Introduction
Evaluation of the Hypothalamic-Pituitary-Adrenal axis (HPA) can be challenging. Concern regarding test reliability and variability in interpretation of investigations due to gender, age and lack of standard assays is well reported.\(^1,2\)

Insulin-induced hypoglycaemia with the Insulin Tolerance Test (ITT) is considered the gold standard assessment of HPA integrity.\(^3\) The Short Synacthen Test (SST) is a relatively simple, low-cost and well tolerated first line test of HPA despite concerns regarding accuracy.\(^4\) The glucagon stimulation test (GST) is often used as an alternative to the ITT. Although less reliable, the GST is particularly useful when induced hypoglycaemia is contra-indicated.\(^5\)

Misdiagnosis of HPA integrity can lead to a lifetime of unnecessary steroid treatment or under-replacement with subsequent ill health and life threatening emergencies; therefore accurate investigation of the HPA is essential. In this audit we evaluated the sensitivity of SST and GST in comparison to ITT for the assessment of patients with clinically suspected HPA insufficiency.

Objectives
We retrospectively audited test results of all patients referred to our unit for the assessment of HPA during a two year period from 2007 to 2009. The audit objectives were:

- To analyse local indicators for HPA assessments.
- To evaluate accuracy of the SST and GST against the ITT with the aim of advising the best method to screen for HPA insufficiency.

Method
During the two year audit period we identified 32 patients who underwent ITT for assessment of HPA, of whom 31 had pre-screening SST and/or GST and were included in the analysis.

Case notes and laboratory results of the 31 patients were reviewed for the indication of HPA assessment and to ensure all three dynamic tests were performed according to the unit protocol.

Appropriate cortisol response was considered as a peak value of ≥500 nmol/L on ITT and GST, and 30 minute value ≥250 nmol/L on standard SST (580 nmol/L in women taking oestrogens/OCP).

Serum cortisol was determined by chemiluminescent microparticle immunoassay (CMIA) using Abbott Architect (Ref 8D15, J840685,R06), Abbott Laboratories, Abbott Park, IL 60064 USA with run precision of approx. CV 4% and total approx. CV 5% and lower limit of detection 22 nmol/L.

Analysis of data was provided by an independent statistician to generate sensitivity and specificity via cross-tabulation.

Results
Sample (n) = 31
21 were females
Average age was 42.9 years (range 19 - 64)

![Image](https://via.placeholder.com/150)

Fig 1. Indication for ITT
- 23 with clinically suspected hypopituitarism
- 6 post-transphenoidal surgery
- 2 with none ACTH-producing pituitary adenoma

The most common indication for assessment of HPA integrity in our sample was investigation of a borderline cortisol which accounted for 59% of all cases, with post-transphenoidal surgery and primary hypopituitarism making 32% of the rest.

In this audit the 30-minute SST cortisol value was more sensitive in predicting HPA insufficiency when compared to the gold standard ITT than the peak cortisol value obtained during GST, with respective sensitivity of 92.8% ( CI 86.1% – 99%) for SST and 75% (CI 75%- 94%) for GST. This result is in line with the finding by Berg et al who compared GST against ITT in adult patients post pituitary surgery and concluded that 51% of the sample tested for HPA integrity would have not been diagnosed with accuracy if GST were used as the standard test.\(^6\) Sensitivity on this study ranged from 32% to 72%.\(^8\)

Both SST and GST in our sample had a low specificity when compared to ITT for producing cortisol values in excess of 16 μg/dL respectively. Attempts on improving specificity by increasing the cut off limit for either test would have led to compromise on sensitivity; a factor which could hinder the validity and utility of these tests as a screening tool for HPA insufficiency.

The limitation of this audit is the small sample, however, we feel it represents a true case mix encountered in the usual clinical practice and reflects the day to day performance of the two common screening tests.

Conclusion
Review of results from this retrospective audit suggest that the standard Short Synacthen Test is a more sensitive screening tool than the Glucagon Stimulation Test in assessing the integrity of the Hypothalamic Pituitary Axis.

Recommendation
SST is a more appropriate screening test for HPA axis and should replace the GST when ITT is contraindicated.

Confirmation of these results in a larger cohort is warranted.

References