

## **Perspectives on the monitoring and clinical utility of hCG measurement in the diagnosis of ectopic pregnancy.**

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The detection of hCG as a marker for pregnancy is one of the most commonly used tests worldwide. We now realise that free subunit expression and the molecular heterogeneity of hCG is more clinically significant than previously expected. With the exception of Down's syndrome screening, obstetricians appear largely unaware of the potential of combined marker approaches involving hCG and hCG variants in clinical diagnosis. The use of hyperglycosylated hCG (H-hCG) alone as a marker in pregnancy is weakened by the overwhelming immunoreactive presence of total hCG. However, in the most part an hCG/H:hCG ratio has been employed in studies looking at pregnancy viability and failure. This algorithm approach to combining multiple tests even on structural variants is yielding diagnostic mathematical models that predict and even diagnose disease.

Ectopic pregnancy still poses a serious threat of morbidity and mortality in women of reproductive age. Currently serial serum hCG in combination with ultrasound is the standard method for the diagnosis of ectopic pregnancy in the UK. There still remains no single biochemical test, combined or otherwise, to provide a quick and reliable diagnosis. We propose a new test for the diagnosis of ectopic pregnancy at presentation, based on hCG/H-hCG and CA-125 may provide a useful screening test for those at high risk.

Urine samples were collected from all women presenting at an emergency department with abdominal pain and/or bleeding with positive pregnancy test. 749 Study sample aliquots were stored frozen immediately and the routine clinical tests were carried out with the patients treated accordingly. Subsequently we assayed 350 samples for hCG, hCG $\beta$ , CA125, progesterone. H-hCG was also quantified in 149 samples where sufficient material remained.

In a previous study we examined the efficacy of different isoforms of hCG in the diagnosis of ectopic pregnancy and the quantification of free hCG $\beta$  appeared to just outperform total hCG as a single time point predictor of ectopic versus viable pregnancy. In a subsequent study CA-125 was able to distinguish spontaneous termination from true ectopic whilst progesterone provided little benefit in distinguishing either. As a combination the measures of hCG and CA-125 gave a high prediction of the risk of the patient having an ectopic pregnancy on the day the patient presents emergency departments. Similarly H-hCG values for the ectopic population were significantly different from those of the viable pregnancies ( $P < 0.0001$ ). While there was no significant difference between H-hCG in ectopic pregnancy and spontaneous miscarriage.

Combination mathematical algorithms are being examined to improve on the diagnostic/at risk performance of this test.