The diagnostic performance of ultrasound in the detection of ectopic pregnancy

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ABSTRACT

BACKGROUND: Accurate diagnosis of ectopic pregnancy is essential in reducing maternal mortality and morbidity. Transvaginal ultrasound (TVUS) is the accepted imaging modality of choice for the diagnosis of ectopic pregnancy (EP).

AIMS: To assess the effectiveness of transvaginal ultrasound (TVUS) in the detection of EP in consecutive women presenting for ultrasound to a radiology department with a clinical suspicion of EP.

METHODS: Retrospective analysis of 585 women presenting for TVUS over a 2.5-year period was performed. Women were classified as having a confirmed EP on the basis of surgery and histology. Women with a suspected EP who were treated medically or expectantly were also included.

RESULTS: Eighty-seven women had a confirmed EP and 29 women had a suspected EP. The sensitivity and specificity of ultrasound for the detection of confirmed EP was 88.5% and 96.5% on the initial TVUS and 93.1% and 95.7% with an additional rescan.

CONCLUSION: TVUS in the radiology setting of a tertiary hospital has excellent diagnostic performance for the detection of EP.

Accurate and timely diagnosis of ectopic pregnancy is essential in reducing maternal mortality and morbidity in the first trimester. Pain, vaginal bleeding and inappropriately rising βHCG in early pregnancy typically raise suspicion of an underlying EP. In the last two decades, transvaginal ultrasound (TVUS) has become the imaging investigation of choice in patients presenting with suspected EP primarily due to its accessibility, excellent diagnostic performance, safety, repeatability and relatively low cost. Ultrasound, however, is an operator-dependent modality and the success of an ultrasound examination is influenced by many factors including the operator’s level of experience.

We assessed the diagnostic performance of ultrasound in the diagnosis of EP in a tertiary hospital in New Zealand (Waikato Hospital, Hamilton). The study was retrospective in nature and the data therefore reflect the normal operating characteristics of ultrasound under common workplace conditions. Examinations were performed by qualified sonographers in the radiology department, rather than by dedicated O&G sonographers working in a subspecialist or research unit. We examined ultrasound performance in patients with a surgically and histologically confirmed EP (“confirmed EP” category) and we also analysed patients who were treated medically or expectantly (“presumed EP” category).

Method

We performed a retrospective audit of all patients who presented for ultrasound at Waikato Hospital (Hamilton, New Zealand) with a clinical suspicion of EP over a two and a half year period between 1 January 2013 and 26 June 2015. The study was approved by the Waikato DHB Research Office in consultation with the Health and
Disability Ethics Committees, Ministry of Health, New Zealand. Patients were referred for ultrasound from the emergency department or from a hospital-based early pregnancy assessment clinic. All patients were scanned in the radiology department by general sonographers with a minimum of postgraduate ultrasound qualification or by trainees or radiology registrars under direct supervision of a sonographer. Patients’ electronic and hard-copy records were reviewed, including: ultrasound reports, clinic notes, discharge summaries, surgical reports, histology reports and repeat admissions.

Patients were included in the study if the referral for the ultrasound included any of the following clinical query terms: “ectopic”, “pregnancy location” or “PUL”. Patients were excluded if they were referred for a scan before a blood pregnancy test was performed and this subsequently proved negative, or if they arrived with a working diagnosis of an EP based on an outpatient scan performed elsewhere.

Classification of ultrasound scan results:

For the purpose of statistical analysis, ultrasound was classified as positive for EP when the conclusion of the ultrasound report contained positive or affirmatory statements such as:

- “consistent with ectopic pregnancy”,
- “suspicious for ectopic pregnancy”,
- “suggestive of ectopic pregnancy” or
- “ectopic should be considered”.

Ultrasound was classified as negative for EP when the conclusion of the report did not mention ectopic pregnancy or contained non-affirmatory statements regarding ectopic pregnancy such as:

- “pregnancy of unknown location”,
- “no evidence of ectopic”,
- “no convincing features of ectopic” or
- “ectopic pregnancy cannot be excluded”.

Classification of clinical outcomes:

The patient’s outcome was classified as “confirmed ectopic pregnancy” (confirmed EP) if the patient underwent a diagnostic laparoscopy and an EP was identified and was histologically confirmed. The patient’s outcome was classified as “presumed ectopic pregnancy” (presumed EP) if the referring team treated the patient as an ectopic pregnancy medically (methotrexate) or expectantly such as in the context of a clinically stable woman with inappropriately rising βHCG. The confirmed and presumed EPs were also pooled together for analysis.

Results

Over the study period, 585 women met our inclusion criteria. The patient’s age ranged between 15 and 47 years with a median age of 28 years. Eighty-seven patients had a surgically and histologically confirmed EP pregnancy (prevalence rate 14.9%) and an additional 29 patients were treated as a presumed EP (prevalence rate 5.0%). In women diagnosed with confirmed EP, 21.8% (19/87) had a previous history of EP.

The majority of the EPs were tubal in location (83/88), of which three were live EPs. Of the tubal EPs, 40 were on the right and 42 on the left. A small number of EPs (5/88, 5.6%) were identified in other locations:

- two cornual EPs
- one ruptured cornual EP in the horn of a bicornuate uterus
- one abdominal EP in the pouch of Douglas and
- one abdominal EP adherent to the anterior abdominal wall

The sensitivity and specificity of ultrasound in the diagnosis of confirmed and EP was 88.5% and 96.5% on the initial ultrasound. The addition of a second examination increased the sensitivity to 93.1% but did not improve the specificity (95.7%). The addition of a third examination did not substantially improve the diagnostic performance of ultrasound any further with a combined sensitivity of 94.2% and specificity of 95.7%.

All patients in whom an EP was missed on the first ultrasound were initially diagnosed as pregnancies of unknown location (PUL). Of these patients, 80% (8/10) required a second TVUS for further evaluation, of whom 62.5% (5/8) were diagnosed with EP. Only one of the 87 patients with a confirmed ectopic pregnancy escaped detection despite three ultrasound examinations. This patient had three ultrasound examinations over the course of 21 days, all with a diagnosis of PUL, but slowly rising βHCG. Subsequent laparoscopy identified an unruptured right tubal EP.
An additional 29 patients did not have surgery, but were treated by the referring team medically or expectantly as presumed, possible or likely ectopics. We classified these patients as “presumed EPs”. While some of these pregnancies probably represent true EPs, others may represent entities such as persisting pregnancies of unknown location (PULs) or failed early pregnancies with an incidental adnexal mass. When the presumed EPs pregnancies were pooled with the confirmed EPs, the sensitivity and specificity of ultrasound decreased, reflecting the diagnostic and clinical uncertainty in these patients. Table 1 summarises the performance of the initial ultrasound and additional follow-up ultrasounds in the detection of EPs.

Overall, the majority of patients in our study (79%) required only one ultrasound examination. A second examination was required in 21% of patients and of these a further 26% required a third examination. When only patients with confirmed EPs were analysed, 82.8% required only one ultrasound examination, 16.0% a second examination and only one patient required a third examination. The median time from the first to the second ultrasound in patients with confirmed ectopic pregnancies was five days.

The distribution of patients' presenting βHCG levels is shown in Table 2. In patients with a confirmed EP, presenting βHCG level at the first ultrasound examination ranged from 70 IU/l to 79,600 IU/l, with a mean value of 4705 IU/l and median value of 1430 IU/l. In our series, 32 confirmed EPs (36%) had a presenting βHCG level was <1000 IU/l units, a level considered discriminatory for the diagnosis of an intrauterine gestational sac in live intrauterine gestations.

Discussion

The diagnosis of EP can be challenging. Women present with variable symptoms, at differing times during early gestation, sometimes not knowing they are pregnant or with uncertain dates making the interpretation of βHCG values in the clinical context difficult. Symptomatology of women with EP often overlaps significantly with other early pregnancy complaints such as painful hemorrhagic corpora lutea, implantation bleeding, early pregnancy failure and miscarriage. While some women with EP present with convincing constellation of symptoms and become haemodynamically unstable requiring urgent surgical management, the majority of women present with less convincing symptomatic patterns.

<table>
<thead>
<tr>
<th>Initial ultrasound (one scan only)</th>
<th>Confirmed EP</th>
<th>Confirmed and presumed EP pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>88.5%</td>
<td>80.2%</td>
</tr>
<tr>
<td>Specificity</td>
<td>96.5%</td>
<td>84.1%</td>
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<table>
<thead>
<tr>
<th>Initial ultrasound + one follow-up ultrasound</th>
<th>Confirmed EP</th>
<th>Confirmed and presumed EP pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>93.1%</td>
<td>87.1%</td>
</tr>
<tr>
<td>Specificity</td>
<td>95.7%</td>
<td>82.8%</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Initial ultrasound + two follow-up ultrasounds</th>
<th>Confirmed EP</th>
<th>Confirmed and presumed EP pooled</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>94.3%</td>
<td>87.9%</td>
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<tr>
<td>Specificity</td>
<td>95.7%</td>
<td>82.6%</td>
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clinical signs to their primary care doctors and these patients are then streamlined through regional emergency departments and specialist early pregnancy clinics that heavily rely on diagnostic ultrasound.\textsuperscript{1,5–8} Advances in transvaginal ultrasound over the last 20 years have enabled early and accurate diagnosis of ectopic pregnancy and have contributed to a marked reduction in maternal mortality and morbidity.\textsuperscript{9} The prevalence of ectopic pregnancy varies in different patient populations, depending on the population characteristics and study selection criteria.\textsuperscript{5–7} In this study, the prevalence of confirmed ectopic pregnancy in patients specifically referred with clinical suspicion of ectopic pregnancy to a tertiary hospital typical of other institutions in Australasia was 15%.

Our results indicate that the diagnostic performance of a single initial transvaginal ultrasound scan performed by general sonographers in a radiology department within a tertiary hospital carries a high sensitivity (88.5\%) and specificity (96.5\%) for the diagnosis of ectopic pregnancy. Other large prospective studies have shown comparable results with sensitivity ranging from 73.9\%–90.9\% and specificity 99.8–99.9\%.\textsuperscript{5–8}

Table 2: Distribution of $\beta$HCG levels at presentation in patients with confirmed ectopic pregnancies.

<table>
<thead>
<tr>
<th>$\beta$HCG level (IU/l)</th>
<th>Number of confirmed EP</th>
<th>Percent of confirmed EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;250</td>
<td>4</td>
<td>4.6%</td>
</tr>
<tr>
<td>250–500</td>
<td>11</td>
<td>12.6%</td>
</tr>
<tr>
<td>500–1,000</td>
<td>17</td>
<td>19.5%</td>
</tr>
<tr>
<td>1,000–2,000</td>
<td>15</td>
<td>17.2%</td>
</tr>
<tr>
<td>2,000–5,000</td>
<td>23</td>
<td>26.4%</td>
</tr>
<tr>
<td>5,000–10,000</td>
<td>10</td>
<td>11.5%</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>7</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

While the vast majority of EPs can be successfully diagnosed by a single initial TVUS, some women will require clinical reassessment, repeat $\beta$HCG and a follow-up ultrasound examination.\textsuperscript{2–4} Missed cases of EP (false negative ultrasounds) are initially diagnosed as PULs. The addition of a second follow-up ultrasound modestly improves the diagnostic performance of ultrasound. In our series of 87 patients with confirmed ectopic pregnancy, only one evaded detection despite multiple scans. The patient was eventually diagnosed with an unruptured right tubal EP. Overall, 21\% of patients presenting to our department with a clinical suspicion of ectopic pregnancy needed a repeat ultrasound examination. The rate of repeat examinations in patients with confirmed ectopics pregnancies was lower (17.1\%) and was especially low for third re-examination (1.1\% versus 26\%). This suggests that patients who harbor an EP are somewhat easier to diagnose than those presenting with other early pregnancy problems such as miscarriage or persisting PUL.

In women with an initial diagnosis of PUL, 7.8\% (10/129) were subsequently diagnosed with a confirmed EP. It is likely these EPs were too small to be visualised at the time of the initial TVUS. A further challenge in the diagnosis of small unruptured ectopic pregnancies is the paucity of associated imaging findings that normally suggest the presence of a non-visualised underlying ectopic pregnancy such as free fluid, particulate fluid, organised haematoma or blood clots in the pelvis.

Non-surgical management of ectopic pregnancy in clinically stable patients has become commonplace.\textsuperscript{10–12} For this reason, apart from the surgically and histologically diagnosed EPs pregnancies in the confirmed EP category, we also included in our analysis those pregnancies that were treated by the early pregnancy clinic team medically or expectantly “as if” they harbored an unruptured EP (presumed EP category). While some of these pregnancies do represent true ectopies, others may represent other entities such as persisting PULs or failed
early pregnancies with an incidental adnexal mass. There is no way to know how many presumed EPs were in fact true EPs pregnancies and how many represented other entities. Given that ultrasound has a very high sensitivity for the detection of EP in patients proven to harbor an EP, it is reasonable to suppose that the vast majority of the women in the presumed EP category did indeed harbor an EP.

A common clinical dilemma in the early pregnancy clinic involves patients who are symptomatic but stable and in whom an initial ultrasound is inconclusive (PUL).

In our analysis, we pooled patients from the confirmed EP and presumed EP category to help answer a useful clinical question: “if there is anything that the clinicians need to worry about in terms of surgery, methotrexate or at least expectant management of an underlying ectopic pregnancy, what is the probability that an ultrasound scan will identify it?”

When the presumed EPs were pooled with the confirmed EPs, the sensitivity and specificity of ultrasound reduced. This reduction in apparent performance is not unexpected and does not necessarily reflect underperformance of ultrasound in these patients, but rather, it highlights the lack of observable findings, diagnostic uncertainty and the lack of a gold standard.

The diagnosis of EP can be particularly challenging when the βHCG level is <1000 IU/l. This is because the non-visualization of an intrauterine gestational sac at this level does not exclude an early intrauterine pregnancy. In our series, over a third (36.7%) of the patients with confirmed EP presented for the initial ultrasound with β<1000 IU/l. The lowest βHCG level at which an ectopic pregnancy was successfully diagnosed by TVUS was only 79 IU/l.

This study has several limitations. Firstly, our patient population was pre-selected based on the geographical location of our centre and the level of service (tertiary teaching hospital). Secondly, in order for patients’ radiology reports to be statistically analysed, we needed to classify the terminology used in radiology reports as positive or negative for EP even though the reports sometimes did not provide such a clear binary distinction. We encountered a wide range of reporting styles with varying levels of diagnostic certainty and diagnostic hedging. The reports did not conform to the recently published consensus statements on the nomenclature and definitions in pregnancies of unknown location. Even though we applied strict criteria, process of classifying radiology reports may have introduced unexpected biases. Thirdly, the sonographers who performed the scans were not blinded to the patient's clinical information, blood test results and patients' symptomatology. Instead, the sonographers and radiologists considered each case in its clinical context and used all available clinical information to assist them in the formulation of a diagnostic impression. It should therefore be acknowledged that this study did not evaluate the standalone performance of sonography in the diagnosis of ectopic pregnancy, but rather, the performance of ultrasound combined with clinical information, symptomatology, βHCG as well as the expertise and clinical judgment of the sonographer. Finally, we considered the retrospective nature of this study an advantage. This is because our study reflects the standard operating characteristics of a normal busy radiology department rather than the stringent parameters associated with a prospective study performed by subspecialist experts in a research unit. The sonographers who assessed the patients in our study did not know their performance was going to be scrutinised in the future.

**Conclusion**

Ectopic pregnancy continues to present a clinical and imaging challenge. The performance of ultrasound in the diagnosis of EP in the setting of a general radiology department within a tertiary hospital in New Zealand is excellent and on a par with international literature. The vast majority of patients can be successfully diagnosed on the first examination with a small number of patients requiring further reassessment with modest diagnostic delays. The likelihood that a clinically significant EP will escape detection on repeat ultrasound examinations is very low.
REFERENCES:


