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Faktor Risiko Hasil Janin/Bayi pada Wanita Hamil dengan Kanker di Jawa Timur Indonesia: Studi Epidemiologi

Risk Factors of Fetal/Infant Outcome in Pregnant Women with Cancer in East Java Indonesia: Epidemiological Study

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ABSTRAK

Latar Belakang: *Kanker selama Kehamilan merupakan kejadian langka meskipun jarang, kejadiannya saat ini terus meningkat di seluruh dunia.*
Tujuan: *Penelitian ini bertujuan untuk menjelaskan data yang tersedia mengenai ibu hamil penderita kanker di Jawa Timur-Indonesia, kondisi yang dialami ibu pasca kelahiran dan fetal outcome, serta mengetahui faktor risiko infant outcome yang buruk yang terjadi pada ibu hamil dengan kanker dari sudut pandang epidemiologi.*
Metode: *Penelitian ini merupakan studi kuantitatif observasi dengan Cross-sectional desain. Pengumpulan data pada kasus ibu hamil dengan kanker diperoleh dari data sekunder (laporan medis di bagian Obgyn RS Dr. Soetomo tahun 2016 – 2020). Peneliti mengunakan SPSS versi 25 untuk analisis statistik.*
Hasil: *Hasil penelitian menunjukkan bahwa dari tahun 2016 hingga tahun 2020 telah dilakukan ekstraksi 54 kasus ibu hamil penderita kanker dengan angka kejadian 0,8%. Angka kejadian Kanker Non-Obgyn (55,6%) lebih tinggi dibandingkan kanker Obgyn (44,4%). Angka kejadian tertinggi pada Kanker Non-Obgyn adalah Kanker Payudara (7,5%) dan Leukemia (3,7%), sedangkan angka kejadian tertinggi pada Kanker Obgyn adalah Kanker Serviks dan Ovarium (8,4%). Tidak ada hubungan antara jenis kanker dan hasil janin. Sedangkan, ada hubungan antara stadium kanker dan hasil bayi (berat badan).*
Kesimpulan: *Tingkat kanker dapat menjadi faktor risiko hasil janin pada ibu hamil dengan kanker di Indonesia.*

Kata kunci: *Kanker, Kehamilan, Hasil janin, Epidemiologi*

ABSTRACT

Background: Cancer during pregnancy is a rare event, despite its rarity, its incidence nowadays keeps on increasing worldwide.
Objective: This study aims to describe the available data on pregnant women with cancer in East Java- Indonesia, maternal outcomes and fetal outcomes, and knowing the risk factors of bad fetal outcomes in pregnant women with cancer from an epidemiological point of view.
Method: This is a quantitative observational study of pregnant women with cancer in East Java Indonesia. Its design is a Cross-sectional study. Data collection was obtained from secondary data (the medical report in the Obgyn department at Dr. Seotomo Hospital from 2016 – 2020). Data were analyzed statistically by using SPSS program version 25.
Result: The results showed that from 2016 to 2020, 54 cases of pregnant women with cancer had been extracted with an incident rate 0.8%. The incident rate of Non-Obgyn Cancer (55.6%) is higher than Obgyn Cancer (44.4%). The highest incident rates in non-Obgyn Cancer are Breast cancer (7.5%) and Leukemia (3.7%), while the

highest incident rates in Obgyn Cancer are Cervical and Ovarian (8.4%). There was no relationship between cancer type and fetal outcomes, while there is a relationship between cancer stage and fetal outcomes.
Conclusion: Cancer stage could be risk factor for fetal outcomes in Indonesian pregnant women with cancer.

Keywords: Cancer, Pregnancy, Fetal outcome, Epidemiology

INTRODUCTION

Pregnant women having cancer is a rare event, occurring approximately once per 1,000 pregnancies annually, corresponding to 0.07% to 0.1% of all malignant tumors (Stensheim et al., 2009). Global estimates show rising incidence rates in both developed and developing countries. In Europe, this number translates yearly into 3000–5000 new patients with cancer diagnosed during pregnancy (Azim, 2016). Melanoma, Breast cancer, cervical cancer, lymphomas, and leukemia are the most frequently occurring cancers in pregnancy (Eibye, Kjær and Mellemkjær, 2013). De Haan and others state in their international cohort study of 1170 women "the most common invasive cancers in pregnancy are breast cancer (39%), cervical cancer (13%), lymphoma (10%), Ovarian (7%), and leukemia (6%)" (de Haan et al., 2018).

Despite its rarity, its incidence nowadays keeps on increasing worldwide. The prevalence of cancer during pregnancy has increased because many women postpone pregnancy until a later age (Parazzini et al., 2017). Other factors contributing to the increase in the rate of pregnancy-associated cancer over time may be improvements in diagnostic techniques and detection and increased interaction with medical services during pregnancy. It has also been hypothesized that the hormones and growth factors necessary for fetal growth may accelerate tumor growth (Azim, 2016).

The maternal health condition during pregnancy has a great impact on the fetal or newborn baby outcome. Smorti and others state in their research that maternal prenatal anxiety and depression negatively affect the clinical aspects of the labor experience and, indirectly, the Apgar index(Smorti, Ponti, and Tani, 2019). Also, there is a cross-sectional study on the effect of smoking during pregnancy on birth weight(Kataoka et al., 2018), and the result shows a significant weight reduction in full-term infants, compared with infants born to non-smoking mothers. The birth weight decreased as the category of cigarette number per day increased. In another study (Widiyanto and Lismawati, 2019), the result shows that there is a relationship between maternal age and anemia with birthweight, as they affected the low birth weight of newborns.

According to the latest World Health Organization (WHO) report of Indonesia Cancer Profile, the most common cancer case in 2018 among females is breast cancer with an incidence of 16.7% which increases to 44% in 2020. In the second stage cervical cancer with an incidence of 9.3 % also increases to 24.4%. Ovarian cancer increased from 3.8% in 2018 to 10 % in 2020 (WHO, 2020, 2021). Limited data are available regarding cancer during pregnancy and its maternal and fetal outcomes in Indonesia. Therefore, this study aims to know the prevalence of cancer during pregnancy in East Java – Indonesia, to determine their cancer characteristics, and to know the risk factors of fetal outcomes in pregnant women with cancer from an epidemiological point of view.

METHOD

This is a quantitative observational study of pregnant women with cancer in East Java Indonesia. Its design is a Cross-sectional study. This research was conducted in Dr. Soetomo Hospital, as it is one of the most important referral hospitals in East Java (from 37 districts), which is located in Surabaya (the capital city of east Java), from the period between May to August 2022. The study population was all pregnant women with cancer in East Java, from 2016 to 2020. The study sample was all pregnant women with cancer who were delivered or consulted in the Obgyn department at Dr. Seotomo Hospital from 2016 to 2020. Excluding criteria were the loss of follow-up cases, the cases of cancer history before pregnancy, and the incomplete medical report. The sample size was the total number of samplings found in the hospital for 5 years. The data of these cases were extracted from the hospital medical reports (Obgyn department).

The variable for this study consists of independent and dependent variables:

Dependent variable: the dependent variable for this study was fetal outcome including condition (survived – dead), birth weight, and Apgar Score (Appearance, Pulse, Grimace, Activity, Respiration)

Independent variables: the independent variable for this study were the type of cancer, and the stage of cancer.

Data collection on the cases of pregnant women with cancer was obtained from secondary data (the medical report in the Obgyn department at Dr. Seotomo Hospital from 2016 – 2020. Data processing was done by entry and categorization. During data entry, study variables were retrieved

from CRF (Case Report Form) and entered into Microsoft Excel, categorized then transformed into SPSS version 25 for statistical analysis of frequencies of each variable. The relationship between the independent variables and the dependent variable was estimated using the Chi-square test and Fisher's Exact Test. The level of significance was set at P≤0.05 with a 95% confidence level. This study got Ethical Approval (No: 153/EA/KEPK/2022).

RESULT AND DISCUSSION

From the medical reports from 2016 - 2020, 54 cases of pregnant women with cancer had been extracted. The incident rate decreased from (1%) in 2016 to (0.7 %) in 2018, then ascended again in 2019 to (0.9%), and finally decreased again in 2020 to (0.6%). Generally, the incident rate of Non-Obgyn Cancer (55.6%) is higher than Obgyn Cancer (44.4%) (Fig. 1).

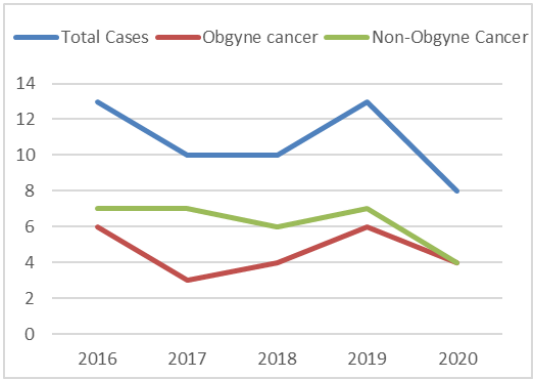

Figure 1. Total Cases of Pregnant Women with Cancer

From 2016 – 2020, the Obgyn Cancer cases during pregnancy, that are found, are 23 cases divided into Cervical (8.4% = 9 cases), Ovarian (8.4% = 9 cases), Uterine (3.7%= 4 cases), and Vaginal (0.9%= 1 case), while Non-Obgyn Cancer cases are 31 cases divided into Breast Cancer (7.5% = 8 cases), Leukemia (3.7% =4 cases), Thyroid Cancer (2.8% = 3 cases), Tongue Cancer (2.8%= 3 cases), Lymphoma system (2.8% = 3 cases), Bone (1.9% = 2 cases), Brain (1.9% = 2 case), Colon (0.9% =1), Muscles+ Lung (0.9%= 1 case), Skin (1.9%= 1 case), Nasopharynges (0.9%= 1 case), Liver (0.9% = 1 case), Parotid (0.9%= 1 case). From that, the highest incident rate in Obgyn cancer among pregnant women is Cervical Cancer and ovarian cancer (8.4%), while the highest incident rate in non-Obgyn Cancer is Breast Cancer (7.5%). The highest types of cancer in Obgyn Cancer are Cervical, and Ovarian, while in Non-obgyn Cancer are Breast Cancer, Leukaemia. Stages of cancer could be categorized as suspected, begging stage I/II, and advanced stage III/IV. In some Non-Obgyne cancer cases, the report just mentions the name of cancer without any stage, like leukemia, skin, bone, colon, muscles, lung, ……et. The result shows 15 cases (26.7%) Advanced stage, 8 cases (14%) begging stage, 12 cases (21.4%) suspect, and 19 cases (33.9 %) not mentioning the stage. As for the stage of cancer for Obgyne and non-Obgyne Cancer shown in (Fig. 2).

For obgyn cancer, cervical cancer had the highest rate (47%) for the advanced stage. While for non- obgyn cancer, Breast cancer had the highest rate with (20%). On the other hand, the highest rate in the suspect stage is from Obgyn cancer: Ovarian (42%) and Uterine (33%). In the Beginning stage, Ovarian has the highest rate with (38%) and NHL with (25%). As for fetal condition (lived – dead), Out of 54 cases of pregnant women with cancer, 17 (31.4%) cases had fetal Mortality, and 37 cases (68.5%) had fetal survival. The highest rate of fetal mortality was in the 2nd trimester (9 cases), while the 1st trimester had 5 cases, and the 3rd trimester had only 3 cases (preterm birth <37 weeks) (Tab 1.).

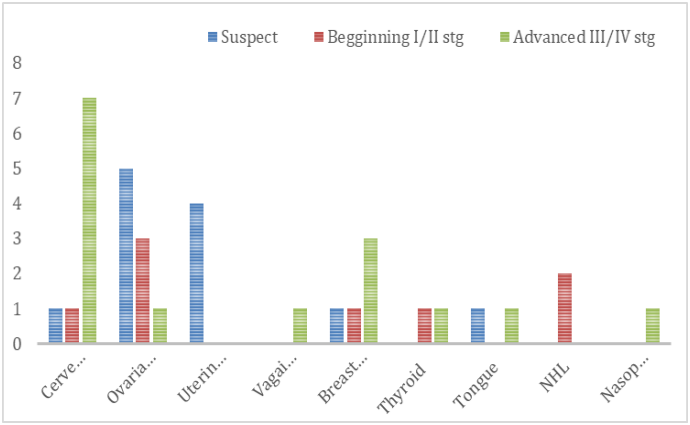

Figure 2. Cancer Stage for Obgyn & Non-obgyn Types

Table 1. Fetal Mortality

Gestational Age	*Cancer Type*				*Total*	
	Obgyn		**Non-obgyn**			
	n	**%**	**n**	**%**	**n**	**%**
1st trimester	3	60	2	40	5	100
2nd trimester	3	33.3	6	76.7	9	100
3rd trimester	1	33.3	2	76.7	3	100
Total	7	41.2	10	58.8	17	100

Table 2 Infant Weight and Cancer Type Crosstabulation

Cancer Type	**Infant Weight**				**Total**	
	≥ 2450g		**< 2450g**			
	n	**%**	**n**	**%**	**n**	**%**
Obgyn Ca.	8	47.1	9	52.9	17	100
Non-obgyn Ca.	10	50	10	50	20	100
Total	18	48.6	19	51.4	37	100

On the other hand, all lived cases were in the 3rd trimester (17 cases 45.9% with Maternal Obgyne cancer, 20 cases (54.1%) with Maternal Non - Obgyne cancer). Also, there were 22 cases of preterm (<37 weeks), and 15 cases of in-term birth (> 37 weeks). As for birth weight, Out of 37 fetal survival cases, the fetal outcome of weight could be also divided as the maternal cancer type Obgyne or Non-obgyn. The infant weight is categorized as above or equal to the normal weight average of 2450g and below the normal average. The result showed that there were 18 cases ≥ 2450g (48.6 %), which could be divided into 10 maternal cases (55.6%) with Non-obgyn cancer and 8 maternal cases (44.4%) with Obgyne cancer. Also, there were 19 cases < 2450g (51.3%), which could be divided into 10 maternal cases (52.6%) with Non-Obgyne cancer and 9 Maternal cases (47.4%) with Obgyne cancer (Tab. 2).

As for APGAR Score (Appearance, Pulse, Grimace+ Activity+ Respiration) could be divided into three categories Low (4 cases = 3.7 %), Middle (9 cases = 8.4%), and Normal (24 cases = 22.4 %). On the other hand, the AS could be divided according to the Maternal cancer type as shown in (Tab. 3).

As for the relationship between fetal outcomes and cancer types, the results show there is no relationship, as the P value of all sub-variables is > 0.05, as shown in (Tab. 4). On the other hand, the results show there is a significant relationship between the stage of cancer and the infant's birth weight only (P < 0.05) as shown in (Tab.5).

Table 3: Infant AS and Cancer Type Crosstabulation

Cancer Type	**Infant AS**							
	Low 0-3		**Moderate 4-6**		**Normal 7-10**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Obgyn Ca.	2	50	3	33.3	12	50	17	100
Non-obgyn Ca.	2	50	6	66.7	12	50	20	100
Total	4	10.8	9	24.4	24	64.8	37	100

Table 4: Relationship of Fetal/Infant outcomes with Cancer type

Cancer type	**Birth condition**				**Infant Weight**				**Infant AS**					
	Dead		**Lived**		**≥ 2500g**		**< 2500g**		**Low 0-3**		**Moderate 4-6**		**Normal 7-10**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Obgyne Ca	6	26.1	17	73.9	8	47.1	9	52.9	2	11.8	3	17.6	12	70.6
Non-obgyne Ca	11	35.5	20	64.5	10	50	10	50	2	10	6	30	12	60
P- Value	0.462				0.858				0.678					

The level of significance was set at $P \leq 0.05$ with a 95% confidence level.
P- Value ≥ 0.05 = there is no relationship

Table 5. Relationship of Fetal/Infant outcomes with Cancer stage

Cancer stage	***Birth condition***				***Fetal Weight***				***Fetal AS***					
	Dead		**Lived**		**≥ 2500g**		**< 2500g**		**Low 0-3**		**Moderate 4-6**		**Normal 7-10**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
-	7	36.8	17	63.2	6	50	6	50	2	16.7	3	25	7	58.3
Suspect	6	50	6	50	1	16.7	5	83.3	1	16.7	3	50	2	33.3
Beginning I/II stg	2	25	6	75	6	100	0		0		0		6	100
Advanced III/IV stg	2	13.3	17	86.7	5	38.5	8	61.5	1	7.7	3	23.1	9	69.2
P- Value	0.183				**0.008**				0.217					

The level of significance was set at $P \leq 0.05$ with a 95% confidence level.
P- Value ≥ 0.05 = there is no relationship
P- Value < 0.05 = there is a relationship (Fetal Weight)

The epidemiology of pregnant women with cancer is difficult to follow up all over the world, as registered data of patients do not consist of obstetrical and oncological data together. For example, miscarriages or abortions due to cancer did not report in both data (Maggen et al., 2020). In Indonesia, previous researches focus on a case study or serial case not an overall view of the epidemiological profile of pregnant women with cancer in Jawa Timur (Octovianus, Kuntari, and Djatmiko, 2015; Jayalie, Priantono, and Amin, 2018; Vanessa Martono et al., 2021). According to the results, the incidence of cancer during pregnancy increased from 2017 to 2019 but decreased during 2020. This may be because of the beak wave of the Coronavirus Pandemic, which affects the healthcare system and healthcare management for many diseases.

Many researchers discussed the impact of COVID-19 on maternal and prenatal care, especially the decrease in antenatal care (ANC) visits (Kotlar et al., 2021; Meaney et al., 2022) that may cause late cancer diagnoses, and the unavailability of healthcare facilities due to the lockdown during the Pandemic and all the hospitals were consecrated for treating Covid-19 cases. That generally affects Cancer treatment and management during the pandemic as what happened in America and South Africa (Nnaji and Moodley, 2020; Patt et al., 2020). In Dr. Seotomo hospital – Surabaya, some Pregnant women with cancer cases lost follow-up during 2020, after diagnoses, and took some chemotherapy sections. This may be due to the pandemic restrictions.

Reproductive cancer (obgyn cancer) did not affect women's fertility. As seen from the results, during pregnancy there were two types of cancer Obgyn and Non-obgyn with an almost 11.2% difference in incidence. According to the literature review (Weiderpass and Labrèche, 2012), lifestyle and occupational factors increased the risk of cancers in the female reproductive system. For example, using hormonal contraceptives, smoking, or exposure to x radiation, chemical material, and gasoline. Cancer didn't affect fertility, it only gets affected with cancer treatment including surgery, chemotherapy, and radiation (Waimey et al., 2015). Therefore, it is possible to get pregnant and have cancer at the same time or after. Which sometimes caused a delay in Cancer diagnoses, because of the similarity of symptoms (Voulgaris, Pentheroudakis, and Pavlidis, 2011). This explains why there are many cases which diagnose with cancer in the late stage of cancer or in the 3rd trimester of pregnancy (during delivery), or in both the late stage of cancer and in the 3rd trimester. Examples of symptoms similar between Cancer and pregnancy, early stage of Cervical Cancer during pregnancy almost had no clear symptoms (Beharee et al., 2019). Also, the ovarian cancer symptoms are the same as the physiological changes during pregnancy: Fatigue, anemia, vomiting, and increased abdominal circumference (Dłuski et al., 2020).

Normally during pregnancy, the breast weight increases as preparation for breastfeeding. At the same time, the early stage of breast cancer during pregnancy represents a painless thickening in the breast which makes the diagnosis in clinical examination more difficult (Durrani, Akbar, and Heena, 2018). This may explain the reason for the diagnosis of advanced-stage of cancer during delivery (27.8%). According to the result, (89.3%) of the stillbirth infant had both Low Birth Weight and Small Gestational Age. In another study, the results show that survival infants were more likely to deliver preterm, but did not show a significantly increased risk of low birth weight (van der Kooi et al., 2018). The increased risk of Small Gestational Age (SGA) stillbirth in maternal cancer diagnosed during pregnancy might be due to cancer treatment. Also, cancer itself might also lead to fetal growth restriction and its subsequent stillbirth (Lu et al., 2017).

Even though, the current study shows no relationship between types of cancer and fetal outcomes, another study (Brenner, Avivi, and Lishner, 2012), mentioned that Leukaemia and NHL affect the fetal supplies for Oxygen and nutrition,

which by sequence causes Small Gestational Age (SGA) and Low Birth Weight (LBW). But in the current study, the results show that from 4 cases of leukemia, only two cases had SGA, and LBW, while from 3 cases of NHL, only one case had SGA and LBW. On the other hand, the result shows there were 3 cases with Choriocarcinoma (fast-growing cancer in the Uterus) and one case of leiomyoma uterus suspected Malignancy, all cases complain of active bleeding and miscarriage condition. Generally, Cancer during pregnancy and the type of treatment had a relationship with fetal outcomes (SGA, Preterm birth, infant mortality, LBW, low AS) (Weisz, Schiff and Lishner, 2001; Lu et al., 2017; Momen et al., 2018; Esposito et al., 2021). From that, cancer itself is a risk factor for bad fetal outcomes, regardless of its type. Cancer Stage had an indirect effect on fetal growth and development. As explained in the study by (Amant et al., 2019)that the stage of cancer and the gestational age determent the type of cancer treatment during pregnancy, and some of these treatments had a bad effect on fetal growth. For example, Chemotherapy could cause Bone marrow toxicity and fetal anemia (Wolters et al., 2021). Also, in another study (Zhang et al., 2019), the results show that the chemotherapy had harmful fetal outcomes such as malformations, organ toxicity, and delayed development.

Research strength could be represented in the study focused on pregnant women with all types of cancer to find the risk factors that affect the fetal outcome and to have an overview of cancer during pregnancy, not just a view on one type as other research. Using SPSS Program as an analytic tool to ensure accurate statistical results. In addition, using one of the latest versions of SPSS, version 25 (the last version 27), to have more statistical tools in the program. Total sampling was more than 30 cases, which full fills the assumption of the statistical test(Field, 2017). On the other hand, the study's weakness is First, it is a retrospective study that may be affected by confounding and reporting bias. Second, data is extracted manually from reading the printed weekly report, not from a computerized database which cannot be free from errors.

CONCLUSION

To conclude, the stage of cancer has a significant relationship with the fetal outcome (infant birth weight), so it could be a risk factor for bad fetal outcomes of cancer during pregnancy. Further research on the relationship between cancer treatment and fetal outcomes especially infant birth weight and how to overcome malnutrition due to cancer treatment which affects fetal outcomes.

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