

Meta-Analysis: Effects of Endometriosis and Intrauterine Device Contraceptive on Ectopic Pregnancy

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ABSTRACT

Background: Ectopic pregnancy is an early complication of pregnancy with high morbidity and mortality. Several studies have examined a history of endometriosis and Intrauterine Device Contraceptive (IUD) use as risk factors for ectopic pregnancy, but have shown mixed results. This study aims to analyze the influence of a history of endometriosis and IUD use on the incidence of ectopic pregnancy based on previous primary studies.

Subjects and Method: This was a systematic review and meta-analysis conducted with the PRISMA flow diagram guidelines. The article search process was carried out on the PubMed, Google Scholar, Science Direct, SAGE, JSTOR, and Scopus databases, for articles published from 2005 to 2022. The keywords used were: "Endometriosis" AND "Intrauterine Contraceptive Device" OR "Intrauterine Device" OR "IUD" OR "IUCD" AND "Ectopic Pregnancy" OR "Extrauterine Pregnancy" OR "Tubal Pregnancy" OR "Pregnancy Outcomes" OR "Pregnancy Complications" AND "Multivariate" OR "Multivariable" OR "Adjusted Odds Ratio" OR "aOR ". Analysis was performed with RevMan 5.3 software. Population: pregnant women of reproductive age. Intervention: endometriosis, using the IUD. Comparison: no endometriosis, no IUD use. Outcome: ectopic pregnancy. Inclusion criteria were full-text observational study articles in English and Indonesian, with ectopic pregnancy as the outcome, analyzed multivariately by including adjusted Odds Ratio/aOR. The analysis was carried out using Review Manager 5.3 software.

Results: A total of 11 articles from Asia, Europe, Africa, Australia, and North America were found to meet the criteria and were included in the meta-analysis. The results of the overall analysis of 4 articles consisting of 2 cohort studies and 2 case-control studies were that endometriosis increased the risk of ectopic pregnancy 1.39 times higher than without endometriosis (aOR = 1.39, 95% CI = 1.16-1.68; $p < 0.001$). The results of the analysis of 7 case-control study articles showed that the use of IUDs increased the risk of ectopic pregnancy 1.35 times compared to not using the IUD and was not statistically significant (aOR = 1.35, 95% CI = 0.45-4.03; $p = 0.590$).

Conclusion: Endometriosis is a risk factor for ectopic pregnancy. IUD use increased the risk of ectopic pregnancy but was not statistically significant.

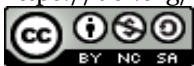
Keywords: endometriosis, intrauterine device contraceptive, ectopic pregnancy, meta-analysis.

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BACKGROUND

Ectopic pregnancy is a complication in the

first trimester of pregnancy with high morbidity and mortality (Taran et al., 2015).

Ectopic pregnancy is an occurrence of pregnancy that occurs both inside and outside the uterus where the fertilized egg (ovum) implants in a place that is not suitable for its development and growth, this condition occurs in 2% of pregnancies with 97% of ectopic pregnancies occurring in the fallopian tube (Jasmy et al., 2020; Fylstra, 2012).

Risk factors for ectopic pregnancy consist of: age more than 40 years, smoking, history of infertility, abortion, history of ectopic pregnancy, more than one sexual partner, history of contraception, history of surgery on the abdomen or pelvis, exposure to diethylstilboestrol (DES), and history of organ disease. Previous gynecology (tubal abnormalities, genital infections, pelvic inflammatory disease, endometriosis, polycystic ovaries, benign ovarian tumors, and leiomyomas) (Farquhar, 2005; Kriebs and Fahey, 2006; Hwang et al., 2016).

Endometriosis is a condition where the endometrial mucosa grows outside the uterine cavity in women of reproductive age which affects about 5% of women of child-bearing age with a peak prevalence at the age of 25-35 years (Vercellini et al., 2014). Endometriosis increases the risk of ectopic pregnancy almost 3 times, which is 2.7 times (Saraswat et al., 2017).

The cohort study by Saetta et al. (2020) concluded that endometriosis is not a risk factor for ectopic pregnancy, in line with the results of a study by Gaskins et al. (2018). The opposite result was presented in the study by Muzaffar et al. (2020), Hwang et al. (2016) and Farland et al. (2019) which states that endometriosis increases the risk of ectopic pregnancy.

Hypersensitivity of endometrial tissue to pregnancy hormones and increased VEGF and proinflammatory cytokines in the tube environment can increase implantation of embryos in the tube, causing an ectopic pregnancy. In addition, in endometriosis,

tubal dysfunction also occurs where there is an alteration of ciliary beat and muscle contractility which can inhibit embryo transport in the tube (Zalecka et al., 2022; Hill et al., 2020).

An Intrauterine Contraceptive Device (IUD) is a contraceptive device that is inserted into the uterus and functions as a protective factor against pregnancy thereby reducing the overall risk of ectopic pregnancy. In cases where IUD failure occurs, there is a higher risk of ectopic pregnancy because the IUD is more effective at inhibiting intrauterine but not extrauterine pregnancies (Gatzke and Johnson, 2014).

The IUD induces local inflammation, increases mucus viscosity, alters cytokine and integrin profiles, impairs sperm motility, and increases leukocytes. About half of ectopic pregnancies appear to be due to slow transport of the fertilized ovum to the uterus (Gabriel et al., 2017; Callahan et al., 2015).

Assouni-Mindjah et al. (2018) conducted a case-control study on 264 women and found that the IUD did not significantly increase the risk of ectopic pregnancy. While Muzaffar et al. (2020) in their study found that IUD use increases the risk of ectopic pregnancy. Meta-analysis by Mol et al. (1995) and Xiong et al. (1995) concluded that IUD use generally reduces the incidence of ectopic pregnancy when not pregnant, but that when a woman with an in-situ IUD becomes pregnant, the risk of ectopic implantation increases.

Based on this background, there is a need for a comprehensive study of primary studies on the effect of endometriosis and IUD use on ectopic pregnancy. This study will be conducted by collecting primary studies and analyzed by systematic review and meta-analysis.

SUBJECTS AND METHOD

1. Study Design

This study is a systematic review and meta-analysis. The article search process was carried out on the PubMed, Google Scholar, Science Direct, SAGE, JSTOR, and Scopus databases, for articles published from 2005 to 2022. The keywords used were: “Endometriosis” AND “Intrauterine Contraceptive Device” OR “Intrauterine Device” OR “IUD” OR “IUCD” AND “Ectopic Pregnancy” OR “Extrauterine Pregnancy” OR “Tubal Pregnancy” OR “Pregnancy Outcomes” OR “Pregnancy Complications” AND “Multivariate” OR “Multivariable” OR “Adjusted Odds Ratio” OR “aOR”.

2. Inclusion Criteria

The inclusion criteria for this study were full-text observational study articles in English and Indonesian, with ectopic pregnancy as the outcome, analyzed multivariately by including the adjusted odds ratio/aOR.

3. Exclusion Criteria

The exclusion criteria for this study are; duplicate articles, non-endometriosis or IUD interventions, and statistical analyzes were bivariate analyses.

4. Operational Definition of Variables

The search for articles was carried out taking into account the eligibility criteria defined according to the PICO. The study population is pregnant women. Intervention: endometriosis, IUD use. Comparison: no endometriosis, no IUD use. Outcome: ectopic pregnancy.

Ectopic pregnancy is a pregnancy that occurs not where it should be, namely in the endometrium in the uterus, it can occur in the fallopian tube, in the endometrium outside the uterus, or other places outside the uterus. The measurement instrument is the result of an ultrasound examination.

Endometriosis is a condition in which the endometrial lining grows in places other than the uterine cavity. The measurement

instrument is a doctor's diagnosis.

The use of the IUD is the use of a contraceptive device in the uterus that serves to delay pregnancy. The instrument used is a questionnaire.

5. Study Instrument

This research was conducted based on the PRISMA flow diagram and assessment of study quality using the Critical Appraisal Checklist for Cohort Study for cohort studies and the Critical Appraisal Checklist for Case-Control Study for case-control studies.

The following 12 questions were used to assess the quality of cohort studies:

1. Does the research address a clearly focused problem?
2. Is the cohort research method appropriate to answer the research question?
3. Are there enough subjects to apply that the findings did not happen by chance?
4. Was the cohort selection based on objective and validated criteria?
5. Is the cohort representative of the defined population?
6. Was the follow-up done in sufficient time?
7. Are the outcome criteria used objective and unbiased?
8. Was an objective and validated measurement method used to measure the variables (endometriosis, IUD, ectopic pregnancy)?
9. Are effect sizes practically relevant?
10. Is there a confidence interval given?
11. Have confounding factors been taken into account such as age, previous ectopic pregnancy, and history of abdominal/pelvic surgery?
12. Can the results be applied to your research?

6. Data Analysis

Data were analyzed using the Review Manager application, namely Revman 5.3 using funnel plots and forest plots to determine the magnitude of the relationship

and heterogeneity of the data.

The following 12 questions were used to assess the quality of a case-control study:

1. Does this study address clearly focused issues?
2. Is the case-control study method appropriate to answer the research question?
3. Were there enough subjects in the study to establish that the findings did not occur by chance?
4. Was the selection of cases and controls based on objective and validated external criteria?
5. Were the two groups comparable at the start of the study?
6. Are the outcome criteria used objective and unbiased?
7. Is there data-dredging?
8. Are the research instruments valid and usable (endometriosis, IUD, ectopic pregnancy)?
9. Was statistical significance assessed?
10. Was a confidence interval given for the main outcome?
11. Are there confounding factors that have not been taken into account such as age, previous ectopic pregnancy, and history of abdominal/pelvic surgery?

12. Are the results applicable to your research?

RESULTS

The search results of research articles are presented according to the PRISMA diagram as can be seen in Figure 1. From a total of 2,161 articles obtained in the database search, exclusion and screening were carried out so that 11 articles were found that were included in the quantitative synthesis process with meta-analysis. The 11 articles came from 5 continents as shown in Figure 2, namely 5 articles from the Asian continent, 2 from the European continent, 2 from the North America continent, 1 from the African continent, and 1 from the Australian continent.

Furthermore, an assessment of the quality of the studies is shown in Table 1 for the cohort study and Table 2 for the case-control study. Table 3 contains descriptions of 4 studies that prove the effect of endometriosis on ectopic pregnancy. Table 4 contains descriptions of 7 studies that demonstrated the effect of IUD use on ectopic pregnancy.

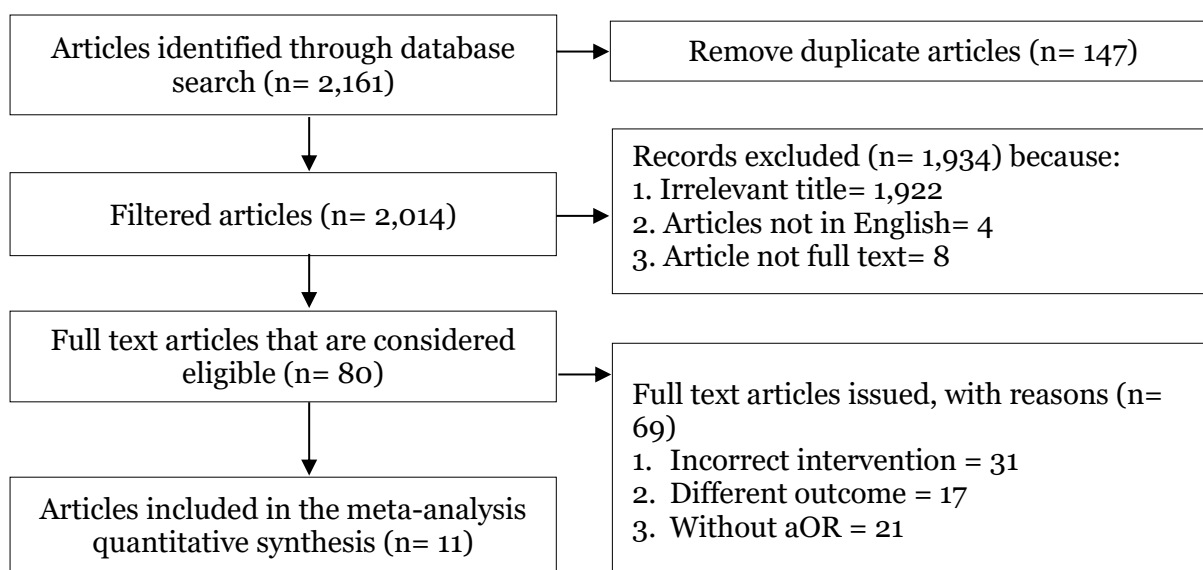


Figure 1. PRISMA Flowchart



Figure 2. Map of the study area the effect of endometriosis and IUD use on ectopic pregnancy

Table 1. Cohort Study Quality Assessment Results

| Primary Study | Criteria | | | | | | | | | | | | Total | |
|-------------------------------|----------|---|---|---|---|---|---|---|---|----|----|----|-------|----|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | | |
| Saraswat <i>et al.</i> (2016) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 12 |
| Rombauts <i>et al.</i> (2015) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 12 |

Note: Answer 1= Yes; Answer 0= No

Table 2. Results of Case-Control Study Quality Assessment

| Primary Study | Criteria | | | | | | | | | | | | Total |
|--------------------------------|----------|---|---|---|---|---|---|---|---|----|----|----|-------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Anorlu <i>et al.</i> (2005) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |
| Barnhart <i>et al.</i> (2006) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |
| Karaer <i>et al.</i> (2006) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |
| Kashanian <i>et al.</i> (2016) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |
| Li <i>et al.</i> (2015) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |
| Parashi <i>et al.</i> (2013) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |
| Zhang <i>et al.</i> (2016) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |
| Jacob <i>et al.</i> (2017) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |
| Clayton <i>et al.</i> (2006) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 10 |

Note: Answer 1= Yes; Answer 0= No

Table 3. Description of the Study of the Effect of Endometriosis on Ectopic Pregnancy

| Author (Year) | Country | Study Design | Total of Sample | I/C (Intervention/ Comparison) | O (Outcome) |
|-------------------------------|--------------------------|--------------|-----------------|-----------------------------------------|-------------------|
| Saraswat <i>et al.</i> (2016) | Scotland | Cohort | 13,655 | I: Endometriosis C: No endometriosis | Ectopic pregnancy |
| Rombauts <i>et al.</i> (2015) | Australia | Cohort | 8,120 | I: Endometriosis C: No endometriosis | Ectopic pregnancy |
| Jacob <i>et al.</i> (2017) | German | Case-control | 100,197 | I: Endometriosis C: No endometriosis | Ectopic pregnancy |
| Clayton <i>et al.</i> (2006) | United States of America | Case-control | 94,118 | I: Endometriosis C: No endometriosis | Ectopic pregnancy |

Table 4. Study Description of the Effect of IUD Use on Ectopic Pregnancy

| Author (Year) | Country | Study Design | Total of Sample | I/C (Intervention/ Comparison) | O (Outcome) |
|-------------------------|--------------------------|--------------|-----------------|----------------------------------------|-------------------|
| Anorlu et al. (2005) | Nigeria | Case-control | 380 | I: use the IUD C: Not using the IUD | Ectopic pregnancy |
| Barnhart et al. (2006) | United States of America | Case-control | 2,026 | I: use the IUD C: Not using the IUD | Ectopic pregnancy |
| Karaer et al. (2006) | Turki | Case-control | 600 | I: use the IUD C: Not using the IUD | Ectopic pregnancy |
| Kashanian et al. (2016) | Iran | Case-control | 924 | I: use the IUD C: Not using the IUD | Ectopic pregnancy |
| Li et al. (2015) | China | Case-control | 4,827 | I: use the IUD C: Not using the IUD | Ectopic pregnancy |
| Parashi al. (2013) | Iran | Case-control | 450 | I: use the IUD C: Not using the IUD | Ectopic pregnancy |
| Zhang et al. (2016) | China | Case-control | 571 | I: use the IUD C: Not using the IUD | Ectopic pregnancy |

The results of the meta-analysis of the effect of endometriosis on the incidence of ectopic pregnancy are depicted in the forest plot in Figure 3. The heterogeneity of the data (I^2) showed 0%, so a fixed effect model was used. The results of a subgroup analysis of the cohort study showed that women with endometriosis had a 2.64-fold risk of ectopic pregnancy compared to women without endometriosis (aOR = 2.64, 95% CI= 1.09 to 6.42; $p= 0.030$). The results of the case-control subgroup analysis showed that women with endometriosis had a 1.35-fold risk of ectopic pregnancy compared to women without endometriosis (aOR= 1.35, 95% CI= 1.12 to 1.64; $p= 0.002$). The results of the overall meta-analysis showed that women with endometriosis had a 1.39-fold greater risk of ectopic pregnancy than women without endometriosis (aOR= 1.39, 95% CI= 1.16 to 1.68; $p < 0.001$).

The funnel plot of the effect of endometriosis on ectopic pregnancy in Figure 4 shows that the distribution of the estimated effects from all the primary studies performed in the meta-analysis is located to the right of the estimated mean vertical line than to the left. Thus, the funnel plot indi-

cates that there is a publication bias that tends to overestimate the true effect. The standard error in the plot on the left is 0 to 1 while the plot on the right has a standard error of 0 to 3.

The results of the meta-analysis of the effect of IUD use on the incidence of ectopic pregnancy are depicted in the forest plot in Figure 5. The heterogeneity of the data (I^2) showed 97%, so a random effects model was used because the study was heterogeneous. The results of the meta-analysis showed that the use of IUDs increased the risk of ectopic pregnancy by 1.35 times compared to those without IUD use, and was not statistically significant (aOR= 1.35, 95% CI= 0.45 to 4.03; $p= 0.590$).

The funnel plot of the effect of IUD use on ectopic pregnancy in Figure 6 shows that the distribution of the estimated effects from all primary studies conducted in the meta-analysis lies more to the right of the estimated mean vertical line than to the left. Thus, the funnel plot indicates that there is a publication bias that tends to overestimate the true effect. The standard error of the plot on the left is 0.2 to 0.4 while the plot on the right has a standard error of 0 to 0.6.

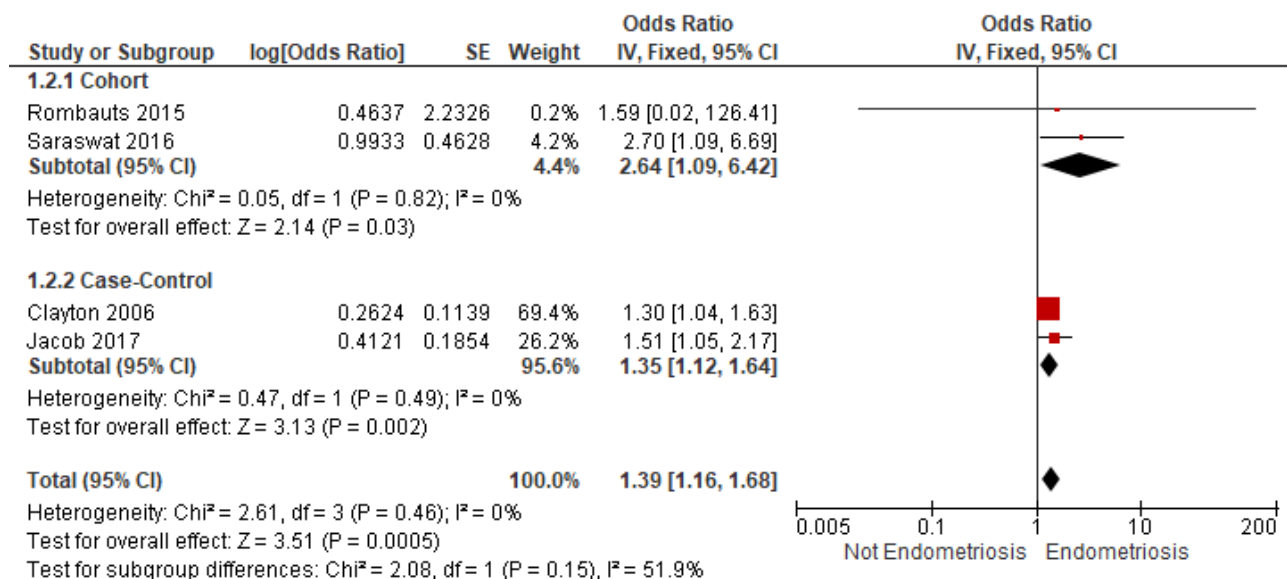


Figure 3. Forest Plot of the effect of endometriosis on ectopic pregnancy

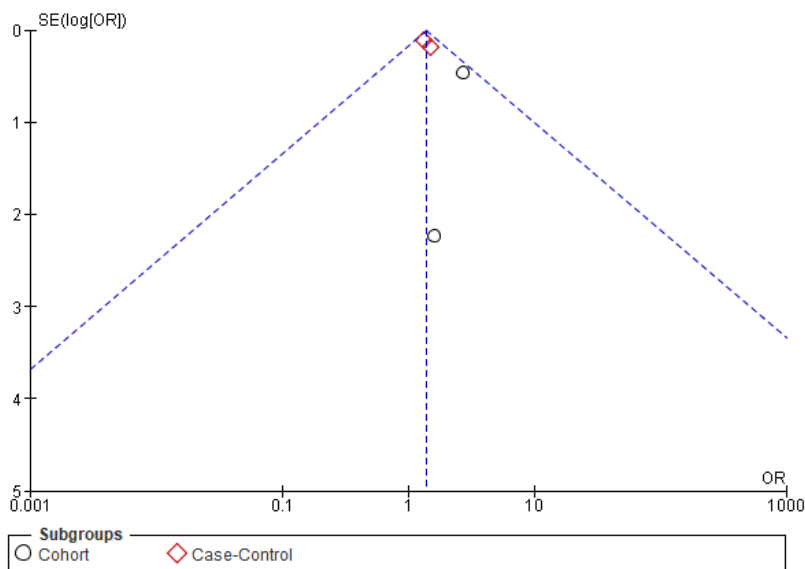


Figure 4. Funnel plot of the effect of endometriosis on ectopic pregnancy

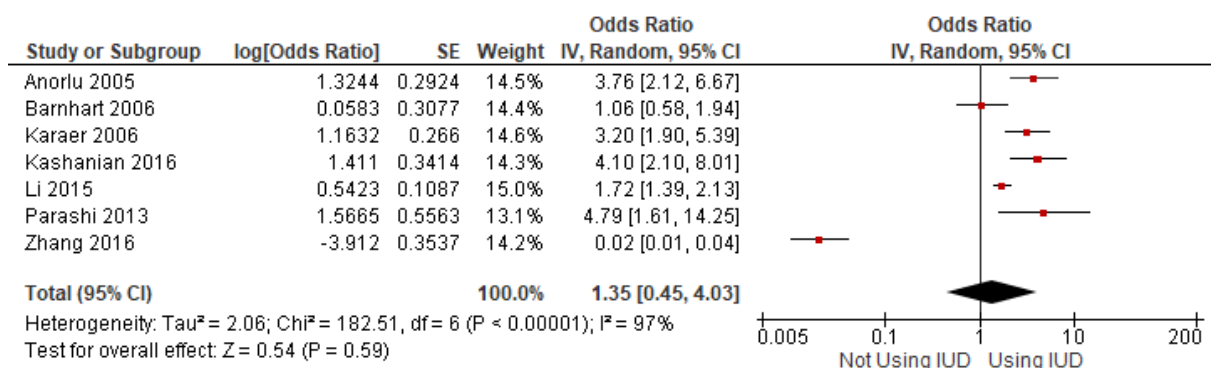


Figure 5. Forest Plot of the effect of IUD use on ectopic pregnancy

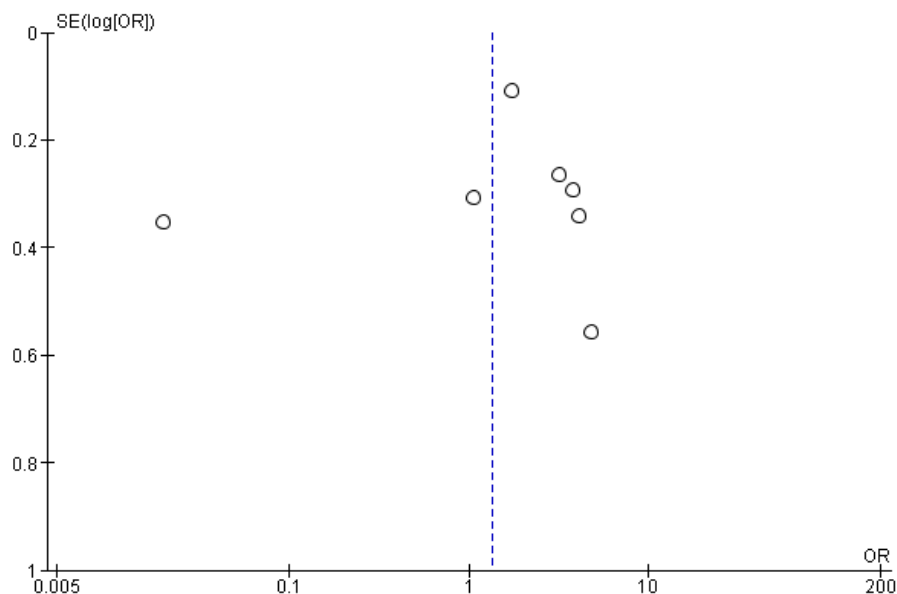


Figure 6. Funnel plot of the effect of IUD use on ectopic pregnancy

DISCUSSION

This systematic review and meta-analysis investigated the effect of endometriosis and IUD use on the incidence of ectopic pregnancy. The independent variables in this study were a history of endometriosis and IUD use. While the dependent variable is the incidence of ectopic pregnancy.

The results of the analysis using the Review Manager 5.3 application are presented in the form of Forest plots and Funnel plots. The results of the overall meta-analysis showed that women with endometriosis had a 1.39-fold greater risk of ectopic pregnancy than women without endometriosis (aOR= 1.39; 95% CI= 1.16 to 1.68; $p < 0.001$), and the asymmetrical graphs in the funnel plots suggest publication bias. The result of $I^2 < 50\%$ indicates homogeneous research data (fixed effect model). The results also showed that IUD use increased the risk of ectopic pregnancy by 1.35 times compared to no IUD use, and was not statistically significant (aOR= 1.35, 95% CI= 0.45 to 4.03; $p = 0.590$), and the asymmetric funnel plot showed no bias. The heterogeneity of the data (I^2) showed 97%,

so a random effect model was used because the study was heterogeneous.

Various studies have examined the effect of endometriosis and IUD use on ectopic pregnancy and have shown inconsistent results. Yong et al. (2020) in a meta-analysis concluded that endometriosis increased the risk of ectopic pregnancy up to 2 times (OR= 2.16; 95% CI= 1.67 to 2.79; $p < 0.001$). Hjortd et al. (2014) stated that women with endometriosis are more at risk for an ectopic pregnancy regardless of the method of conception (aRR= 1.93, 95% CI= 1.80 to 2.08). Conception with assisted reproductive methods in women with endometriosis was at greater risk for an ectopic pregnancy (aRR= 2.67; 95% CI= 1.42 to 5.02).

Obstruction of the tube both anatomically and functionally is the pathogenesis of ectopic pregnancy. Endometriosis appears to be responsible for this condition due to alterations in ciliary beat and muscle contractility, as well as changes in molecular chemistry in the tubal environment due to inflammation, which causes the embryo to stagnate in the tube (Zalecka et al., 2022; Hill et al., 2020).

Meta analysis by Mayaningrum et al. (2021) showed results in line with the results of this study, namely the use of IUDs increased the risk of ectopic pregnancy (RR= 1.53, 95% CI= 0.48 to 4.80; p= 0.470). While Yanuari et al. (2021) stated that IUD use increased the incidence of ectopic pregnancy by up to 2 times (aOR = 2.28, 95% CI= 1.74 to 2.98; p<0.001).

In general, the use of the IUD as a contraceptive reduces the risk of an ectopic pregnancy, but if the IUD fails, resulting in a pregnancy with an in-situ IUD, it can increase the risk of an ectopic pregnancy (Mol et al., 1995; Xiong et al., 1995). The local inflammatory state induced by the IUD appears to affect the transport of embryos in the fallopian tubes. The IUD works as a contraceptive with local inflammatory induction mechanisms, changes in mucus viscosity, and changes the cytokine and integrin profiles in the tubal environment due to inflammation (Gabriel et al., 2017)

It can be concluded that in this meta-analysis, endometriosis and IUD use were risk factors for ectopic pregnancy after controlling for various confounding factors. In this study, researchers encountered several obstacles due to language bias where only English or Indonesian articles were included, it is hoped that further researchers will be able to eliminate language barriers. The results of this meta-analysis are expected to be a reference contribution for future researchers and a reference for health practitioners in educating and treating patients at risk for ectopic pregnancy, and in providing the best contraceptive options for patients.

AUTHOR CONTRIBUTION

Afifa Intifadha Habibatullah is the main researcher who chooses the topic, conducts exploration and collects research data. Uki Retno Budihastuti and Vitri Widyaningsih played a role in data analysis and review of

research documents.

FUNDING AND SPONSORSHIP

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CONFLICT OF INTERESTS

There is no conflict of interest in this study.

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