Point-of-care testing for human chorionic gonadotrophin (hCG)

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Clinical Question:

In pregnant patients presenting to Primary Care or to an Early Pregnancy Assessment Unit with bleeding and pain, what is the accuracy and utility of a point-of-care quantitative hCG test compared to standard laboratory measurement?

Background, Current Practice and Advantages over Existing Technology:

Bleeding and pain in early pregnancy are very common presentations to Primary Care, Emergency Departments and to specialist Early Pregnancy Assessment Units. The first line of investigation for these women is an ultrasound scan to determine the location and the viability of the pregnancy (1). In up to 42% of cases no intrauterine pregnancy is seen on scan (and no ectopic pregnancy is identified) and this is known as a 'pregnancy of unknown location' (PUL) (2). The possible clinical outcomes of a PUL are:

- An ongoing intrauterine pregnancy
- A failing intrauterine pregnancy
- An ectopic pregnancy
- A persistent PUL

The aim of subsequent investigations is to distinguish between these outcomes. The main clinical concern in cases where the pregnancy location has not been determined is whether there is an ectopic pregnancy, a potentially life threatening condition. Its incidence varies between 11 and 20 per 1000 live births in developed countries (3-5).

The use of serial quantitative human chorionic gonadotropin (hCG) measurements is a mainstay of practice in Early Pregnancy Assessment Units (EPAUs) to aid in the management of these patients. The change in hCG over 48 hours gives an indication as to whether the pregnancy is likely to be ongoing (intrauterine or ectopic), or whether it is more likely to be a failing pregnancy (either intrauterine or ectopic). The current clinical pathway involves patients being seen in secondary care and having a blood sample sent to the laboratory. Serial hCG measurements are therefore used, not to determine the location of the pregnancy, but to predict viability of the pregnancy.

NICE have concluded that a rise of more than 63% in 48 hours is likely to be an ongoing pregnancy and a decline of more than 50% is likely to be a failing pregnancy. In cases where there is a change in serum hCG between these values, clinical review is essential to determine the likelihood of an ectopic pregnancy (6). In most cases patients are asked to wait until the following day for the result of the hCG test. This not only causes a delay in determining the management plan, it may also result in unnecessary hospital admission (in women deemed to be at high risk of ectopic pregnancy) and almost certainly increases patient anxiety. However most women undergoing serial hCG testing are not admitted to hospital but managed in the community until a definitive diagnosis is made.

The possible advantages of a point-of-care (POC) test over the existing technology are that:

1) It would provide a rapid result, helping to aid prompt and effective clinical decision making.
2) It is likely to improve patient satisfaction by reducing waiting time for results and clinical decisions and enabling immediate feedback of the results to the patient.
3) It may be more cost effective than current laboratory methods.
4) It may help diagnoses to be made in primary care especially in the context of increasing availability of ultrasound scanning in the community setting.
5) It may allow follow-up in primary care rather than in secondary care.

Details of Technology:

Although there are several qualitative point-of-care hCG devices on the market, we identified only two quantitative POC hCG tests: Abbott Point of Care iSTAT and Radiometer AQT90 FLEX.

The available point of care products that measure quantitative hCG are shown in the table below:

	Type of sample		**Volume**	**Time (mins)**	**FDA approved**	**CE mark**	**Range IU/L**
	Whole Blood	**Plasma**					
iSTAT total β-hCG (Abbott Point-of-Care)	✓	✓	17 µl	10	Yes	Yes	5 to 2000
AQT90 FLEX β-hCG (Radiometer Ltd, England)	✓	✓	0.3-2 ml	18	Not known*	Yes	<1 to 5000

**According to the manufacturer, the AQT90 FLEX immunoassay analyser is not available in US (http://www.radiometer.com/en/products/immunoassay-testing/aqt90-flex-immunoassay-analyzer*

The iSTAT β-hCG uses a two-site enzyme-linked immunosorbant assay (ELISA) method and can detect whole (intact) hCG and the free β-subunit. The test is part of a cartridge system using the handheld iSTAT 1 Analyser System which is a platform for a number of different biochemical analytes (7). Its limitation in the serial measurement of hCG is the relatively low maximum range of 2000 IU/L.

The Radiometer AQT90 FLEX is a bench-top POC device again using ELISA to detect hCG. Its advantage over the only other commercially available device is that the upper limit of detection is

5000 IU/L. This may offer a significant advantage in the measurement of serial hCG. Since this device is a bench-top analyser it is perhaps less likely to be of use in the primary care setting.

Patient Group and Use:

Patients presenting to General Practice, the Emergency Department or an Early Pregnancy Assessment Unit with abdominal pain and/or vaginal bleeding where ultrasound has not identified the location of the pregnancy or is not available.

Importance:

There are more than 10,000 ectopic pregnancies diagnosed in the UK every year (8). Far more women are seen with a pregnancy of unknown location and are monitored with multiple hospital visits to try and establish the site and viability of the pregnancy. A major concern raised in the Confidential Enquiry into Maternal Deaths was the difficulty diagnosing an ectopic pregnancy. Delayed diagnosis of ectopic pregnancies can lead to rupture, with unstable patients requiring emergency operations that may be out of normal working hours which are known to have worse patient outcomes. There were 6 maternal deaths reported due to ectopic pregnancies during the period 2006-8 (9).

Previous Research:

Accuracy compared to existing technology

1. <u>iSTAT</u>

One hospital antenatal clinic-based study analysed 40 samples of blood (heparinised whole blood and serum) from pregnant women at ≤6 weeks gestation using the iSTAT POC analyser compared to the laboratory Beckman Coulter UniCel Dx1800. Analysis of the 40 paired whole blood and serum samples on the i-STAT and DxI800 respectively showed excellent correlation (r^2 = 0.994). Of note however was the finding that a Hook effect (whereby false negative results may be the result of high concentrations of the analyte saturating detection antibodies) was shown at elevated hCG levels (>218,000 IU/L) in cases of gestational trophoblastic disease as well as normal pregnancy (10). (In these cases the reader displayed numerical values below 2000 IU/L when the results should have been reported as ">2000 IU/L"). A further study analysed whole blood, plasma and serum samples collected from non-pregnant volunteers with added hCG (from a variety of sources, including residual clinical serum or plasma from physician-ordered hCG testing samples and commercial hCG preparations) on the iSTAT compared with three laboratory methods (Architect Total β-hCG; DxI Total βhCG, Beckman Coulter, Inc.; and Cobas e601 hCG+β, Roche Diagnostics). Imprecision was highest with whole blood (CV = 16.0% and 6.7% at 10 and 1184 IU/L, respectively) and lowest in serum (CV = 8.1% and 4.3% at 11 and 1305 IU/L, respectively) (11). The i-STAT results agreed most closely with the Architect Total β-hCG assay while greater differences were observed with Beckman

DxI Total βhCG and Roche Cobas e601 hCG+β assays (mean differences 9.3% and 12.3%, respectively). Once again, a Hook effect was seen at high hCG concentrations (>400, 000 IU/L).

2. Radiometer AQT90 FLEX

We did not identify any published studies assessing the accuracy of this test.

Impact compared to existing technology

There is no literature that has reported the actual impact for clinical care using a POC hCG test compared to existing technology. One previous study has shown that a (non-commercially available) POC test is faster and simpler than conventional methods but did not mention any impact on clinical care (12).

In the secondary care setting it is highly likely that a POC hCG test will improve the time to diagnosis, allow for immediate management planning with patients and improve the patient experience. However as yet this has not been established. It is feasible that with the increasing availability of ultrasound scanning in primary care, and the drive to increase the type of care provided in the community setting, that a POC hCG device would facilitate the safe management of women with a pregnancy of unknown location in the community.

Guidelines and Recommendations

The use of a specific POC hCG test in the management of early pregnancy problems has to date not been included in any guidelines. Measurement of laboratory-based serial hCG is however recommended by both the NICE guidelines and the Royal College of Obstetrics and Gynaecology Guidelines for the management of suspected ectopic pregnancy (6, 8).

Research Questions:

1) What is the accuracy of all available POC devices compared to a standard laboratory hCG test?
2) What is the impact of a POC hCG test on patient experience in terms of waiting time, decision making, diagnoses and hospital admissions?
3) What is the cost-effectiveness of a POC hCG test compared to current standard practice in the secondary care setting?
4) Would fast accurate POC hCG testing enable the transfer of care for patients with a pregnancy of unknown location into the community setting?

Suggested next steps:

1. Studies using patient samples in the intended setting to compare the accuracy of the different available tests to each other and to standard laboratory tests.

2. Data mining of current records to identify the current number of presentations and the resources expended in the management of these patients, e.g. number of visits to primary and care care facilities, number of hospital admissions, and length of stay.
3. Decision analytic modelling and economic evaluation of the use of POC hCG compared to standard laboratory tests when introducing the test in existing services or in new settings such as primary care.
4. Studies to compare the patient experience when POC devices are used in the management of pregnancy of unknown location compared to standard laboratory tests.

Expected outcomes:

The use of a POC hCG test could improve efficiency of diagnosis or exclusion of ectopic pregnancies and improve patient satisfaction.

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