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Systematic Review

The diagnostic value and accuracy of ultrasound in diagnosing hydatidiform mole: A systematic review and meta-analysis of the literature

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ABSTRACT

Introduction: Hydatidiform moles are the most common type of gestational trophoblastic disease. Internationally the incidence of hydatidiform moles is 1–2:1000 pregnancies. Early detection of women with hydatidiform moles is preferential, as these women are at a higher risk of developing other gestational trophoblastic disease. Despite Ultrasound being the most common modality used to diagnose hydatidiform moles, its diagnostic value and accuracy throughout all trimesters remains uncertain. Thus, the aim of this review was to explore and evaluate the diagnostic value and accuracy of Ultrasound in diagnosing hydatidiform mole throughout all trimesters of pregnancy.

Methods: The databases MEDLINE and CINAHL were searched between 2004 and 2021. Included studies were quality assessed using the Mixed Methods Appraisal Tool.

Results: A total of 8 studies were included. The narrative synthesis identified four themes: Misdiagnosis, Complete and Partial molar pregnancy, Operator dependency and Gestational age. The meta-analysis highlighted although the sensitivity of ultrasound for diagnosing hydatidiform moles is relatively low at 52.2%, the specificity was high at 92.6%.

Conclusion: While histological examination remains the gold standard for detecting hydatidiform moles, our review made evident that ultrasound is a beneficial diagnostic tool in the detection of Hydatidiform moles, especially alongside other diagnostic investigations. This review has highlighted and collated the main barriers and facilitators to diagnosing hydatidiform moles using ultrasound.

Implication for practice: Findings suggest that although sonographic detection of hydatidiform moles remains a diagnostic challenge, seeking a second opinion or repeating scans before making a final diagnosis should be embedded into clinical practice.

Introduction

Gestational trophoblastic disease (GTD) are rare benign and malignant disorders associated with malformed pregnancies.[1,2] Histologically, GTD includes premalignant mole, complete hydatidiform mole (HM), malignant invasive mole, choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour.[3] HM is a benign form of trophoblastic tumour and accounts for 80% of GTD.[4] HM is commonly referred to as a 'mole', or molar pregnancy; is a rare complication of pregnancy, and is characterised by the abnormal growth of trophoblasts, which are the cells that normally develop into the placenta.[5] Based on their genetic and histopathological features, HM can subdivide into 'complete' moles (CM) or 'partial' moles (PM).[6] Internationally the incidence of HM is 1–2:1000 pregnancies.[7] Within the UK, HM complicates around 1:1000 for CM and 3:1000 for PM.[8] The numbers of HM are rising, thought to be due to the increase of women having pregnancies at a later age.[7,9]

The classic clinical appearance of HM includes vaginal bleeding, hyperemesis, an enlarged uterus and early pre-eclampsia.[10] Before the use of current sonographic techniques such as harmonic imaging and 3D technology, the sonographic characteristic appearance of HM was first described by Donald in the 1960's, as a 'uterus

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full of dots' or a 'snowstorm' appearance.[7] GTD most commonly follows HM but may develop after any gestation.[11] The accurate identification of HM is of major clinical importance,[12] and early detection of HM is preferential, as these women are at a higher risk of developing other GTD for example, choriocarcinoma.[3] It is estimated that after complete molar (CM) and partial molar (PM), GTD develops in 15%–20% (CM) and 1%–4% (PM) of women, respectively.[13] A pregnancy test can be performed three weeks after a miscarriage to exclude persistent GTD,[14] however without the initial diagnosis of HM, denies women appropriate follow up in these subsequent pregnancies.[15] Both transvaginal and transabdominal ultrasound (US) are recognised as the gold standard in investigating pregnancy complications,[16] however, the diagnostic value and accuracy of US across all trimesters remains uncertain.[4] Despite individual studies there is currently no comprehensive overview of this area. Thus, there is a need to collate current evidence to develop an overall understanding to assess the diagnostic value and accuracy of US in diagnosing HM throughout all trimesters of pregnancy.

Aim

To explore and evaluate the diagnostic value and accuracy of Ultrasound in diagnosing hydatidiform mole throughout all trimesters of pregnancy.

Search strategy

Preliminary searches were conducted to provide an insight into key terminology and allowed relevant and appropriate terms to be collected. Two electronic databases were searched: MEDLINE and CINAHL. The search was limited to studies published in English language. The search was restricted to published data from 2004 to 2021 when seminal guidelines for the diagnosis of HM came into force,[17] and to account for the evolution in technology.[18]

Table 1 below details the search strategy used as well as the Boolean search terms used. Additionally, reference lists of relevant papers, guidelines and policy papers were searched. The search was conducted on the 18th of July 2021. No location restrictions were placed on the search as due to US being used internationally for the detection of HM.

Table 1
Search Strategy.

Elements	Alternatives
1. Diagnosing	Detecting Investigating Diagnose "Diagnostic value" Sensitivity Specificity "Positive predicted value" "Diagnostic accuracy"
2. Ultrasound	Ultrasonography* Sonography* "Sonographic Imaging" Ima* "Transvaginal Ultrasound" "Transabdominal Ultrasound"
3. "Hydatidiform Mole"	"Molar pregnancy*" "Complete hydatidiform mole*" Pregnancy* 'Partial hydatidiform mole*' "Gestational trophoblastic disease" "Gestational neoplasms" "Placental site trophoblastic tumour" "Placental Molar*" "Invasive mole" "Complete molar pregnancy*" "Partial molar pregnancy*"
Boolean Operators	1. Diagnosing OR Detecting OR Investigating OR Diagnose OR "Diagnostic value" OR Sensitivity OR Specificity OR "Positive predicted value" OR "Diagnostic accuracy" 2. Ultrasound OR Sonography OR "Sonographic imaging" OR Ima OR "Transvaginal Ultrasound" OR "Transabdominal Ultrasound" 3. "Molar Pregnancy*" OR "Hydatidiform mole" OR "Complete hydatidiform mole*" OR Pregnancy OR "Partial hydatidiform mole*" OR "Gestational trophoblastic disease" OR "Gestational neoplasms" OR "Placental site trophoblastic tumour" OR "Placental Molar*" OR "Invasive mole" "Complete molar pregnancy*" OR "Partial molar pregnancy*"

Eligibility criteria

The literature was firstly screened based on the title and abstracts. Following the initial screening a full text screening was undertaken for relevancy. The literature was reviewed utilising the inclusion and exclusion criteria displayed in Table 2. Manual screening was also included. Reference lists of papers that were initially found were searched by the same process and by hand searching the grey literature. A full range of mixed method studies, quantitative studies, and qualitative studies were included.

Table 2
Eligibility criteria.

Studies must include qualitative and quantitative elements, describing the statistics and value of transvaginal and transabdominal ultrasound.	To develop an understanding of the accuracy of ultrasound in diagnosing HM.
Date limit: 2004–2021.	The Royal College of Obstetricians and Gynaecologists original guideline for the management of Gestational Trophoblastic Neoplasia was released in 2004. Technology has evolved appreciably since this date.
Exclude studies that explore the roles of other imaging modalities investigating HM.	Given the aim of the review, other imaging modalities did not contribute to the results.

Quality assessment

Quality assessment was carried out initially by the first author I.N. using the Mixed Methods Appraisal Tool (MMAT) which can be used to assess the quality of quantitative, qualitative and mixed method studies. Each study following the screening process was measured against the criteria set out in the tool. The quality assessment process was cross checked by A.S. and B.S. Any disagreements were discussed, and if no agreement on a quality score could be reached it was settled by the fourth author K.S. Study quality was graded from 0% to 100% with 0%–20% being (very low), 20%–50% (low), 50%–70% (moderate) and 70%–100% (high).

Data extraction

I.N. carried out the data extraction, and A.S, K.S and B.S. crossed checked the data to minimise selection bias. To extract relevant studies, title screening was used. If the titles did not provide enough detailed information to determine relevance, then the abstract was read. Only abstracts that met the eligibility criteria were included (Table 2).

Data synthesis

Due to the nature of this study, both a narrative synthesis and meta-analysis was carried out. Narrative synthesis is used to contrast the data from multiple studies as well as identifying common areas across the studies.[19] Moreover, narrative synthesis can be used to synthesise heterogeneous data,[20] this is important given that the studies included were mixed methods often presenting a wide range of data.

Some of the statistics and figures extracted from a proportion of the included studies were homogenous enough to conduct a meta-analysis. A meta-analysis is a quantitative technique that uses specific measures to indicate the strength of variable relationships and trends for the studies included in the analysis.[21,22] A meta-analysis was performed to explore and establish the statistical significance across all 8 studies that might otherwise seem to be conflicting results.[23]

Sensitivity: 1st, 2nd, 3rd and 4th quartiles and standard deviations were calculated of the sensitivity, the P-value was calculated using a 2-tailed, paired, t-test between CM and PM, combined was not included in the inferential statistical comparison, as this was a combination of the complete and partial datasets, and so could not be independently compared. Specificity: 1st, 2nd, 3rd and 4th quartiles and standard deviations were calculated of the specificity of 4/8 studies. Positive Predictive Value (PPV): 1st, 2nd, 3rd and 4th quartiles and standard deviations were calculated of the PPV of 4/8 studies.

The narrative synthesis was initially carried out by I.N. who explored common themes and relationships within the extracted data. This process was triangulated by all the authors. The meta-analysis was initially carried out by I.N. and K.S. and was cross checked by A.S. and B.S.

Results

Study selection

A total of 8 studies were included: all were mixed method designs and provided quantitative data, describing statistical results such as sensitivity, specificity, positive predictive value. The assessment sites were routine US screening (2 studies) and early pregnancy units (EPU) (5 studies) and a GTD unit (1 study). 5 studies were based in the UK, and 3 studies were international. A full detailed description of each included study is provided in Table 3 The meta-analysis and narrative synthesis are presented below (Fig. 1):

Meta-analysis

Meta-analysis was performed to calculate the sensitivity, specificity and PPV of HM diagnosis using US. See Tables 4, 5, and 6; Figs. 2, 3, and 4.

Narrative synthesis

Narrative synthesis revealed four key themes: misdiagnosis; complete and partial molar pregnancy; operator dependency; and gestational age.

Misdiagnosis

This theme is centred around the misdiagnosis of HM using US.

When comparing sample sizes, Ross et al.[15] had a smaller sample size of 180, yet 70 (38.8%) were misdiagnosed with US. Fowler et al.[24] had a larger sample size of 1053, with the misdiagnosis rate of 38.5%. This close similarity in proportion suggests the data for misdiagnosis is reliable. The sample sizes are markedly different as each study length and setting varied considerably. Fowler et al.[24] study was conducted over a 3-year period with the largest sample size, possibly due to his retrospective method taking place at a GTD unit. The main limitation with a long length study is the variation of old and new equipment and operators used accompanied by the evolution of US technology. Several studies illustrate the importance of current US equipment,[15,24,30] and how there has been significant US technological improvements in the past decade.[2] Savage et al.[6] describes how the variation and age of equipment can compromise the sensitivity of HM due to the changes in spatial resolution.

Kirk et al.[25] and Johns et al.[27] had similar methods as they were carried out in a EPU setting. The patients included in these studies warranted a first trimester emergency referral due to self-reported symptoms. With warranting symptoms, there is a higher expectancy for abnormal US findings.[28] Stamatopoulos et al.[26] study highlights that EPU have a higher detection rate for HM, and therefore it can be assumed that the misdiagnosis rate should be lower. Yet, this statement does not support the descriptive data, as there was no correlation between the studies performed at the EPU having a lower misdiagnosis rate compared to routine US screening. A limitation regarding the EPU studies would be that not all women with HM would go to the EPU as their first form of contact, and the results may not be a true representation of the population.

All 8 studies used a slightly different US criteria for detecting HM, which could negatively impact the diagnosis of HM. For example, if the US findings did not meet the criteria, was there a higher chance HM was misdiagnosed or even missed. Moreover, all 8 studies illustrate how PMs are misdiagnosed more often than CM. In Johns et al.[27] study, out of the 18 cases (39%) that were not suspected prior to evacuation, 17 (95%) were PM and (5%) were CM. In Kirk et al.[25] it was highlighted that only one case of CM was misdiagnosed yet thirty-three cases of PM were misdiagnosed, however, these findings are limited as the study only investigated suspected HM.

Other studies investigated all suspected GTD, such as Ross et al.[15]

It is apparent that most sonographic diagnoses were misdiagnosed as a miscarriage, and HM was identified only when the histology was performed.[6] A sub-theme identified was an empty sac. Johns et al.[27] discusses how PM was easily mistaken for an empty sac, due to its similar sonographic features. Kirk et al.[25] supports this theme and describes how 8/34 (24%) of women were diagnosed as an empty sac yet histological examination revealed HM.

Complete molar and partial molar pregnancies

The underlying incidence of PM is generally thought to be 50% more common than CM[6]. Fowler et al.[24] found that 29% were CM, with 71% were PM, supporting this position that PM are more common than CM, but with a difference in proportion. However, it was apparent that US was more sensitive in the diagnosis of CM compared to PM, as all 8 studies discussed the sensitivity being greater for complete versus partial moles diagnosis. The descriptive data supported this theme, giving a calculated sensitivity average of 81.5% for CM, and a calculated average of 32.1% for PM.

Sampling differences may account for some disparities in the data. Ross et al.[15] included a retrospective review of HM cases that were diagnosed on histopathology but were not originally diagnosed on US, as well as those cases diagnosed sonographically, unlike the other 7 authors, affecting sensitivity of detection overall. The review was unblinded, introducing bias when reviewing the images, which could then have increased the sensitivity. Boutron

Table 3
Final included study selection.

Author(s)	Aim/Objectives	Study	Method(s)	Results	Quality Score
Alushani et al., 2014	To assess the role of ultrasound examination in the diagnosis of Molar pregnancy in Albania.	Mixed methods design: Cross sectional study.	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.	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.	high
Johns et al., 2005	To examine the relationship between ultrasound and histological features in screening for molar pregnancies.	Mixed methods design: Prospective study	A prospective cohort study was conducted on all missed miscarriages, with features suspicious of molar pregnancy, on transvaginal ultrasound and/or on histological examination over a 5-year period, at an EPU.	51 cases of suspected molar pregnancy were referred to the regional centre for further histological opinion and follow-up, and five cases were subsequently excluded. In 33 cases a molar pregnancy was suspected at the initial scan. 78.8% were confirmed on histology, resulting in a 56% detection rate using ultrasound alone.	high
Folwer et al., 2005	To examine the accuracy of sonographic findings of routine ultrasound examinations in patients proven histological diagnosis of complete or partial hydatidiform mole.	Mixed methods design: Retrospective review	Review of cases referred to a trophoblastic disease unit from June 2002 to January 2005 with a diagnosis of probable hydatidiform mole in whom results of a pre-evacuation ultrasound were documented.	1053 cases were examined. The median age was 31, and the median gestational age was 10 weeks. 859 had a hydatidiform mole (82%), 253 (29%) were complete moles, 606 (71%) partial moles, 194 (18%) were misdiagnosed.	high
Jauniaux et al., 2020	To evaluate the accuracy of ultrasound signs suggestive to complete hydatidiform mole and partial hydatidiform mole.	Mixed methods design: A qualitative study	198 patients presenting at the early pregnancy unit. All ultrasound images were anonymised, and a retrospective examination was completed were the blinded to the histological results. STATA software was used to perfume statistical analysis.	Detection rates are up to 95% for women with a complete molar pregnancy, 50% of partial molar pregnancies are undetected during Ultrasound examinations.	high
Ross et al., 2017	To establish what proportion of ultrasonically suspected molar pregnancies were proven on histological examination.	Mixed Methods design: Retrospective Observational study.	Retrospective study conducted in the early pregnancy unit over an 11-year period. Cases of ultrasonically suspected molar pregnancies were compared with the final histopathological diagnosis.	182 women had suspected GTD.106 (58%) had confirmed hydatidiform mole. The sensitivity of ultrasound was 70.7%, with an estimated specificity of 99.8%. 88.2% of complete molar pregnancy, compared to 56% of partial moles.	high
Kirk et al., 2006	To assess the first trimester ultrasonographic findings in all women suspected of having hydatidiform mole on ultrasound.	Mixed methods design: Retrospective analysis.	A retrospective study that examined all cases of sonographically suspected HM over a 4-year period. Patients were examined in the early pregnancy unit after being self- referred, referred by a GP/Accident and emergency department.	The overall sensitivity for the ultrasound diagnosis of hydatidiform mole was 44%, and the positive predicted value was 48%. For partial hydatidiform mole the sensitivity was 20% and specificity was 22%.	high

Table 3 (*continued*)

Author(s)	Aim/Objectives	Study	Method(s)	Results	Quality Score
				Whilst complete molar pregnancy was 95% sensitivity and 40% specificity.	
Stamatopoulus et al., 2020	To assess the performance of per-operative transvaginal ultrasound to predict hydatidiform mole.	Mixed methods design: Quantitative study	A retrospective study of women who presented to the early pregnancy unit. All women were subject to a transvaginal ultrasound only, and participants were only included when the results were histologically confirmed.	The sensitivity, specificity, PPV and NPV of transvaginal ultrasound in predicting HM were 60%, 99.1%, 63.2%, 99%.	high
Savage et al., 2016	To assess the prospective sonographic diagnosis of molar pregnancy and compare sonographic features of complete versus partial molar pregnancy.	Mixed methods design: A chart review.	A retrospective chart review conducted between 2001 and 2011 identified 70 women with molar pregnancies with available images at a routine hospital. Clinical data, images and reports were reviewed.	Detection rates of complete molar pregnancy was 58% –95%, whilst partial molar pregnancies ranged from 17% to 29%.	high

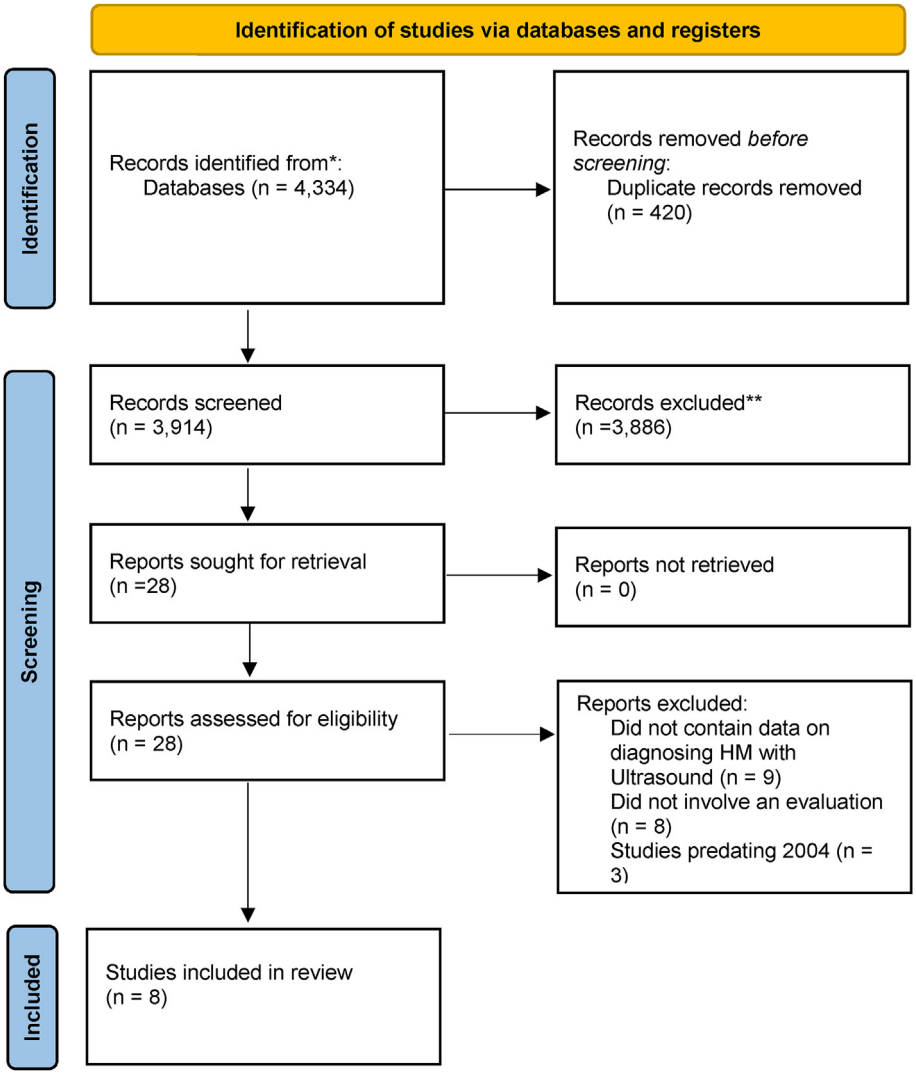

Figure 1. PRISMA - Study Selection flow chart.

Table 4
Sensitivity of HM.

Paper	Sensitivity		
	Complete	Partial	Overall (HM)
Alushini	92	29	31
Stamatopoulos	79.1	37.5	60
Fowler	79	29	44
Ross	88.2	56	70.7
Kirk	95	20	44
Johns	90	48.5	56
Jauniaux	69.9	29.5	50.5
Savage	58.5	23	53
Average	81.5	34.1	51.2
Max	95.0	56.0	70.7
Min	58.5	20.0	31.0
Stdev	12.5	12.5	11.9
Quart 25%	72.2	24.5	44.0
Quart 50%	83.7	29.3	51.8
Quart 75%	91.5	45.8	59.0
P value (complete vs partial)	0.0000025		

Table 5
Specificity of HM.

	Specificity
Alushini	97.3
Stamatopoulos	99.1
Fowler	74
Ross	99.8
Kirk	
Johns	
Jauniaux	
Savage	
Average	92.6
Max	99.8
Min	74.0
Stdev	12.4
Quart 25%	79.8
Quart 50%	98.2
Quart 75%	99.6

Table 6
Positive predicted value of HM.

True Positives	PPV
Alushini	91.9
Stamatopoulos	63.2
Fowler	88
Ross	
Kirk	48
Johns	
Jauniaux	
Savage	
Average	72.8
Max	91.9
Min	48.0
Stdev	20.8
Quart 25%	51.8
Quart 50%	75.6
Quart 75%	90.9

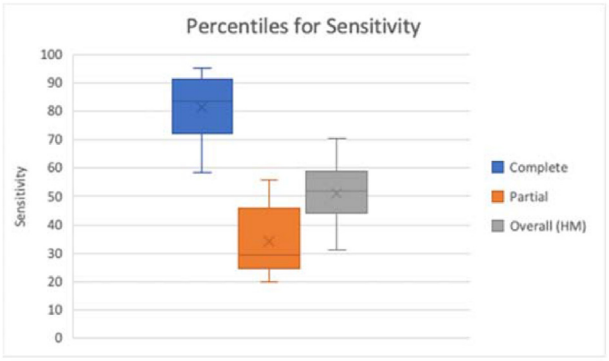

Figure 2. Percentiles of sensitivity of HM.

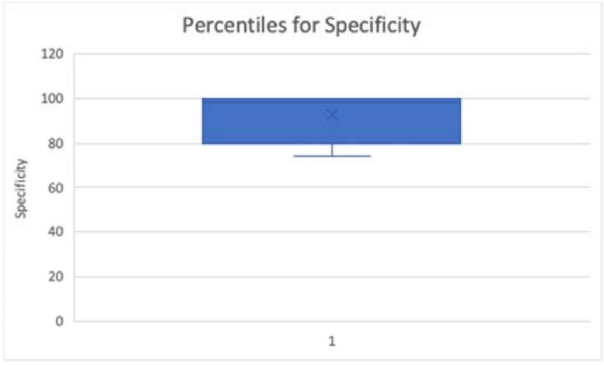

Figure 3. Percentiles for specificity of HM.

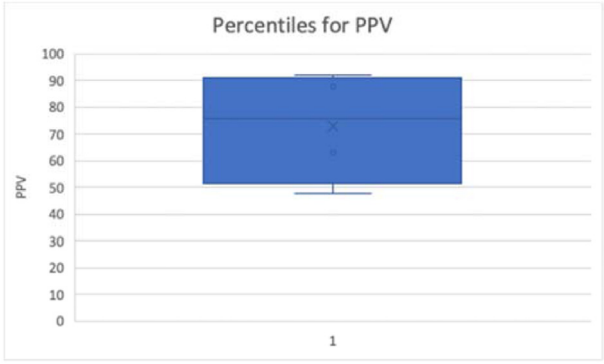

Figure 4. Percentiles for positive predicted value of HM.

et al.[28] suggests that having access to reports during a retrospective study can influence the final diagnosis.

Fowler et al.[24] undertook a retrospective search of the trophoblastic disease unit, whereby the cases represented both those examined at specialist centres such as EPU units, and in routine district general hospitals. This allows for the highest possible ascertainment for patients with HM, unlike other settings.

Stamatopoulos et al.[26] and Alushani et al.[30] had methodologies that varied from the others as they investigated transvaginal US (TVU) only, reducing the available sample size. The descriptive data supports this as there were only 40 cases in Stamatopoulos study.[26] The other studies included both transabdominal and TVU scans, giving a better representative sample of US in the detection of HM.

Operator dependency

The 8 included studies all declared that a high percentage of HM were missed due to the operator. This theme is supported by Fowler et al.[24] study who describes the increase in detection rates of HM when the scans are performed by senior sonographers specialising in obstetrics. Fowler et al.[24] who conducted the study at a trophoblastic disease unit, had the largest sample size of 1053 cases. The study identified 194 cases (18%) being false negatives due to the operator not detecting the disease that was visible on the

images. The false negative rate from the retrospective unblinded review of Ross et al.[15] highlights 21.4% (44 out of 182 cases) of GTD were missed during the US scan.

Differences in methodologies could introduce variation in results when considering false negative rates. Another limitation of the Ross et al.[15] methodology was that there was a range of practitioners performing the scan, which could influence the false negative rate in such an operator dependent modality.[31] Kirk et al.[25] and Stamatopoulos et al.[26] had similar methods and declared that specialising Sonographers or Radiologists performed the reviews and or undertook the initial diagnosis, which could reduce the false negative rate. When considering false negative rates, Jaunxiaux et al.[29] findings are limited as it was not declared who reviewed the images.

Kirk et al.[25] had a smaller sample of 95, with only 61 women having a confirmed HM, and 34 cases (35%) of not suspected mole. This suggests that the sample size does not influence the rate of false negatives due to operators. Ross et al.[15] agrees with this suggestion and states HM could have been detected in more cases by a more senior or experienced Sonographer. Ross et al.[15] reported that a HM was missed due to lack of detail within the report, suggesting it was not explicit enough in the description of GTD. This suggests that the reports' written content can heavily influence the sensitivity and therefore the management of HM.

Another factor contributing to the results, was the criterion used to confirm HM sonographically. All 8-studies sonographic criteria varied slightly and are displayed in the supplementary material. This could have impacted the false negative rates due to the US scan not meeting the specific criteria, therefore increasing the chance of the practitioner misdiagnosing or simply missing HM.

Gestational age

It was apparent that the gestational age (GA) influenced the sensitivity of US when diagnosing HM. There is a trend toward improved sonographic sensitivity when US is performed at a later GA. 7 of the studies highlight a directly proportional relationship between GA and US diagnosis, with a later GA corresponding to a higher US sensitivity. However, Jauniaux et al.[29] did not agree with this finding, but their methodology varied from the other studies, only investigating HM in patients with a GA of less than 13 weeks and giving an overall lower US sensitivity. Fowler et al.[24] study agreed and highlighted there was no significant difference in sensitivity across the GA prior to 14 weeks. The remaining studies shared similar methods as they were conducted with no restriction on GA; therefore, the results were able to detect HM at a varied GA and display a positive trend with US sensitivity and a GA of over 14 weeks.

Another limitation in Jauniaux et al.[29] method was the multiple US scans performed. 92/198 (46%) of participants had multiple US scans, which could influence the sensitivity and make the results unreliable in comparison to the methods of the other 5 studies. The true accuracy of US in the initial diagnosis of Jauniaux et al.[29] study could not be determined as not all studies had multiple examinations. However, the sensitivity was greater in the secondary examination, which supports the theme of the higher sensitivity due to the later GA. Kirk et al.[25] and the 3 other studies that were conducted at an EPU share similar findings with later GA and sensitivity. This supports the third theme of operator dependency, as these sensitivities remain within limits of other literature, raising the question of whether the GA or the operator is the reason for the reduced sensitivity.

Discussion

Synthesis identified four main themes: Misdiagnosis, Complete and Partial Molar Pregnancies, Operator dependency and Gestational Age. Although the diagnosis of HM using US is already an established technique,[1,15] the synthesis of literature presented in this review has collated and highlighted the main barriers and facilitators to diagnosing HM using US as well as identifying areas requiring further research. For example, it was found limited experience and knowledge of operators compounded by equipment/technology variations had an impact on the diagnosis of HM with US, however with the increase of EPU's and specialising staff HM can be detected across all trimesters. These results may therefore help to inform policy, practice and research in relation to HM diagnosis using US. Meta-analysis supports the use of US being an established method to diagnose HM. Although the sensitivity of US for diagnosing HM is relatively low at 52.2%, the specificity was high at 92.6%, making it an appropriate modality to rule out HM.

It is well documented the HM can present in similar ways or even mimic a miscarriage,[33] with the most common symptom being vaginal bleeding.[13]

Stamatopoulos et al.[26] suggests this being the reason practitioners misdiagnose HM for a miscarriage, alongside the lack of sonographic characteristics that suggest the disorder. Farquharson & Stephenson[34] illustrate how PM can be easily misdiagnosed for an empty sac, which can be explained by the enlarged placenta or cystic changes within the uterus that mimic a HM.[33]

Current Royal College of Obstetrics and Gynaecologists guidelines[35] (RCOG) state that medical management of miscarriage is acceptable, however, medical method of uterine evacuation is not recommended for suspected HM. Usually, patients who are diagnosed with a miscarriage on US, do not undergo a histological exam.[31] As the majority of HM is misdiagnosed as a miscarriage, patients are receiving not only the incorrect diagnosis, but are undergoing inappropriate management and treatment. A study by Johns et al.[27] highlights the importance of a histological exam to diagnose GTD. This systematic review agrees with Johns et al.[27] study as the US detection rates alone is not high enough to definitively diagnose HM. However, US is an essential diagnostic tool to work alongside other diagnostic investigations, especially if there is insufficient villous tissue available for a histological exam. The results of US specificity when detecting HM will support this, with an average of 92.6%, therefore, US is a better imaging modality to rule out HM, rather than diagnose it.

US can detect features indicating both CM and PM. Savage et al.[6] made it evident that CM was easier to detect due to its strikingly abnormal snowstorm appearance, with the main characteristic being a larger gestation sac. PM still remains a prospective US challenge, due to its subtle abnormalities and broad range of US appearances,[6,31] however, research suggests there has been some improvement over the past 20 years.[33] Boutron et al.[28] demonstrate similar findings and suggest this improvement can be explained due to improved spatial and contrast resolution which assist in better detection of subtle placental cystic changes.

The sensitivity of PM does increase with later GA; however, the detection rate of PM alone is still low sonographically. Interestingly, Chudleigh et al.[5] illustrates how PM includes both abnormal placental and foetal appearances, with the placental appearances similar to those of CM. PMs are 50% more common than CM[6], and have similar appearances, which would suggest them having a similar detection rate. However, the results from this review do not support this suggestion and there is no definitive reason to why PM is significantly lower to detect sonographically other than its subtle appearances, which raises the question of the issue being related to operator dependency.

US is known for its operator dependency, however, there are many factors affecting the quality of US examinations, including training, experience, and the equipment itself.[32,34] Research suggests how detection rates are heavily influenced depending on the

operator.[15] Over the past 20 years, more women are presenting with HM giving practitioners a greater awareness of the disorder.[12] Joneborg et al.[4] suggests that this is one factor of the increase in detection rates. In Stamatopoulos et al.[26] study a Radiologist or senior Sonographers specialising in obstetrics reviewed the images, there was a reduced proportion of false negatives, which could be explained due to the increased experience, knowledge and training these practitioners hold.[30,36] Kirk et al.[25] agrees with this theory and suggests how the low detection rates with US is purely due to the poor sonographic technique rather than sonographic features. Even when common HM features are pronounced on US, and at a later GA, the diagnosis is missed by inexperienced operators, especially in non-specialised units, which has been explained due to the disorder being an uncommon US finding.[24]

Due to advancements in both US equipment and training in specialised sonographers, HM can be diagnosed in the first trimester.[7,15] Early diagnoses of HM is of great importance, as more medical complications arise with later GA,[4] however earlier presentation of HM has made the US diagnosis of HM more challenging.[31] When US examinations are conducted at an earlier GA, the key sonographic features are not as pronounced compared to a later GA. It is apparent that HM features on US may be different across all trimesters, often in the first trimester there is sparse hydropic change and rare cistern formation, making it difficult to detect sonographically.[24] Johns et al.[27] highlights other sonographic changes through gestation such as morphological features, including villus size and proliferative activity of trophoblast.

Limitations

The main limitation is the heterogenous meta-analysis, due to different countries and settings. Another limitation of the international studies, was the broad range of criterions for suspecting HM. It is well recognised that restricting the literature to English language, could have potentially excluded relevant literature from the review. Furthermore, every study reviewed was a retrospective analysis, and are thus more prone to recall bias compared to prospective studies.

Conclusion

This review has provided an overview of the value and accuracy of US in diagnosing HM. Although the use of US in the diagnosis of HM is already an established technique, this review has highlighted and collated the main barriers and facilitators to diagnosing HM using US. For example, it was found limited knowledge and experience of operators compounded by equipment/technology variations had an impact on the diagnosis of HM with US. However, with the increase of EPU's and specialising staff HM can be detected across all trimesters. Furthermore, seeking the opinion of senior/specialised staff before making the final diagnose should be embedded into clinical practice.

Thus, while histological examination remains the gold standard for detecting HM, our review made evident that US is a beneficial diagnostic tool in the detection of HM, especially alongside other diagnostic investigations. Lastly, this review has highlighted a need for further research exploring Sonographers' confidence in diagnosing HM and the impact of specialist training and variations in equipment on diagnostic accuracy.

Author contributions

I.N and A.S. was responsible for the planning, design, conduct and reporting of the work. I.N and A.S. performed the study selection and data extraction. I.N, A.S. and B.S. were involved in the study appraisal process. All authors were involved in the data analysis and synthesis process. All authors contributed and agreed to the final manuscript.

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Data management and sharing

All relevant data are within the manuscript. Any other data are available upon request from the corresponding author.

Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radi.2022.06.005.

References

1. Ngan H, Seckl M, Berkowitz R, Xiang Y, Golfier F, Sekharan P. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynecol Obstet* 2018;**143**:79–85.
2. Brown J, Naumann R, Seckl M, Schink J. 15 years of progress in gestational trophoblastic disease: Scoring, standardisation, and salvage. *Gynecol Oncol* 2017;**144**(1):200–7.
3. Ning F, Hou H, Morse A, Lash G. Understanding and management of gestational trophoblastic disease. *F1000research* 2019;**8**:428.
4. Joneborg U, Epstein E. Sonographic characteristics of post-molar gestational trophoblastic neoplasia (GTN) in relation to chemo-resistant disease. *Ultrasound Obstet Gynecol* 2018;**52**:47.
5. Chudleigh P, Smith M, Cumming S. *Obstetric and gynaecological ultrasound*. 4th ed. Edinburgh: Elsevier Limited; 2017. p. 382.
6. Savage J, Maturen K, Mowers E, Pasque K, Wasnik A, Dalton V, et al. Sonographic diagnosis of partial versus complete molar pregnancy: a reappraisal. *J Clin Ultrasound* 2016;**45**(2):72–8.
7. Chan E,G, Grant F,K, Chen Y,M, Jayasinha M, Gulati D. *Early first-trimester appearance of Hydatidiform mole on sonography: the snowball sign*. 2016. p. 1610–2.
8. Tantengco O, De Jesus F, Gampoy E, Ornos E, Vidal M, Cagayan M. Molar pregnancy in the last 50 years: a bibliometric analysis of global research output. *Placenta* 2021;**112**:54–61.
9. Soto-Wright V, Bernstein M, Goldstein DP, Berkowitz RS. The changing clinical presentation of complete molar pregnancy. *Obstet Gynecol* 1995;**86**:775–9.
10. Sun S, Melamed A, Joseph N, Gockley A, Goldstein D, Bernstein M. Clinical presentation of complete hydatidiform mole and partial hydatidiform mole at a regional trophoblastic disease center in the United States over the past 2 decades. *Int J Gynecol* 2016;**26**(2):367–70. Cancer.
11. Franciscis P, Schiattarella A, Labriola D, Tammaro C, Messalli E, La Mantia E. A partial molar pregnancy associated with a fetus with intrauterine growth restriction delivered at 31 weeks: a case report. *J Med Case Rep* 2019;**13**(1).
12. Eagles N, Sebire N, Short D, Savage P, Seckl M, Fisher R. Risk of recurrent molar pregnancies following complete and partial hydatidiform moles. *Hum Reprod* 2015;**30**(9):2055–63.
13. Horne G, Akhtar M. Hydatidiform molar pregnancy following assisted reproduction. *J Assist Reprod Genet* 2019;**36**:667–71.
14. Sebire N. Recurrent GTD and GTD coexisting with normal twin pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2020;**167**(87–98).
15. Ross J, Unipan A, Clarke J, Magee C, Johns J. Ultrasound diagnosis of molar pregnancy. *Ultrasound* 2017;**26**(3):153–9.
16. Whitworth M, Bricker L, Mullan C. Ultrasound for fetal assessment in early pregnancy. *Cochrane Database Syst Rev* 2015;(7):1–59. https://doi.org/10.1002/14651858.CD007058.pub3.

17. Seckl M, Sebire N, Fisher R, Golfier F, Massuger L, Sessa C. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;**24**:vi39–50.
18. Ploquin M, Basarab A, Kouamé D. Resolution enhancement in medical ultrasound imaging. *J Med Imaging* 2015;**2**(1):017001.
19. Campbell M, Thomson H, Katikireddi S, Sowden A. Reporting of narrative synthesis in systematic reviews of public health interventions: a methodological assessment. *Lancet* 2016;**388**:S34.
20. Weatherspoon D. *Medical research: systematic review and meta-analysis*. Retrieved from, https://www.medicalnewstoday.com/articles/281283. [Accessed 18 January 2022].
21. Borenstein M, Hedges L, Higgins J, Rothstein H. *Introduction to meta-analysis*. 2nd ed. Oxford: Wiley; 2021.
22. Sundler A, Lindberg E, Nilsson C, Palmér L. Qualitative thematic analysis based on descriptive phenomenology. *Nursing Open* 2019;**6**(3):733–9.
23. Stone D, Rosopa P. The advantages and limitations of using meta-analysis in human resource management research. *Hum Resour Manag Rev* 2017;**27**(1):1–7.
24. Fowler D, Lindsay I, Seckl M, Sebire N. Routine pre-evacuation ultrasound diagnosis of hydatidiform mole: experience of more than 1000 cases from a regional referral centre. *Ultrasound Obstet Gynecol* 2005;**27**(1):p56–60.
25. Kirk E, Papageorghiou A, Condous G, Bottomley C, Bourne T. The accuracy of first trimester ultrasound in the diagnosis of hydatidiform mole. *Ultrasound Obstet Gynecol* 2006;**29**(1):pp70–5.
26. Stamatopoulos N, Espada Vaquero M, Leonardi M, Nadim B, Bailey A, Condous G. Pre-operative classification of molar pregnancy: how good is ultrasound? *Aust N Z J Obstet Gynaecol* 2020;**60**(5):698–703.
27. Johns J, Greenwold N, Buckley S, Jauniaux E. A prospective study of ultrasound screening for molar pregnancies in missed miscarriages. *Ultrasound Obstet Gynecol* 2005;**25**(5):493–7.
28. Boutron I, Page M, Higgins J, Altman D, Lundh A, Hrobjartsson A. Considering bias and conflicts of interest among the included studies. *Cochrane Handbook for Systematic Reviews of Interventions* 2019:177–204.
29. Jauniaux E, Memsta M, Johns J, Ross J, Sebire N, Jurkovic D. Ultrasound diagnosis of complete and partial hydatidiform moles in early pregnancy failure: an inter-observational study. *Placenta* 2020;**97**:pp65–7.
30. Alushani, M., Kasa, E., Toci, E., Manoku, N. Role of Ultrasound examination in the diagnosis of molar pregnancy in Albania: a retrospective study. Albanian Medical Journal, 3.
31. Wang P, Rodgers S, Horrow M. Ultrasound of the first trimester. *Radiol Clin* 2019;**57**(3):617–33.
32. [Internet] *Standards for the provision of an ultrasound service*. Rcr.ac.uk; 2022. Retrieved from, https://www.rcr.ac.uk/system/files/publication/field_publication_files/BFCR_814. [Accessed 3 April 2022].
33. Winder A, Mora A, Berry E, Lurain J. The "hoot effect" causing a negative pregnancy rest in a patient with an advanced molar pregnancy. *Gynaecologic Oncology Reports* 2017;**21**:34–6.
34. Farquharson R, Stephenson M. *Early pregnancy*. 2nd ed. Cambridge: Cambridge University Press; 2017.
35. Royal College of Obstetrics and Gynaecology. *The management of gestational trophoblastic disease*. Retrieved from, https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_38.pdf. [Accessed 18 January 2022].
36. Hoskins P, Martin K, Thrush A. *Diagnostic ultrasound*. Boca Raton: CRC Press; 2019.