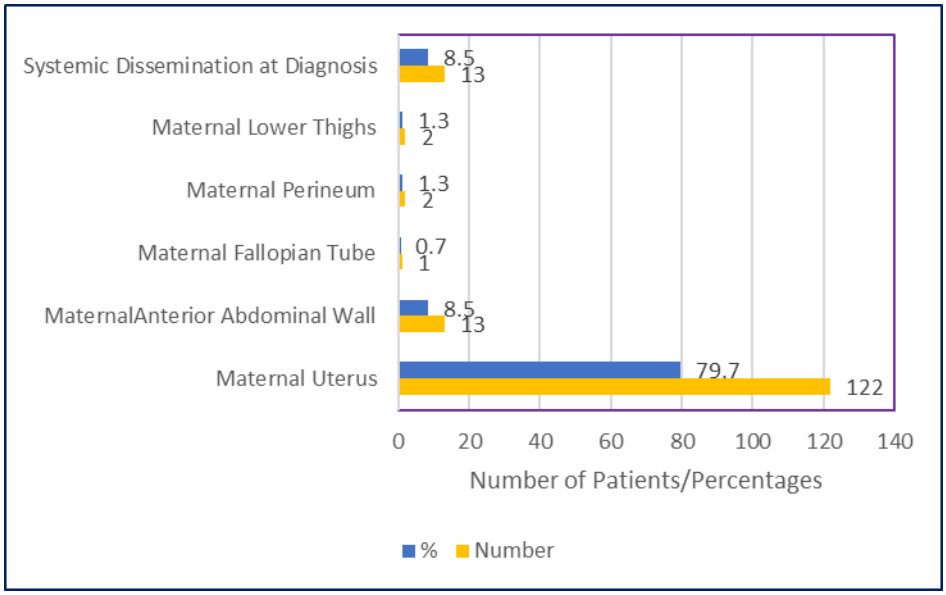

Figure 2 Sites of primary Infection in the cases treated with gas gangrene in pregnancy, abortions and parturition; number and percentages.

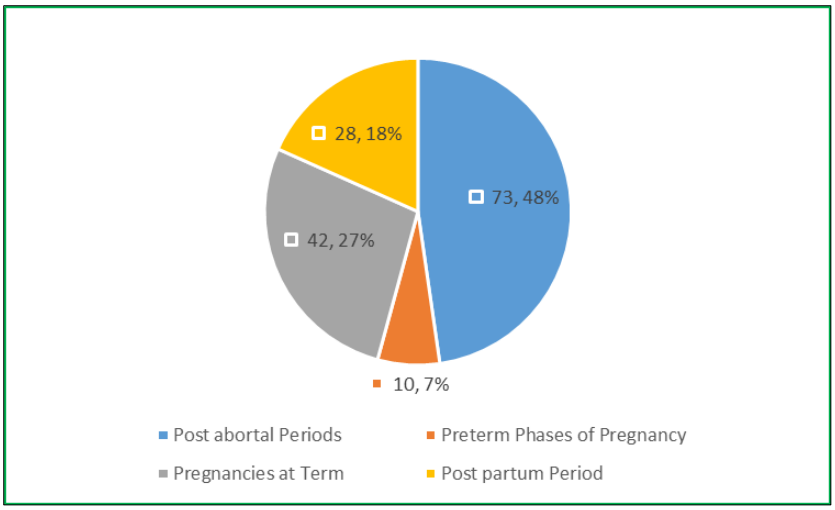

Figure 3 Phases of pregnancy, delivery and abortion at which gas gangrene occurred in the patients.

Table 1 Period of study, site of primary infection and, methods of treatment and outcome

Period of study (DECADES)	**Site of primary infection/morbidity/ Number of patients**	**Treatment method**	**Outcome Survival**	**Mortality**
1966 – 1975	Maternal anterior abdominal wall, 13; maternal uterus 9; Morbidity: Uterine fibroids, •Chorion carcinoma chemotherapy, •POL, abruption of placentae, •Puerperal endometritis •renal failure	Conservative 2 TAH 4 C/S 1	7	Maternal deaths 4, Fetal deaths 6,
1976 – 1985	Uterus post C/S or post-abortion postpartum infection Maternal thigh (2) + leg IUFD	TAH (2)+ Antimicrobials Hip disarticulation (2)	3	Fetal deaths at term (2) Maternal deaths
1986 – 1995	Maternal uterus 17 Maternal extremities: 2 Upper thigh 1, Perineum 3	TAH Hip disarticulation 1	2	Fetal deaths at term 2
1996 – 2015	Maternal uterus – 32 •Intra-myometrial abscess •Spontaneous abortions •Post C/S endometritis •Toxic shock syndrome	Conservative 7 IV Immunoglobulins for GAS TSS in the puerperium TAH 10		
2016 – 2025	Spleen + Liver and the Vaginal + the cerebellum	Splenectomy + C/S •Induction of labor + vaginal delivery	Septic shock DIC + Depression, Hypertension proteinuria	•IUFD •Fetal death •Maternal death postpartum

Table 1: TAH, total abdominal hysterectomy; C/S, Cesarean section; DIC, disseminated intravascular coagulation; GAS, Group A streptococcus; TSS, toxic shock syndrome; IUFD, intrauterine fetal death; POL, prolonged obstructed labor; IV, intravenous.

Table 2 Features of Gas Gangrene in Pregnancy, Parturition and Abortions with References (Authors' Names and Year of Publication

S/n	Author/ journal/ year of publication	Diagnostic/ pathogenic features/ / research efforts on the subject/ symptom, signs, tests
1	Rimawi BH et al. Case Rep Obstet Gynecol 2014 Apr[3]	**C septicum necrotizing Fasciitis after term C/S delivery:** Fever chills, pyrexia (Temperature 38.5^{o}c Abdominal pains and tenderness; elevated liver enzymes (transaminases); Leukocytosis severe anaemia; uterine tissue DNA extract used for diagnosis of C. septicum Alpha-toxin by PCR
2	Mc Donald RE et al BMJ case Rep 2012 Jun [4]	C**. septicum infection in a young woman**; **early features in pregnancy:** Fever, pyrexia, low blood pressure palpitations, tachycardia, generalized abdominal pain; pain and oedema at the site of primary infection**; USS** features-air in pelvic veins, lucencies due to air in myometrium and uterine cavity
3	Patchell RD et al. Obstet Gynecol, 1978 [5]	**Post-partum clostridial myonecrosis.** Abdominal USS features:- uterine gas shows as echo lucencies. Features of fetal viability; Plain X-Ray Exam. Gases shadows in tissues
4	Kirkpatrick CJ et al. Arch Gynecol 1982 [6]	**Fatal C. perfringens sepsis after term pregnancy; features.** Age of patient 22yrs, vomiting (only once), suprapubic pain, Hypotension, tachycardia, renal injury. Died < 15 hours of the first symptom (vomiting)
5	KanakoAbe, Hiromi Hamada et al. Available at https://doi.org/10.1016/j.tjog. 2016.06.006Get right and content [7]	**Fatal gas gangrene in the fetus and the mother**. Age of patient 23yrs.: Features –She was Japanese, was hypertensive, Other features: - coma, brown foul-smelling vaginal discharge, suprapubic pain, depression, panic disorder. Plain X-ray radiographic features AP view: singleton pregnancy, intrauterine gas. CT scan findings: Fetal intracranial, thoracic, abdominal and soft tissue gas; apparently normal maternal uterus
6	Roggentin P et al. Clin C him Acta 1988 Apr [8]	**Experimental study** of early diagnosis of clostridial infection, using polyclonal antibodies produced in response to clostridial sialidase enzyme by clostridium-infected animal hosts. Tests are (l) sialidase inhibition test and (ll) Enzyme protein ELISA test. In one animal model, clostridial infection was diagnosed in 8 to 12 hours of infection
7	Barrett JP et al. Obstet Gynecol; 2002, May [9]	**Features of severe post- abortal clostridial perfringens infection**: (l) The patient had the following: - spontaneous abortion at 6-8 weeks of pregnancy, abdominal pains, vaginal bleeding, hypotension, tachypnea, was not febrile at presentation. She also had a closed cervical os, intravascular hemolysis anuria, and coagulopathy. USS features: - Uterine cavity gas showed as echo-lucencies. The patient died in spite of treatment
8	Nadisauskiene R et al. Gynecol Obstet Invest 2008 Epub Aug 2007 [10]	**Puerperal sepsis, post-Cesarean section**, massive intravascular hemolysis, intermittent leukocytopenia. Death of patient in spite of treatment
9	Katayama S. et al. Anaerobe 2009 Aug [11]	**Experimental study**; Detection of two fibronectin-binding proteins that enhance clostridial attachment to tissue cells, fibronectin-binding protein A (fbpA), and fibronectin-binding protein B (fbpB). Cellular binding promotes infection and myonecrosis
10	Plachouras N et al Obstet Gynecol, 2004 Dec [12]	**Features of post- invasive diagnostic test clostridial infection**: History-amniocentesis at 15weeks and cordocentesis at 20weeks of gestation; Repeat cordocentesis at 21weeks. Vaginal bleeding, PROM, IUFD, intravascular coagulopathy, (DIC), MOF, prolonged hospital stay (34 days).
11	Steven DL et al. J Infect Dis 2004 Aug [13]	**Experimental study**: The virulence factor in C. perfringens infection is the alpha toxin. The study is experimental. To test the effectiveness of murine vaccines to the clostridial alpha-toxin. Alpha toxin is phospholipase - C

12	Stiles BG. et al Toxins (Basel) 2013 Nov [14]	**Characterization/Description of toxins of clostridia:** Literature on animal immunization with animal models of vaccines.
13	Gafumbegete Evariste. et al. IDC cases Nov 2021 [15]	**Features of fatal C. perfringens sepsis:•** Age of patient = 29yrs Gravida 2 para 1; • Normal pregnancy and medical history • Right hypochondriac pain at 37 weeks • Thready pulse, Hypovolemic shock with non-record- with severe hypotension sudden collapse at the emergency room. • Had cardiopulmonary resuscitation with emergency C/S • Intraperitoneal hemorrhage • Perforated spleen, gas in retroperitoneum; Patient died; child born dead • Histology of tissues/ autopsy • Method of culture: Anaerobiasis is with Schaedler Agar with 5% sheep-blood- streaked at 35^{o}c. organism: clostridium perfringens **Autopsy Findings: -** Ruptured spleen, lacerated splenic artery; gas in retroperitoneum gas splenic parenchyma, gas along the abdominal aorta. Histology of tissues: C. perfringens organisms in the spleen, gall bladder, blood vessels renal arteries colonic crypts

C/S, Caesarean section; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction; C, Clostridium; yrs. Years; CT scan, computerized axial tomographic scan; ELISA, enzyme-linked immunosorbent assay; PROM, premature rupture of fetal membrane; IUFD, intrauterine fetal death; DIC, disseminated intravascular coagulation; MOF, multiple organ failure.

4 Discussion

There is a general belief that gas gangrene in pregnancy and its outcome may be limited to certain countries with limited opportunities. The distribution of study reports and patients with this condition observed in this study is worldwide. What this report could not examine were the local conditions at the various hospitals and localities from where each report emanated. It was observed in our previous study that most of the cases of gas gangrene in pregnancy were caused by clostridia, and occurred as complications of diagnostic and therapeutic procedures in pregnancy and abortions [2]. It is therefore trite to surmise that the incidence of the disease might have a relationship with the total number of invasive interventions in pregnancy. The number of reports may relate to invasive procedures in pregnancy and abortions. Seventy-three (73, 48%) of cases were complications of abortions.

4.1 Clinical Features

Clinical Features (Initial Presentation): The disease may initially be latent. Clinical presentations are variable and depend on the stage of disease at the time the patient presents for treatment. Other factors that could affect clinical presentation include previous interventions, the virulence of the organisms involved, and the presence or absence of comorbidities. In Table 2, early and late clinical features of the disease reported from different patients are presented. The features, as also observed in the literature, simulate many common febrile illnesses. However, it is possible to recognize the early onset of the disease with a good index of suspicion, and by studied attention to details of the patient's history of the onset of the first symptom and exclusion of co-morbidities. In gas gangrene, common symptoms appear exaggerated in terms of rapidity of onset, and the short duration it takes to deteriorate from mild to severe manifestations. When the primary infection occurs at a cutaneous maternal site, the first symptoms are characterized by local pain and swelling at the site. Initially, the skin over the site may be normal, but it rapidly becomes erythematous, swollen, and tender on palpation. The surrounding skin may be crepitant or foamy due to subcutaneous emphysema. The severity and speed of deterioration of Initial symptoms should raise suspicion of possible clostridial or streptococcal infection. When systemic inflammatory responses have set in, features include fever chills, night sweats, and exaggerated local pains. These may deteriorate to severe late complications with multiple organ involvement [16]. Koransky J et al studied features of Clostridium septicum bacteremia, and reported that the features included fever, palpitations, pyrexia, hypotension, sweatiness, listlessness, and generalized body pains [17, 18]. In a patient that developed fetal Clostridium perfringens infections 19 hours after amniocentesis, Hendrix WN et al reported the onset of fever hours after the procedure, reduced fetal movements, slight vaginal bleeding, passage foul-smelling vaginal discharge with altered color, and intrauterine fetal death [19]. Different other workers similarly summarized symptoms and signs of early disease to include pyrexia, tachypnea, [20,21], hypotension, spontaneous abortions, vaginal bleeding,

abdominal pains, tachycardia, and pelvic tenderness[3, 22]. However, in one case of postpartum Clostridium perfringens infection of the uterus the features of "hypotension, suprapubic pains, tachycardia, and renal injury" were so severe and rapid that the patient died in less than 15 hours of the first symptom (vomiting [6]. In the absence of treatment, these early signs and symptoms do not abate but usually worsen with the advancement of the course of the disease. They will still manifest or worsen with advanced stages of infection. Features of advanced pathology, severe systemic toxicity, multiple organ involvement, and intravascular hemolysis include jaundice, rapidly increasing anemia, hypotension, hemoglobinuria, proteinuria, depression, peripheral edema, and hepatosplenomegaly [23, 24].

The pattern of treatment from 1966 to 2022 appears the same. There was an emphasis on aggressive surgical excision of involved tissues, antibiotics administration and fluid resuscitation, management of pain, nutritional deficiencies, and concurrent infections. The implication of this trend is that many of the treated patients reported in the literature either died of complications of severe metabolic responses to very invasive surgeries or survived with extensive loss of excised body parts. It could be imagined that such patients probably had grossly diminished health-related qualities of life (HRQoL), and might have had a dependent, handicapped existence, with unacceptable functional, psychological, and cosmetic complications.

The most commonly involved genital organ in this study was the uterus, and total abdominal hysterectomy (TAH) was the most frequently reported excisional surgery of the genital organs. A typical case of extensive invasive surgery was reported in a Danish study of a 33-year-old mother that had necrotizing fasciitis. This was the complication of perforated appendicitis in her pregnancy which was near-term. Clostridial myonecrosis involved her right thigh [25]. For this complication, she had right hip disarticulation [26]. Another was a report from the Netherlands in which a 27-year-old female developed fatal post-abortion shock syndrome and other fatal complications of the deadly Clostridium septicum infection. She had clostridial myonecrosis of both thighs and required emergency amputation of the involved thighs, and other supportive treatments to survive [27]. With the current inclination toward minimal access procedures, a global trend of less invasion of the body in surgical operations is more desirable. A progressive inclination towards prevention and minimally invasive treatments should be pursued in the management of this deadly disease.

Few cases seen in this study were managed conservatively. Many of these cases were highly selected on clinical grounds to ensure post-treatment survival. Lichtenberg ES et al reported their successful conservative management of bacteriologically confirmed uterine and blood-borne clostridial organisms in 5 patients who had abortions [28]. However, these cases were reported to have had no overt clinical manifestations of sepsis. Their experience, however, suggested that with adequate antibiotic management, and scrupulous attention to treatment details, the incidence of this disease might decrease.

Based on the pathogenesis of this disease, and findings in the literature that the lethal and systemic complications of the disease were mediated in most cases by clostridial exotoxins [14], we advocate the vigorous pursuit of a pre-pregnancy immunization program against clostridium exotoxins for women of childbearing age. With global efforts, this may be the most effective method of controlling and preventing this disease.

Another pattern that seemed important in this study was that each report in the Literature was made on an average of one to two (1 to 2) patients. This trend was reproduced when the approximately 60-year period of this study was broken down to the two 30-year periods. The number of reports significantly positively correlated with the number of patients treated (vide supra). The clinical significance of low report/ patient ratio is that, worldwide, clinical experience with management of this condition may be generally limited. This is because for most conditions, it is expected that the greater the number of cases of a particular disease actively managed by a particular clinician, the greater should be his, or her clinical exposure and experience with various presentations of the disease.

5 Conclusion

The distribution of gas gangrene in pregnancy is global with most of the study reports emanating from European countries and North America. The maternal uterus was primarily involved in 122 (79.7%) of patients in this study. The disease is inadequately reported worldwide. This is corroborated by the finding in this study of only 95 study reports in 58 years. These reports were made on 153 patients, with an average of 1 to 2 patients per report. This dearth of study reports and records of treated patients suggests that, generally, clinicians worldwide may have limited experience with the disease.

The pattern of treatment over the nearly 60-year period of 1966 to Dec 2023 has remained virtually the same, with emphasis on prompt radical excision of all involved tissues, fluid resuscitation, antibiotic therapy, nutritional support, pain relief, and other ancillary measures. Radical excisional surgeries left some patients with loss of body parts, with

poor functional and cosmetic complications. World attention needs to be drawn to the disease, with a focus on pre-pregnancy immunization of women of childbearing age against clostridial exotoxins. In the interim antibiotic prophylaxis and extended use of appropriate antibiotics, based on local clinical experience, are advocated for all invasive perineal and pelvic procedures in pregnancy, and in the puerperium.

Limitations

This study has some limitations. There is reliance on secondary data generated in previous studies. Any error in the different studies might have been inherited in this study design. Areas of the world where reports were not made might have been erroneously assumed not to have had the disease. Perhaps national surveillance registers of the disease obtained from all countries, if such existed, would probably have been more informative. Secondly, many study reports might not have been listed in the computerized databases which formed our study frame. We, however, believe that the results of this study are reliable at least as a sample of the actual whole world population of all patients who had this disease during the study period.

Compliance with ethical standards

Acknowledgments

We are grateful to the Head of the Department of Obstetrics and Gynecology, Rivers State University Teaching Hospital, Port Harcourt, for allowing us access to patients' records.

Disclosure of conflict of interest

There is no conflict of interest.

Statement of ethical approval

Ethical approval of the study was obtained from the University of Port Harcourt Teaching Hospital Ethics Committee. The study does not contain any human or animal experimentation by any of the authors.

The study was carried out in accordance with the stipulated ethical standards.

Statement of informed consent

Informed consent was obtained from all individual participants included in this study.

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