



## **Pelvic inflammatory disease: A silent threat to female fertility**

DOI: 10.56238/eSvjH3N3-003

Receipt of originals: 04/12/2024

Acceptance for publication: 05/02/2024

### **Giovanna Abe Rodrigues de Melo**

Medical Student at the University Center of Brasília

Email: giovanna.melo@sempreceub.com

### **Marcelo de Araújo Lopes Júnior**

Medical Student at the University Center of Brasília

E-mail: marcelo.araujo@sempreceub.com

### **Juliana Smidt Costa**

Medical Student at the University Center of Brasília

E-mail: juliana.smidt@sempreceub.com

### **Thiago Alberto Brasil Fraga**

Medical Student at the University Center of Brasília

E-mail: thiago.brasil@sempreceub.com

### **Victor Fernandes Feitosa Braga**

Medical Student at the University Center of Brasília

E-mail: viictorbraga@sempreceub.com

### **João de Sousa Pinheiro Barbosa**

PhD in Health Sciences and Technologies from the University of Brasília

Professor in the Medicine course at the University Center of Brasília

E-mail: joao.barbosa@ceub.edu.br

### **ABSTRACT**

Pelvic inflammatory disease (PID) represents a clinical condition of significant importance, given its potential to generate serious sequelae if not properly identified and treated. Among these sequelae, infertility stands out, whose relationship with the presence of PID is well established. The incidence of infertility is particularly exacerbated by persistent, recurrent and inadequately treated infections, leading to considerable psychological distress for affected women and couples. The proactive approach in the early identification and treatment of PID is key to mitigating the risk of infertility and its emotional repercussions. In addition, raising awareness of risk factors and adopting preventive measures are equally crucial in promoting women's reproductive health and reducing the incidence of complications related to PID.

**Keywords:** Pelvic Inflammatory Disease, Infertility, Chlamydia, Gonorrhea, Prevention.



## 1 INTRODUCTION

PID is an inflammatory and infectious clinical syndrome caused by microorganisms that ascend the vaginal canal, spontaneously or as a result of manipulation, reaching the upper genital tract, compromising the endometrium, fallopian tubes, ovaries, pelvic peritoneum and contiguous structures. As a result, inflammations such as endometritis, oophoritis, parametritis, myometritis, salpingitis, pelviperitonitis, may occur. (1)

The most prevalent pathological agents of the disease include: *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Bacteroides* sp. (2)

In addition, the main causes for the rise of these microorganisms in the vaginal canal involve their spontaneous canalicular dissemination, insertion of an intrauterine device (IUD), endometrial biopsy and curettage. (1)

The consequences of PID represent one of the main reasons for reproductive morbidity in women of childbearing age, and can lead to ectopic pregnancy, chronic pelvic pain and infertility. About 18% of women report infertility even after treatment for the disease. (3)

Infertility is a consequence that can lead to psychological suffering for the woman and the couple (4) and is defined as the absence of clinical pregnancy after one year of unprotected sexual intercourse on a regular basis, that is, with a frequency of two to three times a week during this period. (5)

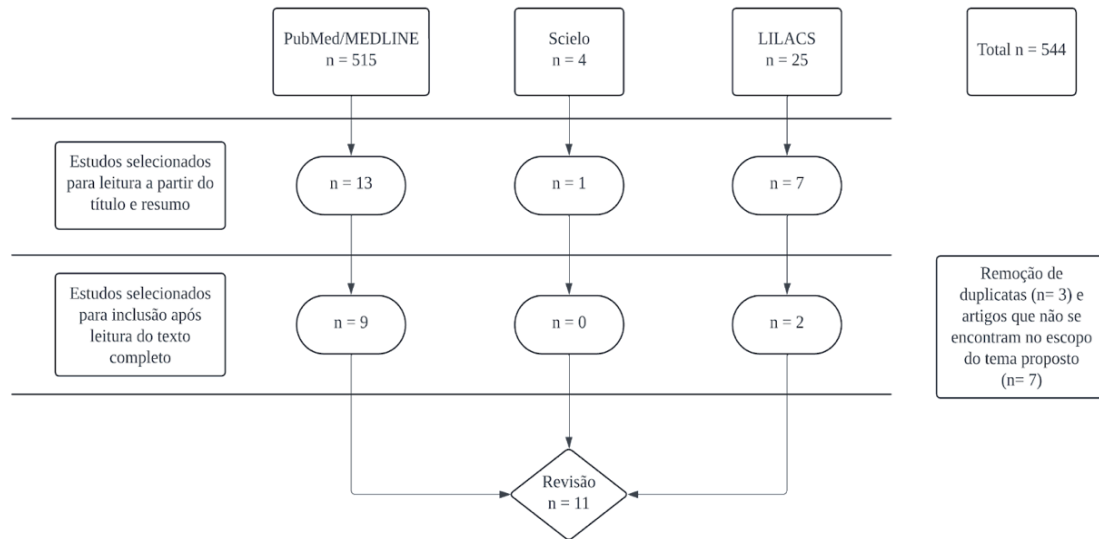
In view of the social panorama of reproductive disability and PID as a possible culprit, this article aims to elucidate what is most current in the literature regarding PID and its effects on infertility.

## 2 METHODOLOGY

This article is a literature review, using the PubMed/MEDLINE, Scielo and LILACS databases. The following descriptors were used in health sciences in isolation and combined through Boolean operators: pelvic inflammatory disease and infertility. As inclusion criteria, articles from the last 5 years were used, in Portuguese and English.

Articles with a publication date older than five years were excluded from the search. After the initial search, the articles were screened by reading the title and abstract, followed by the removal of duplicates in more than one database and articles whose content did not correspond to the theme under study. The diagram expressed in figure 1 demonstrates the methodological process applied in this article.

Figure 1. Quantitative and qualitative results of the database search.



### 3 RESULTS

The initial search in the database resulted in a total of 544 articles in the 3 electronic databases. A priori, 515 articles were found in the PubMed/MEDLINE database, 4 articles in Scielo and 25 articles in LILACS 25, of which, with the reading of the title and abstract, 13, 1 and 7 articles, respectively, relevant to our theme were delimited. Subsequently, with the removal of duplicates and reading of the full text, 11 articles were used to carry out the work in question, represented in the table below.

Table 1. Articles used for the preparation of this review.

Authors	Title	Objective	Conclusion
Anyalechi GE, Hong J, Kreisel K, Torrone E, Boulet S, Gorwitz R, Kirkcaldy, Bernstein K.	<b>Self-Reported Infertility and Associated Pelvic Inflammatory Disease Among Women of Reproductive Age-National Health and Nutrition Examination Survey, United States, 2013-2016</b>	To analyze the determinants of infertility in women who participated in the national survey (NHANES) in the United States in the years 2013 to 2016 with a focus on ethnic difference and its relationship with IPD.	It was observed that 13.8% of women of reproductive age in a national sample reported a history of infertility. Pelvic inflammatory disease (PID) has been linked to infertility, especially in young women. Annual screening for chlamydia and gonorrhea can help prevent PID and consequently reduce the impact of infertility in the United States.
Lijun Liu, Changchang Li, Xuewan Sun, Jie Liu, Hepeng Zheng, Bin Yang, Weiming Tang,	<b>Chlamydia infection, PID, and infertility: further evidence from a case-control study in China.</b>	To evaluate the relationship of chlamydia infection with PID and infertility in a case-control study in	The previous occurrence of PID significantly increases the risk of infertility, especially tubal infertility. Therefore, there is an emphasis on the need for highly sensitive and specific biomarkers for prior chlamydia infection. This highlights the importance of

Cheng Wang.		Guangdong province, China.	early diagnosis and proper treatment of chlamydia to prevent future complications such as infertility.
Ravel, J., Moreno, I., e Simón, C.	<b>Bacterial vaginosis and its association with infertility, endometritis, and pelvic inflammatory disease.</b>	To review the literature relating bacterial vaginosis to infertility, endometritis, and PID.	Diagnosis and treatment of bacterial vaginosis, chronic endometritis, and pelvic inflammatory disease prior to attempted conception may be important components of preconception care for symptomatic women to improve natural and assisted reproduction outcomes.
Amy Curry, Tracy Williams, Melissa L. Penny.	<b>Pelvic Inflammatory Disease: Diagnosis, Management, and Prevention</b>	To propose an updated literature review on the diagnosis, management and prevention of PID.	Hospitalization is recommended for patients who are pregnant, critically ill, have failed treatment, or in cases of tubo-ovarian abscess. Treatment does not vary for patients with intrauterine devices or HIV. Treatment of sexual partners is advised, with expedited options where legally possible. Prevention of PID involves screening for <i>C. trachomatis</i> and <i>N. gonorrhoeae</i> in young and at-risk women.
L.M. Stewart, C.J.R. Stewart, K. Spilsbury, P.A. Cohen, S. Jordan	<b>Association between pelvic inflammatory disease, infertility, ectopic pregnancy and the development of ovarian serous borderline tumor, mucinous borderline tumor and low-grade serous carcinoma</b>	Prospective cohort study with data from women born in Western Australia, to evaluate the association of PID and infertility, ectopic pregnancy, and tumors.	The association with PID supports the hypothesis that inflammatory processes in the upper part of the gynecological tract and/or peritoneum may predispose to the development of borderline serous tumors and serous carcinoma.
Hunt, Sarah, and Beverley Vollenhoven.	<b>Pelvic Inflammatory Disease and Infertility</b>	Describe the pathogenesis, clinical evaluation and management of DIP with a focus on management of long-term fertility-related sequelae	Tubal infertility is not an uncommon sequelae of the DIP. The approach is individualized, based on patient factors, disease severity, and patient preferences. Given the high incidence of long-term complications, public health initiatives to prevent sexuality and communicable infections, as well as detection, diagnosis, and treatment, are goals to reduce the morbidity of the disease.
Casper D. J. den Heijer, Christian J. P. A. Hoebe, Johanna H. M. Driessen, Petra Wolffs	Casper D. J. den Heijer, Christian J. P. A. Hoebe, Johanna H. M. Driessen, Petra Wolffs	<b>Chlamydia trachomatis and the Risk of Pelvic Inflammatory Disease, Ectopic Pregnancy, and Female Infertility: A Retrospective Cohort Study Among Primary Care Patients</b>	To assess the risk of pelvic inflammatory disease (PID), ectopic pregnancy, and infertility in women with diagnóstico prévio de <i>Chlamydia trachomatis</i> (CT).  An association was shown between positive TC tests and three adverse reproductive health outcomes. In addition, the risk increased with repeated CT infections. The use of effective antibiotics in CC did not show decreased

				risks of subsequent PID, regardless of CT history. Our results confirm the burden of CT on reproductive health, which requires appropriate public health interventions
Hui Ye, MD, Yilan Tian, MD, Xiuzhang Yu	Hui Ye, MD, Yilan Tian, MD, Xiuzhang Yu	<b>Association Between Pelvic Inflammatory Disease and Risk of Endometriosis: A Systematic Review and Meta-Analysis</b>	Conduct a meta-analysis of studies published up to May 21, 2022 regarding this relationship.	14 studies with 747,733 patients. The mean prevalence of PID in women with endometriosis was 33.80%. Our quantitative synthesis revealed that endometritis was associated with a significantly increased risk of endometriosis. (OR: 1.63, 95% CI: 1.53–1.74, I2 = 59%)
Fan, L., Liu, Z., Zhang, Z., Li, T., Li, H., Chen, J., Zong, X., Zhang, X., Chen, X., Bai, H., Wang, F., & Shang, C	Fan, L., Liu, Z., Zhang, Z., Li, T., Li, H., Chen, J., Zong, X., Zhang, X., Chen, X., Bai, H., Wang, F., & Shang, C	<b>Identifying the clinical presentations, progression, and sequela of pelvic inflammatory disease through physiological, histological and ultrastructural evaluation of a rat animal model.</b>	To evaluate the inflammatory and uterine tissue response in animal models, by inoculating a contaminated solution in the endometrial tissue of the same.	Elucidated the characteristics and progression of PID in an animal model. The detailed evidence has increased our understanding of the pathogenesis and progression of the disease and may be useful for future studies on this topic.
Sandra A. C., MD1, Amanda N. Kallen,	Sandra A. C., MD1, Amanda N. Kallen,	<b>Diagnosis and Management of Infertility: A Review</b>	Gather current evidence with respect to the diagnosis and treatment of infertility.	Approximately 1 in 8 women aged 15 to 49 years receive infertility services. While success rates vary by age and diagnosis, accurate diagnosis and effective therapy, along with shared decision-making, can facilitate the achievement of fertility goals in many couples treated for infertility.

<p>Maria Luiza B. M., Paulo C. G., Iara M. L., Neide A. T. B., Mayra G. A.</p>	<p>Maria Luiza B. M., Paulo C. G., Iara M. L., Neide A. T. B., Mayra G. A.</p>	<p><b>Brazilian Protocol for Sexually Infected Infections Communicables 2020: pelvic inflammatory disease.</b></p>	<p>To propose an updated protocol consistent with the Brazilian reality for the IPD.</p>	<p>The protocol represents an important instrument to improve the management and prevention of pelvic inflammatory disease in Brazil. The recommendation of screening for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i> as a preventive strategy emphasizes the commitment to public health and technological advances in the early detection of these etiological agents, contributing to the promotion of women's sexual and reproductive health.</p>
--	--	--	--	---

#### 4 DISCUSSION

PID is a condition in which several studies show the presence of a relationship with infertility, according to the Brazilian STI protocol, 10 to 50% of women with PID will have infertility as a sequelae (1). In Anyalechi's study, a four-fold higher relative risk of infertility was found in the group of women who had a diagnosis of PID compared to the group who did not. (6). In the study by Lijun Liu, the group with a previous diagnosis of this disease had a six-fold higher prevalence of infertility than did the control group. (7). In another, by Casper D. J., a five-fold increase in the incidence of PID was identified for women who tested positive for *Chlamydia trachomatis* infection and a three-fold relative risk for infertility in this group, much higher rates when compared to the group with negative results. (8)

Considering that this condition leads to female reproductive disability, it becomes essential to understand what predisposes women to develop PID. Ravel's study makes an important relationship between bacterial vaginosis (BV) and the development of the disease, since women with BV have an increased risk of acquiring sexually transmitted infections (STIs). (9) In addition, there are other risk factors such as: age under 25 years, new or multiple sexual partners,

relationship with a symptomatic partner, sex before the age of 15 years, previous history of STIs or PID. (1,10)

Endometriosis is another complication associated with infertility and the disease that is the subject of this article, in which in a study by Hui Ye, women with PID had a relative risk of 1.53 for the development of this condition. (11)

Regarding the pathophysiology of this inflammatory disease and its connection to infertility, two studies were found. Stewart's study demonstrates a hypothesis that the inflammation caused by PID can lead to functional changes in female reproductive structures (12), a hypothesis reinforced by Linyuan's study, in which an animal model was used to assess the progression of the disease, in which a Th1 and Th2 inflammatory response mediated by inflammatory factors (mainly IFN- $\gamma$ , IL-1 $\beta$ , IL-2, and IL-4) can lead to tissue injury. (13)

In addition, prolonged, recurrent, and silent cases lead to higher probabilities of sequelae such as infertility, borderline serous tumors, and borderline mucinous tumors. (12, 14). Specifically, infertility correlates with the degree of damage caused to the fallopian tubes, which was verified through laparoscopy in women with PID. (14)

In order to avoid infertility due to a possibly recurrent and prolonged state of inflammation, effective management and screening of PID becomes essential. (6 ,7, 10, 14, 8)

The management of PID begins with the identification of active disease by clinical diagnosis based on complete physical and specular examinations. (1, 10, 14) The diagnostic criteria must be met by three major criteria associated with a minor or elaborate criterion, specified in Chart 2. (1)

Table 2. Adapted from the Brazilian Protocol for Sexually Transmitted Infections 2020: Pelvic Inflammatory Disease.

Criteria	Description
Larger	Hypogastrium pain
	Pain on palpation of the appendages
	Pain on cervical mobilization
Smaller	- Axillary temperature >37.5°C or rectal temperature >38.3°C
	Vaginal contents or abnormal endocervical discharge
	Pelvic mass
	More than 10 leukocytes per immersion field in endocervix material
	Leukocytosis in peripheral blood
	Elevated C-reactive protein or erythrocyte sedimentation rate
	Laboratory evidence of cervical infection with gonococcus, chlamydia, or mycoplasmas

Made	Histopathologic evidence of endometritis
	Presence of tubo-ovarian or cul-de-sac Douglas abscess on imaging study
	Laparoscopy with evidence of pelvic inflammatory disease

After diagnosis, antimicrobial treatment should be started immediately, without the need to wait for complementary tests in order to avoid infertility and other complications (1, 12, 11, 14, 15). Initially, the first option treatment should be done with ceftriaxone 500mg, intramuscular, in a single dose, associated with doxycycline 100mg, twice a day, for fourteen days in cases without the need for hospitalization. (1, 10) In cases with hospitalization criteria, defined in Chart 3, ceftriaxone 1 g, intravenous, once a day, associated with doxycycline 100 mg, orally, twice a day for fourteen days, should be used as the first option. (1)

Table 3. Adapted from the Brazilian Protocol for Sexually Transmitted Infections 2020: Pelvic Inflammatory Disease.

Criteria for indication of hospital treatment of PID
Tube-ovarian abscesso
Pregnancy
Absence of clinical response 72 hours after the start of treatment with oral antibiotic therapy
Intolerance to oral antibiotics or difficulties with outpatient treatment
Severe general condition, with nausea, vomiting, and fever
Difficulty in excluding surgical emergency (e.g., appendicitis, ectopic pregnancy)

The prevention of PID consists of the surveillance and control of the disease. Counseling aimed at patients and their sexual practices should be included in order to minimize risk factors for STIs, testing for HIV, syphilis, hepatitis B and C, and in some cases vaccination against hepatitis A and B (1, 10, 14, 15). Sexual partners should be counseled and evaluated, but treated only if there is sexual intercourse up to two months before diagnosis. (1)

The U.S. Centers for Disease Control and Prevention recommends annual screening for women under 25 years of age, or over 25 years of age with risk factors, for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, with proven efficacy in reducing cases of PID. (1, 10, 14)

In Brazil, screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* is performed at the first prenatal visit in pregnant women up to 30 years of age, people diagnosed with STIs, living with HIV or using pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), as well as sexual violence and people with receptive anal sex without the use of condoms. (1)





## 5 CONCLUSION

The relationship between PID and infertility is a significant concern, particularly among young women. The previous presence of the disease is strongly associated with an increased risk of infertility, especially related to tubal dysfunction. The results point to a significant increase in the risk of infertility in women diagnosed with PID, especially when considering additional risk factors such as women under the age of 25, multiple sexual partners, relations with symptomatic partners, bacterial vaginosis and endometriosis.

The pathophysiology of PID suggests that chronic inflammation plays a crucial role, leading to changes in reproductive structures and potentially causing irreversible damage.

It is imperative that effective management and screening strategies are implemented to avoid the devastating consequences of infertility arising from PID, underscoring the importance of prevention, early diagnosis, and appropriate treatment of this condition to preserve women's reproductive health and mitigate the associated risk of infertility.



## REFERENCES

MENEZES, Maria Luiza Bezerra, et al. “Protocolo Brasileiro Para Infecções Sexualmente Transmissíveis 2020: Doença Inflamatória Pélvica.” *Epidemiologia E Serviços de Saúde*, vol. 30, no. spe1, 2021, <https://doi.org/10.1590/s1679-4974202100011.esp1>.

MELO, Gabriel Henrique Resende, et al. “Doença Inflamatória Pélvica: Fisiopatologia, Investigação Diagnóstica e Manejo Terapêutico”. *Brazilian Journal of Development*, vol. 7, no. 10, 19 Oct. 2021, pp. 98440–98453, <https://doi.org/10.34117/bjdv7n10-251>.

Manejo Inicial da Paciente Infértil Pelo Ginecologista. São Paulo: *Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO)*, 2023. (Série, Orientações e Recomendações FEBRASGO, no.2). iv, 76p.

DEMARQUE, Renata, et al. “Infertilidade feminina.” *Debates em Psiquiatria*. <https://doi.org/10.25118/2236-918X-4-4-4>.

DE FARIA, Luisa, et al. “Revisão Integrativa: Causas de Infertilidade e Tratamentos de Fertilização.” *Brazilian Journal of Health Review*, vol. 6, no. 5, 19 Oct. 2023, pp. 25242–25253, <https://doi.org/10.34119/bjhrv6n5-366>.

ANYALECHI, G. E. et al. “Self-Reported Infertility and Associated Pelvic Inflammatory Disease Among Women of Reproductive Age” - *National Health and Nutrition Examination Survey*, United States, 2013–2016. *Sexually Transmitted Diseases*, v. 46, n. 7, p. 446–451, jul. 2019. <https://doi.org/10.1097/OLQ.0000000000000996>.

LIU, L. et al. “Chlamydia infection, PID, and infertility: further evidence from a case–control study in China.” *BMC Women’s Health*, v. 22, n. 1, 15 jul. 2022. <https://doi.org/10.1186/s12905-022-01874-z>.

DEN, Heijer, Casper D J, et al. “Chlamydia Trachomatis and the Risk of Pelvic Inflammatory Disease, Ectopic Pregnancy, and Female Infertility: A Retrospective Cohort Study among Primary Care Patients.” *Clinical Infectious Diseases*, vol. 69, no. 9, 24 Aug. 2019, pp. 1517–1525, <https://doi.org/10.1093/cid/ciz429>.

RAVEL, Jacques, et al. “Bacterial Vaginosis and Its Association with Infertility, Endometritis, and Pelvic Inflammatory Disease.” *American Journal of Obstetrics and Gynecology*, vol. 224, no. 3, 1 Mar. 2021, pp. 251–257, <https://doi.org/10.1016/j.ajog.2020.10.019>.

CURRY, Amy, et al. “Pelvic Inflammatory Disease: Diagnosis, Management, and Prevention.” *American Family Physician*, vol. 100, no. 6, 15 Sept. 2019, pp. 357–364, [www.aafp.org/pubs/afp/issues/2019/0915/p357.html](http://www.aafp.org/pubs/afp/issues/2019/0915/p357.html).

HUI, et al. “Association between Pelvic Inflammatory Disease and Risk of Endometriosis: A Systematic Review and Meta-Analysis.” *Journal of Women’s Health*, 17 Oct. 2023, <https://doi.org/10.1089/jwh.2023.0300>

STEWART, L.M., et al. “Association between Pelvic Inflammatory Disease, Infertility, Ectopic Pregnancy and the Development of Ovarian Serous Borderline Tumor, Mucinous Borderline Tumor and Low-Grade Serous Carcinoma.” *Gynecologic Oncology*, vol. 156, no. 3, Mar. 2020, pp. 611–615, <https://doi.org/10.1016/j.ygyno.2020.01.027>.



FAN, L., Liu, Z., et al “Identifying the clinical presentations, progression, and sequela of pelvic inflammatory disease through physiological, histological and ultrastructural evaluation of a rat animal model.” (2021) *Annals of Translational Medicine*, 9(23), 1710–1710. <https://doi.org/10.21037/atm-21-3345>

HUNT, Sarah, and Beverley Vollenhoven. “Pelvic Inflammatory Disease and Infertility.” *Australian Journal of General Practice*, vol. 52, no. 4, 1 Apr. 2023, pp. 215–218, <https://doi.org/10.31128/AJGP-09-22-6576>.

CANSON, S. A., & Kallen, A. N. “Diagnosis and Management of Infertility: A Review.” (2021). *JAMA*, 326(1), 65–76. <https://doi.org/10.1001/jama.2021.4788>.