Accuracy of a point-of-care test for quantifying human chorionic gonadotrophin (hCG) in the management of pregnancy of unknown location in an abortion service

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ABSTRACT

Introduction Women may seek abortion at gestations when there is no visible intrauterine pregnancy on ultrasound scanning. Clinical protocols for pregnancy of unknown location (PUL) require measurement of serum human chorionic gonadotrophin (hCG), with the National Institute for Health and Care Excellence recommending that values above 1500 IU/L be further investigated to exclude ectopic pregnancy. Our aim was to determine whether a point-of-care test (POCT) could be used instead of laboratory serum hCG measurement.

Methods Over 12 months, women who presented to an abortion service with a PUL had a POCT for blood or urine hCG and laboratory serum hCG measurement. The POCT machine used provides a discrete hCG value below 1000 IU/L and above this gives results as a range. The sensitivity and specificity of the POCT in identifying cases where laboratory serum hCG results were above 1500 IU/L were calculated.

Results A total of 118 women presented with a PUL, of whom 70 had a POCT on blood (n=49) or urine (n=21) and a corresponding laboratory serum hCG. The sensitivity of the blood POCT was 0.67 (95% CI 0.38 to 0.87) and the specificity was 0.97 (95% CI 0.83 to 0.99). The sensitivity of the urine POCT was 0.25 (CI 0.01 to 0.78) and the specificity was 0.94 (CI 0.69 to 0.99).

Conclusion Although both the blood and urine POCTs had a high level of specificity, neither test was acceptably sensitive. While promising, this POCT for hCG is not sufficiently reliable to replace laboratory serum hCG testing in the management of women with PUL in an abortion service.

Key messages

- Pregnancy of unknown location is becoming an increasingly frequent diagnosis in abortion services as women may now present at very early gestations.
- Quantitative point-of-care serum human chorionic gonadotrophin (hCG) testing may be beneficial in management, but close agreement with serum hCG is essential to reduce the risk of failure to diagnose ectopic pregnancy.
- The point-of-care testing device assessed in this study was not sufficiently sensitive to be relied upon to exclude ectopic pregnancy.

INTRODUCTION

Just over 200 000 abortions took place in England, Wales and Scotland in 2017.[1 2] The availability of highly sensitive urinary pregnancy tests that can be bought 'over the counter', coupled with better access to abortion services, has led to women presenting for abortion at earlier gestations than previously.[1]

There are many benefits to earlier access to abortion services, including availability of early medical abortion methods and the greater efficacy of medical abortion at early gestation.[3] However, with very early presentation to abortion services, the proportion of patients with pregnancy of unknown location (PUL) increases, as those attending at earlier gestations may not yet have a pregnancy that is visible on ultrasound imaging (USS).

A pregnancy is confirmed to be intrauterine if a yolk sac is seen within a gestational sac on USS. Protocols have been designed to manage abortion in early pregnancy before a yolk sac is visible on USS,[4] but at very early gestations (before 6 weeks) there may not even be a visible gestational sac.

However, even when an intrauterine pregnancy has not been confirmed, there is evidence that medical abortion is highly effective, with fewer cases of incomplete abortion, when compared with termination at later gestations.[5]

PUL is typically managed by serial monitoring of serum human chorionic gonadotrophin (hCG) levels and repeat imaging until an intrauterine pregnancy is demonstrated. In the setting of abortion services, it becomes counterproductive to delay treatment when so much has been done to broaden early access. Furthermore, serum hCG samples often need to be sent to a laboratory that is not on the same site as the clinic and results may not be available for 24–48 hours. This may be a particular challenge for abortion services in remote or rural locations.

Multi-level semi-quantitative urinary pregnancy tests have been developed and used in various contexts to assess outcome of early medical abortion in the USA[6] and Mexico.[7] These tests show a test line at different bracketed levels of hCG and can allow for a baseline result and then follow-up to confirm the success of abortion. In the context of PUL, where hCG levels may be very low, a discrete quantitative result may be more useful in order to assess the risk that the pregnancy is ectopic. The UK National Institute for Health and Care Excellence (NICE) advises that an empty uterus on USS with a serum hCG greater than 1500 IU/L would require a higher index of suspicion for ectopic pregnancy than an empty uterus with hCG lower than that level, as an intrauterine pregnancy should be visible with that level of hCG.[8] There is some evidence from patients with gestational trophoblastic disease that at low levels of hCG, levels in the urine are similar to serum levels and so urine testing may be appropriate.[9] Furthermore, quantitative point-of-care testing (POCT), particularly for hCG, has been identified as a key area requiring development, investigation and innovation within community healthcare settings.[10]

With this in mind, we introduced a hCG POCT system to our community-based NHS abortion service (Chalmers Centre, NHS Lothian) in an urban UK setting.[11] This service provides care for approximately 2000 women each year requesting termination of pregnancy.[1] Our aim was to use the POCT machine in tandem with sending serum samples to the laboratory, to see if the POCT was sensitive and specific enough to ultimately replace laboratory testing. Our objective was to determine if the POCTs correctly identified women with a serum hCG level greater than 1500 IU/L.

METHODS

This was a service improvement project conducted at the Chalmers Centre, NHS Lothian, Edinburgh, UK and was approved by the local Quality Improvement Team. Given the nature of the project, it was not registered in a clinical trials database and the local scientific ethical officer confirmed that it did not require ethical approval.

Women attending the Chalmers Centre abortion service have an ultrasound scan to confirm the location and gestation of their pregnancy.[11] If the uterus appears to be empty, they are asked to provide a urine sample to conduct a confirmatory high-sensitivity urinary pregnancy test (positive at >25 IU/L hCG). All women have a blood sample taken for full blood count, blood group, HIV and syphilis serology.[11] If they have an empty uterus on USS, an additional blood sample is taken for measurement of serum hCG as per the local clinic PUL protocol.

The use of the POCT was piloted for women with a PUL between December 2016 and December 2017. The POCT machine (VEDA.LAB Easy Reader, Quadratech Diagnostics Ltd, Cooksbridge, UK) was approved by the laboratory services committee of NHS Lothian. The POCT machine has cartridges to test both serum and urinary hCG and generates a quantitative hCG result in approximately 30 s. The POCT machine was used to test a drop of blood (from the blood sample) or a sample of urine for hCG in addition to the standard urine and serum hCG tests for women with a PUL. A single operator (PM) conducted the POCTs and was responsible for regular validation and checks on the functioning of the machine. For levels of hCG below 1000 IU/L, the machine gives a reading as a discrete number, but above 1000 IU/L it gives results as a range: 1000–5000, 5000–50000 or 50 000–250 000 IU/L.

The results of the POCT were not used to inform clinical management during the pilot. Although clinicians were made aware of the POCT result, patient management was based exclusively on the laboratory serum hCG result. In addition, the POCT was not used for serial hCG measurements, as these patients would often have second or third hCG measurements at a different site or over weekends, when POCT was not available. The POCT results were collated and compared with the serum results. POCT results without a corresponding serum sample were excluded.

We calculated the sensitivity and specificity of the POCTs for identifying women with a laboratory serum hCG greater than 1500 IU/L, as this was the threshold recommended by NICE. In order to analyse this, all POCT values above 1000 IU/L were classified as indicating a laboratory serum hCG above 1500 IU/L, because the POCT only reported values above 1000 IU/L as a range. We noted that this will overestimate the sensitivity of the POCTs, while underestimating specificity. Data were analysed using SPSS (Version 23,

Table 1 Sensitivity and specificity analysis for blood point-of-care test

		Serum hCG	
		<1500 IU/L	>1500 IU/L
POCT - blood	<1000 IU/L	n=33 97.1% (95% CI 82.9 to 99.8)	n=5 33.3%
	>1000 IU/L	n=1 2.9%	n=10 66.7% (95% CI 38.7 to 87)

hCG, human chorionic gonadotrophin; POCT, point-of-care test.

IBM 2015) and confidence intervals calculated using the VassarStats (vassarstats.net) online calculator.

Patient and public involvement

Patients and public were not directly involved in the design of this project.

RESULTS

A total of 118 women presented to the service with a PUL between December 2016 and June 2017 and had POCTs. In 48 cases no corresponding serum hCG result was available and so these cases were excluded from the comparison. Consequently 70 results were therefore available for analysis, of which 21 were urine samples and 49 were blood samples.

Tables 1 and 2 display the results of the POCT (categorised as below or greater than 1000 IU/L) cross-tabulated against the serum hCG result (categorised as below or greater than 1500 IU/L). The sensitivity of the blood POCT was 0.67 (95% CI 0.38 to 0.87) and the specificity was 0.97 (95% CI 0.83 to 0.99). The sensitivity of the urine POC test was 0.25 (95% CI 0.01 to 0.78) and the specificity was 0.94 (95% CI 0.69 to 0.99).

DISCUSSION

This quantitative POCT for hCG offered a high level of specificity when testing both urine and blood. However, it had low sensitivity for both sample types, with urine being less sensitive than blood. This means that the result obtained from the POCT may be falsely reassuring that the hCG is at a level below 1500 IU/L and that the risk of ectopic pregnancy is therefore low. This is perhaps unsurprising, as urinary hCG levels are often different to serum hCG levels,[12] and women attending the abortion service may have dilute urine if they are encouraged to drink to fill their bladder prior to a transabdominal USS for gestational age dating.

Table 2 Sensitivity and specificity analysis for urine point-of-care test

		Serum hCG	
		<1500 IU/L	>1500 IU/L
POCT - urine	<1000 IU/L	n=16 94.1% (95% CI 69.2 to 99.7)	n=3 75.0%
	>1000 IU/L	n=1 5.9%	n=1 25.0% (95% CI 1.3 to 78.1)

hCG, human chorionic gonadotrophin; POCT, point-of-care test.

An NHS Horizon-scanning report for hCG POCTs called for studies investigating the accuracy of quantitative POCT devices, particularly the use of these devices in their intended clinical setting.[10] We identified one study where similar devices were tested for their accuracy and sensitivity. However the device we trialled was not included in that analysis and the study was conducted in a laboratory setting rather than a clinical setting.[13] Another study was identified in which a similar hCG POCT was used in an emergency department, but the objective of this study was to compare urine and blood testing in terms of the time taken to analyse results rather than their accuracy.[14] Our study tested both the accuracy of a quantitative POCT and its use in a 'real-life' clinical scenario, and is one of the first studies to do so.

Strengths and limitations

The study used a single operator to test baseline hCG for our entire patient cohort presenting with PUL during the study time frame. PUL is a relatively uncommon problem, involving approximately 2% of patients attending our centre, so although the number of patients in this study is small, it is representative of our population.

The study showed that the POCT used does have limitations, particularly that it cannot give a discrete value above 1000 IU/L and instead gives a range result of 1000–5000 IU/L. The 'cut-off' level of hCG recommended by NICE at which an intrauterine pregnancy should be visible on USS is 1500 IU/L.[8] This means that patients with an empty uterus on USS with an hCG in the range 1000–1500 IU/L cannot be distinguished from those with hCG levels of 1500–5000 IU/L, so all patients with that range result would need to be referred for serial hCG measurements to exclude ectopic pregnancy. Additionally, as this POCT has a low sensitivity, even using the lower threshold of 1000 IU/L as a cut-off for referral, there would be a high proportion of women who are not referred for further investigation but who would, in fact, have a serum hCG level greater than 1500 IU/L.

We only assessed the value of the POCT for single baseline hCG estimations, rather than for serial hCG levels. This was a pragmatic decision as patients often needed to attend an early pregnancy unit on a different clinical site if serial hCG monitoring was required. As mentioned previously, the POCT provides results above 1000 IU/L as a range rather

than a discrete figure. It may therefore not be useful for serial measurements, as it may not be possible to observe an increase or decrease if the values lie within the same range. For example, an increase from 2000 to 4000 IU/L would read as 1000–5000 IU/L for both results.

Future research

As already stated, NICE has advised that the significant hCG threshold for suspicion of ectopic pregnancy in patients with PUL is 1500 IU/L.[8] Future research could investigate use of a qualitative low-sensitivity urinary pregnancy test[15] or a multi-level semi-quantitative urinary pregnancy test[6 7] in this context, but no such test currently available has a 1500 IU/L threshold. However, there are other quantitative POCTs that can discriminate at 1500 IU/L hCG[16] and these should be investigated for their fidelity to laboratory-measured serum hCG at low levels.

CONCLUSIONS

Although both the blood and urine POCTs had a high level of specificity, neither test was acceptably sensitive. The lack of discrete values up to the threshold of hCG that is important in determining the likelihood of ectopic pregnancy (1500 IU/L) further limits its use in aiding clinical decision-making in PUL. While promising, the particular POCT that was the subject of this study is not sufficiently reliable to replace laboratory serum hCG testing in the management of women with PUL in an abortion service.

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