# A prospective Study of Ultrasound Screening for Molar Pregnancies in Missed Miscarriages in Eastern Region of Afghanistan

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## ABSTRACT

**Introduction** Miscarriage is the natural death of an embryo or fetus before it is able to survive independently. The most common symptom of a miscarriage is vaginal bleeding. About 80% of miscarriage occur in the first 12 weeks of pregnancy.

**Objective:** The aim of this study was to prospectively evaluate the role of ultrasound examination in screening for molar changes in women diagnosed with a first-trimester miscarriage. In addition to examine the relationship between ultra- sound and histological features in the screening for molar changes in missed miscarriage.

**Methods:** A prospective cohort study was conducted on all missed miscarriages, with features suspicious of molar pregnancy, on transvaginal ultrasound and/or on histological examination in Nangarhar University Teaching Hospital over a 2-year period. All cases of molar pregnancy diagnosed histologically were examined and cross-referenced with cases diagnosed on ultrasound and with the supplementary report from the regional referral center. When available, maternal serum β-human chorionic gonadotropin (hCG) levels were recorded.

**Results:** seventy-one cases of suspected molar pregnancy were referred to the regional center for further histological opinion and follow-up, and nine cases were subsequently excluded from the final analysis because of the diagnosis of hydropic abortion (HA). In 45 cases a molar pregnancy was suspected at the initial scan. Of these, 35 (77.7%) were confirmed on histology, resulting in a 56% detection rate using ultrasound alone. In 20 cases hCG results were available, of which twelve were greater than two multiples of the median.

**Conclusions:** The diagnosis of both complete (CHM) and partial (PHM) hydatid form moles in first-trimester miscarriages is difficult. hCG is significantly higher in both CHM and PHM and, in conjunction with transvaginal ultrasound, could provide the screening test required to enable clinicians to counsel women more confidently towards non-surgical methods of management of their miscarriage, where histopathological examination is not available.

**KEYWORDS**: histopathology; miscarriage; mole; placenta; ultrasound.

## INTRODUCTION

Miscarriage, also known in medical terms as a spontaneous abortion and pregnancy loss, is the natural death of an embryo or fetus before it is able to survive independently. The most common symptom of a miscarriage is vaginal bleeding with or without pain. Sadness, anxiety and guilt may occur afterwards. Tissue and clot-like material may leave the uterus and pass through and out of the vagina. About 80% of miscarriages occur in

the first 12 weeks of pregnancy (the first trimester). The underlying cause in about half of cases involves chromosomal abnormalities. Diagnosis of a miscarriage may involve testing blood levels of human chorionic gonadotropin (hCG), and an ultrasound. Routine histopathological examination in sporadic miss- carriage has generated a lot of debate and controversy mainly because of the inaccuracy of histological criteria in identifying the cause of a miscarriage in very early pregnancy. It is well established that more than 50% of sporadic miscarriages are associated with a chromosomal defect of the conceptus and that the incidence of chromo- some abnormality increases with increasing maternal age and decreasing gestational age1,2. Most of these abnormalities are numerical chromosomal abnormalities and less than 10% are caused by structural abnormalities or other genetic mechanisms3. The overall recurrence risk of numerical chromosomal abnormalities is low and the risk of live born trisomy following an aneuploidy early pregnancy failure is around 1%4. Within this context, the role of routine histology of sporadic miscarriage is limited. Molar pregnancy is an abnormal form of pregnancy in which a non-viable fertilized egg implants in the uterus and will fail to come to term. It is characterized by the presence of a hydatidiform mole (or hydatid mole, mola hydatidosa). Molar pregnancies are categorized as partial moles or complete moles; however, a molar pregnancy is a condition that needs to be detected because of the potential long-term risk to the mother.

The estimated incidence of partial hydatidiform mole (PHM) is 1 in 700 pregnancies whereas the incidence of complete hydatidiform mole (CHM) is around 1 in 1500 – 2000 pregnancies[5,6]. The vast majority of CHM and PHM pregnancies miscarry spontaneously during the first 3 – 4 months of pregnancy resulting in an incidence of molar placenta of 1 in every 41 miscarriages[5]. Following uterine evacuation, approximately 10 – 20% of women with a CHM develop persistent gestational trophoblastic disease (GTD)[7]. The incidence of this complication after a PHM ranges between 0.5% and 11%[7–10] and is almost certainly underestimated since many early PHM, and therefore persistent trophoblastic disease, will escape diagnosis.

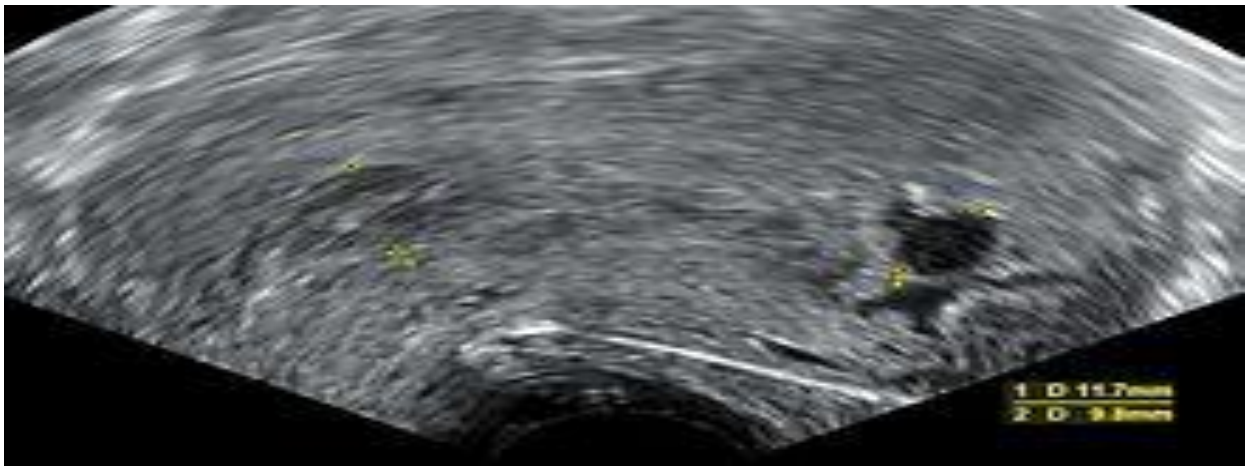

**Figure 1**; Transvaginal ultrasonography, with some products of conception in the cervix (to the left in the image) and remnants of a gestational sac by the fundus (to the right in the image), indicating an incomplete miscarriage.

Placental molar changes can now be detected from the third month of pregnancy by ultrasound which typically reveals a uterine cavity filled with multiple, sonolucent areas of varying size and shape (‘snowstorm appearance’) without associated embryonic or fetal

structures in the case of CHM[11]. In the case of a PHM, the early ultrasound diagnosis may be more difficult because the placental changes may be limited to a few molar villi and/or an increase in placental thickness[12,13] (Figure 2). The aim of this study was to prospectively evaluate the role of ultrasound examination in screening for molar changes in women diagnosed with a first-trimester miscarriage. In addition, when available, we measured preoperative maternal serum β-human chorionic gonadotropin (hCG) to examine the additional role hCG may play in improving diagnostic accuracy.

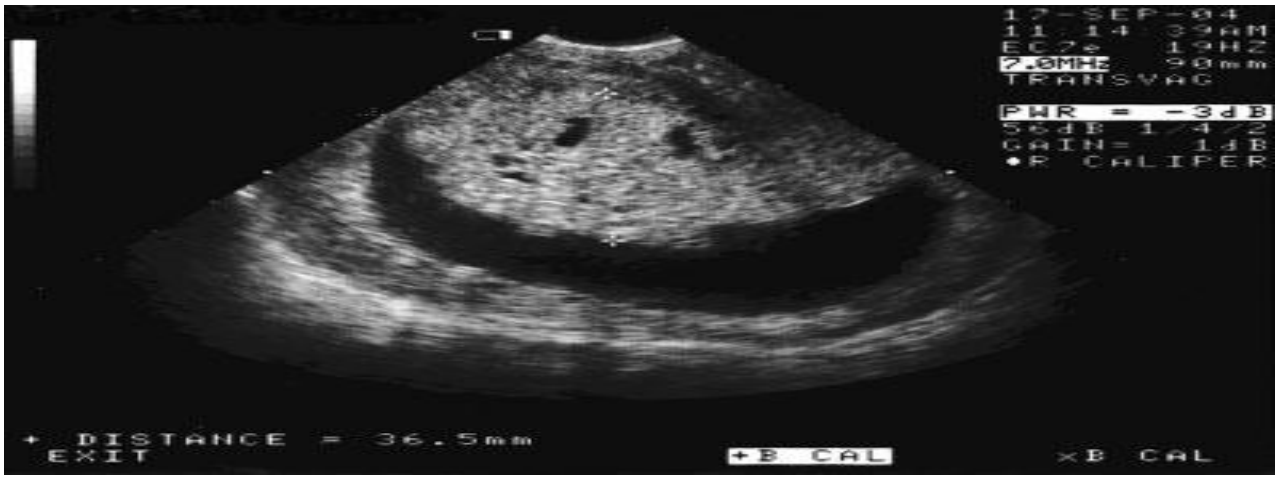


**Figure 2;** Transvaginal ultrasound image of a partial molar pregnancy at 9 weeks' gestation demonstrating increased placental thickness and molar cystic changes.

## METHODS

The study group comprised all women presenting to the unit over a 2-year period from April 2018 to March 2020. All women presenting to the obs and gynae ward of Nangrahar university teaching hospital with symptoms of miscarriage were offered transvaginal ultrasound (TVS) as part of their medical assessment. All scans were performed by the same operators using an Acuson XP/128 ultrasound machine equipped with a 7- MHz transvaginal probe (Siemens, Mountain View, CA, USA). Referrals were received from general practitioners or patients had presented via the accident and emergency department.

All women with suspected molar pregnancy on TVS were recommended surgical evacuation of the uterus (ERPC) and tissue was sent for histological examination and karyotyping where possible in our local histopathology department. Preoperative hCG levels were recorded in 20 women suspected of having a molar pregnancy on ultrasound. All cases of molar pregnancy diagnosed histologically were examined and cross-referenced with cases diagnosed on ultrasound. Twenty-five cases of missed miscarriage, where a preoperative serum hCG was taken and histology was performed, that were collected in the same time period were used as a control group for comparison of serum hCG levels.

The diagnostic criteria used for the diagnosis of a molar pregnancy included, on ultrasound, in the case of CHM, the typical cystic or 'snowstorm' appearance within the uterine cavity, in the absence of recognizable fetal tissue12,14. PHM was diagnosed in the presence of a non-viable fetus or missed miscarriage together with an enlarged placenta with or without cystic change.

## RESULTS

A total of 3025 women were seen in the obs and gynea ward over the 2-year period. There were 1107 (36.6%) miscarriages of which 221 (20%) were incomplete, 619 (56%) complete

and 265 (24%) missed miscarriages. The rate of ERPC was approximately 70% for every year of the study period corresponding to 340 cases in 2 years, all of which had a specimen sent for histological examination. The remaining 30% were women presenting with an incomplete miscarriage or very early missed miscarriage with a maximal sac diameter of 20 mm and no evidence of molar changes. Five cases were excluded from the final analysis when the diagnosis was confirmed as hydropic abortion (HA). In 45 cases a molar pregnancy was suspected at the initial scan. Of these, 36 (78.8%) were subsequently confirmed on histology resulting in a 56% detection rate on ultrasound alone. Thirteen (38%) were CHM and 22 (62%) were PHM, with detection rates of 90% for CHM and 48.5% for PHM.

Table 1 presents the results of the preoperative hCG measurements in 20 cases of suspected molar pregnancy. In twelve cases the hCG was greater than 2 MoM (multiples of the median). Nine of these cases were CHM. In two cases the initial ultrasound diagnosis was of missed miscarriage and the preoperative hCG levels were 0.4 and 0.6 MoM. Initial histological diagnosis had been suggestive of molar change but was subsequently confirmed as HA. Of the 18 (39%) cases that were not suspected prior to evacuation, 17 (95%) were found to be PHM and one (5%) CHM.

Table 2 presents the serum hCG levels for the molar pregnancies compared with the missed miscarriages for each gestation represented. For all gestations the serum hCG levels were considerably lower in the missed miscarriages compared with the molar pregnancies, and were more than half of the median levels for normal pregnancies in all cases.

Table 1 Preoperative human chorionic gonadotropin (hCG) results in 20 cases suspected of having a molar pregnancy on ultrasound.

| Case | Gestation By LMP (Weeks) | Gestation By LMP (Weeks) | Scan | Diagnosis | HCG | |
|---|---|---|---|---|---|---|
| | | | | | IU/L | MoM |
| 1 | 8 | NA | CHM | CHM | 401 900 | 5.00 |
| 2 | 10 | NA | CHM | CHM | 195 280 | 2.75 |
| 3 | 6 | 6 | Missed | HA* | 11 793 | 0.40 |
| 4 | 10 | 10 | PHM | PHM | 765 500 | 10.80 |
| 5 | 7 | 7 | Missed | HA* | 35 319 | 0.60 |
| 6 | 10 | NA | CHM | CHM | 287 565 | 4.00 |
| 7 | 10 | 6 | PHM | PHM | 67 178 | 0.95 |
| 8 | 7 | 5 | PHM | PHM | 61 401 | 1.05 |
| 9 | 7 | NA | PHM | PHM | 17 972 | 0.30 |
| 10 | 9 | NA | CHM | CHM | 325 200 | 3.55 |
| 11 | 5 | 5 | CHM | CHM | 34 275 | 4.26 |
| 12 | 11 | 7 | PHM | PHM | 82 088 | 1.40 |
| 13 | 7 | NA | CHM | CHM | 181 801 | 3.10 |
| 14 | 6 | 6 | CHM | CHM | 77 699 | 2.60 |
| 15 | 8 | NA | PHM | PHM | 359 299 | 4.50 |
| 16 | 6 | 6 | CHM | CHM | 34 275 | 4.26 |
| 17 | 10 | 10 | PHM | PHM | 82 088 | 1.40 |
| 18 | 8 | 7 | CHM | CHM | 181 801 | 3.10 |
| 19 | 7 | NA | PHM | PHM | 17 972 | 0.30 |
| 20 | 5 | 5 | PHM | PHM | 359 299 | 4.50 |

*Cases that were initially suspected as being molar pregnancies on histology but subsequently confirmed to be hydropic abortions (HA). CHM, complete hydatidiform

mole; LMP, last menstrual period; Missed, missed miscarriage; MoM, multiple of the median; NA, not applicable; PHM, partial hydatidiform mole.

Table 2 Preoperative human chorionic gonadotropin in multiples of the median (MoM) for molar pregnancies compared with missed miscarriages.

| Gestation (weeks) | MoM | | |
|---|---|---|---|
| | PHM | CHM | Missed miscarriage |
| 5 | NA | 4.26 | NA |
| 6 | NA | 2.60 | 0.40* |
| 7 | 1.05<br>0.30 | 3.10 | 0.60* |
| 8 | 4.5 | 5.0 | 0.13<br>0.24<br>0.18<br>0.14<br>0.19 |
| 9 | NA | 3.55 | 0.52<br>0.12<br>0.06<br>0.25<br>0.05 |
| 10 | 0.95<br>10.80 | 4.00<br>2.75 | 0.25<br>0.05<br>0.15 |
| 11 | 1.40 | NA | 0.44<br>0.38<br>0.25<br>0.08<br>0.06 |
| 12 | 4.5 | 5.0 | 0.13<br>0.24<br>0.18 |
| 13 | 1.05 | 3.10 | 0.60* |

*Cases that were suspected on initial histology to be molar pregnancies but later confirmed to be hydropic abortions. CHM, complete hydatidiform mole; NA, not applicable; PHM, partial hydatidiform mole. were more than half of the median levels for normal pregnancies in all cases.

## DISCUSSION

We have demonstrated that the combination of ultrasound and quantitative serum hCG could be used as a screening tool to help determine which cases of first-trimester missed miscarriage are molar pregnancies. This is becoming more important as women are presenting earlier in pregnancy, when histopathological diagnosis of molar pregnancy is less accurate. In addition, there is an increasing demand from women for conservative or medical management of missed miscarriages where histopathological examination is not available, and the use of simple screening and follow-up techniques may reduce the number of cases that go unrecognized.

Histological examination of early products of conception will identify about 60–70% of molar pregnancies14. The distinction between CHM and PHM was made in the late 1970s on the basis of gross morphological, histological and cytogenetic criteria in second- and third-trimester pregnancies15,16. The complete or classical hydatidiform mole has been defined as a conceptus with a placenta showing generalized swelling of the villi and diffuse trophoblastic hyperplasia, in the absence of an ascertainable fetus17. The PHM has been characterized by focal trophoblastic hyperplasia with focal villous hydrops and identifiable embryonic or fetal tissue. The clinic pathological picture of the two molar syndromes overlap to a degree since both the phenotype and natural history of the PHM seem to represent a mild, bland version of those of the CHM18.

Morphological features, including villus size and proliferative activity of trophoblast, change with gestation and need to be taken into account when examining specimens of varying gestations19. Difficulties arise when differentiating between PHM, CHM and HA, particularly when there is prolonged postmortem retention in utero in missed miscarriage for example14 and where there are focal hydropic changes found in aneuploidies. It has been suggested that PHM in the first trimester are frequently missed on ultrasound, with detection rates as low as 17%20, and that pathological examination should remain the mainstay of diagnosis9. The debate surrounding whether or not tissues obtained after evacuation of the uterus should be sent for routine histological examination has been long and is still unresolved21. Routine histological examination of products of conception is expensive and time consuming and the histological features of molar pregnancy are also different in the first trimester. Misclassification occurs due to the absence of strict morphological criteria in the first trimester22. The classical pathological features are more subtle in early CHM than at later gestations23. Again, diagnosis is even more difficult in PHM, where features of molar change can be absent. In PHM the trophoblastic hyperplasia is often focal involving the syncitiotrophoblast only14,18 and this may result in errors due to insufficient sampling of the placenta. PHM are practically always triploid, having inherited two sets of chromosomes from the father and one from the mother24. Triploid diandric partial moles are certainly more common in early pregnancy loss than non-molar digynic triploidies25 but seem to be associated with a lower risk of persistent GTD than second-trimester triploid PHM9. Triploid pregnancies are more common in the first trimester26 and the vast majority of CHM and PHM miscarry in the first trimester, resulting in the possibility that a large group of women at risk of GTD may be not be diagnosed and followed up if these pregnancies are not screened.

Since the introduction of early ultrasound, the classification of molar pregnancies has become more difficult because they are evacuated earlier and before the stage of development at which they have obvious macroscopic features. PHM usually presents as a missed or incomplete miscarriage in the first trimester and the diagnosis is often only made after histological examination of the products of conception6,20,27. Typical ultrasound features may or may not be present, with the diagnosis of PHM often being difficult even in later gestations, presenting with fetal growth restriction or subtle placental changes. Ultrasound features of CHM may also be different at earlier gestations and accuracy of diagnosis varies between studies28,29. Until recently, up to 50% of women with CHM aborted spontaneously before the diagnosis was made. Several ultrasound features have been proposed that might increase ultrasound detection of molar change in missed miscarriages in the first trimester. These include gestational sac diameter ratios, cystic changes in the placenta, and increased echogenicity of the maternoembryonicinterface30–32. The ultrasound diagnosis of CHM usually poses little

problem from the third month of pregnancy onwards and can be made prenatally in around 80% of cases11,28,29,33. In contrast, the ultrasound diagnosis of PHM is less accurate and around 70% of those cases will be missed antenatally33. In the present series, of the 18 cases that were not detected pre-evacuation, 17 (95%) were PHM. Despite this, of the cases that were detected, 62% were PHM, demonstrating that detection, even early in the first trimester, is possible. Pre-evacuation hCG levels may be a useful adjunct to histology in first trimester spontaneous miscarriages, in particular in cases with unusual ultrasound appearances18. In the present series, 9/13 molar pregnancies in which a preoperative hCG was available demonstrated an hCG of 2.6 to 10.8 MoM (Table 1). The two cases of HA had very low hCG levels. Disappointingly, in three cases of PHM, the MoM was low. This may be explained by the fact that there was a significant discrepancy between gestational age from the date of the last menstrual period and the dates suggested by the ultrasound scan. This would suggest prolonged postmortem retention and trophoblast degeneration, explaining the low hCG. Even lower levels of hCG were found in non-molar missed miscarriages (Table 2). In none of these cases was the hCG level above 0.6 MoM, whereas the cases of PHM were all 1 MoM or above. In a study of triploid partial moles, all cases had increased hCG MoM (intact and free β-hCG)34. Ongoing CHM are associated with β-hCG levels of 10–200 MoM and PHM with levels of 10–60 MoM13. In the case of CHM, the typical ultrasound features in association with a high hCG are highly suggestive of molar pregnancy even before histological diagnosis confirms this11.

Our data also suggest that in our unit there is a false positive rate of up to 20% in the diagnosis of PHM on ultrasound. Whilst this is reassuring as it suggests that there is a high level of vigilance, the addition of hCG will inevitably refine the screening process in these cases. The use of serum hCG as a screening tool to identify those women with missed miscarriages who are at risk of molar pregnancy would not only help to refine the diagnostic process, but also enable us to counsel women more confidently towards non-surgical methods of management if the hCG is low. It would also provide us with a useful follow-up tool for those cases in which histopathological assessment is not possible for technical reasons or after termination of pregnancy where it is restricted by cost constraints.

## CONCLUSION

The diagnosis of both complete (CHM) and partial (PHM) hydatid form moles in first-trimester miscarriages is difficult. hCG is significantly higher in both CHM and PHM and, in conjunction with transvaginal ultrasound, could provide the screening test required to enable clinicians to counsel women more confidently towards non-surgical methods of management of their miscarriage, where histopathological examination is not available.

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