RESEARCH ARTICLE

Malignancy Risk Scoring of Hydatidiform Moles

Heru Pradjatmo[1]*, Djaswadi Dasuki[1], Ery Kus Dwianingsih[2], Ediati Triningsih[2]

Abstract

Background: Several risk factors leading to malignant transformation of hydatidiform moles have been described previously. Many studies showed that prophylactic chemotherapy for high risk hydatidiform moles could significantly decrease the incidence of malignancy. Thus, it is essential to discover a breakthrough to determine patients with high risk malignancy so that prophylactic chemotherapy can be started as soon as possible. Objectives: Development of a scoring system of risk factors as a predictor of hydatidiform mole malignant transformation. Materials and Methods: This research is a case control study with hydatidiform mole and choriocarcinoma patients as subjects. Multiple logistic regression was used to analyze the data. Odds ratios (OR), attributable at risk (AR : OR-1) and risk index (ARxβ) were calculated for develoipment of a scoring system of malignancy risk. The optimal cut-off point was determined using receiver operating characteristic (ROC) curve. Results: This study analyzed 34 choriocarcinoma cases and 68 benign hydatidiform mole cases. Four factors significantly increased the risk of malignancy, namely age ≥ 35 years old (OR:4.41, 95%CI:1.07-16.09, risk index 5); gestational age ≥ 12weeks (OR:11.7, 95%CI:1.8-72.4, risk index 26); uterine size greater than the gestational age (OR:10.2, 95%CI:2.8-36.6, risk index 21); and histopathological grade II-III (OR:3.4, 95%CI:1.1-10.6, risk index 3). The lowest and the highest scores for the risk factors were zero and 55, respectively. The best cut-off point to decide high risk malignancy patients was ≥31. Conclusions: Malignant transformation of hydatidiform moles can be predicted using the risk scoring by analyzing the above four parameters. Score ≥ 31 implies high risk patients so that prophylactic chemotherapy can be promptly administered for prevention.

Keywords: Hydatidiform moles - choriocarcinoma - prophylactic chemotherapy - malignancy risk - risk scoring

Asian Pac J Cancer Prev, **16 (6)**, 2441-2445

Introduction

In the past five decades there have been a lot of progress in the treatment of hydatidiform moles, especially in developed countries, resulting in improved disease prognosis. There are three major advances in the management of the trophoblastic disease, first advances in the hospital management system; second, an advance in technology that produces powerful tools as support facilities for diagnosis; and third, the discovery of drugs that have been able to introduce a new way of therapy. The characters of most hydatidiform mole in the developing countries and Indonesia either is disadvantages, because the patients often come to the hospital in bad general condition, suffer from bleeding, severe anemia or shock, or even develop malignant degeneration of the advanced stage (Abdullah and Prabowo, 1985; Wardhani el al., 1991; Audu et al., 2009; Khanum and Shamsher, 2010).

The incidence of hydatidiform mole varies greatly around the world, The incidence of hydatidiform mole has been relatively constant in the United States and Europe at 1 to 2 per 1000 pregnancies (Cunningham et al., 2010). Population studies have suggested a worldwide range of hydatidiform mole between 0.5-2.5/1,000 pregnancies (Audu et al., 2009). In Sweden the incidence is reported 1.2 cases per 1,000 births (Salehi et al., 2011). The highest incidence are in several Asian countries between 1 to 10 per 1,000 pregnancies (Altieri et al., 2003; Olzalp et al., 2014). The high different may have largerly reflected discrepencies between population-based and hospital-based data collection. The frequencies of hydatidiform mole in Indonesia was 9.9 per 1,000 pregnancies compared to other countries this ranks Indonesia is the highest (Kurman, 1995). In Indonesia this is very significant because its high incidence of malignant degeneration was 10-23% (Kampono et al., 1995) and mortality was 8.4% (Sanusi unpublished data) to 35.9% (Aziz et al., 1995). It has been said that benign hydatidiform moles could be malignant within 1 week to 3 years, with an average of 1 year after the evacuation of hydatidiform mole. After molar evacuation, local uterine invasion occur in 15% of patients and metastasis occurs with in 4% (Berkowitz and Goldstein, 2007).

Hydatidiform mole is seen as a benign trophoblastic disease, which has a tendency to be malignant for complete mole were 9% to 20% and incomplete mole 1% (Ngan et al., 2012). Up until recently it has not yet known why some hydatidiform moles change to be malignant. Risk factors

*[1]Department of Obstetric and Gynecology, [2]Department of Anatomical Pathology, Faculty of Medicine, Universitas Gadjah Mada, Jogjakarta, Indonesia *For correspondence: pradjatmo@yahoo.com, herupradjatmo@gmail.com*

that can be recognized so far are age above 40 years old, excessive uterine enlargement, hCG level of more than 100,000 mIU/ml, lutein cysts more than 6 cm (Berkowitz and Goldstein, 2007), age of gestation (Aziz et al., 1995).

Studies in Indonesia reported that there was a relationship of histopathological classification to the occurring malignancy (Barnas and Aziz, 1982). Hertig and Mansell found that there was a correlation between anaplasia of trophobastic cells and the incidence of malignancy. Review of 858 patients with complete mole revealed that two fifth patients had marked trophoblastic proliferation (Berkowitz and Goldstein, 2007). On hydatidiform mole, it is concluded that if there is a higher histopathological grading level of hydatidiform mole then it is more likely that there will be a higher chance of malignant degeneration (Barnas and Aziz, 1982; Bernirschke et al., 2012).

β-HCG level played an important role, not only for diagnosis but also for prognosis and for further follow up. Unfortunately, β-HCG examination cannot be performed in all areas of Indonesia; the examination can generally be done only in the laboratories of major cities, in addition to the relatively high cost of examination for middle-low earners. As a result the patients will not comply for routinely assesment, it is an obstacle to follow up for patients with hydatidiform mole and early diagnosis of malignant changes of hydatidiform mole.

In Indonesia the incidence of malignant degeneration was10-23% (Kampono et al., 1995) and mortality was 8.4% (Sanusi, 1991) to 35.94% (Aziz et al., 1995). Several risk factor for malignant changes had been known, however, each patient may be had different number of risk factor, then they had different potential for malignant changes. The administration of prophylactic chemotherapy is aimed to reduce or inhibit the proliferation of trophoblastic cells so this will prevent metastasis but also reduced incidence and morbidity of local uterine invasion. (Berkowitz and Goldstein, 2007). The use of prophylactic chemotherapy at the time of molar evacuation is controversial. The purpose is mainly to prevent GTN development in high-risk patients who are unlikely to be compliant or for whom β-HCG surveillance is not available. Many studied found that prophylactic chemotherapy to high risk hydatidiform mole significantly decreased the incidence of malignant degeneration. Its seem that giving prophylactic chemotherapy is more beneficial in the high risk patients than the low risk ones for decreasing the incidence of persistent trophoblastic disease. However, in clinical practice to differentiate or to classify of high-risk correctly is difficult, as there is no universally accepted combination of risk factors that accurately predict GTN development. Prophylactic chemotherapy is not routinely offered in the United State and Europe. However, prophylactic chemotherapy is generally only used in those countries with limited resources to perform follow-up after evacuation (Uberti et al., 2009).

To reduce of giving unnecessary chemoprophylactic chemotherapy to prevent GTN development it is necessary to discover a breakthrough to determine which patients have a high-risk of hydatidiform mole to develop GTN, and then treat them with prophylactic chemotherapy.

The objectives of this study was to determine the risk factors of malignancy in patients with hydatidiform mole in Indonesia and determine the contribution of risk factors and develop the scoring system of risk factors to determine which patients are at low-risk and high-risk as candidates for giving prophylactic chemotherapy.

Materials and Methods

This was a case-control study in which choriocarsinoma patients preceded with complete hydatidiform mole pregnancies were as the cases and the controls were patients with complete hydatidiform moles who did not experience malignant degeneration and had recovered one year from the time of the evacuation. The study population was patients of hydatidiform mole and choriocarsinoma treated at Dr Sardjito Hospital in Yogyakarta and Suradji Tirtonegoro Hospital in Klaten, Middle Java of Indonesia. Data was collected from the hospital medical records and if necessary completing data retrieval by correspondence or home visits. Inclusion criteria were all of those patients which had a history of diseases, diagnosis criteria of complete mole and all variables which were needed can be found. Bivariate analysis using Chi Square test and Multivariate analysis using Logistic Regresion and construct ROC curve were used to determine the best cut off point of the risk score.

Results

In a period of 8 years 78 cases of choriocarcinoma were found. Of the 78 cases, 34 cases met the inclusion criteria and complete the necessary data. There were 303 patients with hydatidiform mole as the control group selected at random (systematic random) as many as 68 cases of hydatidiform moles or 2 times of choriokarsinoma cases.

Table 1. shows the bivariate analysis of several variables assumed to be risk factors for the change towards malignancy such as age, number of pregnancies, gestational age, fundus height or uterine size and the grade of histopathological differentiation of hydatidiform mole. Of the five variables analyzed, the variable of number of pregnancies did not seem to be a risk factor for malignancy in which OR was 1.55 and p value was 0.34, whereas age, gestational age, fundus height or uterine size and the grade of histopathological differentiation of hydatidiform mole had effects on the occurrence of malignancy with OR of 3.16 and p value of 0.02, OR of 5.28 and p value of 0.006, OR of 13.92 and p value of <0.001, and OR of 4.69 and p value of <0.001 respectively.

Risk factors that were significant in bivariable analysis were then performed multivariable analysis using logistic regression. Multivariate analysis results in Table 2. show that the four variables were the risk factors that increased malignancy in which patients aged more than 35 years increased the risk of malignancy 4.4 times compared to those aged ≤ 35 years (OR 4.41 with p=0.03), gestational age ≥ 12 weeks increased the risk 11.7 times than that <12 weeks (OR 11.73 with p=0.008), uterine size greater than the age of the pregnancy increased the risk 10.2 times higher than patients with smaller uterine size or

Table 1. Bivariate Analysis of Relationship between Hydatidiform Mole and Choriocarcinoma Patients with Several Variables of Patient Age, Number of Pregnancies, Gestational Age, Uterine Size and Degree of Hydatidiform Mole Differentiation

Risk Factors		Hydatidiform Mole		OR	95% CI	p
		Malignant	No Malignant			
Age	≤35 years	22 (64%)	58 (85%)	1		
	>35 years	12 (35%)	10 (14%)	3.16	1.19-8.36	0.020
Gravidity	1-3	11 (67.6%)	16 (23.5%)	1		
	≥4	23 (32.4%)	52 (76.5%)	1.55	0.57-4.25	0.341
Gestational age	<12	2 (8.8%)	23 (33.2%)	1		
	≥12	31 (91.2%)	45 (66.2%)	5.28	1.34-24.28	0.006
Fundus height	≤gestational age	5 (14.7%)	48 (70.6%)	1		
	>gestational age	29 (85.3%)	20 (29.4%)	13.9	4.71-41.11	<0.001
Grade of HM	Grade I	10 (29.4%)	45 (66.2%)	1		
	Grade II-III	24 (70.6%)	23 (33.8%)	4.69	1.92-11.46	<0.001

Table 2. Multivariate Analysis with Logistic Regression on Risk Factors: Patient Age, Gestational Age, Uterine Size and Histopathological Grade of Hydatidiform Moles

Risk Factors	OR	CI (95%)	β	p
Age of patient				
> 35 years	4.41	1.07-16.09	1.48	0.03
Gestational age				
≥ 12 weeks	11.73	1.89-72.48	2.46	0.008
Fundus height				
> gestational age	10.22	2.85-36.67	2.32	0.004
Histopathological grade				
Grade II-III	3.42	1.10-10.63	1.23	0.03

Table 3. Weighting Index Calculation of Risk Factors for Malignancy in Hydatidiform Moles

Risk Factors	OR	Attributable at Risk (OR-1)	Coeff. β (AR x β)	Risk Index
Age of patient:				
≤35 years	1			0
>35 years	4.41	3.41	1.48	5
Gestational age:				
<12 weeks	1			0
≥12 weeks	11.73	10.73	2.46	26
Uterine size:				
Smaller/appropriate	1			0
Greater than GA	10.22	9.22	2.32	21
Histopathology grade:				
Grade I	1			0
Grade II-III	3.42	2.42	1.23	3

according to the age of the pregnancy (OR 10.22 with p=0.004) and the grade of histopathological differentiation of hydatidiform mole grade II-III increased the risk 3.4 times compared to patients with hydatidiform mole grade I (OR 3.42 with p=0,03).

With the identified risk factors, the contribution of each factor in increasing the risk of malignancy in hydatidiform mole was not the same. Each individual patient did not have all four risk factors and the combination was of course different; thus, it was certainly necessary to assess the contribution of each risk factor. For it, the weighting of each risk factor was made with the calculation, weighting index is equal to Attributable at Risk (AR) x β where Attributable at Risk (AR) is equal to Odd Ratio (OR)-1 and β is the β value of logistic regression results. Weighting index calculation results are shown in Table 3. The weighting results of patient age, number of pregnancies, gestational age, fundus height or uterine size and the grade of histopathology differentiation of hydatidiform mole boosted the risk of 5, 26, 21, 3, respectively while the weight index of reference was 0.

Table 4. Sensitivity and Specificity Analysis Result of Each Total Risk Score of Hydatidiform Moles

Score	Sensitivity	Specificity
0	1	0
3	1	0.17
5	1	0.35
8	1	0.42
21	0.97	0.47
24	0.94	0.47
26	0.88	0.54
29	0.85	0.75
31	0.82	0.82
32	0.79	0.82
34	0.79	0.83
47	0.73	0.83
50	0.55	0.89
52	0.23	0.97
55	0.17	0.98
55	0.17	0.98

From the weighting results, scoring was done on all study subjects and the results were calculated their sensitivity and specificity if the score was as "cut of point" as listed in Table 4. From the results, the best "cut of point" was chosen from the score with the distance between sensitivity and specificity was the most narrowed (Table 4). with the score of 31 sensitifity was 0.82 and specificity was 0.82). Subsequently, ROC curve was made with the vertical axis as sensitivity and the horizontal axis as 1-specificity as plotted in Figure 1. The best "cut of point" is the plot point closest to the top left corner with sensitivity value=1.

The results of this study found that patient age, gestational age, fundal height or uterine size and the grade of histopathology differentiation in patients with hydatidiform mole were risk factors for malignancy. The four risk factors were calculated their weighting contribution in increasing the risk of malignancy. The weighting results were used to conduct scoring on the research subjects and the ROC curve was made to determine the best "cut of point" to distinguish hydatidiform mole patients with high risk and low risk of having the possibility of malignancy. This study obtained

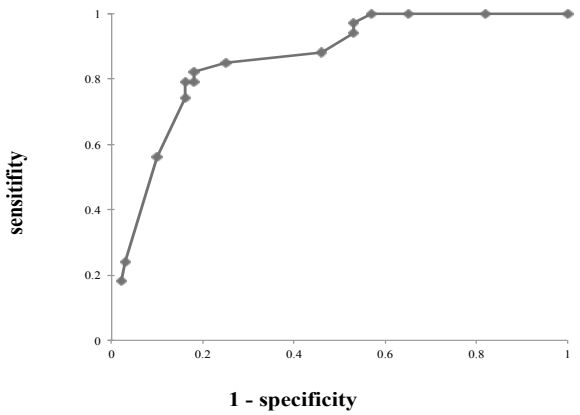

Figure 1. Receiver Operating Characteristic (ROC) curve of Malignant Risk Scoring of Hydatidiform Moles. The risk scores of hydatidiform moles patients plotted from Table 4

a score of 31 as a "cut of point". Thus, if a patient with the four risk factors and the total score is 31 or more, then the patient is at risk of malignancy and can be given chemoprophylatic with methotrexate or actinomycin D to prevent the development of choriocarcinoma.

Discussion

Women aged over 35 years show an increased risk of the incidence of complete mole. This is caused the ovum of older women frequently experience abnormal fertilizations. At age over 35 years, the risk of the complete mole increases 2 times, while over 40 years the risk can increase up to 7.5 times (Berkowitz and Goldstein, 2007). The older patient results in the lower body immunity; the lower body immunity causes tumor cells to undergo proliferation and differentiation of cells. In older women, cellular immunological response is diminishing so that tumor cells grow progressively and an angioinvasion occurs.

The fundus height or uterine size larger than gestational age is a classic sign of a complete mole found to be approximately 50% of cases. The growing endometrial cavity is filled by chorionic tissues. The size of the uterus growing faster is generally associated with high hCG levels as a result of a rapid growth of trophoblast (Berkowitz and Goldstein, 2007). At 14 weeks of gestation, complete moles undergo a rapid rise of hCG levels. This circumstance distinguish normal pregnancies that show hCG level to begin to decrease. A rapid rise in hCG levels show rapid activities of trophoblast and it is a risk factor for malignant degeneration (Berkowitz and Goldstein, 2007). The condition of rapid trophoblast growth and the size of the uterus larger than gestational age might result in spontaneous expulsion at gestational age of 12-14 weeks or 12-16 weeks (Audu et al., 2009).

Histopathologically, the classification of hydatidiform moles by Hertig and Mansell is as follows: Grade I: apparently benign, that is, the microscopic profile in accordance with hydatidiform mole without or with mild proliferation of trophoblastic cells. Grade II: Potentially malignant, that is, the microscopic profile accordance with hydatidiform moles, accompanied by moderate proliferation and mild to moderate anaplasia of trophoblastic cells. Grade III: Apparently malignant, that is, the microscopic profile in accordance with hydatidiform moles, accompanied by intense proliferation and severe anaplasia of trophoblastic cells. The previous studies on the relationship of histopathological classification to malignant degeneration have obtained different results (Bernirschke et al., 2012). Studies in Indonesia reported that there was a relationship of histopathological classification to the occurring malignancy (Barnas and Aziz, 1982). Hertig and Mansell (1953) found that there was a correlation between anaplasia of trophobastic cells and the incidence of malignancy. In this study found that grade of histopathological differentiation had significantly increased risk with OR 3.4. However, due to grade of histopathological differentiation have been shown to be inconsistent and not predictive of malignancy, there was a sugestion that if a scoring system is to be universal value it should not include histological grading of hydatidoform mole.

The administration of prophylactic chemotherapy to high risk hydatidiform mole is aimed to reduce or inhibit the proliferation of trophoblastic cells so this will prevent malignant changes (Berkowitz and Goldstein, 2007; Hoffman et al., 2012). Prophylactic chemotherapy is given particularly to the patients of high risk complete moles. A randomized study to 71 patients with complete hydatidiform moles assaign into two groups, one group of 39 patients was treated with single course of methotrexate and citrovorum factor resque as chemoprophylaxis group, the other group of 32 patients was not treated as a non chemoprophylactic group. The result after evacuation and follow up found four patients from the treated group (10.3 %) and ten patients from the untreated group (31.3 %) developed persistent trophoblastic disease. They also found the incidence of persistent trophoblastic disease among the high risk patients in the treated group than in the untreated group (14.3 *vs* 47.4% and $p < 0.05$) (Kim et al., 1986). Its seem that giving prophylactic chemotherapy is more beneficial in the high risk patients than the low risk ones for decreasing the incidence of persistent trophoblastic disease (Kim et al., 1986; Berkowitz and Goldstein, 2007).

A study of 247 pregnant patients with complete hydatidiform moles was carried out and they received Actinomycin D at the time of curettage evacuation with the dose of 12 mg/kg/day intravenously given 3 days before the evacuation and 2 days after the evacuation. In the moles with expulsion, the same procedure was given 5 days after the evacuation. The result showed the incidence of local invasion in 10 patients (4%) and not any metastasis (Berkowitz and Goldstein, 2007) . Side effects and toxicity of therapy or prophylactic chemotherapy with Actinomycin D or Methotrexate were reported mild, including nausea, vomiting, abdominal pain, and fever but those were disappeared after treatment (Wardani et al., 1991; Samadan-Cagayan, 2008). Other study evaluated 420 patients with molar pregnacy, 293 patients with prophylactic chemotherapy and 127 without prophylactic chemotherapy. They found that 22 patients (7.5 %) in the treated group and 23 patients (18.1 %) in the untreated

group developed secondary trophoblastic disease and it was significantly different ($p<0.01$) (Khasimura et al., 1986). Andrijono and Muhilal (2010) in Indonesia found that administration vitamin A 200,000 IU per day after evacuation of mole tissue up to a regression or degeneration of malignant trophoblastic disease (MTD), the incidence rate of malignant trophoblastic disease was 6.3% in treatment group compare to 28,6% in the placebo group.

Its clear that prophylactic chemotherapy to hydatidiform moles will significantly decrease incidence of malignant changes and its seem that prophylactic chemotherapy is more beneficial to the patients with high risk moles (Kim et al., 1986; Berkowitz and Goldstein, 2007). Several risk factors were mentioned, in clinical practice very difficult to determine which one she is a high-risk patients. It is known that each patient might have different combination of risk factors and the potential of malignant changes is different. This study tried to make the scoring and to find the best cut off point to decide which of the hydatidiform moles is high-risk and appropriate to give prophylactic chemotherapy. Thus the desicion of giving prophylactic chemotherapy is more accurate only to the high risk patients. However, it is sugested that before the scoring is used universally it is necessary to use a separate and independent sample to determine its predictive value so that other researchers might be able to perform the study to test this scoring system to determine the predictive value. Then if the scoring system has a high predictive value it could help confince us what patients with hydatidiform mole will benefit from prophylactic chemotherapy.

In conclusion, *i)* Results of this study identified four risk factors for the development of hydatidiform mole to be GTN, namely patient age, gestational age, fundal height or uterine size and the degree of histopathology differentiation; *ii)* The weight of each risk factor was 0 and 5, 0 and 26, 0 and 21, and 0 and 3, respectively; *iii)* The best 'Cut of point' of total score of four risk factors to determine whether the patients were at low-risk or high-risk was 31, where a score of less than 31 was at a low-risk and a score of ≥ 31 was at a high-risk of developing into GTN. In the future, addition of other features like blood profile (Guzel et al., 2014) may allow even more accuracy.

References

Abdullah NM, Prabowo RP (1985). Hasil pengobatan neoplasma tropoblas ganas di RS. Dr. Soetomo Surabaya (1981-1983). Neoplasma tropoblas gestational, epidemiologi, diagnosis, pengobatan, pencegahan, Prognosis: 42-5.

Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C (2003). Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol*, **4**, 670-8.

Andrijono A, Muhilal M (2010). Prevention of post-mole malignant trophoblastic disease with vitamin A. *Asian Pac J Cancer Prev*, **11**, 567-70

Audu BM, Takai IU, Chama CM, Bukar M, KyariI O (2009). Hydatidiform mole as seen in a university teaching hospital: A 10-year review. *J Obstet Gynaecol*, **29**, 322-5.

Aziz MF, Kompono N, Samil RS (1995). Neoplasma trofoblas, faktor risiko tinggi dan prognosis. *Neoplasma Trofoblas Gestational*, 35-54.

Barnas B, Aziz MF (1982). Hubungan klasifikasi histologik mola hidatidosa dengan penyakit trofoblas ganas. *J Obstet Gynecol*, **8**, 168-72.

Berkowitz RS, Goldstein DP (2007). Gestational tropoblastic disease. *Berek Novaks Gynecology*, **14**, 2376-405.

Bernirschke K, Burton GJ, Baergen RN (2012). Pathology of the Human Placenta. 6th Ed, Springer-Verlag Co, 687-723.

Cunningham FG, Leveno KL, Bloom SL, et al (2010). Gestational Trophoblastid Disease. in Williams Obstetrics, 23th Ed. Mc Graw Hill Co, 257-65.

Guzel AI, Kokanali MK, Erkilinc S, et al (2014). Predictive role of the neutrophil lymphocyte ratio for invasion with gestational trophoblastic disease. *Asian Pac J Cancer Prev*, **15**, 4203-6.

Hertig AT, Mansell H (1956) Hydatidiform Mole and Choriocarcinoma. in: Atlas of Tumor Pathoogy. Armed Forces of Pathology. Washington, DC

Kampono N, Aziz MF, Sjamsudin S, Barnas B (1995). Pengobatan profilaksis pada mola hidatidosa dengan Actinomycin D. neoplasma trofoblas gestational. 62-7.

Khanum F, Shamser S (2010). Gestational trophoblastic disease: experience at a tertiary care hospital of peshawar. *JPMI*, **94**, 127-32.

Khasimura Y, Khasimura M, Sugimori H, et al (1986). Prophylactic chemotherapy for hydatiform mole, five to 15 years follow-up. *Cancer*, **58**, 624-9.

Kim DS, Moon H, Kim KT, Moon YJ, Hwang YY (1986). Effect of prophylactic chemotherapy for persistent trophoblastic disease in patients with complete hydatidiform mole. *Obstet Gynecol*, **67**, 690-4

Kurman R (1995). Gestational tropoblastic disease. 4th Ed, Arcata Graphics, 1067-86.

Lurain J (1987). Gestational trophoblastic disease. Clinical manual of gynecology. 2nd ed. Beckman Ling (Edit.). Mac Graw Hill Inc. 543-56.

Ngan HYS, Kohorn EI, Cole LA, et al (2012). Trophoblastic disease. *Inter J Gynecol Obstet*, **119**, 130-6

Ozalp SS, Telli E, Oge T, et al (2014). Multicenter analysis of gestational trophoblastic neoplasia in Turkey. *Asian Pac J Cancer Prev*, **15**, 3625-8.

Salehi S, Eloranta S, Johansson ALV, Bergstrom M, Lambe M (2011). Reporting and incidence trends of hydatidiform mole in Sweden 1973-2004. *Acta Oncologica*, **50**, 367-72.

Samadan-Cagayan MSF (2008). Efficacy of methotrexate as primary single agent therapy for non metastatic gestational trophoblastic neoplasia at the university of the Philippine-Philippine general hospital (UP+PGH). *Cancer Therapy*, **6**, 611-6.

Uberti EMH, Fajardo MDC, da Cunha AVG, et al (2009). Prevention of post molar gestational trophoblastic neoplasia using prophylactic single bolus dose of actinomycin D in high-risk hydatiform mole: a simple, effective, secure and low cost approach without adverse effects on compliance to general follow-up or subsequent treatment. *Gynecol Oncol*, **114**, 299-305

Wardhani H, Faisal Y, Nuria SM, Saleh AZ, Pohan HS (1991). Karakteristik kasus mola hidatidosa di RSU Palembang selama 2 tahun (1989-1990). *POGI J*, 67-72.