Role of ultrasound examination in the diagnosis of molar pregnancy in Albania: a retrospective study

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Abstract

Aim: Molar pregnancy (MP), the most common form of gestational trophoblastic disease, is statistically associated with an increased risk of gestational choriocarcinoma. Routine use of ultrasound examination has dramatically changed the clinic of MP. In Albania there is scarce information about the effectiveness of ultrasound in early detection of MP. In this context, our aim was to assess the role of ultrasound examination in the diagnosis of MP in Albania.

Methods: A cross-sectional survey was carried out in Tirana among 584 subjects who showed up in "Queen Geraldine" obstetric-gynecologic university hospital with signs and symptoms of missed abortion during 2010-2012. Ultrasound and biopsy examination was carried out and results were compared. Basic demographic information and full history of present and past pregnancies was also retrieved.

Results: The overall prevalence of MP detected by ultrasound and biopsy was 17% and 50%, respectively. The sensitivity of ultrasound examination to detect MP was 31%. According to the type of MP (complete or partial MP), the sensitivity of ultrasound compared to biopsy was 92% and 29%, respectively. Results of ultrasound and biopsy were of moderate strength (Spearman's rho=0.382, P<0.001). Increased age of mother (>40 years) significantly increased the risk of detection of MP via ultrasound by more than five folds (OR=5.4, P=0.002).

Conclusions: Ultrasound examination detects about one third of MPs in Albania. This figure is low compared to the European and world standards where about half of MPs are detected. It is necessary to strengthen diagnosing capacities of molar pregnancies in Albania.

Keywords: Albania, biopsy, hydatidiform mole, sensitivity, ultrasound.

Introduction

Gestational trophoblastic disease (GTD) comprises several proliferative disorders varying from hydati)-diform mole (HM) (complete or partial) to other neoplastic entities such as choriocarcinoma (1,2) with HM being the most common form of GTDs (3). Complete HM is shown to statistically increase the risk of choriocarcinoma (4).

The incidence of HM varies greatly with geography being higher in south-eastern Asia (5,6) with around 6-7 new cases per 1,000 pregnancies and lower in North America (7) and Europe (8) with approximately less than 2 new cases per 1,000 pregnancies.

Risk factors of HM include the extreme age of the mother (either too young, under 20 years of age, or older than 35 years) (2,9,10), previous molar pregnancies (11,12), ethnic group (5-8), genetics (13), and general lower socioeconomic conditions (14,15).

In the past the diagnosis of MP was difficult. The major clinical manifestation of HM in over 85% of patients was vaginal bleeding usually during the second trimester of pregnancy (16), as well as hyperemesis, toxemia and pulmonary emboli (17) whereas preeclampsia was present in about one fourth of HM patients. But recent developments have dramatically changed the situation. The introduction and quick spread of ultrasound examination was decisive for the early detection of GTDs so that any patient presenting with abnormal hemorrhage and other signs of missed abortion was referred to ultrasound examination in order to exclude a GTD diagnosis (18). Today, the clinical manifestations of HM described above are very rare (17) and most patients with this condition present with signs and symptoms of missed abortion during the first trimester of pregnancy (19), that is before classical signs and symptoms of GTDs develop.

The histopathologic examination of gestational tissue remains the gold standard for the diagnosis of HM (16), even though in up to 50% of difficult cases even biopsy might fail (18) and there is no consensus among professionals (20).

The information about GTDs in Albania is relatively low. A study among 100 patients with ectopic pregnancy during 2007-2009 reported a GTD prevalence of 1.5 cases per 1,000 live births (21). Another study from Albania was a case-report about a 28 year-old patient who presented at a private clinic with signs of spontaneous abortion but the diagnosis was ectopic pregnancy in the right fallopian tube with characteristics of partial HM (22). Another publication suggested the prevalence of GTDs to be 0.8 cases per 1,000 live births during 2007-2011 (23).

Yet another report suggested that the prevalence of partial HM among 513 patient undergoing abortion was 16.4% and no association was found between partial HM and mother's age (24).

Despite some data available, mainly about the prevalence of GTDs in Albania, there is no information about the comparison of different tests for the diagnosis of hydatidiform mole in this Balkan country. Therefore, our aim was to compare the results of ultrasound examination against biopsy data in order to evaluate the sensitivity of this easy-to-operate instrument in the diagnosis of HM in Albania.

Methods

This is a cross-sectional study conducted among 584 patients who were either self-referred or referred by a doctor to the premises of the "Queen Geraldine" obstetric-gynecologic university hospital during 2010-2012. The patients included in the study had signs and symptoms suggestive of missed abortion. We included only patients for whom the results of biopsy and ultrasound examinations were available. The inclusion criteria therefore was: showing up in the "Queen Geraldine" hospital with the following signs and symptoms: vaginal bleeding (light or heavy, constant or fluctuant), pain (pelvic cramps, pain in the lower back) accompanying vaginal bleeding, and/or fetal tissue parts or coagula coming out from the vagina. Apart these signs and symptoms, the patient should have had the results of ultrasound and histopathologic examinations as well in order to be part of the study.

Data collection involved the initial consultation with health personnel and retrieving information from the clinical chart. Besides basic socio-demographic data, ultrasound examination of the patient and histo-pathologic examination of fetal tissues was performed

as well. The initial consultation explored in detail the history of previous pregnancies of the patient including the number of birth, abortions and a thorough history of actual complaints.

In order to set the diagnosis, an initial transvaginal ultrasound examination was performed using ACUSON X300 and Siemens Sonoline Sienna equipment. The conduction of the histopathologic examination of fetal tissues was done using the standard hematoxylin-eosine (HE) staining method by selecting the softest, most spongious, non-hemorrhagic parts of the fetal tissue. All membranous elements or fragments without content were removed. The International Federation of Gynecology and Obstetrics (FIGO) staging systems were used to classify the hydatidiform moles (25).

Arithmetic mean and standard deviation was used to describe the scale variables included in the study. For categorical variables absolute numbers and respective percentages were reported. Chi-square test was used to compare differences in proportion of mole detected by ultrasound and biopsy. Measures of criterion validity (sensitivity, specificity, false negative rate, false positive rate, positive predictive value and negative predictive value) of ultrasound examination against results of biopsy (golden standard) were reported. To determine the factors associated with the likelihood of having a mole detected by ultrasound we used the Binary Logistic Regression statistical procedure. Two models of Binary Logistic Regression were used: model 1, reporting crude (unadjusted) odds ratios and Model 2, reporting odds ratios adjusted for mother's age and age of pregnancy. A p-value of ≤ 0.05 was regarded as statistically significant. Spearman's rho coefficient was used to assess the direction and the strength of the bivariate associations between results of ultrasound examination with results of biopsy examination. Statistical Package for Social Sciences (SPSS), version 19.0, was used for all the statistical analyses.

Results

Table 1 displays general information about the study participants. The mean age of study subjects was

Table 1. General information about study participants

Variable	Number	Percentage
Age (in years)*	28.6 ± 6.9	
Age-group		
≤20 years	63	10.8
21-30 years	324	55.5
31-40 years	156	26.7
≥41 years	41	7.0
Employment status		
Employed	140	24.1
Unemployed	442	75.9
Socioeconomic status		
Low	375	64.2
Average	190	32.5
High	19	3.3
Pregnancy age (weeks)*	8.2 ± 1.8	
Gestational age		
≤7 weeks	194	33.2
7.1-8 weeks	159	27.2
>8 weeks	231	39.6
Ultrasound results		
Mole	99	17.0
Non mole	485	83.0
Biopsy results		
Mole	290	49.7
Non mole	294	50.3
Type of mole in biopsy		
Partial mole	279	95.9 †
Complete mole	12	4.1
Total	584	100.0

* Mean value ± standard deviation.

† Proportion within total number of moles detected in biopsy (n=290).

28.6±6.9 years. Around one in ten participants was 20 years old or younger whereas 7% of subjects were at least 41 years old. One quarter of subjects was employed and around 33% were of average socioeconomic status at the time of the survey. The average gestational age was 8.2±1.8 weeks (Table 1).

Table 2 shows the measures of criterion validity for ultrasound examination. The sensitivity of ultrasound to detect molar pregnancy was 31.4%, specificity was 97.3%, positive predictive value was 91.9% and negative predictive value was 58.9%.

Table 2. Results of ultrasound examination by results of histopathologic examination (biopsy)

Variable	Total	Results of biopsy		P-value
		Non mole	Mole	
Results of ultrasound				
Non mole	485 (83.0)	286 (97.3)*	199 (68.6)	<0.001†
Hydatidiform mole	99 (17.0)	8 (2.7)	91 (31.4)	
Total	584 (100.0)	294 (100.0)	290 (100.0)	
Validity measures of ultrasound examination against biopsy examination				
Sensitivity		91/290 = 31.4%		
Specificity		286/294 = 97.3%		
False Negative rate		199/290 = 68.6%		
False Positive rate		8/294 = 2.7%		
Positive Predictive Value		91/99 = 91.9%		
Negative Predictive Value		286/485 = 58.9%		

* Number of subjects and column percentage (in parenthesis).

† P-value (value of statistical significance) according to chi square test.

Table 3 details the information about measures of criterion validity according to the type of hydatidiform mole. It can be noticed that ultrasound examination has a sensitivity of 91.7% in detecting complete hydatidiform mole and a sensitivity of 28.8% for the detection of partial hydatidiform mole compared to the results yielded by biopsy examination.

Table 3. Results of ultrasound examination by results of histopathologic examination (biopsy) according to type of mole

Variable	Total	Biopsy results			P-value
		Non mole	Partial mole	Complete mole	
Ultrasound results					
Non mole	485 (83.0)*	286 (97.3)	198 (71.2)	1 (8.3)	<0.001†
Hydatidiform mole	99 (17.0)	8 (2.7)	80 (28.8)	11 (91.7)	
Total	584 (100.0)	294 (100.0)	278 (100.0)	12 (100.0)	

* Number of subjects and column percentage (in parenthesis).

† P-value (value of statistical significance) according to chi square test.

Table 4 explores the association of ultrasound detected mole with selected variables. It can be noted that, in mother's age and duration of pregnancy' adjusted models, the higher age of the mother increases significantly the likelihood of a mole being detected by ultrasound. For instance, mothers aged 40 years or older are approximately 5 times more likely to be diagnosed with hydatidiform mole by ultrasound compared to mothers aged 20 years or younger (OR=5.37, P=0.002)

whereas mothers aged between 21 and 30 years old have significantly lower likelihood of being diagnosed with a hydatidiform mole in ultrasound examination (OR=0.39, P=0.023). Also, subjects with positive biopsy for MP were 19 times more likely to be also positive in ultrasound examination (OR=18.6, P<0.001). The association with gestational age was not significant.

Table 4. Association of ultrasound diagnosed mole with selected variables; odds ratio (OR) from binary logistic regression

Variable	Model 1[§]		Model 2[‡]	
	OR (95% CI)[*]	P-value	OR (95% CI)	P-value
Biopsy				
Non mole	1.00 (reference)	**<0.001**	1.00 (reference)	**<0.001**
Mole	16.3 (7.8-34.4)		18.6 (7.1-48.7)	
Age-group		***<0.001** (3)*[†]		***<0.001** (3)*[†]
≤20 years	1.00 (reference)	-	1.00 (reference)	-
21-30 years	0.44 (0.22-0.87)	**0.018**	0.39 (0.17-0.88)	**0.023**
31-40 years	0.73 (0.36-1.51)	0.400	0.53 (0.32-1.81)	0.532
≥40 years	4.05 (1.73-9.52)	**0.001**	5.37 (1.82-15.80)	**0.002**
Gestational age		***0.007** (2)*		***0.126 (2)***
≤7 weeks	1.00 (reference)	-	1.00 (reference)	-
7.1-8 weeks	1.05 (0.62-1.76)	0.861	1.27 (0.66-2.42)	0.474
>8 weeks	0.47 (0.27-0.80)	**0.006**	0.63 (0.33-1.21)	0.166

* Odds Ratio (OR) and 95% confidence interval (in parenthesis).
† P-value and degrees of freedom (in parenthesis).
§ Model 1: unadjusted (uncontrolled) for any factor; crude ORs and 95% CIs.
‡ Model 2: adjusted (controlled) simultaneously for age of the mother and age of pregnancy.

Discussion

This study for the first time provided a detailed picture about the effectiveness of ultrasound examination in the diagnosis of molar pregnancy and, more specifically, in the diagnosis of complete and partial moles against the results of biopsy among pregnant women showing up with vaginal bleeding and other signs of missed abortion. Our study is amongst few studies reporting data about the distribution of HMs among women with clear clinical signs of problematic pregnancy, mainly during the first trimester of pregnancy. Previous studies in Albania tackling similar issues have focused on HM among ectopic pregnancies whereas we included a wider range of problems affecting pregnancy.

As we mentioned earlier, information about GTDs in Albania is relatively low. A study among 79 ectopic pregnancy patients for which biopsy was available during 2007-2009 reported that the prevalence of partial and complete mole was 13.9% and 8.9%, respectively (21) whereas in our study we reported a prevalence of 47.6% and 2.1%, respectively. Another study published by Tasha et al., which covered the period 2007-2011 (23), reported that the prevalence of partial mole was 8.7% among 103 ectopic cases for whom biopsy results were available (23). Our results differ greatly from those reported by Tasha et al. which could be due to different population used in each study. It is possible that completely different selective factors have determined the population of women showing up in each of the study sites and, consequently, have affected their chances of being included in each of the studies. For example, the mean age of participants in our study was almost 29 years whereas in the study by Tasha et al. this figure was 23 years (21). However, the discrepancies are very high and warrant careful investigation in future studies.

Another study reported on the incidence of partial

mole, diagnosed through biopsy of fetal tissue, among 513 patients hospitalized with the diagnosis of missed abortion, blighted ovum, incomplete abortion and dead embryo (24). In this case the mean age of patients was 34 years. The prevalence of partial HM was 16.6% (24). The authors did not find an association between mother's age with partial mole (24) whereas in our study we found such an association. It can be noted that the informations about the prevalence of HM in Albania are very heterogeneous, even in studies conducted by the same authors in different time periods. Therefore, future studies should be conducted in order to shed light and to clarify the situation about these health conditions in our country.

However, it was not our aim to come with representative figures about the prevalence of molar pregnancy in Albania. Rather, our focus was on the effectiveness of ultrasound examination in detecting molar pregnancies among patients with signs of missed abortion. No previous study in Albania has addressed this issue. Therefore, our data can only be compared with those being reported in the international literature. The correct diagnosis of complete and partial molar pregnancies is very important from the clinical perspective because such anomalies increase the risk of developing into other more serious diseases, including choriocarcinoma. These diseases occur in about 15% of subjects with previous complete HM and about 0.5% of those with previous partial HM (26).

As regards the comparison of ultrasound and biopsy results reported in our study, the figures are comparable to those reported in the international literature, even though the sensitivity of ultrasound examination in our study was lower. For example, it is suggested that ultrasound might detect up to 50% of moles compared to biopsy result. However, a number of factors might hinder the sensitivity of ultrasound in detection of molar pregnancies. The most important factor here is the gestational age: the lower the gestational age the lower the sensitivity of ultrasound to detect a molar pregnancy (27). In a study involving four women with very early complete mole (gestational age between 6.5 and 11 weeks) reported that in all cases the ultrasound examination had miss-classified the entity as missed abortion (27) and the diagnosis was set only through biopsy (27). This information is very important in order to understand the results of our study. If we recall the gestational age of our study subjects, we see that in around 60% of cases the gestational age was 8 week or less (therefore, within the first trimester) and in 95% of cases the gestational age was less than 11 weeks with a mean value of 8.2 weeks. Therefore, in our study about 70%-80% of moles were very early hydatidiform moles. In this context, it is understandable why the ultrasound examination struggles to set the correct diagnosis: because it is too early for the typical molar changes to be detectable by ultrasound. Even in international literature it is recognized that ultrasound detection of very early moles is problematic (28,29), because of the poor clinical manifestations and few histopathologic findings (28). Changes in this stage of pregnancy are so subtle that even biopsy finds it challenging to put the right diagnosis (28,29).

The fact that molar pregnancies today are usually seen during the first trimester of pregnancy, as evidenced also by our study where over 95% of subjects had a gestational age under 12 weeks, has a logical explanation: because they are detected earlier thanks to the massive use of ultrasound examination (30-32), even though it has not a high sensitivity in detecting molar pregnancies (31). Today, the main clinical feature of molar pregnancies is the vaginal bleeding, and very rarely one can present with enlarged uterus, anemia, pre-eclampsia, hyperemesis and hyperthyroidism (30,31).

Different studies have reported about the success rate of ultrasound in detection of molar pregnancies against biopsy. For example, a study among 90 women suspected to have HM during 2002-2006 reported that the prevalence of biopsy confirmed mole was 61 cases or 68% (31). Among these 61 cases, 67% had partial mole and 33% complete mole (31). The corresponding figures in our study were 49.7%, 95.9% and 4.1%, respectively.

Sensitivity of ultrasound in the study by Kirk et al. was 44% for moles in general, but it was 95% for complete moles and 20% for partial moles (31). In our study, these figures were 31.4%, 91.7% and 28.8%, respectively. Therefore, our results are comparable to those reported in the literature as regards the rate of detection of partial and complete moles, but the overall detection rate is obviously lower (31% in our study vs. 44% in the study by Kirk et al.). Another study published in 2006 reported figures which were similar to those in our study. In this study involving 1053 patients suspected for HM, ultrasound and biopsy examination was performed (32). Mean age of participants was 31 years (in our study: 29 years). The prevalence of HM confirmed by biopsy was 82% (29% complete mole and 71% partial mole) (32). The sensitivity of ultrasound for the diagnosis of moles in general, complete and partial moles in this study was 44%, 79% and 29% respectively (32), being similar to those reported by our study. Yet another study comparing ultrasound and biopsy results regarding the diagnosis of molar pregnancies reported that the sensitivity of ultrasound for the detection of molar pregnancy, complete and partial moles was 34%, 58% and 17%, respectively (19). Other studies reported corresponding sensitivity of 56%, 90% and 48.5%, respectively for molar pregnancy, complete and partial mole (29) whereas a recent study reported that the sensitivity of ultrasound examination for the detection of complete mole and partial mole was 73% and 35%, respectively (33).

It can be concluded that around 50% of molar pregnancies can be detected by ultrasound examination. Obviously the rate of detection is much higher for complete moles (up to 90%) than for partial moles (up to 50%) (29,32,33).

Although ultrasound has low sensitivity for the detection of HM, especially during the first trimester of pregnancy, it has played a big role toward the changing of the clinical manifestations of hydatidiform moles, as discussed earlier. However, it is difficult to predict if the sensitivity of ultrasound will be improved in the future since the changes occurring in early molar pregnancies are too subtle to be detectable by ultrasound examination (34). On the other hand, since the medical treatment of missed abortion is usually not followed by fetal tissue taking for biopsy purposes, then a considerable number of women with early signs of problematic pregnancies could actually experience HM but will be misclassified as missed abortion by ultrasound examination and therefore will be inadequately followed-up (32).

In summary, the sensitivity of ultrasound for detecting molar pregnancies in Albania is lower compared to the practices in the international arena. There is need to strengthen the diagnosing capacities of local professionals in order to improve the detection rates of HM in our country.

Conflict of interest: None declared.

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