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Risk Factors Associated with the Incidence of Ovarian Cancer

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Abstract

Ovarian cancer is the biggest malignancy problem in female reproduction today. Dr. Hospital H. Abdul Moeloek as a referral center hospital in Lampung province has data that ovarian cancer is the most gynecological cancer with cases that have continued to increase over the past 3 years. The purpose of this study was to determine the risk factors associated with the incidence of ovarian cancer in RSUD Dr. H. Abdul Moeloek Lampung Province. This type of research is quantitative with a case-control design. The population was all patients treated in the gynecology room with 70 case samples taken using total sampling and 70 control samples using simple random sampling. The results showed that the factors related to the incidence of ovarian cancer in RSUD Dr. H. Abdul Moeloek included age (p-value = 0.001 and OR = 13.5 with 95% CI = 6.01-30.31), history of breastfeeding (p-value = 0.009 and OR = 2.684 with 95% CI = 1.326 -5.432), and a history of contraception (p-value = 0.001 and OR = 3.882 with 95% CI = 1.855-8.126). While the age of menarche and parity has no relationship with the incidence of ovarian cancer. From the research results expected, the high incidence of ovarian cancer in Lampung province can be socialized properly in society, so that people understand and can prevent ovarian cancer early.

Keywords

age; breastfeeding; contraception

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Introduction

Cancer is currently the leading cause of death in the world and is the most common obstacle to achieving desired life expectancy in most countries(Momenimovahed et al., 2019). Ovarian cancer is a group of cells that grow abnormally in the ovarian cells and damage the surrounding tissue(Canadian Cancer Society, 2019)and is the biggest malignancy problem in the female reproductive organs. The National Comprehensive Cancer Network (NCCN) states that in one day there are more than 28 women in the world who are diagnosed with ovarian cancer, so it can be accumulated that every year more than 200,000 new diagnoses are found.(Gajjar et al., 2012)the predictive value of symptoms remains very low. The aim of this paper is to obtain the views of general practitioners (GPs. The number of new cases of ovarian cancer in 2018 ranks 18th based on general gender and age classification and 8th on the specific classification of cancer that occurs most often in women in the world. The incidence rate was 295,414 cases with a death rate of around 184,799 cases (62.56%). Based on the order of countries with the highest incidence rates, Indonesia is in fifth place with a total incidence of 13,310 cases. In Indonesia alone, ovarian cancer is in third place after breast cancer and cervical cancer(Globocan, 2019), but survival is three times worse than other cancers(Momenimovahed et al., 2019).

The term "ovarian cancer" is not a single diagnostic description, but rather a general term for various types of cancer that affect the ovaries, fallopian tubes, and the main cavity of the peritoneum. It is estimated that more than 30 different types of ovarian cancer have been discovered(Bhatla & Jones., 2018)However, the etiology is still unclear until now. Several hypothetical theories have been widely published, including the incessant ovulation hypothesis (non-stop ovulation theory) (Busmar, 2010), gonadotropin stimulation hypothesis(Sumanasekera, 2018)endometrioid, mucinous and clear cell; in each subtype, low and high grade. The large majority of ovarian cancers are diagnosed as high-grade serous ovarian cancers (HGS-OvCas, androgen stimulation hypothesis(Busmar, 2010), progesterone hypothesis, and estrogen hypothesis(Sumanasekera, 2018)endometrioid, mucinous and clear cell; in each subtype, low and high grade. The large majority of ovarian cancers are diagnosed as high-grade serous ovarian cancers (HGS-OvCas. According to the World American Cancer Institute, ovarian cancer occurs due to repeated damage and repair to ovarian cells during the ovulatory cycle. This triggers cells to continue to proliferate (grow and develop) thereby increasing the potential for spontaneous mutations.

Risk factors related to the incidence of ovarian cancer can be divided into two groups, namely predisposing (triggers) and protective (protectors). Age is an important factor in the incidence of ovarian cancer. The risk of ovarian cancer increases with age, supporting the theory of the incessant ovulation hypothesis, which states that as women get older, the number of ovulations that have occurred also increases. The risk of ovarian cancer increases at the age of 45-54 years(Widayati et al., 2011)but the peak is at the age of 50 years(Zheng et al., 2018). Meri Yanti's research at Zainoel Abidin Hospital, Aceh (2017) illustrates that maternal age is related to the incidence of ovarian cancer with p value=0.046 and an odds ratio (OR) of 2.250 with 95% CI=1.105-5.639(Yanti, 2018).

Menarche age <12 years (early menarche) also appears to support the incessant ovulation hypothesis theory because it increases the number of ovulatory cycles(Montes et al., 2012). Several epidemiological studies show that the odds ratio (OR) of early menarche on the incidence of ovarian cancer is 1.1-1.5(Montes et al., 2012)and the results of research by Rian Pasaoran et al stated that the highest incidence of ovarian cancer was in the menarche age group of 11 years(Simamora et al.,

2018). Meri Yanti's research at Zainoel Abidin Hospital, Aceh (2017) shows that there is a relationship between early menarche and the incidence of ovarian cancer, proven by p value = 0.016 and OR = 2.700 with 95% CI = 1.194-6.103(Yanti, 2018).

Parity is associated as a protective factor for ovarian cancer because nulliparous women tend to have more ovulatory cycles than multiparous women. Pregnancy causes anovulation and suppresses pituitary gonadotropin secretion thereby confirming the incessant ovulation hypothesis and the gonadotropin hypothesis. Parous women have a 30%-60% lower risk than nulliparous women(Reid et al., 2017). Full ovulation every year indicates an increased risk of ovarian cancer by 6%. These findings are particularly relevant in the 20 to 29 year age group, where there is a 20% increase in risk. Women with last birth after age 30 to 35 years had a 58% lower risk of ovarian cancer compared with nulliparous women(Montes et al., 2012).

Apart from parity, a history of breastfeeding and the use of hormonal contraception are also considered protective factors for ovarian cancer because they can suppress ovulation in women. The relationship between breastfeeding and a reduced risk of ovarian cancer is related to the contraceptive mechanism of the lactational amenorrhea method (MAL). Research by Adisasmita et al (2016) shows that there is an 83% reduction in the risk of ovarian cancer in women who have a history of breastfeeding (OR=0.17 with 95%CI=0.08-0.39)(Adisasmita et al., 2016).

Overall, use of any type of hormonal contraception has a protective effect against ovarian cancer compared to never using hormonal contraception with relative risk (RR)=0.66 with 95%CI=0.58-0.76. The results of a reanalysis of 45 epidemiological studies indicate that oral contraceptive use provides long-term protection against ovarian cancer by preventing approximately 200,000 ovarian cancers and 100,000 ovarian cancer-related deaths, in both carriers and non-carriers of the BRCA 1 mutation(Montes et al., 2012).

Dr. Hospital H. Abdul Moeloek is the highest referral hospital in Lampung province. Pre-survey results show that ovarian cancer is the most common gynecological cancer with the number of cases continuing to increase over the last 3 years, followed by cervical cancer and endometrial cancer. In 2016, the number of patients diagnosed with ovarian cancer was 43, cervical cancer was 80, and endometrial cancer was 25. In 2017 the number of ovarian cancer patients was 105 patients, 102 patients with cervical cancer, and 28 endometrial cancer patients. In 2018 the number of ovarian cancer patients increased to 146 patients, 124 patients with cervical cancer and 21 endometrial cancer patients. As of September 2019, the number of new cases of ovarian cancer registered in the gynecology room at Dr. H. Abdul Moeloek has added 70 cases. Based on the problems above, further research was carried out regarding the risk factors associated with the incidence of ovarian cancer at RSUD Dr. H. Abdul Moeloek Lampung Province.

Methods

This type of research is quantitative research with a case control design that is hospital based analytical in nature.The population of this study were all patients treated in the gynecology room at Dr. H. Abdul Moeloek Lampung Province registered 358 patients from January to September 2019, then divided into two groupsincluding a group of ovarian cancer sufferers as cases of 70 patients and a group of non-ovarian cancer sufferers as controls of 288 patients. Researchers used a 1:1 ratio in determining the sample size so that in the case group a total sampling technique was used and in the control group a simple random sampling technique was used via the Random Sample Generator mobile application after the samples were filtered using predetermined inclusion and exclusion criteria.

This research uses secondary data

sourced from patient medical records. The resulting univariate analysis is a percentage frequency distribution and the bivariate analysis uses the chi square statistical test. Researchers also assessed the strength of the risk relationship between variables by calculating the odds ratio (OR). Data collection was carried out in March-April 2020 at RSUD Dr. H. Abdul Moeloek, Lampung Province and has passed the ethical feasibility test issued by the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University with number 23/EC/KEPK/FK-UNDIP/II/2020.

Results and Discussion

Table 1 on the age variable shows that the age category has a higher risk in the case group (ovarian cancer), namely 56 respondents (80%) from the control group (no ovarian cancer), namely 16 respondents (22.9%), whereas for the no age category at risk, the case group was lower (20%) than the control group (77.1%). The variable age at menarche shows that both groups (cases and controls) are mostly not at risk (menarche≥12 years). The number of respondents in the case group at risk was 13 respondents (18.6%) while in the control group the number of respondents at risk was 10 respondents (14.3%) and in the control group the number respondents who were not at risk were 57 respondents (81.4%) while the case group was 60 respondents (85.7%). The parity variable shows that the results in the two groups have differences that are not very significant. The number of parities at risk (parity < 2) was more common in the case group than in the control group. The number of parities at risk in the case group was 38 respondents (54.3%) while in the control group there were 33 respondents (47.1%) and the number of parities not at risk (parity ≥ 2) in the case group was 32 respondents (45.7%) while the control group was 37 respondents (52.9%). Respondents in the breastfeeding history variable who were at risk because they did not provide exclusive breastfeeding were more in the case group, namely 51 respondents (72.9%) while in the control group there were 35 respondents (50%) and

Table 1. Frequency Distribution of Variable Characteristics and Factors Associated with the Occurrence of Ovarian Cancer at RSUD Dr. H. Abdul Moeloek Lampung Province

Risk Factors	Case (Ovarian Cancer)		Control (Not Ovarian Cancer)	
	n	%	n	%
Age				
At risk (age ≥ 40 years)	56	80	16	22.9
No Risk (age < 40 years)	14	20	54	77.1
Menarche Age				
At risk (<12 years)	13	18.6	10	14.3
No Risk (≥ 12 years)	57	81.4	60	85.7
Parity				
At risk (parity < 2)	38	54.3	33	47.1
No Risk (parity ≥ 2)	32	45.7	37	52.9
Breastfeeding History				
Risky (not giving exclusive breast milk)	51	72.9	35	50
No Risk (exclusive breastfeeding)	19	27.1	35	50
Contraception History	55	78.6	34	48.6
Risky (not using hormonal contraception)				
No risk (using hormonal contraception)	15	21.4	36	51.4

those who were not at risk (giving exclusive breastfeeding) in the case group were only as many as 19 respondents (27.1%) and the control group were 35 respondents (50%). There were more respondents who had a history of risky contraception (not using hormonal contraception) in the case group, namely 55 respondents (78.6%) compared to the control group, 34 respondents (48.6%) and respondents who had a history of not using hormonal contraception (using hormonal contraception).) in the case group were fewer, namely 15 respondents (21.4%) compared to the control group, namely 36 respondents (51.4%).

Table 2 shows that for the education category more than half of the respondents in the case group had elementary school education (55.7%) while in the control group the highest level of education was high school (41.4%) and for the employment category, both case and case group respondents The control group was mostly housewives (IRT).

Table 3 shows that respondents who were at risk (age ≥ 40 years) in the case group were higher (80%) than in the control group (22.9%), while respondents who were not at risk (age < 40 years) were in the cases was lower (20%) compared to the control group (77.1%). The chi square test results obtained p value=0.001 and OR of 13.5 with 95%CI=6.01-30.31. These data show that there is a relationship between age and the incidence of ovarian cancer at Dr. H. Abdul Moeloek and respondents aged ≥ 40 years were 13.5 times more at risk of developing ovarian cancer than respondents aged < 40 years.

The relationship between age and the incidence of ovarian cancer is related to the incessant ovulation hypothesis (the theory of non-stop ovulation) which states that as women get older, the number of ovulations that occur in women also increases.(Widayati et al., 2011)and the gonadotropin hypothesis which states that many ovarian cancer sufferers are diagnosed during menopause and post menopause because at that time circulating gonadotropin hormones (FSH and LH) are at their highest levels due to the lack of

Table 2. Frequency Distribution of Respondent Characteristics at RSUD Dr. H. Abdul Moeloek Lampung Province based on Education and Employment

Respondent Characteristics	Case (Ovarian Cancer)		Control (Not Ovarian Cancer)	
	n	%	n	%
Education				
TS (No School)	2	2.9	0	0
elementary school	39	55.7	13	18.6
JUNIOR HIGH SCHOOL	14	20.0	19	27.1
SENIOR HIGH SCHOOL	12	17.1	29	41.4
PT (College)	3	4.3	9	12.9
Total	70	100	70	100
Work				
IRT	45	64.3	53	75.7
Farmer	17	24.3	3	4.3
Laborer	6	8.6	1	1.4
Employee	2	2.9	8	11.4
ART	0	0	2	2.9
Seamstress	0	0	1	1.4
Trader	0	0	1	1.4
Self-employed	0	0	1	1.4
Total	70	100	70	100

Table 3. The Relationship Between Age, Age of Menarche, Parity, Breastfeeding History, and Contraception History with the Occurrence of Ovarian Cancer at RSUD Dr. H. Abdul Moeloek Lampung Province

Variable	Case (Ovarian Cancer)		Control (Not Ovarian Cancer)		P value	OR (95%CI)
	n	%	n	%		
Age						
At risk (age ≥ 40 years)	56	80	16	22.9	0.001	13.5 (6.01-30.31)
No Risk (age < 40 years)	14	20	54	77.1		
Menarche Age						
At risk (<12 years)	13	18.6	10	14.3	0.648	-
No Risk (≥ 12 years)	57	81.4	60	85.7		
Parity						
At risk (parity < 2)	38	54.3	33	47.1	0.499	-
No Risk (parity ≥ 2)	32	45.7	37	52.9		
Breastfeeding History						
Risky (not giving exclusive breast milk)	51	72.9	35	50	0.009	2,684 (1,326-5,432)
No Risk (exclusive breastfeeding)	19	27.1	35	50		
Contraception History						
Risky (not using hormonal contraception)	55	78.6	34	48.6	0.001	3,882 (1,855-8,126)
No risk (using hormonal contraception)	15	21.4	36	51.4		

negative feedback by ovarian steroids (estrogens). High gonadotropins are involved in inhibiting cellular apoptosis (death) and aberrant expression of the p53 gene (suppressor gene) thereby triggering malignancy which causes a worsening of the prognosis of ovarian cancer(Sumanasekera, 2018)endometrioid, mucinous and clear cell; in each subtype, low and high grade. The large majority of ovarian cancers are diagnosed as high-grade serous ovarian cancers (HGS-OvCas.

However, researchers believe that the cause of the high incidence of ovarian cancer in RSUD Dr. H. Abdul Moeloek is very complex. The results of the analysis of the characteristics of respondents in the case group showed that the median age of ovarian cancer sufferers at RSUD Dr. H. Abdul Moeloek is 49 years old, more than half of the respondents have elementary school education (55.7%) and work as housewives (64.3%). Meanwhile, the results of the analysis of the characteristics of respondents in the control group showed that the median age of the control group was 30 years, the highest level of education was high school (41.4%), and the highest profession was housewife (75.7%).

The median age of ovarian cancer sufferers at Dr. H. Abdul Moeloek differs from the results of research conducted by Zheng et al (2018) through the Swedish Family-Cancer Database which shows that the median age of ovarian cancer sufferers shifted from 63 years to 65 years.(Zheng et al., 2018). The low median age of ovarian cancer sufferers at RSUD Dr. H. Abdul Moeloek estimated that this was due to the low quality of a healthy lifestyle and was influenced by the socio-economic status of the community.

Socioeconomic status is a predictor of the incidence and survival of ovarian cancer patients(Momenimovahed et al., 2019). The results of the study show that there is a positive correlation between life expectancy and income and the incidence of ovarian cancer, but there is a negative correlation between education level and the incidence of ovarian

cancer.(Razi et al., 2016).

The observed relationship between education level and income on the incidence of ovarian cancer is explained by the complex interaction between several underlying factors such as access to quality health examinations, lifestyle factors, diet, comorbidities (comorbidities) and a person's awareness of the symptoms that arise.(Præstegaard et al., 2016). A low quality healthy lifestyle causes an increase in the body's oxidative stress and premature aging of cells. If the intensity of the cell oxidation process is higher, more DNA damage will be caused.(Arthur et al., 2019).

The results of the findings in the field showed that 20% of respondents from the case group had a history of ovarian cysts, 8.6% of respondents had a history of colon cancer, cervical cancer, peritoneal cancer and uterine tumors and 5.7% of respondents had a family history of cancer (breast, leukemia, and bone cancer). Meanwhile, in the control group, information regarding family history and previous medical history was not found in the respondents' medical records. Supporting this, the gonadotropin hypothesis states that high concentrations of the gonadotropin hormone cause ovarian epithelial cells to become trapped in the surrounding connective tissue, causing the formation of inclusion cysts in the ovaries.(Su et al., 2013), due to environmental factors and continuous exposure to hormones, cells continue to grow and change towards malignancy, causing the cyst wall to thin and cancer cells to migrate to the peritoneal cavity, therefore ovarian cancer usually metastasizes to several organ sites. intraperitoneal, and vice versa(Furuya, 2012).

Other findings also show a picture of the time interval from the onset of symptoms to the first treatment for ovarian cancer sufferers at RSUD Dr. H. Abdul Moeloek 40% < 6 months since symptoms appeared, 17.1% 6 months to 1 year, and 42.8% > 1 year. Symptoms that arise mostly include abdominal pain, difficulty defecating, getting tired easily, bleeding, shortness of breath, and swelling of the stomach. The results of this research support the theory that poor awareness and interpretation of symptoms that occur in people with low socioeconomic status causes a tendency to ignore and deny the symptoms that arise so that they escalate into malignancy.(Præstegaard et al., 2016).

The results of research on the age of menarche variable showed that in both groups (cases and controls) the number of respondents who experienced menarche <12 years was less than respondents who experienced menarche ≥12 years. The chi square test results obtained p value = 0.648, which means there is no relationship between menarche age with the incidence of ovarian cancer at RSUD Dr. H. Abdul Moeloek.

Although there are many hypotheses regarding ovarian cancer, the etiology is still unclear at this time(Sumanasekera, 2018) endometrioid, mucinous and clear cell; in each subtype, low and high grade. The large majority of ovarian cancers are diagnosed as high-grade serous ovarian cancers (HGS-OvCas. Menarche is defined as the first menstrual period in a woman's life which indicates the maturity of ovarian and other endocrine functions related to reproductive ability. Over the past few decades, the age of menarche has shifted downward as a result of socioeconomic increases and chemical exposure(Lee et al., 2019). The relationship between menarche age less than 12 years (early menarche) and ovarian cancer appears to support the theory of incessant ovulation because ovulatory cycles that occur earlier cause a greater number of periods, although several studies have shown inconsistent results.(Gong et al., 2014).

Other findings showed that 50% of respondents in the case group had a history of menstrual disorders which included dysmenorrhea and irregular menstrual cycles. Meanwhile, in the control group, 27% of respondents had a history of menstrual disorders, most of which were dysmenorrhea. However, the data from the two groups was

not explained in detail regarding how long menstruation lasts and the distance between menstrual cycles.

Several epidemiological research results explain that women who experience irregular menstrual cycles and chronic anovulation can increase the risk of ovarian cancer, this explains the effect of shorter, longer and irregular cycles as an expression of symptoms of hyperandogenism or polycystic ovary syndrome (PCOS) with risk marker for more malignant ovarian cancer. This contradicts the incessant ovulation hypothesis which postulates that infrequent ovulatory cycles can reduce the risk of ovarian cancer. (Cirillo et al., 2017)but supports the androgen stimulation hypothesis which states that women with high androgen levels are more at risk of developing ovarian cancer(Busmar, 2010).

Androgens are a collection of hormones produced in the ovaries, adrenal glands, and through peripheral conversion of androgen precursors which will later be used to produce estrogen by the aromatase enzyme. Androgens can directly influence ovarian carcinogenesis through androgen receptors in the ovarian epithelium or through estrogen precursors resulting from the conversion of testosterone by the aromatase enzyme which results in a higher ratio of estrogen in the body compared to progesterone.(Ose et al., 2018). The results of in vitro research explain that androgens and estrogens act as mitogens (chemical compounds that stimulate cell division) which increase proliferation in ovarian epithelial cells.(Eric R. Craig et al., 2016).

The results of research on the parity variable show that the number of parities at risk (parity < 2) in the case group is higher (54.3%) than the control group (47.1%), while the number of parities not at risk (parity ≥ 2) in the case group is higher. lower (45.7%) than the control group (52.9%). The results of the chi square test obtained p value = 0.499, which means there is no relationship between parity and the incidence of ovarian cancer at RSUD Dr. H. Abdul Moeloek.

There are several hypotheses linking parity to ovarian cancer, but the etiology is still unclear. A large number of parities is considered to be a protective factor against ovarian cancer because during pregnancy the ovulation process does not occur, causing no damage to the ovarian epithelial cells and reducing the exposure of the ovaries to possible gene mutations due to continuous repair of epithelial cells after ovulation every month. Pregnancy causes inhibition of the ovulation process and an increase in the hormone progesterone which is thought to have protective properties against ovarian cancer because it is a suppressor gene.(Sumanasekera, 2018)endometrioid, mucinous and clear cell; in each subtype, low and high grade. The large majority of ovarian cancers are diagnosed as high-grade serous ovarian cancers (HGS-OvCas.

The results of the analysis of the characteristics of respondents in the case group illustrate that of the 70 respondents, 38 respondents had parity<2 with the classification of 21 respondents as nullipara and 17 respondents as primipara, the remaining 32 respondents had parity ≥2, while in the control group of 70 respondents, as many as 14 respondents were nulliparous. , 19 primiparous respondents, and 37 multiparous respondents. This supports research conducted by Montes et al that nulliparous women tend to have more ovulatory cycles than multiparous women, full ovulation every year shows an increased risk of ovarian cancer by 6%(Montes et al., 2012). The incidence of ovarian cancer is also higher in women with ovulation disorders, endometriosis and infertility. This relationship is strengthened with age, the higher the age, the greater the risk of occurrence(Lundberg et al., 2019).

The breastfeeding history variable shows that the number of respondents who did not provide exclusive breastfeeding was higher in the case group (72.9%) than the control group (50%) while the number of respondents who provided exclusive breastfeeding in the case group (ovarian cancer) was lower (27.1%) than the control group (50%).

The results of the chi square test obtained p value=0.009 and an OR of 2.684 with 95% CI=1.326-5.432, which means that there is a relationship between a history of breastfeeding and the incidence of ovarian cancer at RSUD Dr. H. Abdul Moeloek and respondents who did not give exclusive breastfeeding had a 2.684 times higher risk of developing ovarian cancer than respondents who gave exclusive breast milk, so it can be concluded that exclusive breastfeeding is a protective factor against ovarian cancer.

This is in line with the results of hospital-based research by Adisasmita et al (2016) at the Gynecology Polyclinic at Dharmais Cancer Hospital which shows that there is a relationship between exclusive breastfeeding and a reduced risk of ovarian cancer by 83% compared to women who have never breastfed in their lives (OR= 0.17 with 95% CI=0.08-0.39). However, analysis of menopausal ovarian cancer status versus breastfeeding showed that there was no significant difference between the effect of breastfeeding and the incidence of ovarian cancer diagnosed during pre-menopause or post-menopause.(Adisasmita et al., 2016).

Exclusive breastfeeding is giving only breast milk without additional food to babies aged zero to 6 months. The reduced risk of ovarian cancer due to exclusive breastfeeding is associated with delayed ovulation and prolonged periods of amenorrhea due to the contraceptive process of the lactational amenorrhea method (MAL). This causes a reduction in the number of ovulatory cycles in women. Lactation suppresses ovulation by increasing the concentration of prolactin, which inhibits the secretion of gonadotropins (FSL and LH) so that proliferation of ovarian epithelial cells does not occur due to repeated repair of the results of the ovulation process.(Su et al., 2013).

It is possible that the high failure rate of exclusive breastfeeding in the case group is due to the low level of knowledge of respondents regarding the importance of exclusive breastfeeding so that parents provide food other than breast milk to their babies early.

The contraceptive history variable shows that respondents with a history of contraception are at risk (not using hormonal contraception) in the case group is higher (78.6%) compared to the control group (48.6%) while respondents with a history of contraception are not at risk (using hormonal contraception). in the case group it was lower (21.4%) than in the control group (51.4%). The results of the chi square test obtained p value=0.001 and OR of 3.882 with 95% CI=1.855-8.126, which means that there is a relationship between history of contraception and the incidence of ovarian cancer at RSUD Dr. H. Abdul Moeloek and respondents who did not use hormonal contraception had a 3,882 times greater risk of developing ovarian cancer than respondents who used hormonal contraception. The low use of hormonal contraceptives in the case group was associated with the large number of respondents who were classified as nullipara (30%) and primipara (24.3%) who were older. The results of the chi square test obtained p value=0.001 and OR=3.882 (95% CI=1.855-8.126) which means there is a relationship between history of contraception and the incidence of ovarian cancer at RSUD Dr. H. Abdul Moeloek and respondents who did not use hormonal contraceptives had a risk of developing ovarian cancer 3,882 times that of respondents who used hormonal contraceptives.

Overall, the use of any type of hormonal contraception has a protective effect against ovarian cancer, especially epithelial, endometrioid, mucous and serous cancer compared to those who have never used hormonal contraception with a relative risk (RR) = 0.66 (95%CI = 0, 58-0.76). However, recent research shows that the reduction in risk of ovarian cancer with single progesterone contraceptive products is lower than using combined hormonal contraceptives, and the protective factor is stronger with increasing duration of contraceptive use. (Iversen et al., 2018). The mechanism of hormonal contraception, namely the continuo-

us use of estrogen and progestin, will inhibit the secretion of GnRH and gonadotropins in such a way that no follicular development occurs and ovulation does not occur. The function of estrogen is to inhibit (inhibit) the release of FSH and progesterone to inhibit the release of LH so that the maturation of follicles in the ovaries can be prevented. The use of hormonal contraception will cause estrogen and progesterone levels in the blood to remain high, so that the feed back mechanism will work (inhibition of FSH and LH release)(Cooper & Mahdy, 2019).

Although many studies show that hormonal contraception can reduce the risk of ovarian cancer, there are still pros and cons to using it. Other research shows that there is a significant relationship between the use of hormonal contraception and an increased risk of breast cancer because the estrogen contained in it causes hypertrophy and continuous abnormal proliferation of breast cancer stem cells directly in the ducts of the breast glands. Estrogen can also increase fat deposits in the body. Excessive fat storage causes estrogen synthesis to increase so that exposure to more estrogen and increases breast cell proliferation, besides that estrogen content can also interfere with gene expression in enzymes that regulate splicing (removal) of mRNA which results in loss of control over cell proliferation and regulation of apoptosis so that cells continues to proliferate without any death limit(Nissa et al., 2017).

Referring to this, further study is needed on the use of hormonal contraception, especially in women at high risk (>40 years) of developing ovarian and breast cancer. If the side effects caused are greater than the benefits of using hormonal contraception, the researcher's suggestion is that we need to succeed in a government program policy that directs the use of MKJP contraception based on the consideration that MKJP is more effective (lower level of side effects, complications and failure), efficient (availability of budget and provision of equipment), and saving costs by not visiting health workers too often to get contraceptive services.

Conclusion

The description of each variable (age, age at menarche, parity, history of breastfeeding, and history of contraception) in both groups showed varying results, in the case group most of the respondents were in the risk group, namely aged ≥ 40 years, parity <2, had a history of not giving birth. Exclusive breastfeeding and not using hormonal contraception. Meanwhile, in the control group, most of them were aged <40 years, had a menarche age of ≥12 years and parity ≥2, the number of respondents for the breastfeeding history variable had the same ratio, and more than half of the respondents had a history of using hormonal contraception. Of the five variables studied, three variables were found that had a relationship with the incidence of ovarian cancer at Dr. H. Abdul Moeloek Lampung Province so that this variable can also be assessed for the magnitude of the association with risk exposure. These variables include age (p value=0.001 and OR=13.5 with 95%CI=6.01-30.31), breastfeeding history (p value=0.009 and OR=2.684 with 95%CI=1.326-5.432) and history of contraception (p value=0.001 and OR=3.882 with 95%CI=1.855-8.126). The variables age at menarche and parity have no relationship with the incidence of ovarian cancer so the odds ratio value cannot be determined.

Based on these conclusions, the Lampung Provincial Health Service and related health agencies (community health centers and referral hospitals) are expected to work together to carry out outreach and education (risk factors for ovarian cancer, especially age, breastfeeding history and contraceptive history so that the public knows the importance of exclusive breastfeeding and can determining appropriate and safe contraceptive methods) as well as symptom-based screening of the community regarding the high incidence of ovarian cancer in Lampung Province through routine posyandu

programs, both infant and toddler posyandu and elderly posyandu. Further research is also needed regarding other risk factors that are closely related to the incidence of ovarian cancer.

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