Ultrasound diagnosis of complete and partial hydatidiform moles in early pregnancy failure: an inter-observer study

Eric Jauniaux[1], Maria Memtsa[1], Jemma Johns[2], Jackie A Ross[2], Neil J Sebire[3], Davor Jurkovic[1]

[1]EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London (UCL), London, UK.

[2]Early Pregnancy and Gynaecology Assessment Unit, Kings College Hospital, London, UK.

[3]UCL Great Ormond Street Institute of Child Health and NIHR GOSH BRC, London, UK.

No funding was obtained for this project.

The authors have no conflict of interest to declare.

Word count: 1009

Correspondence to: *Professor Eric Jauniaux,*
EGA Institute for Women's Health, *University College London,*
86-96 Chenies Mews,
London WC1E 6HX, UK.
Telephone numbers: +44/207/3908113
Fax: +44/207/3908115
E-mail: e.jauniaux@ucl.ac.uk

Key Words: Hydatidiform mole; Complete mole; Partial mole; Ultrasound imaging; First trimester; Miscarriage.

Abstract

We retrospectively evaluated the accuracy of the ultrasound signs at the initial examination suggestive of complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM) in a cohort of women with histologically confirmed hydatidiform mole (HM) who presented with early pregnancy failure, including 103 CHM and 95 PHM for which ultrasound images were available. The accuracy of the differential diagnosis was significantly ($p<0.001$) greater during secondary examination compared with the original primary ultrasound examination. The interobserver agreement analysis indicated only a fair to moderate agreement between the two examinations (kappa value 0.41; 95% CI 0.29-0.53). Most HM present as early pregnancy failure and identification of early ultrasound signs at the first scan improve the diagnosis of CHM but around half of PHM remains undiagnosed by ultrasound.

Introduction

Hydatidiform moles (HMs) are defined histologically by trophoblast hyperplasia which may lead to the development of gestational trophoblastic neoplasia (GTN), often within months after the evacuation of the molar tissue [1,2]. Microscopically, complete hydatidiform moles (CHM) are characterised by generalised dysmorphism, hydrops of the villous mesenchyme and absence of a fetus [3]. In partial hydatidiform moles (PHM), there is fetal development and the villous dysmorphic changes are focal [3]. With advances in ultrasound imaging, the diagnosis of HMs has shifted from the second to the first trimester of pregnancy [4-10]. Villous hydrops in HM is a progressive phenomenon and molar changes may not be visible until the end of the first trimester, in particular in PHMs where the molar changes are focal.

The vast majority of HMs miscarry in the first trimester of pregnancy and the combined incidence of CHM and PHM in early pregnancy failure ranges between 1 per 19 cases of clinical miscarriage [9] and 1 per 41 early pregnancy losses examined histologically [11]. The risk of post-molar GTN is not affected by the gestational age at diagnosis or evacuation [12] but women with CHM have a 15-20% risk of GTN compared to 0.5-1% for PHM [1,2].

Women presenting with early pregnancy failure may not be diagnosed with HM if they opt for a conservative or medical management or if there is insufficient villous tissue available for histopathological examination and thus will not benefit from follow-up. Thus, the accuracy of the initial ultrasound examination in these cases can have an impact on the management of women

with HM. In early pregnancy (4-5 weeks of gestation), CHM may appear as a morphologically normal gestational sac containing a chorionic cavity and sometimes a secondary yolk sac [13]. At around 6-7 weeks, the molar tissue often appears as a heterogeneous, mainly dense but often polypoid mass [13-16], before developing into typical generalised hydatidiform mole in the following weeks [13]. In PHM, the first ultrasound sign is often placental enlargement with an abnormally developing fetus and the hydropic changes of some villi are often not visible before 10 weeks of gestation. The purpose of the present study was to evaluate the role of these early ultrasound features in the differential diagnosis between CHM and PHM in women presenting with early pregnancy failure.

Methods

The study group included 198 patients presenting with a missed or incomplete miscarriage at $\leq$ 13 weeks of gestation at the Early Pregnancy Assessment Unit (EPAU) at University College London (UCLH) or King's College Hospital (KCH), diagnosed histologically (Charing Cross Hospital (www.hmole-chorio.org.uk), Imperial College, London) with HM following surgical evacuation, between March 2003 and December 2017. Only cases with ultrasound images available for retrospective review were included in this study. All ultrasound images were anonymised for the analysis and reviewed using previously described diagnostic criteria [9,10,13].The protocol and a waiver of consent were granted a favourable opinion by the NHS Health Research Authority (REC 18/WM/0328).

For the retrospective (secondary) examination, the principal investigators (EJ & MM) were blinded to results of the original (primary) ultrasound examination and whether histopathology diagnosis was CHM or PHM. The comparison was performed for the initial ultrasound examination when the patient presented for care and was diagnosed with a missed or incomplete miscarriage. Stata (STATA software (version 15; StataCorp, College Station, TX) was used to perform the statistical analysis. Categorical variables were compared using chi-squared (χ^2) test. The McNemar test was used to compare the percentage of cases where a correct diagnosis of CHM versus PHM was made between observers at the initial ultrasound examination. Interobserver variability rates were based on each observer's first ultrasound examination. Kappa statistics and percentage agreement are reported according to Landis and Koch [19]. A p value of <0.05 was considered significant.

Results and Discussion

Ultrasound images were available for review in 198 cases of HM including 103 CHM and 95 PHM. Ninety-two patients had more than one ultrasound examinations. Table 1 compares the results of the primary and secondary evaluation at the initial ultrasound examination. Significantly ($p<0.001$) higher correct diagnoses were found during the secondary examination compared with the original primary examination. The overall interobserver agreement between the primary and secondary examinations was moderate for HM (Kappa 0.41; 95%CI 0.29;0.53), slight for CHM (Kappa 0.15, 95%CI 0.03;0.27) and fair for

PHM (kappa value 0.39, 95% CI 0.22-0.57). These suggest that the ultrasound diagnosis of PHM remains difficult even when the images are reviewed by experts.

In the vast majority of CHM, the sonolucent cystic areas corresponding to hydropic molar villi and the loss of a recognisable gestational sac should be identifiable from 9 weeks of gestation on ultrasound examination. In PHM, the hydropic villi are in small numbers often within an enlarged placenta and are difficult to differentiate from the hydropic changes associated with prolonged retention after fetal demise often seen in missed miscarriages. This can explain the higher accuracy of ultrasound imaging in diagnosing CHM compared to PHM in early pregnancy failure at the initial ultrasound examination. The accuracy of the ultrasound diagnosis is also operator dependent and the data of the present study suggest that awareness of the early ultrasound signs of CHM, which we previously described [13] i.e. polypoid heterogeneous hyperechogenic mass (figure 1 A), should improve the detection rate of this anomaly in women presenting with early pregnancy failure.

In conclusion, women with HM are likely to be first seen with clinical symptoms and an ultrasound diagnosis of early pregnancy failure. Awareness of early ultrasound signs by ultrasound operator could improve the overall management for HM with predicted detection rates of up to 95% of CHM at the first ultrasound examination. It is likely that around half of PHM would remain undetected by ultrasound examination, necessitating routine histological evaluation of the products of conception to ensure accurate diagnosis.

References

1. M.J. Seckl, N.J. Sebire, Berkowitz RS. Gestational trophoblastic disease. Lancet (2010);376:717-29.
2. H.Y.S. Ngan, M.J. Seckl, R.S. Berkowitz, Y. Xiang, F. Golfier, P.K. Sekharan, J.R. Lurain, L. Massuger. Update on the diagnosis and management of gestational trophoblastic disease. Int. J. Gynaecol. Obstet. (2018); 143 Suppl 2: 79-85.
3. E. Jauniaux. Partial moles: from postnatal to prenatal diagnosis. Placenta (1999); 20: 379-88.
4. E. Lazarus, C.A. Hulka, B. Siewert, D. Levine. Sonographic appearance of early complete molar pregnancies. J. Ultrasound. Med. (1999); 18: 589-593.
5. C.B. Benson, D.R. Genest, M.R. Bernstein, V. Soto-Wright, D.P. Goldstein, R.S. Berkowitz. Sonographic appearance of first trimester complete hydatidiform moles. Ultrasound. Obstet. Gynecol. (2000); 6: 188-191.
6. D.J. Fowler, I. Lindsay, M.J. Seckl, N.J. Sebire. Routine pre-evacuation ultrasound diagnosis of hydatidiform mole: experience of more than 1000 cases from a regional referral center. Ultrasound. Obstet. Gynecol. (2006); 27: 56-60.
7. E. Kirk, A.T. Papageorghiou, G. Condous, C. Bottomley, T. Bourne. The accuracy of first trimester ultrasound in the diagnosis of hydatidiform mole. Ultrasound. Obstet. Gynecol. (2007); 29: 70-75.

8. D.J. Fowler, I. Lindsay, M.J. Seckl, N.J. Sebire. Histomorphometric features of hydatidiform moles in early pregnancy: relationship to detectability by ultrasound examination. Ultrasound. Obstet. Gynecol. (2007); 29: 76-80.
9. J. Johns, N. Greenwold, S. Buckley, E. Jauniaux. A prospective study of ultrasound screening for molar pregnancies in missed miscarriages. Ultrasound. Obstet. Gynecol. (2005); 25: 493-497.
10. J.A. Ross, A. Unipan, J. Clarke, C. Magee, J. Johns. Ultrasound diagnosis of molar pregnancy. Ultrasound (2018); 26: 153-159.
11. M.D. Jeffers, P. O'Dwyer, B. Curran, M. Leader, J.E. Gillan. Partial hydatidiform mole: A common but underdiagnosed condition. A 3-year retrospective clinicopathological and DNA flow cytometric analysis. Int. J. Gynecol. Path. (1993); 12: 315-323.
12. S.Y. Sun, A. Melamed, D.P. Goldstein, M.R. Bernstein, N.S. Horowitz, A.F. Moron, I. Maestá, A. Braga, R.S. Berkowitz. Changing presentation of complete hydatidiform mole at the New England Trophoblastic Disease Center over the past three decades: does early diagnosis alter risk for gestational trophoblastic neoplasia? Gynecol. Oncol. (2015);138:46-9.
13. E. Jauniaux, M. Memtsa, J. Johns, J.A. Ross, D. Jurkovic. New insights in the pathophysiology of complete hydatidiform mole. Placenta (2018); 62: 28-33.
14. S.I. Jung, M.H. Moon, J.A. Kim, M.J. Song, Y.J. Kim, Y.H. Lee. Characteristic sonographic vesicular pattern of a complete

hydatidiform mole in the early first trimester. J. Reprod. Med. (2008); 53: 865-868.

15. J.L. Savage, K.E. Maturen, E.L. Mowers, K.B. Pasque, A.P. Wasnik, V.K. Dalton, J.D. Bell. Sonographic diagnosis of partial versus complete molar pregnancy: A reappraisal. J. Clin. Ultrasound. (2017); 45: 72-78.
16. S. Chan, E.G. Grant, F.K. Chen, Y.M. Jayasinha, M. Gulati. Early First-Trimester Appearance of a Hydatidiform Mole on Sonography: The "Snowball" Sign. J. Ultrasound. Med. (2016); 35: 1610-1612.
17. E. Jauniaux, R. Brown, R.J. Snijders, P. Noble, K.H. Nicolaides. Early prenatal diagnosis of triploidy. Am. J. Obstet. Gynecol. (1997); 176: 550-554.
18. E. Jauniaux, K.H. Nicolaides. Early ultrasound diagnosis and follow-up of molar pregnancies. Ultrasound. Obstet. Gynecol. (1997); 9: 17-21.
19. Landis J, Koch G. The measurement of observer agreement for categorical data. Biometrics (1977); 33: 159-174.

Figure legend

Fig.1: A: CHM at 7 weeks of gestation. Note the molar changes at the basis of the polypoid mass (*); **B**: PHM at 10 weeks of gestation. The placenta (P) is enlarged and contains molar changes with an adjacent an amniotic sac (AS) containing embryonic remnant (*).