

## Review Article

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# Intrauterine devices & infection: Review of the literature

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**The relationship between use of an intrauterine device (IUD) and pelvic inflammatory disease (PID) has been studied extensively over the past 50 years. Previous research has led to considerable controversy and debate. Numerous limitations in the studies make it difficult to draw any firm conclusions from the past research or to design new approaches to study the topic. The main research barriers include uncertainty of infection/diagnoses, and inappropriate comparison groups for IUD users. Natural history studies of the aetiology of disease and observational research among IUD users suggest that the risk of PID is very low. Research linking previous IUD use to the more distant endpoint of tubal infertility reveals that the risks may be even lower than the risks of PID.**

**Key words** Aetiology - infection - intrauterine device - pelvic inflammatory disease - research limitations

## Introduction

The concern that intrauterine devices (IUDs) might cause or facilitate gynaecologic infection has a long and controversial history, dating to the 1940s<sup>1</sup>. The introduction and rapid adoption of modern IUDs in the 1960s, followed by increased popularity in the 1970s, gave scientists many opportunities to conduct research on IUD-related infections. Despite nearly 50 years of research, we still lack a clear understanding that is accepted by all. Even with modern research methods that employ more sophisticated approaches and strategies that can help eliminate the shortcomings of prior research, we still do not have perfect information.

This article reviews the available information about the relationship between IUD use and gynaecologic infection. Because the majority of pelvic inflammatory

disease (PID) is thought to be caused by unbridled exposure to sexually transmitted bacteria<sup>2</sup>, this review draws from the medical literature on contraceptive use and sexually transmitted infections. It is important to emphasize that this article provides evidence for non-hormonal IUDs only. The levonorgestrel intrauterine system, for example, may have a different effect on the aetiology of infection, compared to copper IUDs.

## Barriers to understanding

Four main barriers prevent complete understanding of the role of the IUD in gynaecologic infections: the asymptomatic nature of many infections, the unknown timing of bacterial exposure in relation to insertion and use of an IUD, lack of an appropriate comparison group for IUD users, and imprecise PID diagnoses. These and other limitations make it difficult to conduct research on this topic<sup>3</sup>.

(i) *Asymptomatic infections*: Because an infection may produce mild or no symptoms, women may be inaccurately characterized as free of disease, flawing research, especially when searching for associations between previous infection and IUD use. This problem is particularly true for *Chlamydia trachomatis*, which can cause a significant number of asymptomatic cervical and upper genital tract infections. The damage may be discovered only years later through diagnostic work-up for infertility or chronic pelvic pain.

(ii) *Timing of bacterial exposure in relation to insertion and use of an IUD*: Documenting the presence of sexually transmitted bacteria in the genital tract, with or without accompanying infection (again possibly asymptomatic) is a necessary first step in understanding how or if the IUD increases risk. Presence of bacteria before the IUD is inserted can have a completely different aetiology compared to bacteria acquired after the IUD is *in situ*. Treatment of detected bacteria removes both the risk of infection and the ability to fully understand the aetiology.

(iii) *Lack of appropriate comparison group*: To obtain valid results, researchers must compare IUD users with women who have the same levels of infection risk. This requirement is difficult to fulfill, for several reasons. First, self-perceived differences in risk of infection often dictate the decision on which birth control method to use. For example, a woman who is unsure of her partner's sexual behaviour might opt for condoms. Or high coital frequency might prompt a woman to seek intrauterine contraception because it is highly effective, but high coital frequency itself increases the risk of infection in general populations.

A woman who chooses sterilization may be at the lowest risk of infection, because often her sexual relationship is likely to be stable and monogamous. Researchers have attempted to control for such confounding factors by collecting information on the number of sexual partners, use of condoms, and other

infection risk factors<sup>4-6</sup>. These measures, which are often ascertained by the subject report, are notoriously unreliable and cannot fully account for the underlying differences in risk among study groups<sup>7-9</sup>.

A second difficulty in comparing risk among women using different contraceptive methods is that some methods reduce risk: condoms may protect women from bacterial exposure, and oral contraceptives may protect women from upper genital tract infection by thickening the cervical mucus barrier<sup>10</sup>. Copper IUDs do neither. Thus, when compared to some contraceptives, the IUD may appear riskier even though these do not add to the intrinsic risk of infection.

(iv) *Imprecise diagnoses*: PID is difficult to diagnose with high sensitivity and specificity, even in a research setting with predefined criteria. Laparoscopic evaluation, the gold standard for diagnosis, is highly invasive for general evaluation of possible acute PID.

### Natural history of gynaecologic infection

Sexually transmitted bacteria that ascend through the genital tract may not produce discrete signs of disease at different anatomic sites. A single bacterial exposure causes chronic infection and the disease begins with the acquisition of bacteria. If host defenses fail, acquisition may lead to cervical infection, followed by PID, and finally tubal infertility.

Although published research provides some clues as to how often one stage of infection develops into the next, the evidence is insufficient to allow definitive conclusions. At each step, the quality of the information varies, making it difficult to understand with confidence the complete aetiology of disease. The evidence as we have it from cervical infection to PID and from PID to tubal infertility is outlined below (Fig. 1).

*Cervical infection to PID*: How often does cervical infection lead to PID? Some evidence comes from studies conducted in the United States that discovered that penicillin was an ineffective treatment for

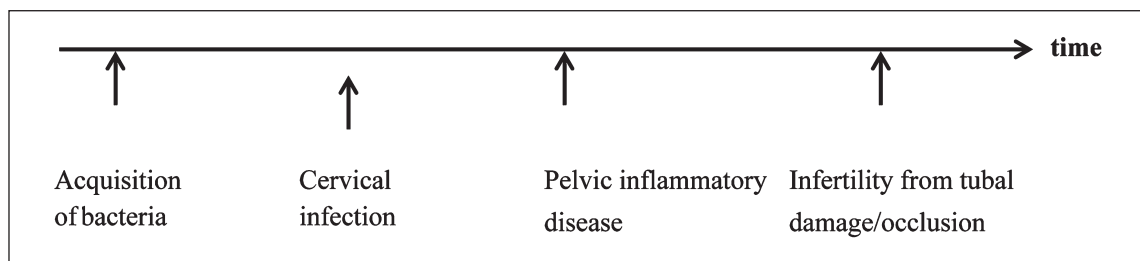


Fig. 1. Aetiology of infection.

chlamydial infection. In two separate studies, 16 and 30 per cent of women with chlamydial infection developed PID<sup>11,12</sup>. In research from The Netherlands, none of the 30 women who had chlamydial infections developed PID<sup>13</sup>. Rahm<sup>14</sup> estimated that either 2 or 5 per cent of participants in a prospective study developed PID secondary to chlamydial cervical infection, depending on whether some PID diagnoses were missed. In a small study of 20 women with chlamydial infection, Paavonen and coworkers<sup>15</sup> found that 20 per cent women developed PID within four weeks. A study of gonococcal exposure that had time to progress during contact tracing and before treatment found that nine of 16 women (47%) developed symptoms consistent with PID (median time of 11 days after exposure)<sup>16</sup>. As noted in two review articles<sup>17,18</sup>, small study sizes, varying quality of the research, and other factors, make it difficult to use existing research to summarize the risks.

**PID to tubal infertility:** How often does PID damage the lumen of the fallopian tubes, resulting in tubal infertility? The best evidence comes from a seminal Swedish study<sup>19</sup> in which women who had laparoscopically confirmed PID were followed up for 6 to 14 yr in the national health system. Among women who had one episode of PID, 13 per cent were diagnosed with tubal infertility. With two episodes of PID, 35 per cent developed PID. With three or more episodes of PID, 75 per cent of women developed tubal infertility. None of the 100 control subjects (negative for PID based on laparoscopy) developed tubal infertility over the same follow up period.

#### ***Aetiology of infection with an IUD***

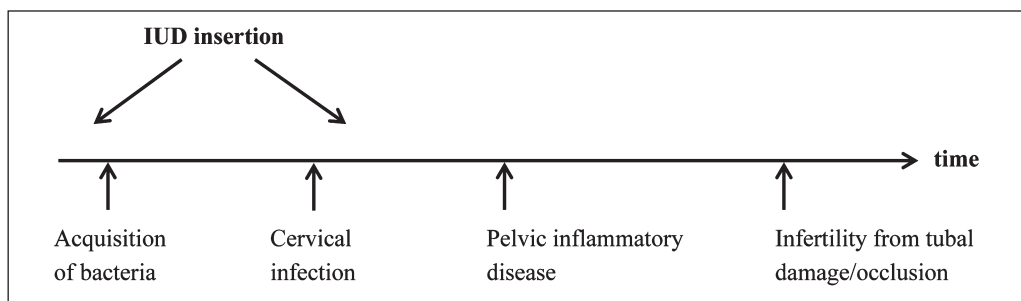
Event rates observed in natural history data outlined above may be altered by IUD use. The risks may also vary, depending on when the IUD is inserted in relation to the different disease steps (Fig. 2). For example, if the IUD is *in situ* prior to bacterial exposure, does the

IUD facilitate infection of the upper genital tract? If the cervix is infected and an IUD is inserted, the chances of upper genital tract infection may be different. If months pass between acquisition of bacteria and IUD insertion (without developing cervical infection), does the insertion procedure increase the risk of lower and upper genital tract infection? We have no evidence to answer most of these questions.

**Background rates of PID among IUD users:** How common is PID in a general population of IUD users? The best evidence comes from a compilation of IUD studies conducted by the World Health Organization<sup>20</sup>. Key points from the study are: (i) 22,908 women received an IUD (75% of the devices were copper-containing), some were followed up to 10 years (Greater than 51,000 person-years of IUD use). (ii) PID defined as oral temperature  $\geq 38^{\circ}\text{C}$ , and abdominal tenderness with guarding, and positive pelvic exam (adnexal or cervical motion tenderness, or palpable adnexal mass), (a) 81 cases of PID were followed up; (b) average incidence was 1.6 events per 1000 person-years; (c) Highest rate in the first month: 4 times higher than the average rate.

This evidence shows that the risk of PID among IUD users is low and similar to the rate in a general population of sexually active women. However, the higher rate during the first month suggests that the insertion procedure may cause additional cases of PID.

**Antibiotic prophylaxis at IUD insertion:** The concern that the insertion procedure might increase PID risk led several groups of researchers to investigate whether prophylactic use of antibiotics could reduce PID incidence. A systematic review and meta-analysis of four randomized trials on this topic<sup>21</sup> found low and equal PID rates between the antibiotic and placebo groups. Thus, with today's focus on careful selection of IUD users (*i.e.*, low risk of acquiring sexually



**Fig. 2.** Aetiology of infection with intrauterine device (IUD).

transmitted infection), PID rates can remain low, without the need for prophylactic medications.

*Insertion through an infected cervix: effect on PID incidence:* If natural history studies show that between 0 and 47 per cent of untreated cervical infections will progress naturally to PID, how does IUD insertion through an infected cervix affect PID risk? In other words, does IUD insertion contaminate the uterus with a clinically significant amount of bacteria? Evidence to answer these questions does not exist. A systematic review by Mohllajee and colleagues<sup>17</sup> at the Centers for Disease Control and Prevention failed to identify any properly designed published research. Because ethical considerations preclude implementation of a study with such a design, it is impossible to know how PID incidence might be altered by inserting an IUD through an infected cervix, compared to simply leaving the cervical infection untreated and providing an alternative method of birth control. The review by Mohllajee and colleagues, however, found six published studies that tallied events after inserting an IUD through an infected cervix<sup>22-27</sup>. These prospective studies lack a comparison group since these involved only IUD users, some of whom had a cervical infection at the time of insertion. Among women who had an IUD inserted through an infected cervix, 0 to 5 per cent developed PID. IUD users who did not have an infection at the time of insertion appeared to have a lower incidence of PID. Still, it is difficult to draw firm conclusions from these studies, for two main reasons. First, because the number of women with infection was small and there were only a few PID events, the confidence intervals around the point estimates were very wide. Second, an unknown proportion of women who had an infection were contacted to return to the clinic for treatment, thus possibly preventing development of PID. In addition, timing of initiation of antibiotic treatments probably varied considerably in the studies.

### **Tubal infertility and IUD use**

The latest research to examine the relationship between IUD use and tubal infertility was conducted in Mexico City<sup>28</sup>. Three key features of this effort distinguish it from past work: a non-litigious society void of IUD controversy; collection of serum samples from participants to detect past exposure to *C. trachomatis*; and any past use of an IUD was limited to copper devices. The case-control study found that women with tubal infertility had used the IUD previously with same frequency as pregnant primigravid controls. Thus the research found that

past use of a copper IUD did not increase the risk of tubal infertility; however, previous exposure to *C. trachomatis* (as determined by presence of chlamydial antibodies) increased the risk more than two-fold. This effort lends support to the theory that sexually transmitted bacteria, and not the IUD, are to blame for tubal infertility. Because the research was conducted among only nulligravid women, the results should be reassuring to women who want to use an IUD before having children.

### **Attributable risk**

The concept of attributable risk, as applied to IUD use and resulting PID, was developed because clinicians often do not know whether a patient has an active cervical infection when inserting a device<sup>29</sup>. Thus, to prevent complete paralysis of IUD services in the face of these unknowns, the attributable risk model gives clinicians a better sense of the magnitude of the risks. Using a hypothetical model and assumptions about risk under worst-case scenarios (10% prevalence of cervical infection in the clinic population; relative risk of PID from IUD use is 2.5 times higher than for the general population; and 5 per cent of cervical infections will progress to PID after an IUD insertion), approximately 1 in 333 insertions would result in PID that was directly attributable to the IUD (less than one-third of 1%). Also estimated in the model was that the attributable risk could be halved (1 in 667 insertions or about 0.15%) if clinicians used simple questions to screen out high-risk women.

### **Conclusions**

We do not know for certain whether the IUD is a cause, facilitator, or innocent bystander in the aetiology of gynaecologic infection. The best evidence suggests that the risk of PID among IUD users is very low. Although research has shown that the insertion procedure may increase the risk of PID, prophylactic use of antibiotics appears unnecessary because PID rates, even in the first month, are low. Recent evidence suggests that any link between IUD use and subsequent infertility is less certain.

### **Conflict of interest**

David Hubacher has served on Scientific Advisory Boards for Bayer HealthCare and Teva Pharmaceutical. He has received product donations from Bayer, Teva, and Merck for his independent and externally-funded research ideas. Bayer has funded an additional year of follow up on participants in



one of Dr Hubacher's NIH-funded research projects (investigator-led R01).

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