

**STUDI LITERATUR: HUBUNGAN ANTARA PEMAKAIAN
KONTRASEPSI HORMONAL SECARA ORAL DENGAN ANGKA
KEJADIAN KANKER OVARIUM**

SKRIPSI

**Untuk Memenuhi Persyaratan
Memperoleh Gelar Sarjana Kedokteran**



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**Diajukan untuk Memenuhi Salah Satu Syarat Guna
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KATA PENGANTAR

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DAFTAR SINGKATAN DAN SIMBOL

<i>LH</i>	:	<i>Luteinizing Hormone</i>
<i>FSH</i>	:	<i>Follicle Stimulating Hormone</i>
<i>GnRH</i>	:	<i>Gonadotropin-Releasing Hormone</i>
<i>PGS-2</i>	:	<i>Prostaglandin Synthase 2</i>
<i>DNA</i>	:	<i>Deoxyribonucleic Acid</i>
<i>CIC</i>	:	<i>Cortical Inclusion Cysts</i>
<i>POP</i>	:	<i>Progesteron Only Pil</i>
<i>RSUP</i>	:	Rumah Sakit Umum Pusat
<i>IUD</i>	:	<i>Intrauterine Device</i>

Original Research Article**Literature Study of The Relationship Between Oral Hormonal Contraception Use With the Incidence of Ovarial Cancer****Satriyo Nugroho¹, Titiek Sunaryati², Ira Idawati³**Mahasiswa Program Studi S1 Kedokteran, Universitas Wijaya Kususma Surabaya¹Dosen Program Studi S1 Kedokteran, Universitas Wijaya Kususma Surabaya²Dosen Program Studi S1 Kedokteran, Universitas Wijaya Kususma Surabaya³

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Ovarian cancer is a condition when the tissue in the ovaries experiences abnormal growth or can be called malignant. Ovarian cancer accounts for around 239,000 new cases and 152,000 deaths annually worldwide. According to the results of research that is in line with the incessant ovulation hypothesis which states that the use of hormonal contraception that is used regularly can reduce the incidence of ovarian cancer. Because of this, this study aims to determine the relationship between the use of oral hormonal contraceptives and the incidence of ovarian cancer. In this study, descriptive research was used using the literature study method. The sources of literature in this study were obtained from Google Scholar, Mendeley, Elsevier, and PubMed which were used as sources for the last 10 years. Based on the results of the study it can be concluded that there is a relationship between oral contraceptives and ovarian cancer so that regular use of hormonal contraceptives can reduce the incidence of ovarian cancer. This is because contraception will prevent the ovulation process from occurring so that there is no inflammation and carcinogenesis in the tissues in the ovaries. In addition, the role of the hormone progesterone has the effect of inhibiting proliferation and causing the process of apoptosis in cells that are still normal or that are about to experience malignancy. The use of oral contraceptives can be used as a preventive measure in an effort to reduce the occurrence of ovarian cancer. However, it is necessary to consider the effects of oral contraceptives on other cancers.

Studi Literatur Hubungan Antara Pemakaian Kontrasepsi Hormonal Secara Oral Dengan Angka Kejadian Kanker Ovarium**Abstrak**

Kanker ovarium adalah kondisi ketika jaringan pada ovarium (indung telur) mengalami pertumbuhan yang tidak normal atau bisa disebut mengalami keganasan. Kanker ovarium menyumbangkan sekitar 239.000 kasus baru dan 152.000 kematian setiap tahunnya di seluruh dunia. Menurut hasil penelitian yang sejalan dengan hipotesis *incessant ovulation* menyatakan bahwa penggunaan kontrasepsi hormonal yang digunakan secara teratur dapat menurunkan angka kejadian kanker ovarium. Dikarenakan hal tersebut, maka penelitian ini bertujuan untuk mengetahui mengetahui hubungan antara pemakaian kontrasepsi hormonal secara oral dengan angka kejadian kanker ovarium. Pada penelitian ini menggunakan penelitian yang bersifat deskriptif dengan menggunakan metode studi literatur, sumber pustaka pada penelitian ini diperoleh dari *Google Scholar*, *Mendeley*, *Elsevier*, dan *PubMed* yang digunakan sebagai sumber pustaka memiliki rentang 10 tahun terakhir. Berdasarkan hasil dari penelitian dapat disimpulkan

bahwa ada hubungan antara kontrasepsi oral dengan kanker ovarium sehingga penggunaan kontrasepsi hormonal yang digunakan secara teratur dapat menurunkan angka kejadian kanker ovarium. Hal ini dikarenakan kontrasepsi akan mencegah terjadinya proses ovulasi sehingga tidak terdapat inflamasi dan karsinogenesis pada jaringan di ovarium. Selain itu, peran dari hormon progesteron yang mempunyai efek menghambat terjadinya proliferasi dan menyebabkan proses terjadinya *apoptosis* pada sel yang masih normal maupun yang akan mengalami keganasan. Penggunaan kontrasepsi oral dapat digunakan sebagai tindakan pencegahan dalam upaya mengurangi terjadinya kanker ovarium. Namun demikian, perlu dipertimbangkan efek kontrasepsi oral terhadap kanker lainnya.

Kata Kunci: kanker ovarium, kontrasepsi, hormonal, ovulasi

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INTRODUCTION

Ovarian cancer is a condition when the tissues in the ovaries experience abnormal growth or can be called malignant. This cancer can spread to other parts of the body, such as the pelvis and abdomen through the vascular system or lymph system. Ovarian cancer is also often known as the "silent killer" because the symptoms are difficult to identify. Symptoms often appear when it has reached an advanced stage. Early detection efforts are needed to prevent the advanced stage phase. Various preventive measures have also been developed to reduce the incidence rate by identifying risk factors. Findings show that many factors can influence the occurrence of ovarian cancer, including family history, age, ethnicity, lifestyle, and environment. (Buckles, Johnson and Trevi, 2012)

Contraception or can be called anticonception is a preventive effort made to prevent fertilization to pregnancy, temporary or permanent. Contraception has several methods, one of which is using hormonal. Hormonal contraceptives are contraceptives based on synthesized hormones in the form of estrogen and progesterone preparations. There are several methods with hormonal contraception, including: injections every 3 months, injections every 1 month, oral every 1 month, and with implants or implants. (Wahyuni, 2017).

Ovarian cancer is a common malignancy in gynecology that ranks third after cervical cancer and uterine cancer. Ovarian cancer accounts for approximately 239,000 new cases and 152,000 deaths annually worldwide. (Reid, Permuth and Sellers, 2017). Reporting from Global Cancer Incidence, Mortality and Prevalence (Globocan) that the incidence of ovarian cancer in Indonesia contributed 14,896 cases and 9,581 cases of death. The incidence rate is expected to increase every year. The five-year life expectancy is less than 45% and there are 15,000 deaths which makes it the eighth leading cause of cancer death.

The highest incidence rate is in Continental Europe. (Webb and Jordan, 2017).

According to the results of research in line with the incessant ovulation hypothesis, the use of hormonal contraceptives used regularly can reduce the incidence of ovarian cancer. This is because contraception will prevent the ovulation process so that there is no inflammation and carcinogenesis in the ovarian tissue. In addition, the role of the hormone progesterone which has the effect of inhibiting proliferation and causing the process of apoptosis in cells that are still normal and that will experience malignancy. So that from this mechanism can protect ovarian epithelial cells from malignancy. (Widodo et al., 2019). The use of hormonal contraceptives, especially oral for 5 years or more, can reduce the risk of ovarian epithelial cancer by 0.5 or reduce 50% of the incidence of ovarian cancer.. (Harsono et al., 2020)

With the low survival rate and high mortality rate caused by ovarian cancer. Therefore, I took preventive measures to prevent ovarian cancer. Thus, my title is "Relationship between Oral Hormonal Contraceptive Use and Ovarian Cancer Incidence Rate."

MATERIAL AND METHODS

This research uses qualitative research through a literature study approach, which is a series of activities using methods of collecting data from literature studies to be managed which will later be used as the result of research conclusions. The sources used come from credible literature sources obtained from books, journals, and various writings related to the phenomenon under study. In searching for literature sources that are in accordance with the topic, researchers use platforms that have a broad scope and are easily accessible. Literature sources were also collected in the mendeley application to facilitate writing citations. Researchers read at the same time as making notes that are relevant to the research problem which will later serve as material and

guidelines for making conclusions that are in accordance with the research objectives.

The first step was to identify the problem described at the beginning, which showed the phenomenon of ovarian cancer incidence. The incidence rate is related to several risk factors such as gene mutation, lifestyle, and contraceptive use. So the researcher carried out a study with the title "The Relationship between Oral Hormonal Contraceptive Use and Ovarian Cancer Incidence Rates."

The next stage is to search for and collect literature sources which will be used as material for discussion in the study. The literature sources were obtained through Pubmed, Google Scholar, and Elsavier. The technique used in obtaining suitable journals is by entering keywords such as ovarian cancer and contraception. The literature sources obtained are journals in Indonesian and English within the last 10 years since the preparation of this study, which is from 2012 to 2022. The search results for literature sources obtained from Pubmed, Google Scholar, and Elsavier totaled 5,133 journals.

In the screening stage, the literature sources that have been obtained will be sorted out in accordance with the inclusion and exclusion criteria, so that the journal discussion is in accordance with the problems in the study. The inclusion criteria in this literature study research used ovarian cancer patients over the past 10 years in the vulnerable years 2012 to 2022, and risk factors for using oral hormonal contraception. Exclusion criteria or those that are not included as research data for this literature study if the risk factor for using contraception with non-hormonal as a hypothesis that affects ovarian cancer, and the journal research year before 2012. Journals that have been screened will be collected in the mendeley application to facilitate writing citations in research.

Study results from previous studies will be used as material for discussion in this literature study by summarizing into important points that are in accordance with the topic. Then recorded into a table as a brief description of the contents of the journal that examines the relationship

between the use of hormonal contraceptives and the incidence of ovarian cancer. Furthermore, it is analyzed descriptively to answer the problem formulation contained at the beginning of this research chapter. The last stage is to make conclusions and suggestions.

RESULT AND DISCUSSION

According to the results of research in line with the incessant ovulation hypothesis, the use of hormonal contraceptives used regularly can reduce the incidence of ovarian cancer. This is because contraception will prevent the ovulation process so that there is no inflammation and carcinogenesis in the ovarian tissue. In addition, the role of the hormone progesterone which has the effect of inhibiting proliferation and causing the process of apoptosis in cells that are still normal and that will experience malignancy. So that this mechanism can protect ovarian epithelial cells from malignancy. (Widodo et al., 2019).

Based on research (Schrijver et al., 2021) with a cohort approach method, there are BRCA1 and BRCA2 carrier mutations with diagnosed ovarian cancer. There are findings regarding the inverse relationship between oral contraceptive use and ovarian cancer risk. For BRCA1 mutation carriers, oral contraceptive use was associated with a reduced risk of ovarian cancer. Cancer risk was reduced to a greater extent with longer duration of oral contraceptive use, and the risk reduction persisted for a long time. The findings for BRCA2 mutation carriers were similar, but the sample size was too limited to draw conclusions. There are findings that oral contraceptive use may increase breast cancer risk. This is based on data, the cumulative risk of breast cancer is 43% in BRCA1 and 35% BRCA2 at age 50 years. While the cumulative risk of ovarian cancer is 8% in BRCA1 and 0% in BRCA2. Although the use of oral contraceptives can be considered as a preventive approach to developing ovarian cancer, their use in BRCA1 and BRCA2 mutation carriers needs to be considered against the possible association of oral contraceptive use with an increased risk of breast cancer.

Based on research (Park et al., 2022) using the meta-analysis method using the Newcastle-Ottawa Scale (NOS) for case control and cohort studies. The use of oral contraceptives is associated with a reduced risk of ovarian cancer. Both short-term and long-term use were associated with reduced risk in BRCA1 mutation carriers, while long-term use was significantly associated with reduced risk in BRCA2 mutation carriers. In conclusion, this meta-analysis of observational studies found that oral contraceptive use in BRCA mutation carriers was significantly associated with increased breast cancer risk and decreased ovarian cancer risk. Therefore, the use of oral contraceptives as ovarian cancer chemoprevention should be considered in BRCA mutation carriers.

Based on research (Buckles, Johnson and Trevi, 2012) with experimental methods with female chicken media showed that the administration of progestins, either alone or in combination with estrogen, reduced the prevalence of ovarian cancer. The hormonal components of oral contraceptives, progesterone and estrogen, are thought to influence the development and/or progression of ovarian cancer. Treatment with progestin alone, or in combination with estrogen, significantly reduces the risk by 91% and 81%, respectively. Progesterone will suppress the development of ovarian tumors. This protective effect may be independent of the effect of progestins on ovulation. This is because women who use oral contraceptives containing only progestin also have a lower risk of ovarian cancer even though ovulation is only suppressed at about 40%. Progesterone/progestin proliferation inhibition and apoptosis induction in oral contraceptive use have protective effects.

Based on research (Li et al., 2012) that evaluated the relationship between reproductive factors, and exogenous hormones, especially oral contraceptives (OC) and hormone replacement therapy (HRT), are recognized as risk factors for breast cancer and ovarian cancer. As major risk factors, unfavorable changes in reproductive factors and the use of oral contraceptives and

hormone replacement therapy may lead to an increase in the incidence of breast cancer and/or ovarian cancer. However, specifically oral contraceptive use has an effect on increasing the risk of breast cancer, especially in young women and a history of oral contraceptive use has also been shown to reduce the risk of ovarian cancer.

Based on research (Jatoi et al., 2015) using the Chi-square method or Wilcoxon rank-sum test by comparing patients who have and who have never used oral contraceptives. shows that the use of oral contraceptives reduces the risk of ovarian cancer. A relative risk reduction greater than 20% appears to occur every 5 years a woman reports using oral contraceptives. This risk reduction is particularly prominent among women who have used oral contraceptives for 10 years or more, and also occurs in high-risk women, such as those with BRCA1 and BRCA2 gene mutations. Ovarian epithelial cancer cells that experience repeated trauma each month from ovulation. They are more likely to have DNA mutations. The more frequent the trauma, the greater the tendency for these cells to develop abnormal DNA mutations. The more DNA mutations, the more aggressive the development of ovarian cancer. Oral contraceptives protect against the development of primary ovarian cancer suggesting that cessation of ovulation may stop the repeated monthly trauma to the ovarian surface, possibly limiting epithelial cell mutation and carcinogenesis. Continuous ovulation is thought to be the start of ovarian epithelial cell DNA damage, which in turn gives rise to carcinogenesis, thus providing a possible mechanism for how ovulation cessation from oral contraceptives may lead to a lower risk of cancer.

Based on the literature (Moorman et al., 2013) by identifying several studies that discuss the use of oral contraceptives and the risk of ovarian cancer in BRCA1 and BRCA2 carriers. The results showed an inverse relationship in the use of oral contraceptives for the combined group of BRCA1 and BRCA2 mutation carriers of (OR, 0.58), which means that the use of OCs reduces the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. However, the overall benefit of oral contraceptives for ovarian cancer prevention in

high-risk women should be compared with the risk of breast cancer. This is because there is an increased risk of breast cancer in oral contraceptive users.

Based on research (Ferris et al., 2014) which showed a statistically significant inverse trend over years of oral contraceptive use with the greatest reduction seen in those using oral contraceptives for 3 years or more. Results showed the greatest risk reduction for those who started use between 20-25 years of age. Oral contraceptive results stratified by BRCA1/2 mutation status, there was a statistically significant inverse association between oral contraceptives and ovarian cancer in BRCA1/2 mutation negatives compared to those with positive BRCA1/2 mutations. In the results of the study by comparing those who had used oral contraceptives with those who had not, the risk of ovarian cancer was 0.58 in the model with control sisters and 0.35 in the model with all cases and controls.

Based on the study (Dayanand and Olivia, et al., 2018) which observed a significant increased risk of ovarian cancer with short-term oral contraceptive use and a non-significant inverse association with oral contraceptive use for 15 years or more. evaluated the use of oral contraceptives by assessing ever and never use and evaluating the duration of contraceptive use. This was due to strong concentration differences and older formulation patterns than previous studies.

Based on research (Vessey and Yeates, 2013) on cancer incidence associated with the total duration of oral contraceptive use. In the results of the study concerning women who had used oral contraceptives, showed a positive association in women who experienced breast and cervical cancer (RR: 3.4, 95% CI: 1.6-8.9). While showing a negative association in uterine cancer (RR: 0.5, 95% CI: 0.3-0.7) and ovarian cancer (RR: 0.5, 95% CI: 0.4-0.7). The studies were mostly related to oral contraceptives containing 50 mcg estrogen, a high dose by current standards, and the analysis took into account the effects of oral contraceptive use. The findings

concluded that oral contraceptive use did not alter the risk of cancers of the thyroid, lung, stomach, urinary tract, gallbladder, and/or the risk of lymphoma, cutaneous melanoma, or central nervous system tumors. Oral contraceptive use increases the risk of liver cancer in populations with a low prevalence of Hepatitis B Virus infection. In colorectal cancer that oral contraceptives with this type of cancer. While there is a slightly increased risk of breast cancer in young women up to 35 years of age. There is a strong positive association between oral contraceptive use and cervical cancer that increases with duration of use and decreases with interval since last use. Oral contraceptives are protective against cervical cancer, that the protective effect increases with duration of use and persists for at least 20 years after discontinuation of use. Similarly, ovarian cancer has a protective effect and will persist for at least 30 years after discontinuation of oral contraceptive use. The conclusion on the findings is in relation to the effects that continue after oral contraceptive use. The beneficial effects on uterine cancer and ovarian cancer clearly outweigh the adverse effects on cervical cancer.

CONCLUSION

Based on literature sources through different research methods with the same subject matter regarding oral contraceptives and ovarian cancer, it can be concluded that there is an association between the use of oral hormonal contraceptives and the incidence of ovarian cancer. The relationship of oral contraceptives is protective against ovarian cancer within a certain duration of use. This can be utilized as a preventive effort in preventing ovarian cancer. The effect of oral contraceptives can be inversely related to breast cancer. So it is also necessary to consider its use in someone who has a risk of breast cancer.

SUGGESTION

The use of oral contraceptives can be used

as a preventive measure in an effort to reduce the occurrence of ovarian cancer. However, it is necessary to consider the effects of oral contraceptives on other cancers. It is necessary to conduct further research specifically on certain types of contraceptives as a reference to medical science, especially in the field of oncology.

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