Levonorgestrel-Releasing Intrauterine Device for the Prevention of Pelvic Inflammatory Disease: A Systematic Review

Jodee L.D. Trivette

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Levonorgestrel-Releasing Intrauterine Device for the Prevention of Pelvic Inflammatory Disease: A Systematic Review

Abstract

Background: Pelvic inflammatory disease is a community-acquired infection accounting for approximately 1.2 million hospital visits and $1.88 billion in cost annually in the United States. Few interventions are available for the prevention of pelvic inflammatory disease. Intrauterine devices are a well-established method of contraception, in addition, levonorgestrel-releasing intrauterine devices may provide a protective advantage against pelvic inflammatory disease. This review aims to evaluate the available evidence to determine if levonorgestrel intrauterine devices, in addition to contraception, provide a protective benefit against pelvic inflammatory disease when compared to other intrauterine devices.

Method: An extensive literature search was performed using the databases MEDLINE, Web of Science, and CINAHL. Duplicate results and non-English articles were excluded. Articles meeting inclusion criteria were analyzed using the GRADE system.

Results: The literature search identified three articles that met inclusion criteria. All studies were randomized comparison trials involving a levonorgestrel intrauterine device compared to one or more forms of copper intrauterine device. Studies showed conflicting evidence supporting the benefit of levonorgestrel intrauterine devices for the prevention of pelvic inflammatory disease. All studies were of very low quality.

Conclusion: Limited very low quality evidence is available to support the potential benefit of levonorgestrel intrauterine devices for the prevention of pelvic inflammatory disease. Research results are conflicting and there is a small amount of very low quality evidence to support this theory. Based on the current research levonorgestrel intrauterine devices for the prevention of pelvic inflammatory disease are not recommended. Further well-designed prognostic studies are needed to determine the protective potential of levonorgestrel intrauterine devices.

Degree Type
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Degree Name
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Levonorgestrel-Releasing Intrauterine Device for the Prevention of Pelvic Inflammatory Disease: A Systematic Review

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2012

Faculty Advisor: James Ferguson, PA-C, MPH

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Information redacted for privacy]
Abstract

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**Conclusion:** Limited very low quality evidence is available to support the potential benefit of levonorgestrel intrauterine devices for the prevention of pelvic inflammatory disease. Research results are conflicting and there is a small amount of very low quality evidence to support this theory. Based on the current research levonorgestrel intrauterine devices for the prevention of pelvic inflammatory disease are not recommended. Further well designed prognostic studies are needed to determine the protective potential of levonorgestrel intrauterine devices.

**Keywords:** intrauterine device, levonorgestrel, intrauterine device copper, pelvic inflammatory disease
Acknowledgements

[Information redacted for privacy]
# Table of Contents

- Biography ................................................................................. 3
- Abstract .................................................................................. 4
- Acknowledgements .................................................................... 5
- Table of Contents ...................................................................... 6
- List of Tables ............................................................................ 7
- List of Abbreviations .................................................................. 7
- Background ............................................................................... 8
- Methods .................................................................................. 10
- Results .................................................................................... 11
- Discussion ............................................................................... 17
- Conclusion ............................................................................... 19
- References ............................................................................... 20
- Tables ..................................................................................... 23
List of Tables

Table I: Characteristics of Reviewed Studies
Table II: Summary of Finding

List of Abbreviations

PID................................................................................................Pelvic Inflammatory Disease
IUD................................................................................................Intrauterine Device
LNG.................................................................................................Levonorgestrel
Cu.................................................................................................Copper
Levonorgestrel-Releasing Intrauterine Device for the Prevention of Pelvic Inflammatory Disease: A Systematic Review

BACKGROUND

Pelvic inflammatory disease (PID) is a community-acquired infection of female reproductive organs caused by a sexually transmitted disease, most commonly Neisseria gonorrhoeae and Chlamydia trachomatis. It may involve the uterus, fallopian tubes, ovaries, or all of these structures. PID is the most common gynecological condition seen in emergency departments in the United States and accounts for approximately 1.2 million hospital visits per year.\(^1\) In addition, an estimated annual cost of $1.88 billion is attributed to PID and its sequelae.\(^2\) Women who are celibate are not at risk for developing PID and women in long-term monogamous relationships are at very low risk.\(^3\) Women at greatest risk for developing PID are those between the ages of 15 to 25, women with multiple sexual partners, those with a male partner with a sexually transmitted infection, and those with a prior history of PID.\(^3-6\) Even with prompt diagnosis and treatment of PID long-term complications often occur. Sequelae of PID include recurrent episodes of PID, infertility, chronic pelvic pain, ectopic pregnancy, and possibly an association with increased risk of ovarian cancer.\(^7\) Long-term effects of PID are thought to be due to the scarring and adhesions that develop as a result of tissue damage caused by infection and the natural healing process. These processes take place even in women with mild infections and resolution of symptoms.\(^8\) Few interventions are available for the prevention of PID. Condoms are the most effective intervention for protecting against PID and may reduce gonococcal and chlamydial infections by as much as 50 percent.\(^9\) However, condom use must be correct and consistent to be
effective in the prevention of PID. Progestin-based contraceptives may decrease the risk of PID. Progestin-based contraceptives increase the viscosity of cervical mucus creating a barrier to sperm ascension into the uterus.\textsuperscript{10} The same mechanism may also create a barrier for ascending infection.\textsuperscript{8}

Intrauterine devices (IUDs) are one of the oldest methods of contraception, dating back to the early 1900s.\textsuperscript{11} They are a very safe and reliable method of contraception and their efficacy has been compared to that of female sterilization.\textsuperscript{12,13} In America there seems to be a persistent preconceived notion among medical providers and the general public, that IUDs cause an increased risk of PID.\textsuperscript{14} This could be due to a model of IUD available in the United States in the 1970s called the Dalkon Shield. This device was later shown to cause an increased risk of PID because the multifilament tail strings of the device were porous and allowed bacteria to ascend easily into the uterus, causing infection. The Dalkon Shield was removed from the market in 1974,\textsuperscript{14} and since that time, studies have shown that the risk of PID in patients with IUDs is similar to the risk of PID in the general population, with only a slight increase in risk for the first 20 days after insertion.\textsuperscript{15} In 2007 the American College of Obstetrics and Gynecology (ACOG) released a Committee Opinion stating that IUDs were an acceptable method of contraception for adolescent and nulliparous women and considered first-line therapy as a contraceptive method in these groups.\textsuperscript{16} Not only does ACOG state that IUDs are acceptable for use in teens and efficacious in preventing contraception, but levonorgestrel-releasing IUDs may actually protect women against PID.\textsuperscript{16} In addition to ACOG, UpToDate and several other articles also make reference to the idea that LNG IUDs may have a protective effect against PID.\textsuperscript{13,17-19}
In the United States there are currently two IUDs available on the market. The first is the Paragard IUD, which consists of a copper wire wound around a T-shaped polyethylene frame. Paragard was approved by the FDA in 1984 and has an effective treatment life of 10 years.\textsuperscript{20} The second is the Mirena IUD, which contains the synthetic hormone levonorgestrel. Mirena, also a T-shaped polyethylene device, contains a hormone reservoir around the vertical stem. The device releases 20 mcg of levonorgestrel daily and has a treatment life of 5 years.\textsuperscript{21} Levonorgestrel achieves its contraceptive effect by acting directly on the endometrial layer causing atrophy and thinning and by increasing the viscosity of cervical mucus in much the same way as progestin-based contraceptives do.\textsuperscript{21, 22}

The prevention of PID is of critical importance to those at risk for developing PID and to those responsible for covering the substantial annual cost of the disease. If levonorgestrel IUDs are shown to reduce the risk of PID in comparison to other IUDs then they may become an important first-line therapy in the prevention of PID. This review aims to determine if the current evidence supports the potential benefit of levonorgestrel-releasing IUDs in decreasing a woman’s risk of developing PID.

METHODS

Search Design

An exhaustive literature search was conducted using the databases MEDLINE (Ovid), Web of Science, and CINAHL (EBSCOhost). Search terms included \textit{intrauterine device}, \textit{levonorgestrel}, and \textit{intrauterine device copper}. Duplicate results were removed and remaining results were screened. In addition to the database search, references of all included studies as well as reputable medical resources were reviewed for additional articles. Medical
resources included UpToDate and Medscape. The abstracts of the articles were analyzed to identify randomized control trials comparing levonorgestrel-releasing and copper-releasing intrauterine devices.

**Inclusion Criteria**

Articles were required to be English language, randomized comparison trials, studies including a direct comparison of levonorgestrel and copper-releasing IUDs, and include pelvic inflammatory disease as an outcome.

**Quality Assessment**

The studies were evaluated for quality and validity of findings using the GRADE system. The GRADE system analyzes studies based on methodology, consistency of results, directness of evidence, and risk of publication bias. The quality of each study was categorized as high, moderate, low, or very low.

**RESULTS**

A total of 331 articles results were found in the search, and thirty-three potential articles were identified after duplicates and irrelevant articles were removed. Of these, three studies met the inclusion criteria. All studies were randomized comparison trials. Two of the studies were open studies in which no blinding occurred. The third study employed only blinding of the study subjects, not the study researchers. All studies compared a levonorgestrel-releasing IUD to one or more forms of copper-releasing IUD. All studies followed patients for a minimum of three years and had low lost to follow up numbers. (See Table I: Characteristics of Reviewed Studies.) The studies by Sivin et al and Andersson et al published articles throughout the course of the research reviewing and
analyzing data as it became available. For the purpose of this review the most recent articles which compile the entirety of that data for each study was used.\textsuperscript{12, 25}

**Baveja et al (1989)**

The Indian Council of Medical Research conducted a study at fifteen Human Reproductive Research Centres throughout India beginning in August 1983. The purpose of the study was to compare the newer levonorgestrel IUDs, and the Copper T 380Ag and Copper T 220C IUDs to the Copper T 200B IUD which was in use in India at the time. The daily dose of levonorgestrel released from the IUD in the study is not described.\textsuperscript{24}

The study design called for 2400 patients, 600 patients per device. Researchers enrolled 1905 healthy female patients age 18 to 40 with proven fertility in the study. Patients were randomized to one of four study groups. The randomization process was concealed using a computer program. Study centres were provided with sealed numbered envelopes containing the devices. Envelopes contained information identifying the device. At the time of device placement patient and researchers became aware of which type of device was received. There were 475 patients randomized to the LNG IUD group, 434 to the Copper T 380Ag IUD, 496 to the Copper T 220C IUD, and 500 to the Copper T 200B IUD. The optimum number of patients outlined in the study design was not achieved due to two factors, one of the centres dropped out of the study and study participant information could not be obtained, and researchers had an inadequate supply of LNG IUDs. Study groups were similar in prognostic factors. Analysis of study group characteristics yielded no statistical difference in characteristics among groups. Loss to follow up was low, ranging from 7.2 to 10.3 percent, with no statistically significant difference between groups.\textsuperscript{24}
The researchers in this study were most concerned with the continuation rate of the various devices and analyzed the reason the devices were discontinued to document the variation. Discontinuation rates between copper devices were similar with 50.4% of the Copper T 380Ag users, 45.4% of the Copper T 220C users, and 45.4% of the Copper T 200B users continuing use at three years. However, discontinuation of the LNG device was higher compared to the other devices and this difference was statistically significant with a P-value <0.01. Only 38.8% of LNG users continued use at three years. The most significant reason for discontinuation of the LNG device was menstrual abnormalities. Unintended pregnancy occurred at different rates between devices. Pregnancy rates per 100 women were 1.0 in the Copper T 380Ag group, 0.3 in the Copper T 220C group, and 1.6 in the Copper T 200B group, with no pregnancies occurring in the LNG group. The difference was not statistically significant according to the study.\textsuperscript{24}

Other reasons for discontinuation of use, in addition to unintended pregnancy and menstrual abnormalities, were expulsion of device, perforation, and pelvic and vaginal infection. Sixteen cases of pelvic infection occurred during the course of the study. There is no significant difference in the rates of PID between devices and confidence intervals are narrow. Over the course of the three year trial PID occurred at a rate of 1.8 (95% CI, 0.4-3.2) per 100 women in the LNG IUD group, 1.2 (95% CI, 0.0-2.4) in the Copper T 380Ag group, 1.7 (95% CI, 0.3-3.1) in the Copper T 220C group, and 1.2 (95% CI, 0.2-2.2) in the Copper T 200B group.\textsuperscript{24}

\textbf{Sivin et al (1994)}

The Population Council’s International Committee for Contraception Research sponsored a multicenter international study to measure and compare the effectiveness as well
as advantages and disadvantages of two types of 20 mcg/day levonorgestrel IUD compared to a copper-releasing IUD. The study took place over the course of seven years. Originally the study was designed to be a five years trial but during the course of the study the 60mg LNG IUD was found to have an effective treatment life of up to seven years and the study was extended.25

Patient enrollment into the study began in September 1981. Researchers enrolled 2246 healthy female patients age 18-38 desiring contraception into the study. A total of 1125 women were randomized to the LNG IUD group and 1121 to the copper IUD group. IUDs were individually packaged in opaque envelopes and numbered. Patients agreed to both randomization and blinding and were randomly assigned a number corresponding to an envelope. Researchers were not blinded in the study. Patients were similar in prognostic factors. Loss to follow up was low, 11.5 percent in the LNG group and 16.2 percent in the copper IUD group.22

Several outcomes related to device discontinuation were evaluated in the study. Reasons for discontinuation of the IUD included pregnancy, expulsion of device, amenorrhea, menstrual concerns/pain, PID, endometritis, planning pregnancy, other personal reasons, and a variety of other medical concerns. Examples of other medical concerns include skin/hair conditions, headache, depression, gastrointestinal tract concerns, and vaginitis. Discontinuation due to pregnancy occurred at a rate of 1.1 (95% CI, 0.1-2.1) per 100 women in the LNG IUD group and a rate of 1.4 (5% CI0.6-2.2) per 100 women in the copper IUD group with no statistically significant difference in rate. Rates of amenorrhea per 100 women occurred at 4.4 in the LNG group and 0.1 in the copper group, which was significant with a P-value <0.001.25
There were a total of 48 cases of PID throughout the study, 24 in each group. Over the course of the study PID occurred at a rate of 0.7 per 100 years in the LNG group and 0.7 per 100 years in the Cu IUD group. There was no statistically significant difference in rates of PID between groups.25-26

**Andersson et al (1994)**

The study was carried out in a total of twelve clinics located in Finland, Sweden, Denmark, Hungary, and Norway. The purpose of the European based study was to compare the contraceptive efficacy and clinical performance of a 20 mcg/day levonorgestrel IUD to the Nova T, a type of copper IUD. Study enrollment began in November 1982 and concluded in December 1984 and patients were followed for 5 years.12

The study design called for a minimum of 1000 patients per group to be able to detect significant differences in contraceptive efficacy between devices. Researchers also decided to allocate the LNG and copper devices in a 2:1 fashion in order to detect more reliably rare side effects that may be associated with the LNG IUD. In the study protocol the diagnosis of PID included salpingo-oophoritis, tubo-ovarian abscess, and pelvic peritonitis. The diagnosis of PID required at least two of the following signs and symptoms; history of lower abdominal pain and temperature greater than 38 Celsius, sedimentation rate above 30 mm/hour, tenderness on pelvic exam, mass on pelvic exam, or evidence on ultrasound or laparoscopy if clinical evidence was controversial. A total of 2758 healthy women ages 18-38 desiring contraception were enrolled in the study. Within the study group 1821 were randomized to the LNG IUD group and 937 to the Nova T group. IUDs were randomized and placed in sealed numbered envelopes at a central location then supplied to the study sites. No
blinding occurred in the study because researchers felt providers would better be able to counsel patients on expected side effects if the device type was known. Patient groups were similar and there was no statistically significant difference in study groups. Loss to follow up was low at 14% in the LNG IUD group and 6.3% in the Nova T group.\textsuperscript{12}

Continuation rates at the end of the five-year study were 44.5\% in the LNG IUD group and 46.9\% in the Nova T group. Reasons for device discontinuation include pregnancy, expulsion of device, bleeding problems, amenorrhea, pain, PID, hormonal side effects such as depression and acne, personal reasons, and other medical reasons including enlarged follicles and hypertension. Pregnancy occurred at a rate of 0.5 in the LNG group and 5.9 in the Nova T group. The difference in rates demonstrated a statistically significant difference with a P-value <0.001. Discontinuation due to amenorrhea occurred at a rate of 6.0 in the LNG group and there were no patients in the Nova T group who discontinued the IUD for this reason. The difference in rates of amenorrhea was also statistically significant with a P-value <0.001.\textsuperscript{12}

Pelvic infection occurred at an overall rate of 0.8 in the LNG IUD group and 2.2 in the Nova T group. The difference in rates is statistically significant, however, the P-value in relation to this data is denoted differently in two separate places. Within the body of the text the P-value is denoted as <0.05, in Table 3 it is listed at ≤0.01. In addition, the difference in rates of PID in the 25 and under age group was even more substantial with a P-value ≤0.01. In this group PID occurred at a rate of 0.3 in the LNG group and 5.6 in the Nova T group over the course of the study. The rates of occurrence outlined are a measure of cumulative gross rates over the course of the seven-year study.\textsuperscript{12}
DISCUSSION

The studies reviewed demonstrate conflicting evidence to support the theory that LNG IUDs protect against PID. All studies reviewed contain their own flaws in methodology and allow for potential bias to be introduced. PID is a secondary outcome in all three studies making the results in regard to this outcome inherently weak. In addition, none of the studies include women under the age of 18 which excludes a large portion of the group most at risk for developing PID (See Table I). Also, only one of the studies clearly outlines their diagnostic criteria for PID which allows their diagnosis of PID to be consistent between providers. The other two studies provide no criteria for the diagnosis of PID allowing for potential variability between providers. There is little variability between studies in regards to patient age range or the types of intervention being studied, however, patient populations are very different in regard to location. It is possible that because patient populations are from a variety of global locations, local cultural practices and beliefs could influence female’s sexual practices in these areas leading to variation in their risk of PID. Overall, these studies are insufficient to prove or disprove the potential protective effect of LNG IUDs. The current available data does not have the power to change the current practice for IUD use. Further well designed and well conducted studies would be needed to determine the actual effect of LNG IUDs on development of PID.

In the article by Baveja et al although the study was a randomized comparative trial there is a lack of blinding of both patients and researchers limiting the effectiveness of their methodology. There are no apparent inconstancies in their results, however, the outcome of PID is a secondary outcome in this study leading to some indirectness of evidence in regards to the question at hand. There is also a lack of precision evident in this study due to the fact
that the calculated optimum number of patients was not enrolled as mentioned earlier. The research organization was examining the possible use of the LNG IUD in India and concluded at the end of the study that they would not change the national use of the copper IUD even though LNG IUD had a higher efficacy at preventing pregnancy. This suggests there is a potential for publication bias because the Indian Council of Medical Research was possibly under pressure to make cost effective decisions for the country. Therefore, the overall GRADE for the quality of this study is very low.

Sivin et al\textsuperscript{25} attempted only single blinding in their randomized control trial, limiting the effect of their methodology. There is no evidence of inconsistencies in their results. There is a degree of indirectness of evidence because PID in this study is also a secondary outcome. In addition, it is unclear if there is a lack of precision in the findings because confidence intervals and standard deviations are not outlined for all outcomes in the study. There appears to be a low likelihood of publication bias\textsuperscript{25} however, due to the characteristics of the study the overall GRADE assessment is very low.

The randomized control trial published by Andersson et al\textsuperscript{12} makes no attempt at blinding study participants or researchers leading to limitations in their methodology. In addition it is unclear from the study how the researchers obtained the numbers they use for their statistical analysis. For example, it is unclear how they extrapolate the gross rate that is outlined in Table 3 based on number of patients who became pregnant during the course of the study, thus leading to concerns about inconsistency in their results. The numbers that are noted for net cumulative rates per 100 per year in Table 2 of the study do not correlate with the cumulative gross rates in Table 3. There is also concern for indirectness of evidence because PID in this study, like the others, is a secondary outcome. Since confidence intervals
and standard deviations are not given there is concern for lack of precision of results.\textsuperscript{12}

Finally, there is some controversy alluding to potential researcher bias that is indicated in statements made by other research teams.\textsuperscript{27} Regardless of the potential for publication bias, the overall GRADE for the quality of evidence outlined in this study is very low as well.

Due to the very low quality of evidence regarding LNG IUDs and their potential protective effect against PID it seems that additional research could have a considerable impact on future practice. Additional studies are certainly needed to determine the actual effect of LNG IUDs on decreasing rates of PID. A randomized comparative trial is not the best study design for a question of this nature. A prognostic study involving women at highest risk for developing PID, those ages 15 to 25, would be ideal. By performing a prognostic study researchers would be able to take a group of women at risk of the target event, in this case PID, who are using either a LNG or copper IUD and follow them over a period of time to determine at what rates each group experiences the target outcome. A prognostic study would more clearly demonstrate the actual effect of LNG on the rates of PID and better guide medical practice in the future.

CONCLUSION

There is minimal low quality evidence available to support the statement that LNG IUDs are protective against PID. Yet, several articles make reference to this theory and in some cases almost as if it is fact. There is a degree of controversy surrounding this idea and we lack the supporting evidence to bring this theory forward into practice. Further investigation of the potential protective effect is needed and could greatly impact the use of the levonorgestrel IUDs in modern medical practice.


# Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Age Range</th>
<th>Number of Study Participants</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Prognostic Factors Similar Among Groups</th>
<th>Follow-up Complete</th>
<th>Loss to Follow-up</th>
<th>Length of Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baveja et al(^{21})</td>
<td>Randomized Comparison Trial</td>
<td>18 to 40</td>
<td>1905 (475 LNG, 1430 Cu)</td>
<td>Adequate</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>7.2 to 10.3% per group</td>
<td>3 years</td>
</tr>
<tr>
<td>Sivin et al(^{22})</td>
<td>Randomized Comparison Trial</td>
<td>18 to 38</td>
<td>2246 (1125 LNG, 1121 Cu)</td>
<td>Adequate</td>
<td>Single (patient only)</td>
<td>Yes</td>
<td>Yes</td>
<td>11.5% in LNG group, 16.2% in Cu</td>
<td>5-7 years</td>
</tr>
<tr>
<td>Andersson et al(^{12})</td>
<td>Randomized Comparison Trial</td>
<td>18 to 38</td>
<td>2758 (1821 LNG, 937 Cu)</td>
<td>Adequate</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>14% in LNG group, 6.3% in Cu group</td>
<td>5 years</td>
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</tbody>
</table>

### Table I continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Precision (CI, p-values, SD)</th>
<th>PID Primary outcome Y/N?</th>
<th>Other Considerations</th>
<th>GRADE</th>
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<tbody>
<tr>
<td>Baveja et al(^{21})</td>
<td>SD, some p-values &lt;0.001, &lt;0.01, and &lt;0.05</td>
<td>No</td>
<td># of study patients lower than optimal #</td>
<td>very low</td>
</tr>
<tr>
<td>Sivin et al(^{22})</td>
<td>p-values &lt;0.001, &lt;0.01, and &lt;0.05, no CI or SD</td>
<td>No</td>
<td>none</td>
<td>very low</td>
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<tr>
<td>Andersson et al(^{12})</td>
<td>p-values &lt;0.001, &lt;0.01, and &lt;0.05, no CI or SD</td>
<td>No</td>
<td>method of statistical analysis unclear</td>
<td>very low</td>
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<td>Study</td>
<td>Rates of PID</td>
<td>P-value</td>
<td>Confidence intervals</td>
<td>GRADE</td>
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<td>----------------</td>
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</tr>
<tr>
<td>Baveja et al²¹</td>
<td>LNG - 1.8</td>
<td>Not significant, P &gt;0.001</td>
<td>LNG: 0.4-3.2</td>
<td>very low</td>
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<td>CuT380Ag: 0.0-2.4</td>
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<td>Cu200B- 1.2</td>
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<td>Cu200B: 0.2-2.2</td>
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<tr>
<td>Sivin et al²²</td>
<td>LNG - 0.7</td>
<td>Not significant</td>
<td>None given</td>
<td>very low</td>
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<td>TCu380Ag- 0.7</td>
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<td>Andersson et al²²</td>
<td>LNG- 0.8</td>
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<td>Nova T- 2.2</td>
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