RESEARCH ARTICLE

Malignancy Risk Scoring of Hydatidiform Moles

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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 development 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

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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 et al., 1991; Audu et al., 2009; Khanum and Shamsheer, 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 (Ngan et al., 2012). Up until recently it has not yet known why some hydatidiform moles change to be malignant. Risk factors of hydatidiform mole vary widely from 9% to 20% and incomplete mole 1% (Ngan et al., 2012). 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. 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 largely reflected discrepancies 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).

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Malignancy Risk Scoring of Hydatidiform Moles
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 trophoblastic 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 assessment, 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 was 10-23% (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 choriocarcinoma 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 choriocarcinoma 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 Regression 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 choriocarcinoma 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                 | 1                 | 0.02 | 58 (85%)      | 0.020 |
| >35 years                 | 1                 | 0    | 10 (14%)      |       |
| Gravidity                 |                   |      |               |       |
| 1-3                       | 1                 | 0    | 16 (23.3%)    |       |
| ≥4                        | 1                 | 0    | 52 (76.5%)    |       |
| Gestational age           |                   |      |               |       |
| <12                       | 1                 | 0    | 23 (33.2%)    |       |
| ≥12                       | 1                 | 0    | 45 (66.2%)    |       |
| Fundus height             |                   |      |               |       |
| <gestational age          | 1                 | 0    | 5 (14.7%)     |       |
| >gestational age          | 1                 | 0    | 48 (70.6%)    |       |
| Grade of HM               |                   |      |               |       |
| Grade I                   | 1                 | 0    | 20 (29.4%)    | <0.001|
| Grade II-III              | 1                 | 0    | 46 (66.2%)    |       |

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

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

| Score | Sensitivity | Specificity |
|-------|-------------|-------------|
| 0     | 0           | 1           |
| 3     | 0.17        | 1           |
| 5     | 0.35        | 1           |
| 8     | 0.42        | 1           |
| 21    | 0.47        | 1           |
| 24    | 0.47        | 1           |
| 26    | 0.54        | 1           |
| 29    | 0.75        | 1           |
| 31    | 0.82        | 1           |
| 32    | 0.82        | 1           |
| 34    | 0.83        | 1           |
| 47    | 0.83        | 1           |
| 50    | 0.89        | 1           |
| 52    | 0.97        | 1           |
| 55    | 0.98        | 1           |
| 55    | 0.98        | 1           |

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, fundal 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.

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 sensitivity 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...
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Potentially malignant, that is, the microscopic profile mild proliferation of trophoblastic cells. Grade II: accordance with hydatidiform mole without or with apparently benign, that is, the microscopic profile in moles by Hertig and Mansell is as follows: Grade I: age of 12-14 weeks or 12-16 weeks (Audu et al., 2009). The condition of rapid trophoblast it is a risk factor for malignant degeneration (Berkowitz and Goldstein, 2007). The condition of rapid trophoblast 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). The fundus height or uterine size larger than gestational age is a classic sign of a 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 trophoblastic 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 suggestion that if a scoring system is to be universal value it should not include histological grading of hydatidiform 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 pregnancy, 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

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 condition of rapid trophoblast it is a risk factor for malignant degeneration (Berkowitz and Goldstein, 2007).

The fundus height or uterine size larger than gestational age is a classic sign of a 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 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).

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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 compared to 28.6% in the placebo group.

It's clear that prophylactic chemotherapy to hydatidiform moles will significantly decrease incidence of malignant changes and it seems 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 suggested 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 convince 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 changes and its seem that prophylactic chemotherapy is more accurate only to the high risk hydatidiform mole: a simple, effective, secure and low cost approach without adverse effects on compliance to general follow-up or subsequent treatment.

For the future, it was significantly different (p<0.01) (Khasimura et al., 1986). Prophylactic chemotherapy for hydatidiform mole, live to 15 years follow-up. Cancer, 58, 624-9.

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