

## The Efficacy of Emergency Contraception to Prevent Pregnancy: A Systematic Review and Meta-Analysis

Tigor Peniel Simanjuntak, Resilia Sihaloho, Batara Imanuel Sirait

Department of Obstetrics and Gynecology, Faculty of Medicine of Universitas Kristen  
Indonesia

Correspondence: Tigor Peniel Simanjuntak, Email: tigorpsimanjuntak@gmail.com

### Abstract

**Objective:** A systematic review and meta-analysis to determine the effectiveness of various emergency contraceptive methods to prevent pregnancy.

**Method:** This study followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) protocol. Data search used four databases, namely *Pubmed*, *Google Scholar*, *Science Direct*, and *Wiley*. Data that met the inclusion criteria were subjected to meta-analysis to analyze the combined proportion of data using MedCalc 20.012 software, calculation of a percentage of 95% Confidence Intervals (CI) and  $P < 0.05$ , and heterogeneity test between studies.

**Results:** There were 6 journals that met the criteria. Some of the contraceptives used as emergency contraception are: the copper IUD (CuIUD) with effectiveness reaching 100% in preventing pregnancy, levonorgestrel (LNG) 52-mg IUS with effectiveness reaching 99.95%, the levonorgestrel (LNG) 52-mg IUD with effectiveness reaching 99.7%, mifepristone 10 mg with effectiveness reaching 99.3%, mifepristone 5 mg with effectiveness reaching 98.8%, ulipristal acetate (UPA) 30 mg in pre-ovulatory women with effectiveness reaching 98.6%, levonorgestrel (LNG) 0.75 mg with effectiveness reaching 98.3%, yuzpe regimen with effectiveness reaching 98.2%, and ulipristal acetate (UPA) 30 mg in post-ovulatory women with effectiveness reaching 97.9%. The results of the proportion meta-analysis showed the proportion of pregnancies after the use of emergency contraceptive, which was 0.231% (95% CI 0.116–0.384) from 4,927 samples in 6 studies, and the results of the heterogeneity test between studies were found to be not meaningful ( $I^2 = 0\%$ ).

**Conclusion:** The emergency contraception used to prevent pregnancy is very effective with the results of a meta-analysis of the proportion of 0.231% (95% CI 0.116–0.384). This suggests that the percentage of pregnancies after emergency contraceptive use is quite low.

**Key words:** Effectiveness, Emergency Contraception

## Efektivitas Kontrasepsi Darurat untuk Mencegah Kehamilan: Tinjauan Sistematis dan Meta-Analysis

### Abstrak

**Tujuan:** Tinjauan sistematis dan meta-analisis untuk mengetahui efektivitas berbagai metode kontrasepsi darurat untuk mencegah kehamilan.

**Metode:** Penelitian ini mengikuti protokol Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA). Pencarian data menggunakan empat database yaitu *Pubmed*, *Google Scholar*, *Science Direct*, dan *Wiley*. Data yang memenuhi kriteria inklusi dilakukan meta analisis dengan analisis proporsi gabungan data menggunakan software MedCalc 20.012, dilakukan perhitungan persentase 95% CI dan  $P < 0.05$ , serta dilakukan uji heterogenitas antar studi.

**Hasil:** Terdapat 6 jurnal yang memenuhi kriteria. Beberapa alat kontrasepsi yang digunakan sebagai kontrasepsi darurat yaitu: AKDR tembaga (CuIUD) dengan efektivitas mencapai 100% dalam mencegah kehamilan, levonorgestrel (LNG) 52-mg IUS dengan efektivitas mencapai 99,95%, levonorgestrel (LNG) 52-mg IUD dengan efektivitas mencapai 99,7%, mifepristone 10 mg dengan efektivitas mencapai 99,3%, mifepristone 5 mg dengan efektivitas mencapai 98,8%, ulipristal asetat (UPA) 30 mg pada wanita pre-ovulasi dengan efektivitas mencapai 98,6%, levonorgestrel (LNG) 0,75 mg dengan efektivitas mencapai 98,3%, yuzpe regimen dengan efektivitas mencapai 98,2%, dan ulipristal asetat (UPA) 30 mg pada wanita post-ovulasi dengan efektivitas mencapai 97,9%. Hasil meta analisis proporsi menunjukkan proporsi kehamilan setelah penggunaan kontrasepsi darurat yaitu 0,231% (95% CI 0,116–0,384) dari 4.927 sampel, serta hasil uji heterogenitas antar studi ditemukan tidak bermakna ( $I^2 = 0\%$ ).

**Kesimpulan:** Penggunaan kontrasepsi darurat sangat efektif dalam mencegah kehamilan dengan hasil meta analisis proporsi yaitu 0,231% (95%CI 0,116–0,384). Hasil tersebut menunjukkan bahwa persentase kehamilan setelah penggunaan kontrasepsi darurat cukup rendah.

**Kata kunci:** Efektivitas, Kontrasepsi Darurat

## Introduction

Contraception is a crucial way to prevent pregnancy from occurring. The word contraception is derived from the combination of two words: contra and conception. Contra means preventing or fighting, while conception is the meeting of a mature egg with a sperm cell. The main purpose of using contraception is to prevent pregnancy due to the meeting of the two cells<sup>1</sup>. Before choosing a contraceptive method, it is important to consider several factors such as reliability, absence of adverse health effects, adjustability, non-interference during sexual intercourse, efficient use, affordability, and acceptance by the couple<sup>2</sup>. There are several methods of contraception including simple contraception like condoms, spermicides, and diaphragms, hormonal contraception like pills, injections, and implants, intrauterine devices, and permanent contraception like tubectomy and vasectomy.<sup>3</sup>

Emergency contraception is defined as the use of contraception used within 72 hours to 120 hours after sexual intercourse without contraception or unplanned contraception to prevent unwanted or unplanned pregnancy.<sup>4</sup>. There are many emergency contraceptive methods that can be used, including levonorgestrel, Cu IUD, mifepristone, yuzpe regimen, and ulipristal acetate<sup>5</sup>. We

were interested in conducting a systematic study that summarizes the effectiveness of various emergency contraceptive methods, as previous studies have reported variations in their effectiveness.

## Method Study Design

This study design is a systematic review carried out by identifying, evaluating, and interpreting various results of research on the topic to be discussed. The method used to determine research articles was the PICO method<sup>6</sup> and a meta-analysis with quantitative analysis in the form of an analysis of the combined proportion of data with a percentage calculation of 95% Confidence Interval (CI) and  $P < 0.05$  to show statistically significant or meaningless results was conducted.

## Search Strategy

Data search used four databases with specified criteria, namely *Pubmed*, *Google Scholar*, *Science Direct*, and *Wiley*. Keywords are stated in Table 1.

## Inclusion and Exclusion Criteria

The inclusion criteria for the journals are: 1) International journals published in

**Table 1 Databases and Keywords**

| Database       | Keywords  | Total Articles |
|----------------|---|----------------|
| Pubmed         | “contraceptives postcoital” or “contraception postcoital” or “emergency contraception” or “emergency contraceptive” and “efficacy” or “effectivity” and “cohort” or “randomize control trial” or “randomize controlled trial” | 79             |
| Google Scholar | “emergency contraception”, “effectivity”  | 43             |
| Science Direct | “contraceptive postcoital” or “emergency contraception” and “effectivity”   | 3              |
| Wiley          | “emergency contraceptive” OR “emergency contraception” and “effectivity”  | 4              |

English; 2) Journals with RCT (Randomized Controlled Trial) and Cohort Study design studies; 3) Journals that examined the effectiveness of various methods of emergency contraception to prevent pregnancy; 4) Journals were searched from the database using predetermined keywords. Hence, the exclusion criteria are: 1) Journals that are not available in a full text form; 2) Duplicate journals using Mendeley software; 3) Journals that are not in accordance with the topic to be discussed; 4) Journals that do not report the percentage of pregnancies and the effectiveness of various methods of emergency contraception to prevent pregnancy.

### Data Extraction

After conducting a thorough search of online journal databases such as Google Scholar,

PubMed, Science Direct, and Wiley, a total of 129 articles were found. Using the Mendeley tool, we were able to identify and remove 3 duplicate articles. From the remaining 126 articles, we screened them by titles and abstracts and excluded 87 articles that did not discuss emergency contraception or related topics. After selecting 39 full-text journals for further research, we excluded 33 journals that discussed emergency contraception but did not focus on its effectiveness. In the end, we were able to obtain 6 articles that would be analyzed in depth.

### Study Quality Assessment

The process of searching and selecting literature in this study used the diagram guide Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA).<sup>7</sup>

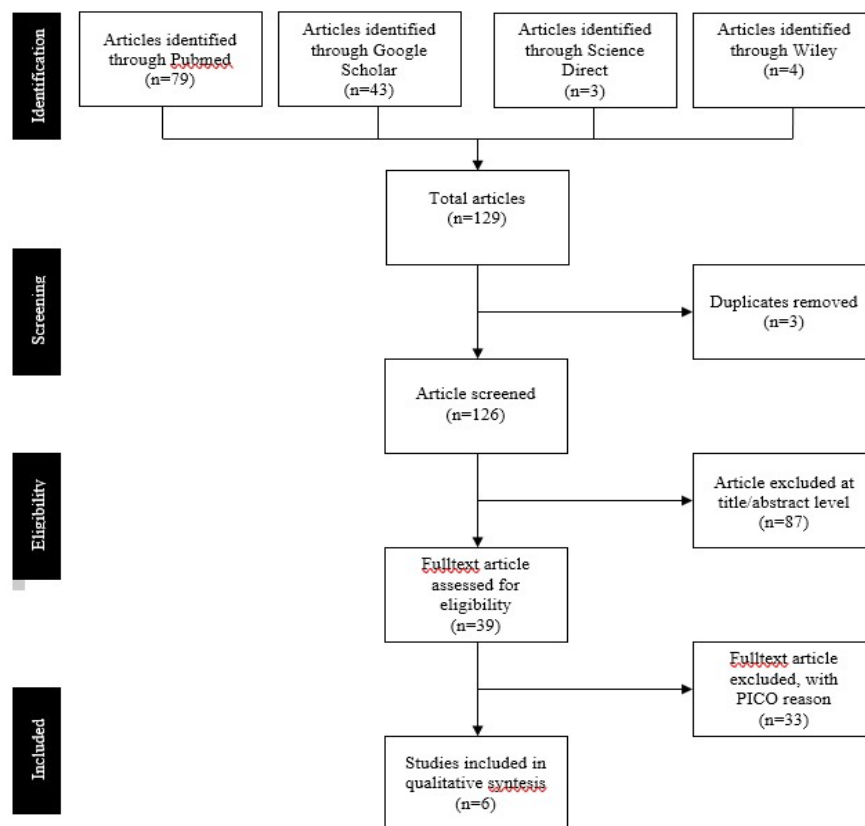


Figure 1 PRISMA Diagram

**Result**

Based on the 6 studies included in reports analyzed, 5 articles were obtained with RCT and 1 article was a cohort study article, as can be seen in Table 2. As for a summary of research journals ranging from the type of emergency contraception, dosage, percentage

of pregnancy, to the number of samples, it can be seen in Table 3.

Based on the results of research from 6 studies, the researchers made a summary of the sequence of emergency contraception that is most effective in preventing pregnancy as listed in table 4.

**Tabel 2 Summary of the Research Journals Regarding the Author, Year of Publication, Region, and Study Design**

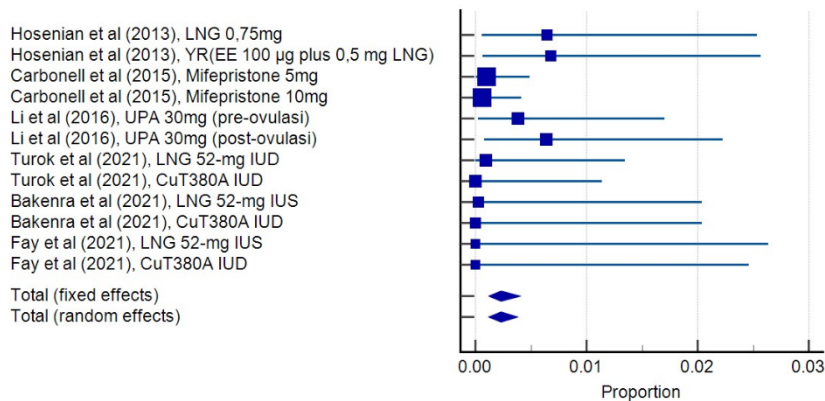
| Authors                       | Year | Region   | Study Design  |
|-------------------------------|------|----------|---------------|
| Hoseini et al. <sup>8</sup>   | 2013 | Iran     | <i>RCT</i>    |
| Carbonell et al. <sup>9</sup> | 2015 | America  | <i>RCT</i>    |
| Li et al. <sup>10</sup>       | 2016 | Hongkong | <i>Cohort</i> |
| Turok et al. <sup>11</sup>    | 2021 | America  | <i>RCT</i>    |
| Bakenra et al. <sup>12</sup>  | 2021 | America  | <i>RCT</i>    |
| Fay et al. <sup>13</sup>      | 2021 | America  | <i>RCT</i>    |

**Tabel 3 Summary of the Research Journals Regarding the Types or Doses of Emergency Contraception, Pregnancy Rates, and Number of Samples**

| Author                        | Emergency Contraception             | Type/Dose   | Pregnancy Rate | Number of Samples |
|-------------------------------|-------------------------------------|---|----------------|-------------------|
| Hoseini et al. <sup>8</sup>   | Levonorgestrel (LNG)                | 0.75 mg   | 1.7            | 263               |
|                               | Yuzpe Regimen                       | Ethinyl estradiol<br>100 µg plus 0.5 mg<br>Levonorgestrel | 1.8            | 266               |
| Carbonell et al. <sup>9</sup> | Mifepristone                        | 5 mg  | 1.2            | 1206              |
|                               | Mifepristone                        | 10 mg   | 0.7            | 1212              |
| Li et al. <sup>10</sup>       | Ulipristal Acetate (pre-ovulation)  | 30 mg   | 1.4            | 364               |
|                               | Ulipristal Acetate (post-ovulation) | 30 mg   | 2.1            | 329               |
| Turok et al. <sup>11</sup>    | Levonorgestrel (LNG)                | 52-mg IUD   | 0.3            | 317               |
|                               | CuIUD                               | CuT380A IUD   | 0              | 321               |
| Bakenra et al. <sup>12</sup>  | Levonorgestrel (LNG)                | 52-mg IUS   | 0.05           | 184               |
|                               | CuIUD                               | CuT380A IUD   | 0              | 179               |
| Fay et al. <sup>13</sup>      | Levonorgestrel (LNG)                | 52-mg IUS   | 0              | 138               |
|                               | CuIUD                               | CuT380A IUD   | 0              | 148               |

**Tabel 4 Sequence Of The Efficacy Of Emergency Contraception To Prevent Pregnancy**

| Emergency Contraception             | Dosage   | Pregnancy Rate (%) | Efficacy (%) |
|-------------------------------------|--|--------------------|--------------|
| CuIUD                               | CuT380A IUD  | 0                  | 100          |
| Levonorgestre (LNG)                 | 52-mg IUS  | 0.05               | 99.95        |
| Levonorgestre (LNG)                 | 52-mg IUD  | 0.3                | 99.7         |
| Mifepristone                        | 10 mg  | 0.7                | 99.3         |
| Mifepristone                        | 5 mg   | 1.2                | 98.8         |
| Ulipristal Acetate (Pre-ovulation)  | 30 mg  | 1.4                | 98.6         |
| Levonorgestre (LNG)                 | 0.75 mg  | 1.7                | 98.3         |
| Yuzpe Regimen                       | Ethinyl estradiol 100 µg plus 0,5 mg Levonorgestre | 1.8                | 98.2         |
| Ulipristal Acetate (Post-ovulation) | 30 mg  | 2.1                | 97.9         |



**Figure 2 The Results of Data Processing in the Form of Forest Plot Graphs.**

| Study  | Sample size | Proportion (%) | 95% CI              | Weight (%) |        |
|--|-------------|----------------|---------------------|------------|--------|
|  |             |                |                     | Fixed      | Random |
| Hosenian et al (2013), LNG 0,75mg                    | 263         | 0.646          | 0.0594 to 2.540     | 5.35       | 5.35   |
| Hosenian et al (2013), YR(EE 100 µg plus 0,5 mg LNG) | 266         | 0.677          | 0.0689 to 2.571     | 5.41       | 5.41   |
| Carbonell et al (2015), Mifepristone 5mg             | 1206        | 0.0995         | 0.00425 to 0.489    | 24.44      | 24.44  |
| Carbonell et al (2015), Mifepristone 10mg            | 1212        | 0.0578         | 0.000371 to 0.415   | 24.56      | 24.56  |
| Li et al (2016), UPA 30mg (pre-ovulasi)              | 364         | 0.385          | 0.0239 to 1.706     | 7.39       | 7.39   |
| Li et al (2016), UPA 30mg (post-ovulasi)             | 329         | 0.638          | 0.0834 to 2.226     | 6.68       | 6.68   |
| Turok et al (2021), LNG 52-mg IUD                    | 317         | 0.0946         | 0.00000100 to 1.346 | 6.44       | 6.44   |
| Turok et al (2021), CuT380A IUD                      | 321         | 0.000          | 0.000 to 1.143      | 6.52       | 6.52   |
| Bakendra et al (2021), LNG 52-mg IUS                 | 184         | 0.0272         | 0.000 to 2.041      | 3.75       | 3.75   |
| Bakendra et al (2021), CuT380A IUD                   | 179         | 0.000          | 0.000 to 2.040      | 3.64       | 3.64   |
| Fay et al (2021), LNG 52-mg IUS                      | 138         | 0.000          | 0.000 to 2.638      | 2.81       | 2.81   |
| Fay et al (2021), CuT380A IUD                        | 148         | 0.000          | 0.000 to 2.462      | 3.02       | 3.02   |
| Total (fixed effects)                                | 4927        | 0.231          | 0.117 to 0.408      | 100.00     | 100.00 |
| Total (random effects)                               | 4927        | 0.231          | 0.116 to 0.384      | 100.00     | 100.00 |

**Figure 3 Meta-Analysis of the Proportion of Pregnancy after Emergency Contraceptive Use**

**Test for heterogeneity**

|                                |               |
|--------------------------------|---------------|
| Q                              | 9.6851        |
| DF                             | 11            |
| Significance level             | P = 0.5589    |
| I <sup>2</sup> (inconsistency) | 0.00%         |
| 95% CI for I <sup>2</sup>      | 0.00 to 52.80 |

**Figure 4 Heterogeneity Test Between Studies**

**Meta-Analysis**

The number of articles combined to analyze the proportion of pregnancy after emergency contraceptive use was 6 articles consisting of 1 cohort study article and 5 RCT articles. The results of a meta-analysis of the proportion of pregnancy after emergency contraceptive use are shown in Figure 2., Figure 3, and Figure 4.

Figure 2 above presents the results of a meta-analysis in the form of forest plots from six studies. The results of the proportion meta-analysis show that the proportion of pregnancy after emergency contraceptive use was 0.231% (95% CI 0.116–0.384) from 4,927 samples in 6 studies. This suggests that the percentage of pregnancies after emergency contraceptive use is quite low. The results of the heterogeneity test between studies were found to be meaningless (I<sup>2</sup> = 0%).

**Discussion**

Based on the results of research from 6 studies, the study of Hoselini et al.<sup>8</sup> reported that the study made a comparison of Levonorgestrel consisting of two kinds; each contained 0.75 mg Levonorgestrel and placebo tablets and pills taken 12 hours apart with a study sample of 263 groups compared with Yuzpe Regimen with a sample of 266 groups. The yuzpe regimen used a dose of 100 µg of ethinyl estradiol plus 0.5 mg of Levonorgestrel separated within 12 hours. In the Hoselini et al.<sup>8</sup> study, it was also

mentioned that 75% of participants in the levonorgestrel group did not experience nausea at all, and 19.8% experienced mild nausea. In contrast, 62% of participants in the yuzpe regimen group experienced mild nausea and splints, which were significantly higher than those of the levonorgestrel group. Participants who received Levonorgestrel experienced significantly lower side effects in cases of nausea, vomiting, and dizziness (P<0.05) and changes in the number and pattern of menstruation were similar in both groups (P>0.05).

The most effective levonorgestrel period for emergency contraception is within the pre-ovulatory follicle. The use of levonorgestrel after the ovulation period and the increased interval between unprotected sexual intercourse and the beginning of treatment have been described as the leading causes of ectopic pregnancy.<sup>14</sup>

The study of Carbonel et al.<sup>9</sup> reported that there were 15/1,206 (1.2%) pregnancies in the 5 mg mifepristone group and 9/1,212 (0.7%) pregnancies in the 10 mg mifepristone group (P = 0.107). The study aimed to assess the efficacy and safety of 5 mg and 10 mg mifepristone for emergency contraception when given up to 6 days after unprotected sexual intercourse. The study of Carbonel et al.<sup>9</sup> showed that there was a significant difference in the number of expected and observed pregnancies between the 5 mg and 10 mg (P<0.001) mifepristone groups. However, there was no significant difference between the two groups in the percentage of



pregnancies prevented ( $P = 0.122$ ). This study suggests using a 10 mg dose of mifepristone for emergency contraception because there is a tendency to show that the failure rate of a 10 mg dose of mifepristone will tend to be more relentless.

During the follicular phase, mifepristone delays estrogen increases, LH surges, and ovulation. In addition, mifepristone also suppresses endometrial development and follicle development. This effect of mifepristone ultimately leads to inhibition of ovulation. Use after ovulation will inhibit the development of the endometrium and block the expression of necessary endometrial receptors. The endometrium remains immature, thus preventing implantation from occurring effectively.<sup>15</sup>

Ulipristal acetate is a progesterone receptor modulator that has been granted market authorization by the European Medicines Agency in 2009 and approved by the United States Food and Drug Administration (FDA) in 2010, so it has been widely used to date<sup>15</sup>. Ulipristal acetate is more effective as emergency contraception when sexual intercourse occurs before ovulation, precisely before the LH surge. Despite this, ulipristal acetate remains effective until LH levels reach their peak. In addition to delaying or inhibiting ovulation, ulipristal acetate also causes a decrease in LH levels, so that the menstrual cycle will lengthen, and endometrium changes that support the prevention of pregnancy occur<sup>16</sup>. Li et al.<sup>10</sup> study discussed the effectiveness of emergency contraceptive ulipristal acetate (UPA) by comparing UPA when given to women before ovulation to UPA when given to women after ovulation. The dosage used was 30 mg. The study found a significantly higher rate in pre-ovulatory subjects (77.6%) compared to post-ovulatory subjects (36.4%). The pregnancy rate observed after UPA administration was significantly higher in the pre-ovulatory group compared to the

post-ovulatory group ( $P < 0.0001$ ). Among the 12 subjects who were pregnant, 5 were in the pre-ovulatory group and 7 were in the post-ovulatory group, citing failure rates of 1.4% (5/364) and 2.1% (7/329) in the pre-ovulatory group and the post-ovulatory group ( $P = 0.564$ ), respectively. Furthermore, more pre-ovulatory subjects (19.1%) experienced subsequent menstrual irregularities of more than 7 days ( $P < 0.001$ ) than post-ovulatory subjects (7.8%). The efficacy of UPA was significantly better when given before ovulation than after ovulation.

Turok et al.<sup>11</sup> analyzed levonorgestrel 52-mg IUDs and copper IUDs and reported pregnancy rates of 1 in 317 cases (0.3%; 95% CI, 0.01-1.7) in the levonorgestrel group and 0 in 321 cases (0%; 95% CI, 0-1.1) in the copper IUD group. The absolute difference between the groups in both analyses was 0.3% (95% CI, -0.9-1.8). This shows that the use of levonorgestrel has an effectiveness unparalleled with copper IUDs. Side effects that resulted in participants seeking medical care in the first month after IUD insertion occurred in 5.2% of participants in the levonorgestrel IUD group and 4.9% in the copper IUD group.

Meanwhile, Bakenra et al.<sup>12</sup> reported on the effectiveness of copper IUD with Levonorgestrel 52 mg IUS. The study of Bakenra et al.<sup>12</sup> assessed pregnancy 1 month after IUD insertion and compared pregnancy risk with one or several episodes of unprotected sexual intercourse and with time (5 days or less before IUD insertion or 6 days or earlier). In the single unprotected sexual intercourse episode, it was found that there were 184 samples using Levonorgestrel (LNG) 52-mg IUS as emergency contraception and there was 1 participant who had been pregnant for 1 month, so in the study, levonorgestrel contraception had a percentage of pregnancy of 0.05% (95% CI, 0.01-3). Meanwhile, there were 179 samples using Copper IUDs but none of the samples had pregnancy for

1 month, so emergency contraception with copper IUDs had a pregnancy perpetration of 0% (95% CI, 0-2).

The copper IUD method is believed to be the most effective form of post-coital emergency contraception and can be used up to 5 days after sexual intercourse. In the pre-fertilization period, the composition of copper can be toxic to the ovum and sperm. In addition, foreign bodies within the uterine cavity induce a chronic inflammatory response that causes the release of cytokines and integrins. These inflammatory markers cause spermicidal effects and inhibit implantation despite fertilization. It is believed that copper IUDs are also effective after fertilization occurs. Although the mechanism is not fully understood, post-fertilization effects occur before the embryo enters the uterus<sup>17</sup>. In addition, the copper IUD has the added benefit of being able to be used for up to 12 years and used as a long-acting form of reversible contraception to prevent future unwanted pregnancies<sup>18</sup>. Fay et al.<sup>13</sup> conducted a study to compare 1-month pregnancy rates among individuals who took Levonorgestrel 52 mg IUS and copper IUS as emergency contraception and reported sexual intercourse within 7 days post-insertion. No pregnancies occurred among levonorgestrel IUS users who reported sexual intercourse within 7 days of insertion (0/138, 0.0%, 95% CI 0.0%, 2.6%) or among users of 380 mm<sup>2</sup> copper IUDs (0/148, 0.0%, 95% CI 0.0%, 2.5%). This indicates that the pregnancy rate after the installation of a copper IUD or the installation of Levonorgestrel 52 mg IUS for emergency contraception is quite low.

## Conclusion

Based on the 6 research reports analyzed, the emergency contraception used to prevent pregnancy is very effective with the results of a meta-analysis of the proportion of 0.231% (95% CI 0.116–0.384). This suggests that the

percentage of pregnancies after emergency contraceptive use is quite low.

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