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Hydatiforme Mole is a Rare Histopathological Diagnosis in Spontaneous Abortion

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Abstract

Introduction: Hydatidiform mole is a rare complication in pregnancy that poses a real challenge in terms of diagnosis and management.

Objective: The aim of this study is to confirm the value of histopathological examination in determining the rare diagnosis of total or partial hydatidiforme mole in spontaneous abortion.

Material and method: This is a retrospective study conducted at both University Obs/Gyn Hospitals in Tirana for the period 2015 - 2019. There are 413 patients included in this study. The data were collected from the statistic department and the laboratory of histopathology.

Results: Hydatidiform mole developed mainly in females aged 25-34 years old. The most frequent clinical diagnosis is missed abortion (74.1%). The most frequent histopathological diagnosis is partialis hydatiforme mole which occurred at 93.7% of total cases. The % of mole (no. = 413) to the total number of abortions (no. = 10,457) in Tirana continues to be a low steady figure over the 5 years with an average of 3.9% per year, while both abortions and mole screening have a decreasing trend during 2015-2019.

Conclusions: Accurate diagnosis of the hydatiforme mole is both important and difficult. Mortality and maternal risk during and after abortion and curettage is zero. Only histopathological diagnosis is definitive so it directs the woman's follow-up until β-HCG neutralization. Therefore, all materials from abortions and curettage must necessarily be sent

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to the laboratory to carry out histopathological examination of the material as well as to perform other auxiliary diagnosis tests, if necessary.

Key words: total and partial hydatidiform moles, histopathology examination, abortion, missed abortion, curettage, trophoblastic gestational disease, choriocarcinoma.

INTRODUCTION

Hydatidiform mole is a rare complication in pregnancy that poses a real challenge in terms of diagnosis and management. Hydatidiform mole is a medical term meaning a cluster of cells filled with fluid (mole - a cluster of cells, hydatid-containing fluid-filled sacs or cysts) (1). The hydatidiform mole is part of a broad spectrum of diseases known as trophoblastic diseases. It is an uncommon complication of pregnancy (2). Mola is characterized by abnormal growth of trophoblast cells that normally develop to form the placenta (3). Some factors increase the probability of a woman developing a hydatiform mole. These include, age (>35 years); previous history of molar pregnancy is also shown to be a risk factor; women of Asian origin are also at higher risks of molar pregnancy (4). Parazzini et al. reports that compared to younger females the risk for a total mole was about twice as high for females over 35 years old and 7.5 times greater for those over 40 years old (7). Women, who have had a previous molar pregnancy, have a 6-fold higher risk of having recurrence while women who have had two previous molar pregnancies have a 120-fold higher risk. It is precisely some genes that determine this increased risk. These genes are named: NLRP7 and KHDC3L (6). The incidence of gestational trophoblastic disease is reported to vary from country to country worlwide. For example: the incidence of molar pregnancy in Japan is about 3 times higher than in Europe or North America. Careful case-control studies have been undertaken to identify risk factors and according to these studies the high incidence of hydatiform mole in some populations is related to nutritional and socioeconomic factors. Case-control studies in Italy and the US suggest that low intake of carotene and animal fats may be associated with increased risk of total mole. Regions with a high incidence of molar pregnancies correspond to geographical areas that have high incidence of vitamin A deficiency. Naming some other risk factors, we may include such as smoking, blood type A, B or AB, unsuccessful completion of a pregnancy beyond 20 weeks, oral contraception use and history of infertility (7).

Possible complications of molar pregnancy may include: change to invasive molar disease or choriocarcinoma; preeclampsia; thyroid problems; molar pregnancy that continues or comes back. In addition, the complications from surgery to remove a molar pregnancy include: excessive bleeding that may possibly require a blood transfusion; side effects of anesthesia, etc.

Histopathology, or shortly histology, involves microscopic examination of tissues. Specimens received from the histopathological laboratory require tissue preparation and then treated and analyzed using appropriate techniques depending on the type of tissue and examination required. As the clinical diagnosis, mostly evident by vaginal hemorrhagia, is not enough to determine the mole disease diagnosis, the role of histopathology in determing in the microscop field the presence of the trophoblastic cells is very important.

Prevalence of hydatidiform mole (HM) is not clearly defined among spontaneuous abortions, partly because most studies have reported different prevalence rates from different regions. However, it is unknown if there is a previous study published about the prevalence and associated risk factors of HM among patients with spontaneous abortion in Tirana. This statistical analysis attends to present such data for Tirana in addition to the confirmation of the important role of histology in the HM diagnosis.

OBJECTIVES

The main objective is to determine the importance of performing histopathological examination in the diagnosis of hydatiforme mole and to find the associated risk factors and the prevalence of HM among patients with spontaneous abortion in Tirana.

MATERIALS AND METHODS

This is a retrospective epidemiologjical study. There have been included 413 patients in this study. Through histopathological examination, they were diagnosed with partial or total hydatiforme mole at both University Obstetric and Gynecological Hospitals in Tirana during the 2015- 2019. The data used for this study were collected from the histopathological examinations register present at the Laboratory of histopathology, from statistic departments and Insitute of Statistics (INSTAT) (18). In this study have been included 413 patients diagnosed with Hydatidiforme Mole. Patients included in the study belong to the age of 17 to 51 years old. All patients were subjected to histopathological examination of tissue specimen obtained after abortion or after the curettage procedure. The data were collected from the statistic departments and the laboratory of histopathology. This study did not include patients who had an abortion but that the final diagnosis by histological examination was not a hydatiforme mole.

Data used in this study include: age of patient, month of histological examanition performed, macroscopic description of the material/clinical diagnosis, histopathological diagnose and abortion statistics.

Methodology of statistical analysis: After obtaining the information from the histopathological laboratory registries and the statistical department, the data were entered for analysis in SPSS statistical software 27. The following technics have been used in this paper: *a. Crosstab and Chi–Square test* for testing the relationship between two variables considered as categorical. *b. Average, Standard Deviation, Minimum, Maximum, Frequency, Percentage* which serve to present a more accurate picture of the results of the data analysis in table and graphical form.

RESULTS

Patients has been grouped based on their age and presented in 4 groups of minimum 9 years each. The study involved 413 patients of which 50.4% (n = 208) belonged to the age group of 25-34 years old, 31% (n = 128) belonged to the age

group of 35-44 years old, 14.0% (n = 58) belong to the age group of 15-24 years old, and 4.6% (n = 19) over 45 years old **(Figure 1)**. It is noted that the highest percentage of cases with hydatiforme mole was in women aged 25-34 years old.

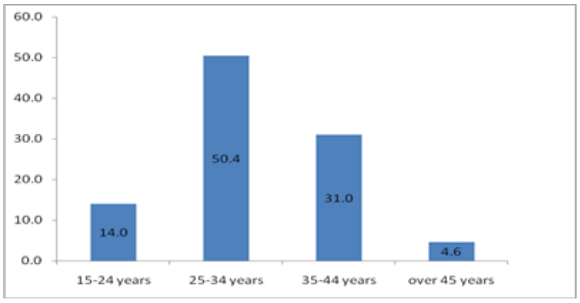

Figure 1. Percentige of each age-groups of patients diagnosed with Mole

In 2019, 53.7% (n = 36) belong to the 25-34 age group, in 2018, 48.8% (n = 39) belong to the 25-34 age group, in 2017, 54.5% (n = 36) belong to the 25-34 age group, in 2016, 50.6% (n = 43) belong to the 25-34 age group and in 2015, 47.0% (n = 54) belong to the 25-34 age group. It is noted that the highest percentage of cases of hydatidiforme mole was seen in women aged 25-34 years old in all 5 years analyzed in this study (Figure 2).

The patients participating in this study are of minimum age 17 years old and maximum of age 51 years old. The average age results to be 30.617 years old with a standard deviation SD=6.7008 (Table 1)

Table 1. Other technics presenting patient age-related data

	No.	Minimum	Maximum	Average	Standard Deviation
Age	413	17	51	30.617	6.7008

In January 7.5%, February 9.2%, March 9.2% April 9.7%, May 13.6%, June 9.4%, July 8.7%, August 6.3%, September 5.6%, October 7.5%, November 6.3%, December 7.0%. (Figure 3)

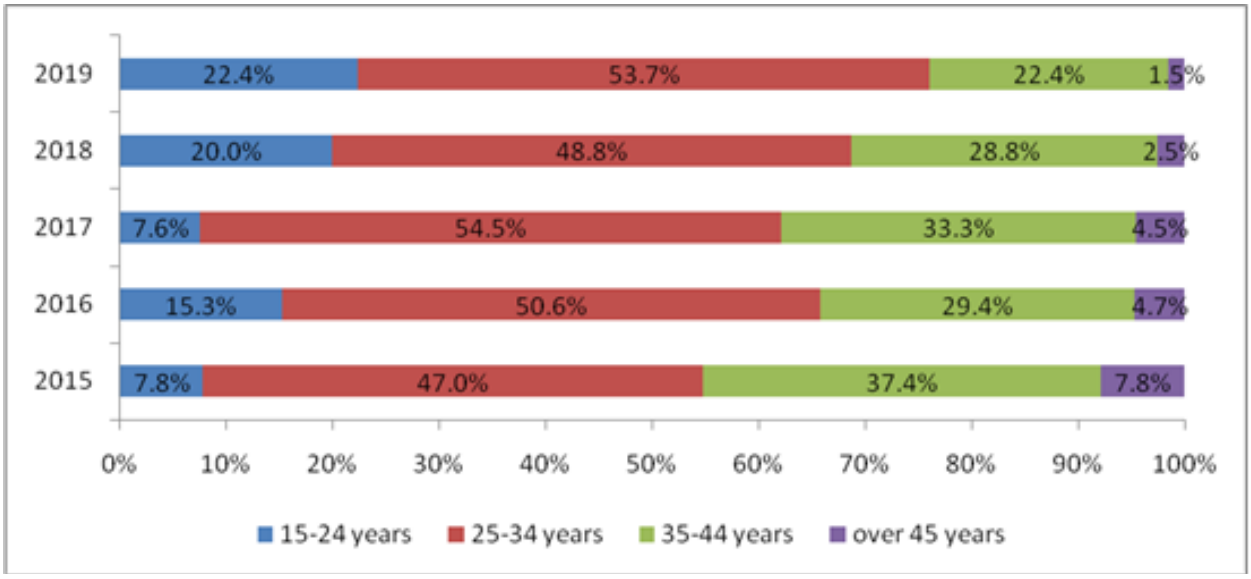

Figure 2. Age-group presented in 4 categories for each of 5 years

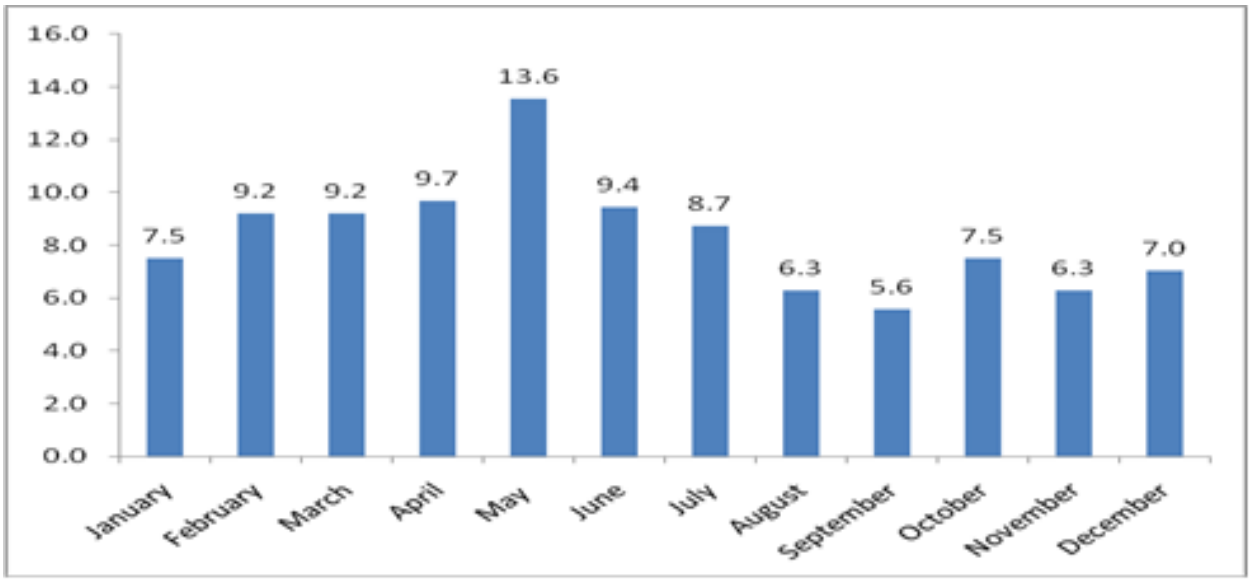

Figure 3. The frequency of mole diagnosis by month of year in %

We note that more histopathological examinations that determined the diagnosis of hydatidiforme mole were performed in April, May and June. There is no data yet on whether the period of the year when a pregnancy begins affects the risk of developing a hydatiforme mole. Referring to the above graphic, it results that the clinical diagnoses have been devided as follows: Abortion 18.6% (n = 77), Missed abortion 74.1% (n = 306) and Mola hydatiforme/Susp. mole Hydatiforme 7.3 % (n= 30). (Figure 4). It is noted that the most frequent clinical diagnosis determined at the time of hospital admission is "Missed abortion", so patients are admitted to the obs/gyn hospital because they have experienced a problem with their pregnancy or termination of their pregnancy without knowing that the cause of this termination is specifically the molar mass presence. Within 7.3% of cases, 2.7 % were diagnosed with hydatiforme mole based on clinical signs and the rest, 4.6% of cases, were diagnosed as suspicious for hydatiforme mole based on the clinical signs/symptoms but confirmation was made through histopathological examination afterwards in all cases.

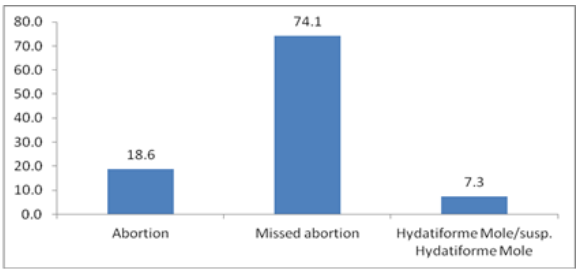

Figure 4. Clinical diagnosis at obs/gyn hospital admission in %

According to the microscopic description, partial hydatiforme mole resulted in 93.7% (n = 387) of cases, tuberous partial hydatiforme mole in 0.5% (n = 2), total hydatiforme mole in 5.6% (n = 23) and necrotic mole in 0.2% (n = 1). (Figure 5). So only after a microscopic examination an accurate diagnosis of the etiology of the abortion has been established in most of the cases.

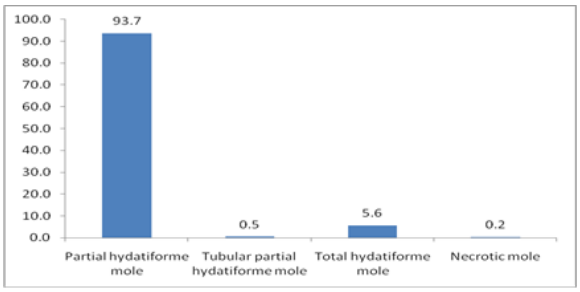

Figure 5. Microscopic/histopathological examination in %

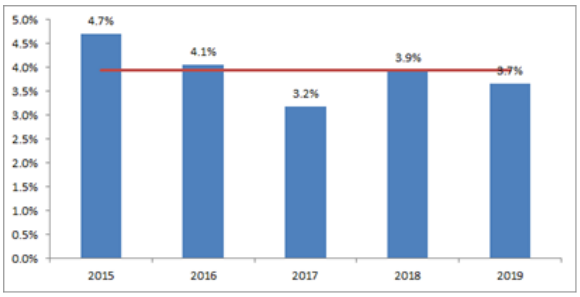

Figure 6. Ratio of Moles at Abortions in a 5 years period

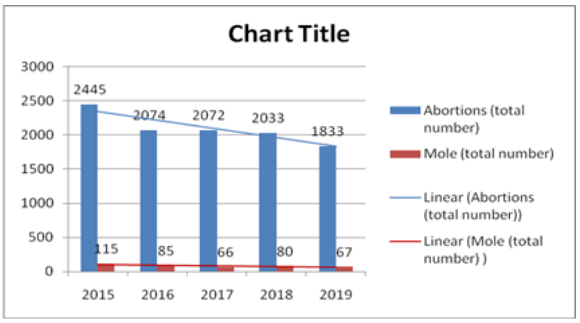

Figure 7. Trend lines of both Abortions and Moles during the 5 years period

It is noted that none of the cases resulted in fatal outcome during abortion or during the curettage procedure for 5 years period. There is no data available from the current records on the risk of developing chorio-carcinoma following total hydatiforme mole diagnosis.

The data we collected from the registry and statistical department make possible the calculation of the prevalence (%) of Hydatiforme Mole (no. = 413) in total number of abortions (no. = 10,457) in Tirana. The average age of pregnancies in Albania is up to 35 years of age, so is the age of spontaneous abortions. The prevalence continues to be steady over the 5 years with an average of 3.9% (Figure 6), while both abortion and mole disease have a decreasing trend during 2015-2019 (Figure 7). There could be severeal reasons to explain the trend of decreased number of abortions and moles consequently and this could be another hypothesis to further investigate about.

DISCUSSION

Hidatiform mola is an uncommon form of pregnancy, which has a low incidence in our country, as in countries worldwide. It can be found in two forms: the total mole with a very low frequency and the partial mole that is much more widespread. The study involved 413 patients whose mean age was 30 years, the youngest age was 17 years old and the oldest age was 51 years old.

The predominant age group of patients included in the study was 25-34 years old, accounting for 50.4% of cases, followed by 35-44 years old, which accounted for 31.0% of cases.

According to a retrospective study conducted at a Tertiary Health Care Center in Nepal (8), more than one-third of patients diagnosed with

hydatidiform mole belonged to the age group of 20-35 years old. Thus, the results of our study are consistent with Nepal's study regarding the data of the age group where the cases of hydatiform mole are most frequently encountered.

On the other hand, according to a case-control study conducted in Chicago, Illinois (9), one of the major risk factors for developing hydatidiform mole is being pregnant in a very young or very old age. However, the highest number of molar pregnancies turns out to be in women of the age group of 20-40 years old, because this age group represents the years with the highest level of reproduction for a woman.

Another study conducted in 2003 (13), concludes that although the risk for a molar pregnancy is higher in patients under 15 and above 45 years old, and based on the fact that the total number of pregnancies in women of this age is much lower, the age group of 18-40 years results to be the group with the highest number of cases of hydatidiform mole.

So the data of our study regarding the age group with the highest incidence of the disease are also consistent with the data of other studies conducted in different countries of the world.

During this study we have also considered a data which has not been taken into consideration very often in other studies on this topic, but it has made a very interesting conclusion. We are talking precisely about the month of histopathological examination of the material. The data show that most of the examinations were carried out during the months: April, May and June, respectively 9.7% in April, 13.6% in May and 9.4% in June. So we note that the highest number of ill-conceived cases is in late winter (February) and during the spring peaking in May. The mechanism or factors that may affect these results are not known, but similar data were also drawn from a study conducted in Morocco, a city with a similar climate to our country; found that weather conditions influenced the occurrence of a higher number of cases of hydatiform mole. The way how weather conditions affect them is not known yet and has not been studied, so we cannot draw an accurate conclusion as to whether climate impacts the risk of developing hydatidiform mole or whether these data are purely coincidental.

The clinical presentation of both total and partial hydatiform moles is a non-typical and therefore the exact diagnosis cannot be established at the time of admission to the maternity.

The most common clinical diagnosis at the first moment of admission is missed abortion or abortion. When analyzing the data, it is noted that the most frequent clinical diagnosis at the time of hospitalization is missed abortion, i.e. a "silent" abortion with no visible clinical signs. We have 74.1% of cases diagnosed with missed abortion, followed by 18.6% of those diagnosed with abortion. On the other hand, the diagnosis of hydatiform mole and suspected mole was present only in 7.3% of all cases. A study conducted at the New England Trophoblastic Disease Center in 1985 (11) concluded that over 90% of study patients were diagnosed with abortion or missed abortion at the time of admission to the maternity

hospital. Only 6.2% of patients were presented with symptoms that make you suspect the presence of hydatiform mole.

So, as can be clearly seen from these data, in most cases the diagnosis of hydatiform mole is not made accurately at the time of admission at the maternity hospital. It is thought that this may be due to the lack of typical signs as well as the lack of other auxiliary diagnostic examinations such as measuring HCG levels or performing ultrasonography for any hemorrhagic emergencies at the time of admission to assist in diagnosis.

A study conducted in 2012 (10) supports the fact that the examination of the hydatiform mole may not be suspected through clinical signs, hCG level or ultrasound examination and therefore a histopathologic examination is required. The study also confirmed that the frequency of the hydatiform mole is low.

Specifically in 50% of the cases included in the study there was no suspicion of hydatiform mole based on these criteria, therefore, accurate diagnosis of the disease requires histopathological examination of the material prepared in advance. So the conclusions drawn from our study are the same as those drawn from studies conducted in different parts of the world in many ways.

According to the microscopic description, 93.7% of patients were diagnosed with partial hydatiform mole, 0.5% with tubular hydatidiform mole, hereas 5.6% with total mole and only one case with necrotic mole (0.2%). As in other studies, our study has a very low percentage of cases of total mole, perhaps this is why the diagnosis of hydatiform mole is difficult to determine based on clinical data or pregnancy follow-up examinations such as hCG measurement or ultrasonography. According to the data of some studies (11), the diagnosis of partial mole is more difficult due to the unusual symptoms and confounding features of the microscopic examination. The diagnosis of partial mole is made after the microscopic examination of the specimen obtained after curettage.

A study conducted in London in 2003 (13) found that 47% of cases were total mole and 53% of cases were partial mole, so there was a predominance of partial mole cases eventhough with a significantly lower difference than in this study. Another study carried out in Tunisia (12) displays conflicting data with our study regarding the frequency of total and partial mole occurrence. Thus in 68.2% of cases there was total mole, while in 31.8% of cases were partial moles. Still it is not known what are the factors affecting the appearance of one or the other form of hydatiform mole to draw a conclusion related to the reason for this difference but what can be said for sure is that cases with total mole have an increased risk for developing choriocarcinoma and in Albania fortunately the number of cases with total moles is low. However, it remains to be further investigated especially in the histopathological aspect by the specialists themselves in this field.

In our study, as in other studies (12,14), is found that none of the cases had a fatal outcome, nor did any of the patients died during the abortion or curettage procedure. Also, in cases where choriocarcinoma has developed the cure rate is very high, especially if the disease is properly managed and followed (12,14). [14].

According to the study, the highest proportion of patients with partial hydatidiform mole belongs to the age group of 25-34 years. This result is thought to be due to the fact that this age group represents the most reproductive age group and the number of pregnancies is higher than in any other age group.

Both patients who developed total mole belong to the 25-34 year old age group.

A large number of studies (6,10,12,16,17) support the fact that the definitive and most accurate diagnosis for hydatiform mole is made through histopathological examination of material obtained after abortion or through a curettage procedure. Despite the fact that ultrasonography, hCG measurement as well as clinical examination can provide an indication for diagnosis, none of them can accurately determine it, nor can them make a differential diagnosis between the total mole, partial and hydropic abortion.

On the other hand, a recent study published in the Polish Journal of Pathology in 2017 (5) concluded that the diagnosis of partial molar pregnancy cannot be based solely on the histopathological examination data of conception product but should use additional molecular techniques to accurately determine the presence of molar pregnancy. This is important for the patient not only because it enables her to know the reason for her abortion but more importantly because it may occur, albeit in rare cases, that persistent gestational trophoblastic disease is developed after a molar pregnancy.

Another study published in the Journal of Clinical Pathology (15) notes that the reported histologic criteria are either not consistently applied or lacking in practical use, so using molecular biology tests would be helpful in diagnosis. According to this study, total mole can be difficult to distinguish from non-molar pregnancy, but both total mole and non-molar pregnancy cannot be easily distinguished from partial mole.

As can be understood from the data of our study, as well as other studies conducted in different parts of the world, we conclude that the best way available in our country for accurate diagnosis of hydatiform mole is histopathological examination of material obtained after abortion or curettage. Other molecular diagnostics tests would undoubtedly be of great help in differential diagnosis, but still they are not available unfortunately in all labs of the public sector, therefore we can call “histopathology” as the golden standard of diagnostics.

CONCLUSIONS

Accurate diagnosis of the hydatiforme mole is both important and difficult; eventhough the hydatiform mole prevalence is low among

spontaneous abortion. Only histopathological diagnosis is definitive because it directs the woman's follow-up until β-HCG neutralization. Therefore, all materials from abortions and curettage must necessarily be sent to the laboratory to carry out histopathological examination of the material as well as to perform other auxiliary diagnosis tests if necessary. A pregnancy should be avoided for about a year after a molar pregnancy. Mortality and maternal risk are zero during and after the abortion and/or curettage procedures.

Acknowledgments

None declared.

Conflict of interest

None declared.

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