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IMPACT OF PELVIC INFLAMMATORY DISEASE ON FEMALE FERTILITY: A COMPREHENSIVE REVIEW ON PREVENTIVE STRATEGIES AND TREATMENT OPTIONS

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Abstract: The objective of this study was to analyze the impact of Pelvic Inflammatory Disease (PID) on female fertility, exploring preventive strategies and therapeutic options. Method: An integrative review was carried out using the PubMed Central (PMC) database, resulting in 182 initial articles. After applying inclusion and exclusion criteria, only 10 were selected as official sources for the study. Discussion: Studies indicate that tissue damage caused by PID can result in infertility, especially due to tubal factors. However, due to the lack of accurate complementary tests, the essential host and pathogen determinants underlying infertility have not yet been identified. Conclusion: The reproductive health of women after PID due to Chlamydia is intrinsically linked to accurate diagnosis and appropriate treatment. To achieve this, it is imperative to include screening programs that make use of biomarkers sensitive to the responsible pathogen.
Keywords: Pelvic inflammatory disease, Female fertility, Women's health

INTRODUCTION

Pelvic Inflammatory Disease (PID) is a condition that results from the invasion of infectious agents, such as bacteria, viruses and fungi, into a woman's upper genital tract. Among the most common microorganisms associated with sexually transmitted diseases, Chlamydia trachomatis, Neisseria gonorrhoeae and, to a lesser extent, Mycoplasma genitalium stand out. These infections can ascend from the vagina, passing through the cervix until reaching the endometrium and fallopian tubes, culminating in the clinical manifestation of PID. Primary infection by Neisseria gonorrhoeae generally begins in the endocervix, which can result in acute PID, such as salpingitis, endometritis and tubo-ovarian abscess. This condition can lead to serious complications such as sterility,

ectopic pregnancy and chronic pelvic pain. Approximately 15% of women diagnosed with PID develop tubal factor infertility (TANG et al., 2020).

The epidemiology of these infections is significant, with estimates of 357 million new cases of curable sexually transmitted infections each year worldwide. Chlamydia trachomatis is responsible for 131 million cases, Neisseria gonorrhoeae for 78 million, syphilis for 5.6 million and trichomoniasis for 143 million. Gonorrhea, in particular, remains one of the most prevalent sexually transmitted infections, representing a global public health challenge (HUNT & VOLLENHOVEN, 2023).

The lack of distinct symptoms in many cases and the possibility of being asymptomatic make PID a substantial concern. The challenge lies in early detection, as late diagnosis can lead to serious complications, including female infertility. The global magnitude of sexually transmitted infections (STIs), especially those caused by Chlamydia trachomatis and Neisseria gonorrhoeae, highlights the relevance of PID as a public health problem. With millions of new cases annually, it is imperative to understand the direct relationship between these infections and subsequent complications, highlighting the urgency of effective prevention and treatment strategies (SMOLARCZYK et al., 2021).

Given this context, this literature review article aims to examine and summarize the impact of PID on female fertility. Furthermore, it seeks to identify effective preventive strategies and review the treatment options available for women affected by this condition, thus contributing to a more comprehensive and informed approach to the management of PID and its repercussions on reproductive health.

METHODOLOGY

This is a bibliographic review conducted according to the criteria of the PVO strategy, an acronym that encompasses the population or research problem, variables and outcome. This approach was used to develop research around the following guiding question: "What is the impact of PID on female fertility, what are effective prevention strategies, and what treatment options can be considered for women affected by this condition?" In this context, according to the parameters mentioned, the population or problem addressed by this research refers to female patients diagnosed with PID, and therapeutic approaches and treatments associated with infertility are investigated.

The search for articles was conducted by searching the PubMed Central (PMC) database. Initially, 182 articles were identified, which were subsequently subjected to rigorous selection criteria. The inclusion criteria covered articles in English published between 2019 and 2023, which addressed the themes relevant to this research. Randomized clinical trial, retrospective cohort and integrative review studies were considered, as long as they were available in full. Duplicate articles, those available only in abstract form, as well as those that were not directly related to the research proposal were excluded. In the end, 10 articles were selected to compose the present study.

DISCUSSION

ETIOPATHOGENESIS AND DIAGNOSIS OF PID

PID is a polymicrobial clinical syndrome that generally results from the rise of infectious microorganisms from the vagina to the uterus and appendages, triggering inflammation in the upper genital tract. The complexity of the etiopathogenesis of PID is compounded

by diagnostic inaccuracy, difficulties in sampling the upper genital tract, frequent superinfection and challenges in identifying the pathogen (AL-KURAN et al., 2021).

The signs and symptoms of PID are often nonspecific, including tenderness to cervical movement, uterine tenderness, and adnexal tenderness to pelvic examination (RAVEL, MORENO & SIMON, 2021). The subclinical/ chronic nature of PID contributes to the underreporting of cases due to diagnostic inaccuracy (AL-KURAN et al., 2021). PID is associated with significant consequences, with chronic pelvic pain and infertility being the most relevant.

The relationship between Chlamydia trachomatis infection and PID is recognized as an important risk factor for female infertility. Chlamydia, a prevalent STI, alone can lead to infertility and is a significant cause of PID, further increasing the risk of infertility (LIU et al., 2022).

Liu et al. (2022) revealed that previous PID increases the risk of infertility, especially tubal infertility, with a six-fold higher prevalence in women with previous chlamydia infection compared to those without the infection. Furthermore, data indicate that N. gonorrhoeae, C. trachomatis and/or M. genitalium are present in 30% of PID cases, while urogenital probiotic bacteria or bacteria associated with bacterial vaginosis (BV) are present in 70% of cases (AL-KURAN et al., 2021).

Studies, such as those by Ravel, Moreno & Simon (2021), corroborate the prevalence of the rise of anaerobic bacteria associated with BV in the etiopathogenesis of PID. BV, characterized by a decrease in lactic acid-producing bacteria and an increase in anaerobic bacteria, increases the risk of STIs and upper genital tract infections due to the rise of bacterial and anaerobic pathogens (RAVEL, MORENO & SIMON, 2021). Treating BV urgently is crucial to prevent sequelae that contribute to an increased risk of infertility, in addition to other complications such as premature labor and spontaneous abortions associated with PID (AL-KURAN et al., 2021).

Chlamydia trachomatis infection, commonly known as chlamydia, is a sexually transmitted infection that affects a significant proportion of women, often asymptomatically. This infection, due to its ability to reach the structures of the upper genital tract, including the fallopian tubes and the uterus, can result in complications such as PID and infertility (ANYALECHI et al., 2021).

The relationship between chlamydia infections, antibiotic treatment and its consequences on women's reproductive health is the subject of analysis. Women who test positive for chlamydia have a significantly elevated risk of developing reproductive tract infection (PID), ectopic pregnancy, and infertility compared to those who test negative. High levels of seropositivity are associated with chlamydia infections, PID and infertility, showing a direct correlation (ANYALECHI et al., 2021).

Furthermore, repeated chlamydia infections and the use of antibiotics are linked to higher risks, as treatment does not effectively reduce the risks of PID and may, in some cases, increase the risk, as found by Den Heijer et al. (2023).

It is crucial to highlight the relevance of trichomoniasis in relation to female fertility. This STD, with a high prevalence in the United States, affects approximately 3.1% of women, being more prevalent than gonorrhea or syphilis, especially in non-Hispanic and post-adolescent black women. More than 70% of infected women may be asymptomatic, increasing the risk of gynecological complications, including PID, HIV transmission, cervical cancer, infertility,

and pregnancy complications. However, the specific relationship between trichomoniasis and PID, as well as its connection with infertility, lacks detailed investigation in prospective studies. The results of these studies highlight the importance of preventive strategies and targeted interventions to address chlamydia and trichomoniasis infections, thus protecting women's reproductive health (WIRINGA et al., 2019). An in-depth understanding of these relationships is essential to guide effective prevention and treatment approaches.

Tao, Xin et al. (2018) demonstrated, through a case-control study, that PID involving several structures increases the risk of infertility, especially in women under 40 years of age. However, the overall probability of all-cause tubal infertility in women with chlamydial infection was relatively low.

Den Heijer et al. (2019) presented results from a cohort study indicating a substantially higher risk of PID, ectopic pregnancy, and female infertility in CT-positive women compared to CT-negative women. Repeated infections further increased the risk, and appropriate treatment did not reduce the risk of subsequent PID.

Wiringa et al. (2019) observed, in a cohort study, that women who tested positive for T. vaginalis were more likely to develop histologically confirmed endometritis, suggesting the potential role of this infection in the pathogenesis of PID. Horner & Patrick et al. (2021) addressed the limited usefulness of serological assays in evaluating the relationship between infertility and Chlamydia infection, due to low sensitivity. However, they highlighted that the use of more sensitive methods, such as ELISA, can provide a more accurate assessment.

The studies reviewed highlight the complexity of the relationship between CT infection, PID and infertility. While some indicate a significant increase in the risk of complications, including infertility, others show a relatively low overall probability. Understanding these discrepancies and searching for more sensitive assessment methods are crucial to guide effective prevention and treatment strategies.

PID TREATMENT AND PREVENTIVE MEASURES

Treatment for PID depends on the severity of the condition. In moderate stages, an outpatient approach is feasible, involving a single intramuscular injection of cephalosporin, followed by oral doxycycline for 14 days. Metronidazole is indicated for 14 days in specific situations, such as bacterial vaginosis, trichomoniasis or recent uterine instrumentation. For more serious cases, hospitalization becomes necessary. Pregnant patients, serious situations, failure in outpatient treatment, presence of tubo-ovarian abscess or when there is a risk of emergency surgery justify this approach. Treatment remains unchanged for patients with intrauterine devices or HIV (CURRY, WILLIAMS & PENNY, 2019).

In addition to direct treatment, the integrated approach involves treatment of the sexual partner, emphasizing a rapid approach within legal limits. PID prevention includes strategies such as screening for Chlamydia trachomatis and Neisseria gonorrhoeae in women under 25 years of age, those at risk or pregnant. Intensive behavioral counseling is recommended for all adolescents and adults who are most likely to contract sexually transmitted infections. Annual chlamydia and gonorrhea screening is advised in sexually active women under age 25 and those at high risk for sexually transmitted infections. However, the effectiveness of bacterial vaginosis screening and treatment in reducing the incidence of PID still lacks clarity and requires further investigation (CURRY,

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WILLIAMS & PENNY, 2019).

The recommended initial therapy for infections caused by Neisseria gonorrhoeae involves the administration of ceftriaxone, 250 mg intramuscularly in a single dose, combined with azithromycin, 1 g in a single dose orally. This double regimen is the first-line choice, and is also applied to pregnant women. Standard treatment for Chlamydia trachomatis infection consists of doxycycline, 100 mg twice a day, for a period of seven days. In cases of contraindication for doxycycline during pregnancy, the first-line alternative is the administration of azithromycin, 1 g orally. For Mycoplasma infections, the recommendation includes azithromycin, 500 mg on the initial day, followed by 250 mg on days 2 to 5. Alternatively, josamycin, 500 mg for 10 days, administered orally, three times a day. In cases of infection complicated with PID, the recommended treatment is moxifloxacin, 400 mg once a day, for a period of 14 days (SMOLARCZYK et al., 2021).

It is scientifically proven that effective treatment of genital infections significantly reduces the risk of infertility. In the case of Pelvic Inflammatory Disease (PID), a frequent sequela of chlamydia and gonococcal infections, treatment is carried out with metronidazole, doxycycline and ceftriaxone, and can occur on an outpatient or hospital basis, adapting to the symptoms, severity and individual conditions of each patient (CURRY, WILLIAMS & PENNY, 2019).

The relationship between bacterial vaginosis and tubal factor infertility, regardless of the presence of chlamydia, is evident, especially in women undergoing in vitro fertilization. However, more investigation is needed into the connection between bacterial vaginosis and PID, endometritis and infertility. Adequate treatment, whether with oral metronidazole or clindamycin vaginal cream, is crucial to avoid possible sequelae (RAVEL, MORENO & SIMON, 2021).

Delay in PID treatment increases the chances of infertility and ectopic pregnancy by up to three times (CURRY, WILLIAMS & PENNY, 2019). Gonococcal, chlamydia, and genital mycoplasma infections can result in a variety of reproductive problems, including ectopic pregnancy, PID, infertility, neonatal infections, postpartum endometritis, and pregnancy loss. The recommended treatment in Brazil includes ceftriaxone and azithromycin for gonococcus, doxycycline (contraindicated in pregnancy) or azithromycin for chlamydia, and azithromycin for genital mycoplasma (SMOLARCZYK et al., 2021). However, antibiotic resistance deserves attention.

Retrospective studies indicate that Chlamydia trachomatis infection, especially when recurrent, increases the risks of adverse reproductive health outcomes, and treatment with antibiotics does not decrease the risk of subsequent PIDs (DEN HEIJER et al., 2019). Another comprehensive analysis, involving a systematic review and meta-analysis, concluded that chlamydia is associated with spontaneous abortion, tubal factor infertility and ectopic pregnancy, mainly in low- and middle-income countries (TANG et al., 2020).

The management of tubal factor infertility depends on the location of the disease, and may include transcervical tubal cannulation, tubocornoal anastomosis microsurgery, salpingostomy with fimbrioplasty and in vitro fertilization (HUNT and VOLLENHOVEN, 2023).

FINAL CONSIDERATIONS

The final considerations highlight that PID represents a clinical syndrome triggered by several pathogens, with emphasis on Chlamydia trachomatis and Neisseria gonorrhoeae. This condition is predominantly manifested by the invasion of these agents into the upper genital tract, triggering

an inflammatory response that results in significant tissue damage, leading to infertility. Research in the field of Gynecology and Infectious Diseases has focused on identifying potential exacerbating factors of female infertility. It is confirmed that infections originating from the rise of strict or facultative anaerobic bacterial pathogens from the vagina to the endometrium represent one of the fundamental causes of infertility in women of reproductive age, especially in the context of tubal infertility. Therefore, it is imperative to implement screening programs, including early screening using sensitive biomarkers capable of anticipating previous chlamydial infections. Furthermore, accurate diagnosis and appropriate treatment of Chlamydia are essential to preserving women's reproductive health.

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