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BREAST CANCER IN PREGNANCY AT DR. KARIADI GENERAL HOSPITAL: A SERIAL CASE

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ABSTRACT

Background Each year 2.1 million women were diagnosed with breast cancer, being the most common type of cancer found and cancer-related cause of death in women worldwide. In Indonesia, especially in Middle Java, more than 80% women diagnosed were already in the late stage. Physiological changes in pregnancy contributes to the delay in diagnosis in pregnant women and pregnancy also resulted in a more complicated approach of therapy. Regarding only few studies were done involving pregnancy with breast cancer, the aim of the study is to provide further knowledge associated with it. **Methods** Medical records of pregnant women with breast cancer in year 2014-2018 at Dr. Kariadi General Hospital were studied. **Results** Based on the 3 cases be studied, patients were referred from class B and C hospitals outside of Semarang city showing stage III (33.33%) and IV (66.67%) breast cancers. Two-third of the patients underwent mastectomy previously and one of them also underwent chemotherapy program prior her pregnancy. Comorbidities varied between patients and therapies were adjusted individually and multidisciplinary. Two of the cases went through transperitoneal caesarean section for delivery and one patient with twin pregnancy died by complications and intrauterine foetal death was also determined. **Conclusion** Overall, all patients were $\geq$ 35 years old and the breast cancers were diagnosed at late stage. Complications by comorbidities such as anaemia, severe malnutrition, and infection, were found. Two pregnancies which were already in third trimester was terminated and a case of maternal mortality was found.

Keywords : *Breast cancer, pregnancy*

INTRODUCTION

Breast cancer is the most common malignancy found in women, yet its occurrence is rare as comorbid in pregnant women. Despite its rarity, its incidence nowadays keeps on increasing worldwide. This trend also occurred in Indonesia, where more than 80% non-pregnant women was diagnosed in late stage breast cancer.[1–7] The delay in diagnosis was also found in pregnant women, which was caused by the physiological changes of the breast during pregnancy which results in difficulties in identifying tumour mass.[8–10] Some studies stated the prognosis of breast cancer between non-pregnant women and pregnant women is similar. However, some studies also stated the opposite where breast cancer in pregnant women showed a higher stage, bigger in size, and increase of hormone receptor-negative tumour.[2,7,9,11–13] These affects the prognosis itself besides the delay in diagnosis. Not postponing therapy is important once a diagnosis been made but the therapy for pregnant women should consider the safety of the foetus in determining the choice of examinations, therapies and when it is given.[2,8,9] According to the guidelines published, management of breast cancer in pregnancy were divided based on the stage of breast cancer and the age of pregnancy which involves when and what type of management recommended to be done.[14] This study provides description of characteristic of pregnancy with breast cancer and its management in Dr. Kariadi General Hospital in compare of clinical guidelines provided.

METHODS

All data used in this serial case study was collected from patients' medical record in Dr. Kariadi General Hospital searched based on the ICD-10 code applied. Ethical clearance of this study was given from Dr. Kariadi General Hospital, Semarang, Indonesia.

CASE PRESENTATION

Based on the ICD-10 number recorded, there were 3 cases of breast cancer in pregnancy at Dr. Kariadi General Hospital.

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Table 1. Pregnancy characteristics with breast cancer

Characteristics	n (%)
Breast cancer in pregnancy, n (%)	3 (100)
Median age (year)	36 (35-37)
Educational status, n (%)	
Finished JHS	2 (66.67)
Finished SHS	1 (33.33)
Mother's address, n (%)	
From Semarang city	0 (0)
Outside Semarang city	3 (100)
Referral hospital, n (%)	
Class C	1 (33.33)
Class B	2 (66.67)
Contraception usage history, n (%)	
Yes	2 (66.67)
No	1 (33.33)
Breast medical problem history, n (%)	
Yes	0 (0)
No	3 (100)
Gestational age, n (%)	
Trimester 1	0 (0)
Trimester 2	1 (33.33)
Trimester 3	2 (66.67)
Parity history	
0	0 (0)
1	0 (0)
2	3 (100)
>2	0 (0)
Histopathology subtype, n (%)	
IDC	2 (66.67)
ILC	1 (33.33)
Others	1 (33.33)
Breast cancer stage, n (%)	
I	0 (0)
II	0 (0)
III	1 (33.33)
IV	2 (66.67)
Breast cancer grade, n (%)	
I	0 (0)
II	0 (0)
III	2 (66.67)
Type of therapy, n (%)	
Chemotherapy	1 (33.33)
Radiotherapy	0 (0)
Mastectomy	2 (66.67)
Maternal mortality, n (%)	
Yes	1 (33.33)
No	2 (66.67)

JHS: junior high school; SHS: senior high school; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma

The 2014 medical record could not be retrieved, and a case turned out to be coded mistakenly, therefore only 3 cases can be studied.

Case #1

A 38-weeks-pregnant women, at the age of 37 years old was referred in November 2018 for a follow up on her breast cancer. Patient was diagnosed with grade III no special type invasive ductal carcinoma (NST-IDC) of the left breast grade III since January 2018. After a mastectomy another mobile mass with solid consistency 8 cm in size was found by her left breast. This pregnancy was considered high risk considering her age and complicated with breast cancer. Patient's laboratory work-up showed moderate anaemia, hypokalaemia, and signs of urinary tract infection (UTI). Patient was transfused 3 packs of packed red cell (PRC) and other conservative therapy was done to improve her general condition. On the next day, patient's membrane ruptured and transperitoneal caesarean section (TCS) was done immediately. The baby was born with low birth weight (1850 grams), since it was diagnosed foetal growth restriction (FGR) before, but without any congenital abnormalities. Echocardiography was suggested for the patient and the result showed no abnormality except mild pulmonary regurgitation. Breastfeeding was postponed and mother was recommended to do chemotherapy with Paclitaxel and Doxorubicin. Unfortunately, the patient and family refused to do the chemotherapy program and patient was sent home after her general conditions had improved.

Case #2

A 36-year-old women, was admitted twice, in September and December 2016, to Dr. Kariadi General Hospital. At 31 weeks gestational age, the patient complained contractions in the lower abdomen. Patient has a history of caesarean section twice, first by indication of uterine cyst and myoma and the second by the low attachment of placenta. The patient came with mild anaemia, signs of UTI and signs of malignancy of the right breast. Initially, tumour was found around March 2016, which progressively grew and later developed a wound increasing in size and bled. Patient was administered analgesics and bandage press was done. Biopsy was done when the patient was admitted and was diagnosed with mixed invasive carcinoma between NST-IDC and invasive lobular

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carcinoma (ILC), grade III, of the right breast. Lungs maturation was done for the foetus and it was planned for delivery by 34 weeks of pregnancy. During the second admission, 34 weeks of pregnancy, the patient's chief complaint was pain by the right breast. Laboratory work-up showed that the mother was mildly anaemic, hypoglycaemic, hyponatraemic, and hypoalbuminemia. After improving patient's general condition, she was prepared for TCS and bilateral salpingo-oophorectomy. However, later, it was found that the left tube had been cut previously and the left ovarium cannot be found. The baby was born preterm with low birth weight (2210 grams).

Case #3

A 35-year-old women was admitted in December 2017 with complaints of right back pain and breathing trouble in the past several days. Patient's pregnancy was by the age of 25 weeks and was a twin pregnancy, it was complicated by the presence of breast cancer. Historically, the tumour mass was acknowledged by the patient since July 2016 and then she underwent mastectomy in the same month. The biopsy examination of the tumour sample showed mucoid adenocarcinoma. Patient was then referred to a higher type of hospital to join chemotherapy program and another surgery. Another chemotherapy was assigned after the second surgery but then it was cancelled since the patient was pregnant. When the patient came to Dr. Kariadi General Hospital, the breast cancer was already at stage IV and was severely malnourished. Patient's laboratory work-up indicated moderate anaemia, increased in liver function test, azotaemia, hypoalbuminemia, hypoglycaemia, and electrolyte imbalance. Radiology imaging showed bone metastasis and pneumonia. Conservative and palliative care was given yet the patient's condition worsened and there was decrease in consciousness. It was caused by intracranial space occupying lesion suspected as brain metastasis, but it could not be confirmed by CT scan because of the pregnancy. No metastasis was found in liver which was confirmed by abdominal ultrasound. In conclusion, patient was diagnosed with breast cancer with comorbidities of bone metastasis, pneumonia, chronic kidney disease (CKD), preeclampsia, UTI, electrolyte imbalance, hyperthyroid, non-overt disseminated intravascular coagulation (DIC), and sepsis. The patient's family gave the permission to let IUFD occur if the condition of the patient worsens by age of pregnancy less than 28 weeks. If by 28-32 weeks of pregnancy the patient's condition worsen then perimortem caesarean section can be performed. DNR (do not resuscitate) form was also signed by the patient's family. Medical and family conference were held but looking at the patient's condition the family decided to bring back home the patient. About 11 days after the patient was sent home, the patient was readmitted with pregnancy age of 27 weeks and the condition was worse from previous admission. Rectal bleeding was found and was suspected as sign of IUFD. Patient's condition progressively deteriorated and unfortunately died by cardiac arrest, breast cancer, and multiorgan failure.

CASE DISCUSSION

Physiological changes in pregnancy resulted in certain considerations on the examinations and treatment used on pregnant women and its effect on the foetus. Breast cancer in pregnancy further complicates in the approach of care yet delay in therapy, regarding a safer outlook for the foetus, may worsen mother's condition.[14–17]

Case #1

Being in a high-risk pregnancy with additional of breast cancer called for a multidisciplinary approach.[2] When the patient came, she was severely malnourished and mildly anaemic. Anaemia can be caused by the haemodilution involved as one of the physiologic changes during pregnancy, low on nutrition intake and the effect from the cancer itself. Recent studies implied that cancer tumour overproduced cytokines which inhibits erythropoiesis in multiple ways. Even though the process was not well-defined yet, it was stated that cancer-related anaemia was caused by shorter erythrocytes life span, hypo-proliferative state of bone marrow with impairment in increasing erythropoiesis to fulfil the body's demand and restore deficiencies, defects in iron reutilization and low erythropoietin (EPO) production. Cancer cells also produced procoagulant factors that caused microangiopathic haemolytic anaemia.[18–20] Infusion of RL and transfusion of 3 packs PRC was given in response to the anaemia.

UTI was confirmed by presence of fever, leucocytosis, leukocyturia, and bacteriuria, hence

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patient was administered Paracetamol and Amoxicillin orally with additional of KSR to treat patient's hypokalaemia state.

The pregnancy was terminated by TCS since it was already full-term, and the membrane has ruptured. TCS was indicated on grade III breast cancer and FGR. Baby was delivered healthy but low in birth weight. Concerning patient's breast cancer, that is stage III NST-IDC, following the delivery, she was recommended to follow through chemotherapy program. According to the algorithm (Figure 1), TCS and recommendation to do chemotherapy was correct since the breast cancer is already in late stage and gestational age is already over 28 weeks.[14]

Patient was also recommended to postpone breastfeeding since researches showed that breastfeeding stimulates tumour growth by producing more proinflammatory cytokines that are angiogenic.[2,21–23]

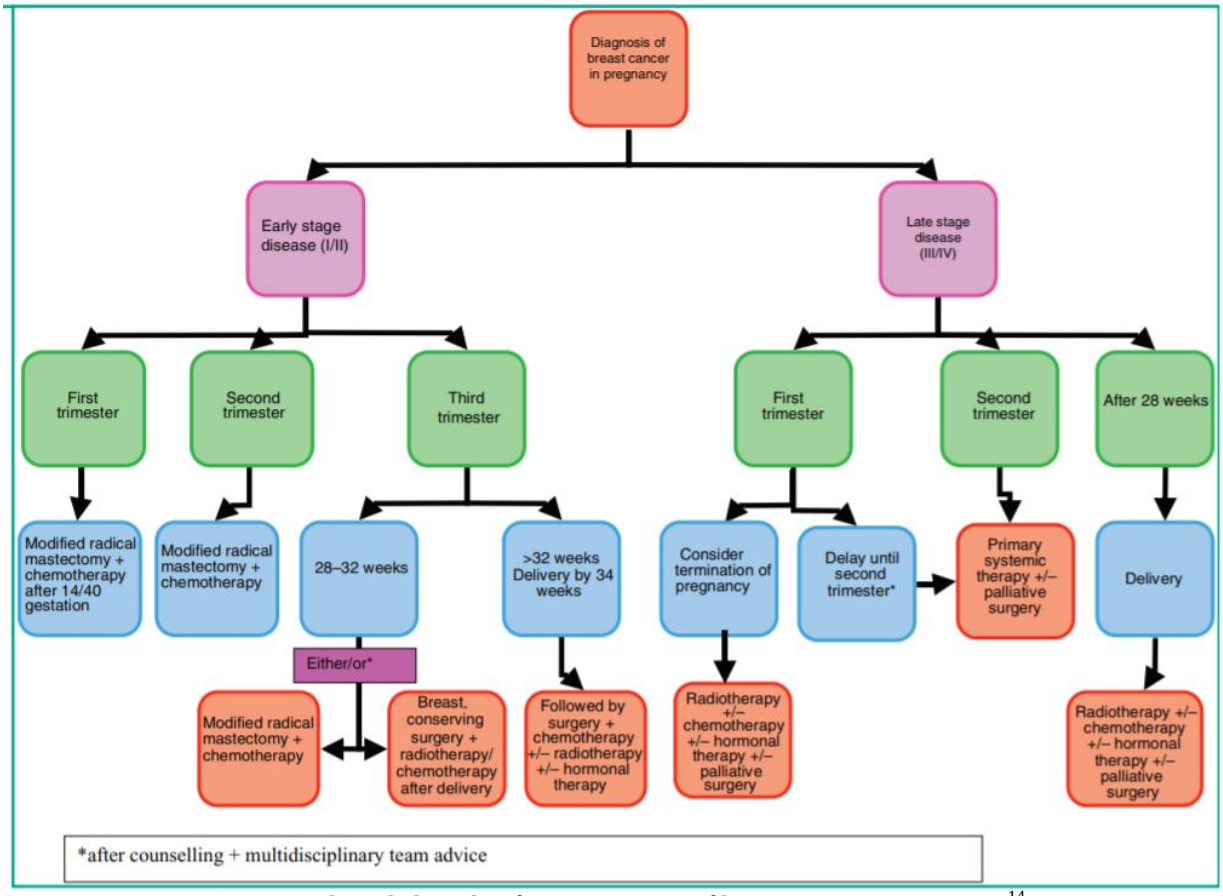

Figure 1. Clinical algorithm for management of breast cancer in pregnancy[14]

Case #2

At first, patient came with complaint of contractions which turned out to be Braxton Hicks. Her nutritional status was good yet was identified with mild anaemia, leucocytosis, and bacteriuria. Breast lesion was found since months ago which progressively grew and then was found wound on the tumour itself which also increasing in size and bled. With suspect of malignancy, biopsy was done. Core needle biopsy or excisional biopsy was the gold standard examination for tissue diagnosis. However, needle cytology has higher risk for false-positive result in pregnancy caused by the hyperproliferative state of the breast tissue. Through biopsy it was recommended to determine the histological grade, receptor and HER2 status, but it is not routinely done.[2,14,17] The biopsy result showed mixed invasive carcinoma between NST-IDC and ILC, grade III with angioinvasion.

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Pain was felt on the tumour and was treated with bandage press and mother was administered analgesic. The cause of pain may be from the cancer growth that already reach late stage, involvement of other deeper organs such as muscle or ribs, metastasis or even from the therapy given. It is important to lessen cancer pain because it affects the quality of life of the patient both physically and psychologically. According to WHO, cancer pain treatment using analgesics hold the principle of 3 step ladder (Figure 2), starts from using non-opioid drugs, then opioid for mild to moderate pain, and last opioid for moderate and severe pain. Opioid usage in high dosage and long-term use can cause numerous side effects so it is best to use non-opioid drugs first. In conclusion, using Ketorolac injection, an NSAID drug, is correct as the initial treatment.[24–27]

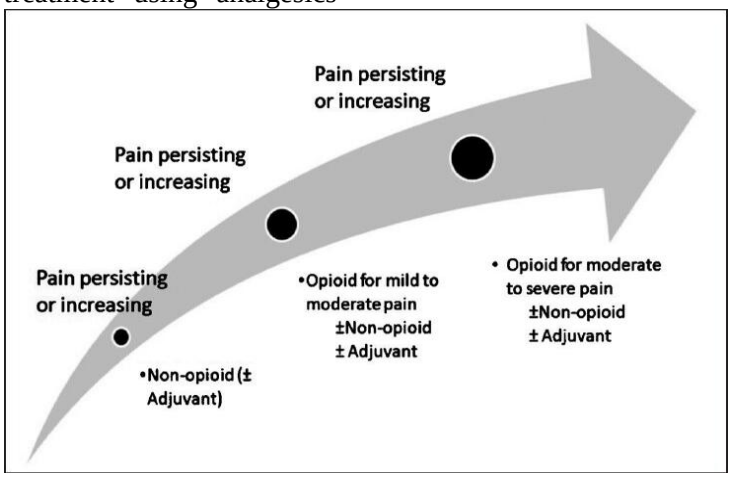

Figure 2. WHO 3 step ladder analgesic usage

Lungs maturation of the foetus was done in considerations of early labour then early treatment for the mother. On the 34 weeks of pregnancy, mother was asked to be readmitted to undergo surgery for labour. Patient came in severe malnutrition which may play a role on her hypoglycaemic state and electrolyte imbalance. After improving mother's condition, TCS and salpingo-oophorectomy was done. TCS was indicated on the history of having caesarean section twice previously which is a relative indication to do caesarean section again.[28] Salpingo-oophorectomy was indicated over right ovarian endometriosis cyst, corpus albicantus and corpus luteum, non-specific chronic salpingitis and paratubal cyst, on the other hand, through this procedure will also suppress hormones which will increase overall survival and disease free survival in breast cancer patients especially with positive hormone receptor tumour.[29–32]

Case #3

Dyspnoea was caused by the pneumonia with infiltrates in the left lungs. Cancer patients are vulnerable to infections as tumour cells produced immunosuppressive factors such as TGF-β (Figure 3). Other than the cancer itself, therapy particularly chemotherapy also caused immunity dysfunction.[33–36] Besides pneumonia, signs of pleural effusion were also found which is a common complication found in late stage cancer patients mainly in lung cancer in men and breast cancer in women. Malignant pleural effusion may involve the cancer directly or indirectly. Cancer will disrupt lymphatic system's integrity or even invade the pleura directly. Indirectly, cancer will stimulate local inflammatory response which increase capillary permeability so more fluid will enter pleural cavity. Symptoms usually in form of dyspnoea yet it may be asymptomatic. Chest X-ray or ultrasound can be used in diagnosis of malignant pleural effusion, but definitive diagnosis was determined by evaluating effusion fluid, with thoracentesis, whether there is presence of malignant cells. Prognosis varies from good to bad depending on the patient's condition. A research stated that patient with pleural effusion that is also leucocytosis, hypoalbuminaemia, and hypoxemia have poorer prognosis with median survival of 42 days. In this case, the mother has all the factors.[37–39]

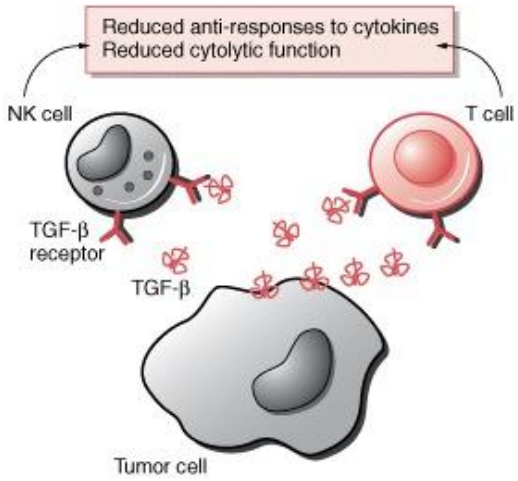

Figure 3. TGF-β role as immunosuppressive factor[33]

Back pain was suspected to be the consequence of bone metastasis of the breast cancer. Mother was diagnosed with breast cancer before her pregnancy, to be precise with mucoid adenocarcinoma. Mastectomy and chemotherapy have been done previously which then ceased because of the pregnancy. Bone metastasis was confirmed with chest X-ray where it is allowed if mother use appropriate abdomen shielding.[2] On the other hand, in this case, suspect of brain metastasis cannot be confirmed through CT scan which was slightly incorrect. A research by J. de Haan et al.[40] revealed that radiology imaging under 100mGy are allowed and considered safe enough if MRI is contraindicated. Radiation exposure to the foetus in chest X-ray is 0,0001-0,43 mGy while head CT scan is 0,005 mGy, both are permitted to be done. However, contrast utilization was still in discussion with the low number of literatures explain about the side effects during pregnancy. Based on Manual on Contrast that are provided by American College of Radiology recommends usage of intravenous contrast was enabled if necessary. The principle in radiology imaging is ALARA (as low as reasonably achievable) therefore the use of non-ionizing radiation modalities is preferable. The patient was suspected of having liver metastasis too since it was found an increase of liver function tests, but no metastasis was found during ultrasound. Abdominal ultrasound of the mother showed increase echogenicity of both kidneys' cortex, multiple cholecystolithiasis, and minimal ascites. Cholecystolithiasis give rise to bilirubin and transaminase, based on a case report.[41] Patient with symptomatic cholelithiasis, cholecystectomy is recommended, while in pregnant women it is recommended to use conservative therapy instead, such as administering ursodeoxycholic acid. However, if symptoms are severe and conservative therapy has failed, it is advised to do cholecystectomy.[42,43]

Severe malnutrition and infection are in a vicious cycle (Figure 4). Malnutrition made body more susceptible to infection while on the other hand, infection will stimulate body immune respond which increase the anabolic energy demand, especially protein, in use of immune components production. However, pro-inflammatory mediators will increase catabolic response in total there is increase of energy demand.[44–46] The recurring hypoglycaemia can also be caused by severe malnutrition, occurring infection or sepsis, or even tumour-induced hypoglycaemia. Infections that are most associated with hypoglycaemia are UTI and pneumonia, which the patient both have. Some studies stated non-pancreas islet tumour hypoglycaemia may be caused by overexpression of IGF-II.[47–49]

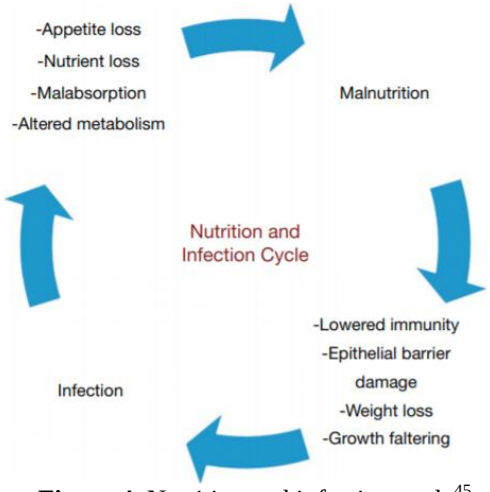

Figure 4. Nutrition and infection cycle[45]

Involvement of CKD also affect mother's appetite therefore there was inadequate intake of total energy and protein. Mother was given high energy and protein formula with 1990 kcal and low-fat diet was recommended in breast cancer patient. Additional pregnancy weight was adjusted based on mother's body mass index before pregnancy. Estimation of additional calories intake in women with twin pregnancies are 600kcal per day but since mother was obese, the calories were reduced.[50,51] Administering high energy and protein formula can be proceeded but with caution because mother has CKD, stage IV. High protein diet (>1.2 protein g/BW/day) will burden the kidneys yet low-protein diet will affect other body system like increase in catabolic metabolism and inflammation.[52] Based on mother's creatinine level which is 2.3 mg/dL, mother's eGFR was 26 ml/minute by MDRD formula[53], the recommendation of protein uptake by ESPEN will be 0,55-0,60 g/BW/day. Mother protein uptake recommendation is 37,4-40,8 g per day, nevertheless, considering other comorbidities protein intake was increased to 60g per day.[54]

DISCUSSION

All the patients were referred from lower class (class B and C) hospitals outside of Semarang city. Considering the age of the mother (≥ 35 years old), the pregnancies above were high-risk, with breast cancer it was further complicated. Late stage breast cancer was diagnosed in each case. Delay in diagnosis can be caused by the little knowledge that the patients have about breast cancer and low educational status may play a role in it since their last education is in high school.[9,13]

Most of the examinations and managements done were correct especially in the multidisciplinary approach care. Patients' safety and convenience has been most upheld by the palliative care given and minimizing the usage of ionizing radiation modalities. However, there are some examinations that are better done for a more accurate choice of therapy such as tumour immunohistochemistry test. This assessment was used to examine the receptors and HER2 status for considerations in treatment planning and prognosis determination, where triple-negative receptor tumour showed poorer prognosis. Grade of cancer tumour can also be examined through this assessment, which in this study was done on two of the cases with the result of grade III tumours and a case with angioinvasion.[2,55]

The most frequent comorbidities found was anaemia mainly moderate anaemia and transfusion of packed red cells was indicated to treat the anaemia.[56] Not only caused by physiologic haemodilution during pregnancy, cancer also played a role in anaemia morbidity since it inhibits erythropoiesis in multiple ways.[18–20] Apart from anaemia, severe malnutrition and infection were also found in every case. Cancer itself cause immunosuppressive state hence patient was more susceptible to infection. Malnutrition and infection are connecting comorbidities; infection can cause malnutrition and vice versa. The chain should be broken by

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improving one or both problems. Both malnutrition and infection involved in delaying improvement of mother's condition.[33,44–46]

Two-third of the cases have history of mastectomy and one of them also undergo chemotherapy which later was ceased because of her pregnancy. On the first and second case, babies were delivered through TCS, as indicated, since they were already in third trimester. On the other hand, on the third case the gestational age is still in second trimester so instead it was attempted conservative therapy until the foetus was full-term, yet the foetuses later were determined IUFD and the mother died because of cardiac arrest, breast cancer, and MOF.[14] Poorer prognosis between breast cancer in pregnant women than non-pregnant women was still debatable as some research showed poorer prognosis and 40% higher mortality, while on the other hand, another showed the prognosis and disease free survival nor overall survival between the two didn't show significant difference.[11,13] Recent studies showed pregnancy has long-term protective factor on breast cancer, but it is said that this protective factor did not directly appear after pregnancy, on the contrary, there was an increase in risk between 3-15 years after the first pregnancy. Aside from that, women diagnosed with breast cancer within the period closer to after delivery, especially the first two years of postpartum, showed increase in mortality. Risk of mortality decrease with every additional year of postpartum.[13,17,57] As been said before, all cases showed late stage breast cancer, this showed that there are delay in diagnosis. Delay in diagnosis will worsen the prognosis because the approach of management will be more complex. This can be prevented by self-breast examination that can be done by women independently and routinely and immediately see a doctor if any abnormality was found.[55]

CONCLUSION

In summary, all patients were referred from lower class hospitals outside of Semarang city. Patients' age were all $\geq$ 35 years old with history of labour, twice. Two out of three patients have contraception usage history, with one of them used pill. This study also showed the breast cancer diagnosed were at late stage with stage IV being the majority. The pregnancies were further complicated by comorbidities such as anaemia, severe malnutrition, and infection. Two-third of the patients have history of mastectomy and the pregnancies which were already in third trimester was terminated by TCS. Being in the stage IV breast cancer with metastases and numerous comorbidities, IUFD and maternal mortality was found in a case. This study was limited by the data provided in the medical records and only three cases can be used. More studies are warranted to investigate other factors affecting the delay in diagnosis of breast cancer during pregnancy as well as how to prevent it and management guidelines of comorbidities or complications arise in breast-cancer-during-pregnancy patients.

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