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Ultrasound diagnosis of molar pregnancy

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Abstract

Introduction: The primary aims of this study were to establish what proportion of ultrasonically suspected molar pregnancies were proven on histological examination and what proportion of histologically diagnosed molar pregnancies were identified by ultrasound pre-operatively. The secondary aim was to review the features of these scans to help identify criteria that may improve ultrasound diagnosis.

Methods: This was a retrospective observational study conducted in the Early Pregnancy Unit at King's College Hospital London over an 11-year period. Cases of ultrasonically suspected molar pregnancy or other gestational trophoblastic disease were identified and compared with the final histopathological diagnosis. In addition, cases which were diagnosed on histopathology that were not suspected on ultrasound were also examined. In discrepant cases, the images were reviewed unblinded by two senior sonographers. Statistical analysis for likelihood ratio and post-test probabilities was performed.

Results: One hundred eighty-two women had gestational trophoblastic disease suspected on ultrasound examination (1:360, 0.3%); 106/182 (58.2%, 95% CI 51.0 to 65.2%) had histologically confirmed gestational trophoblastic disease. The likelihood ratio for gestational trophoblastic disease after a positive ultrasound was 607.27, with a post-test probability of 0.628.The sensitivity of ultrasound for gestational trophoblastic disease was 70.7% (95% CI 62.9% to 77.4%) with an estimated specificity of 99.88% (95% CI 99.85% to 99.91%); 102/143 (71.3%, 95% CI 63.4 to 78.1%) molar pregnancies were suspected on pre-op ultrasound; 60/68 (88.2%, 95% CI 78.2 to 94.2%) of complete moles were suspected on pre-op ultrasound, compared with 42/75 (56.0%, 95% CI 44.7 to 66.7%) of partial moles. On retrospective review of the pre-op ultrasound images, there were cases that could have been suspected prior to surgery.

Conclusion: Detecting molar pregnancy by ultrasound remains a diagnostic challenge, particularly for partial moles. These data suggest that there has been an increase in both the predictive value and the sensitivity of ultrasound over time, with a high LR and post-test probability; however, the diagnostic criteria remain ill-defined and could be improved.

Keywords

Ultrasound, histopathology, hydatidiform, complete mole, partial mole, molar pregnancy

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Introduction

Gestational trophoblastic disease (GTD) comprises a group of disorders including complete (CM) and partial (PM) molar pregnancies, invasive moles, choriocarcinomas and placental site trophoblastic tumours. Molar pregnancies are the commonest and are categorised as complete or partial, occurring in 1:1000 and 3:1000 pregnancies in the UK, respectively.[1] The incidence of molar pregnancy is rising in the UK and Western Europe, in part due to an increasing number of women having pregnancies at a later age.[2]

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The typical clinical presentation of molar pregnancy includes vaginal bleeding, hyperemesis gravidarum, early embryonic demise, an enlarged uterus, early pre-eclampsia, hyperthyroidism and abdominal distension[3]. The characteristic ultrasound appearance of hydatidiform mole was first described by Donald in the 1960s as a 'uterus full of dots' or a 'snowstorm'.[4–6] This traditional description is of the late features of the disease that are seen in the second trimester. Over the last 20 years in the UK, increasingly sensitive home pregnancy tests and Early Pregnancy Units (EPUs) equipped with transvaginal ultrasound have brought the clinical presentation forward to the first trimester, when the symptoms and ultrasound findings are more subtle.

Concurrently, there has been a move away from routine surgical treatment of miscarriage and increasing use of expectant and medical treatments with no histological examination of pregnancy tissue. Although a pregnancy test can be performed three weeks after a miscarriage to exclude persistent GTD, the lack of diagnosis denies women appropriate follow up in subsequent pregnancies. If a woman is known to have had a molar pregnancy, her follow-up is co-ordinated by our UK regional GTD units and she has an increased risk of a recurrent mole in future pregnancies, particularly after a CM.[7] Ultrasound identification of a possible molar pregnancy allows women to choose surgery over other management options allowing histopathological examination of pregnancy remains.

The primary aims of this study were to establish (a) what proportion of ultrasonically suspected molar pregnancies were proven on histological examination and (b) what proportion of histologically diagnosed molar pregnancies were identified by ultrasound pre-operatively. The secondary aim was to analyse the features of the pre-op scans to help identify criteria that may improve ultrasound diagnosis.

Methods

This was a retrospective observational study conducted in the EPU at King's College Hospital London. Women accessed EPU as self-referred patients, referrals from general practitioners, midwives, fetal medicine unit or the emergency department. The EPU is not part of routine antenatal care, but is for women with clinical problems in the first trimester such as abdominal pain or vaginal bleeding. Clinical and ultrasound data were collected prospectively and stored electronically (ViewPoint, GE Healthcare). All patients had a clinical assessment and transvaginal pelvic ultrasound performed by Gynaecologist sonographers working in the EPU (Voluson E6 and/or E8 Expert, GE Healthcare). If the uterus was enlarged, this was supplemented by a transabdominal approach. The ultrasound criteria for suspecting molar pregnancy were cystic changes, irregularity, or increased echogenicity in the decidua, chorionic tissue or myometrium.[8,9] The ultrasound criteria for suspecting malignant GTD were a hypoechoic or heterogenous, predominantly solid tumour within the uterine cavity in the presence of a positive pregnancy test.[10] Patients with histopathologically diagnosed GTDs were identified using electronic patient records and Charing Cross Hospital Trophoblastic Disease Service records.

Inclusion criteria for the primary aims were an ultrasound scan in the first trimester with the diagnosis of a suspected molar pregnancy or other GTD, or histopathological diagnosis of trophoblastic disease confirmed at Charing Cross Hospital over an 11-year period, January 2005 to December 2015.

Unblinded, retrospective review of USS images was performed by two senior sonographers JR and JJ.

Statistical analysis for likelihood ratio and post-test probabilities was performed using University of California's online calculators for scientific research (http://www.sample-size.net/post-probability-calculator-test-new/ accessed 28/03/2017). The study protocol was approved by the local Research & Development team.

Results

There were a total of 65,536 pregnancies during the study period of which 182 had suspected GTD on ultrasound examination (1:360, 0.3%); 106/182 (58.2%, 95% CI 51.0 to 65.2%) had histologically confirmed GTD, including a patient with a pregnancy that was unclassifiable histologically, thought to be most likely to be a non-molar pregnancy, but as an atypical mole could not be excluded, she was followed up as per the molar pregnancy protocol; 70/182 (38.5%, 95% CI 31.7 to 45.7%) were non molar miscarriages on histological examination, 2/182 had ongoing pregnancies in which the placental or decidual cysts resolved by the end of the first trimester and they delivered normal babies at term, 2/182 miscarried spontaneously with no tissue available for histology and 2/182 patients had their surgery in the private sector with no histology results available locally.

There were 44 cases of GTD diagnosed histologically with no documented suspicion of the diagnosis on the pre-operative ultrasound. One of these patients presented with abnormal vaginal bleeding at the age of 54 years, was not known to have a positive urinary pregnancy test and the diagnosis of choriocarcinoma was made by outpatient endometrial sampling. Another had a partial molar tubal ectopic pregnancy.

Details of the histological subtypes of GTD are shown in Table 1. Assuming the approximation that there was no additional GTD in patients with negative scans who did not have histological tissue for analysis, the sensitivity of ultrasound was 70.7% (95% CI 62.9% to 77.4%) with a specificity of 99.88% (95% CI 99.85% to 99.91%). The likelihood ratio for GTD after a positive ultrasound was 607.27, with a post-test probability of 0.628. Considering molar pregnancies alone, 60/68 (88.2%, 95% CI 78.2 to 94.2%) of complete moles (CM) were suspected on ultrasound preoperatively, compared with 42/75 (56.0%, 95% CI 44.7 to 66.7%) of partial moles (PM). Overall, 102/143 (71.3%, 95% CI 63.4 to 78.1%) molar pregnancies were suspected on pre-op ultrasound.

We looked back at examples of the ultrasound images of six of the eight patients with false negative ultrasound scans who had complete moles (Figure 1). Two patients only had scans in the fetal medicine unit and their ultrasound images were not available for review. The cases shown in Figure 1(a) and (b) demonstrated cystic changes in the chorionic tissue typical of molar pregnancies. In case 1(a), the Gynaecologist who performed the scan commented that tissue should be sent for histological examination, but was not explicit in stating that this was to check for GTD. Figure 1(c) to (f) shows more subtle changes; 1(c) shows small cysts in the chorionic tissue and a relatively high proportion of trophoblast for a small gestational sac. 1(d) and (e) shows abundant chorionic tissue with loss of the

Table 1. Histological subtypes of gestational trophoblastic disease 2005–2015 inclusive

	Complete mole	Partial mole	Invasive mole	Choriocarcinoma	Placental site tumour	Unclassifiable
Suspected on USS ($n=106$)	60	42	0	2	1	1
Unsuspected on USS ($n=44$)	8	33	1	1	1	0
total ($n=150$)	68	75	1	3	2	1

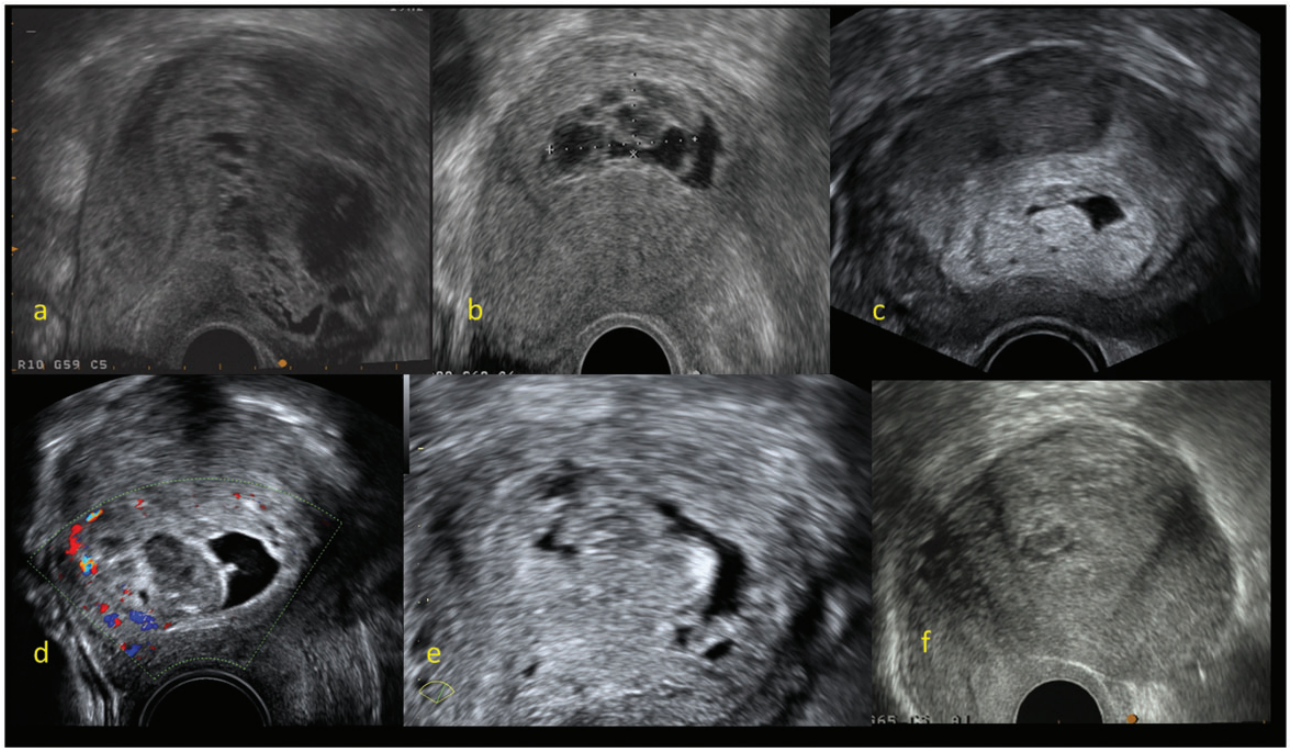

Figure 1. Missed complete moles (false negative ultrasound scans).

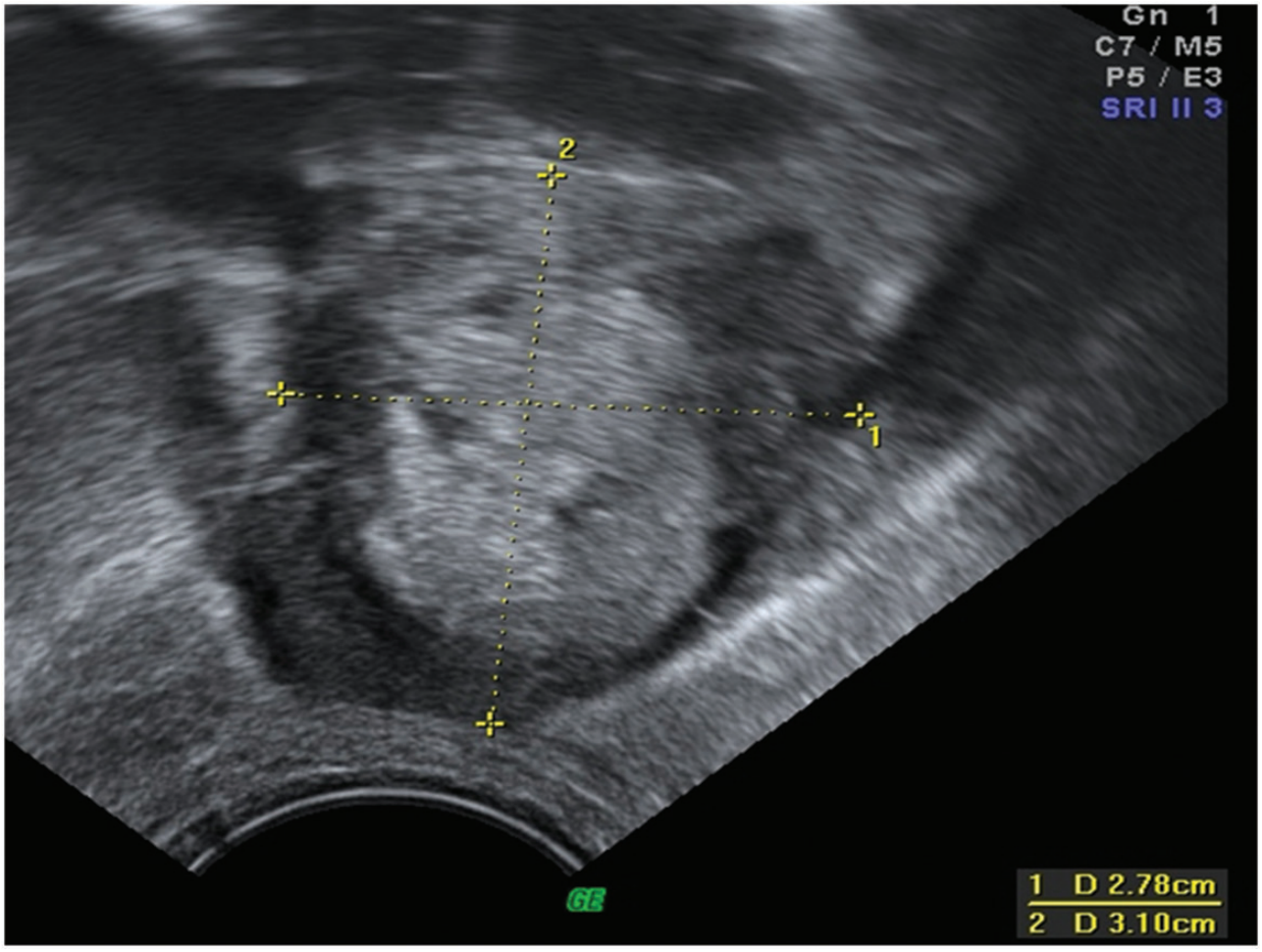

Figure 2. Tubal ectopic partial molar pregnancy.

normal sac-like architecture. Figure 1(f) showed a small irregular gestational sac only and we were unable to see any features that could indicate a complete mole.

There were 33 cases of partial molar pregnancies that were not recorded as having been suspected on pre-operative ultrasound. One of these was the tubal mole. On pre-op ultrasound, this was a 3 cm, predominantly solid ectopic pregnancy. The trophoblast appeared echogenic, but otherwise it was unremarkable (Figure 2). Thirteen cases of PM were referred from the Fetal Medicine Unit and there were six of these with no images available to review. Of the remaining 26 cases, reviewing the images retrospectively and independently, 8/26 had USS features that could have indicated a partial mole (Figure 3). However, the reviewers disagreed in six cases ($k = 0.115$) indicating a generally poor strength of agreement.

Discussion

This study has shown that just over half of the pregnancies, we suspect to be molar on ultrasound are proven to be so, and that we are able to detect a higher proportion of molar pregnancies by pre-operative ultrasound than previously reported in the literature.

An overview of previous studies showed that 533/1210 (44%) of molar pregnancies were suspected on USS pre operatively, with the US sensitivity for CM moles being much higher than for PM (Table 2). The overall increase in ascertainment in the current study was due to a lower proportion of PM in our population compared with other studies. This may reflect an increasing use of non-surgical treatment of miscarriage over time, but our data were fairly consistent year on year. We treat approximately 20% non-surgically, which may be higher than in some other units – and we do not routinely try to collect tissue from non-surgically managed miscarriages for histopathological examination. This means that unsuspected cases of PM may have been missed as they were treated non-surgically. It may also reflect the fact that we have an older EPU population than in some of the other studies, as CM shows a more pronounced increase with age,[14] but these data were not available for comparison.

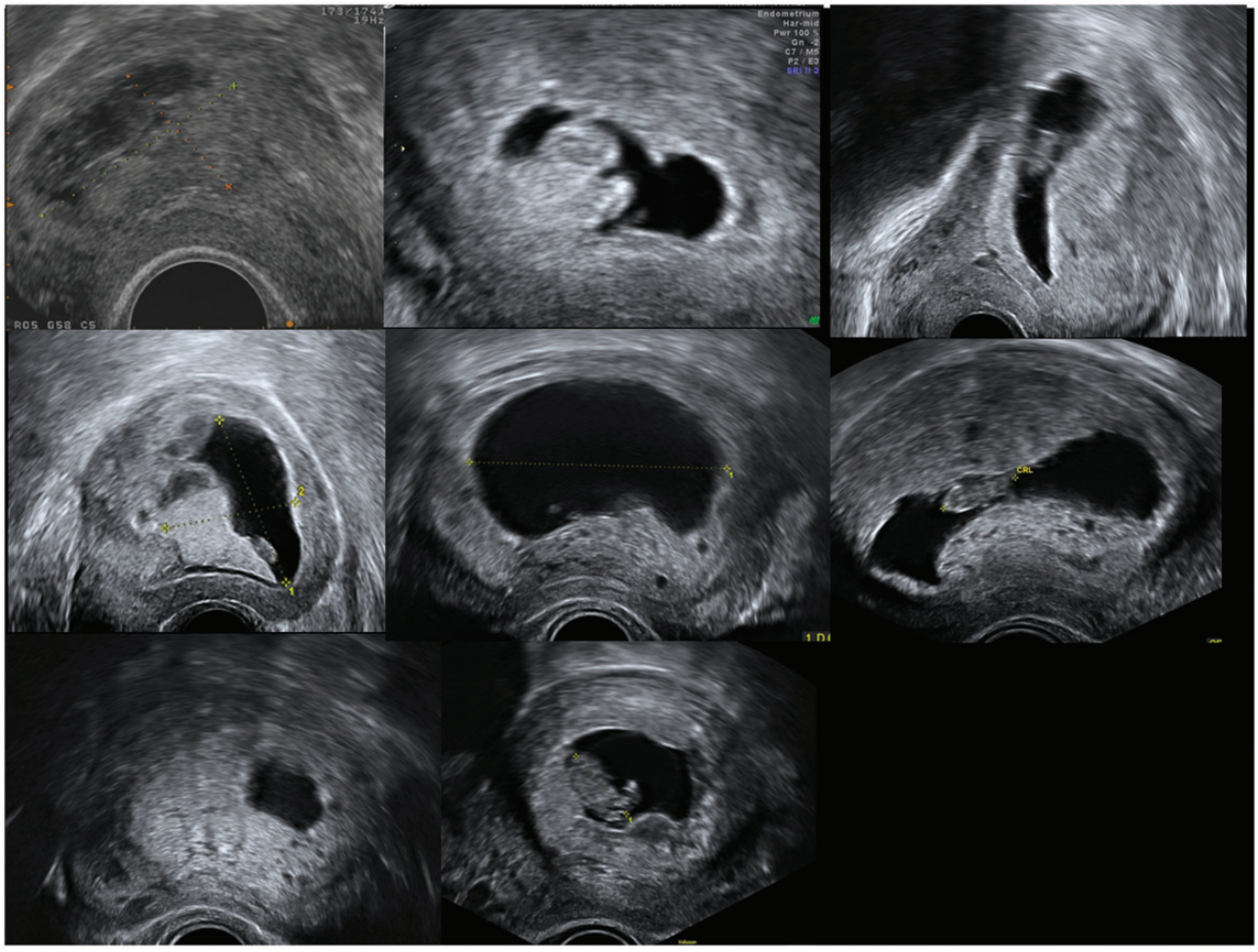

Figure 3. Missed partial molar pregnancies (false negative ultrasound scans).

Table 2. Overview of studies reporting USS detection of molar pregnancies.

Study	CM	CM suspected on US	PM	PM suspected on US
Lazarus 1999[9]	21	57%	–	–
Sebire 2001[11]	64	58%	91	17%
Johns 2005[12]	11	90%	33	49%
Fowler 2006[13]	253	79%	606	29%
Kirk 2007[14]	20	95%	41	20%
Savage 2017[15]	22	86%	48	42%
Ross 2017 (current study)	68	88%	75	56%
Total	459	78%	894	31%

Complete mole (CM); Partial mole (PM); Ultrasound (US)

Since modern transvaginal ultrasound has been used routinely for the assessment of early pregnancies, the proportion of molar pregnancies suspected preoperatively has risen.[11–13] Older studies from the UK relied upon registration data provided by local hospitals, and with paper-based clinical notes and results, the documentation of preoperative ultrasound was likely to have been less reliable than with contemporary electronic systems, so this may also account for some of the increase.

One of the strengths of our study was that we were able to identify and follow-up pregnancies that were thought could be molar on ultrasound and establish whether the diagnosis was proven on histology so as to assess the value of a positive scan. This is important for sonographers and clinicians so that we can counsel our patients regarding the odds of molar pregnancy before they choose the treatment of their miscarriage. Other than Kirk et al. who found a positive predictive value of 48% for the diagnosis of molar pregnancy, previous studies have only looked at cases where the diagnosis of a molar pregnancy was made histologically to give an estimate of sensitivity. It would be interesting to see whether our data are replicated in other units with a different clinical set ups, staffing and degrees of supervision, to see whether this pattern of diagnosis is consistent across modern practice.

Our study was limited by the retrospective analysis of data. We assumed that all pregnancies that were thought to be molar were explicitly stated as such in the ultrasound reports. It is possible that our Gynaecologist sonographers may have recommended surgical management of miscarriage, but not made it expressly clear in the report that this was because they suspected an underlying molar pregnancy and wanted the remains to be examined histologically. We also had to assume that there was no additional GTD in patients with negative scans who did not have histological tissue for analysis. This was likely to be the case for malignant or invasive GTD, but it is quite possible that there were some cases of molar pregnancy that resolved with expectant or medical management of miscarriage without ever being suspected or detected. Without histopathological examination of all miscarriage tissue, the true false negative rate of ultrasound is impossible to gauge.

Can we improve ultrasound detection of molar pregnancy? We have no diagnostic criteria that have been subject to testing for accuracy or reproducibility. Savage et al.[13] retrospectively examined USS images of proven moles in an to attempt to grade the cystic changes in the placenta and vascularity; they found that PM were more likely to have recognisable embryonic and extraembryonic structures, were more vascular and less likely to consist of cystic placental tissue with no recognisable sac. In their study, hCG did not appear to help to distinguish the two. Johns et al.[11] showed that there may be a role for hCG, but it is more likely to be raised in CM than PM, which is easier to diagnose on ultrasound anyway. Our retrospective, unblinded review of images showed that there were some cases of CM that could have been suspected by more experienced sonographers on USS prior to surgery, due to abundant chorionic tissue with loss of the normal architecture of the gestational sac, but that the main diagnostic difficulty is in distinguishing PM from uncomplicated first trimester miscarriage (i.e. early embryonic demise). Without a prospective study using predefined assessment criteria, the diagnostic criteria will never be rigorously assessed.

Do we need to improve ultrasound detection of molar pregnancy, particularly PM? Will it alter how the miscarriage is managed? There is an ongoing debate in the UK about the financial cost and value of histological examination of the tissue obtained from surgical treatment of miscarriage.[15] What is the value of knowing the diagnosis of PM when it is easy to do a urinary pregnancy test after a miscarriage to check for the rare cases of persistent GTD? In the UK, it is no longer advised that women wait six months before conceiving again after a PM, so delaying a pregnancy is no longer a potential reason to check histology, and the risk of a CM after a PM is 0.1%, as recurrent CM is almost exclusively a problem of CM.[7] It may be that knowledge of an underlying PM needlessly increases women's anxiety in future pregnancies, when the risk of recurrence is very low. Making the diagnosis could also have the opposite effect, reducing anxiety; however, there is no data available from which to draw a conclusion as to whether there is any psychological benefit of knowing the diagnosis.

Conclusion

Detecting molar pregnancy by ultrasound remains a diagnostic challenge, particularly for PM. These data suggest that there has been an increase in both the predictive value and the sensitivity of ultrasound over time; however, the diagnostic criteria remain ill defined. Awareness of the possibility of molar pregnancy prior to management of miscarriage will guide treatment and allow appropriate follow-up. The recent increase in non-surgical management of miscarriage may result in missed cases but this may well be almost exclusively in PM where the value of a diagnosis is less clear.

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Contributors

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