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Prematurity and low birth weight may be key indicators for a low peak cortisol on neonatal Short Synacthen Tests

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Abstract

Background: There are multiple indications where evaluation of the Hypothalamic-pituitary-adrenal (HPA) axis in neonates may be considered e.g. hypoglycaemia, hypotension, conjugated hyperbilirubinemia; however permanent neonatal adrenal insufficiency (AI) is rare. Interpretation of results can be challenging due to a paucity of normative reference data in this population. This risks overdiagnosis and unnecessary treatment with corticosteroids leading to the associated iatrogenic harm, including steroid induced AI.

Methods: We undertook a retrospective case note review of all neonates who underwent random and/or stimulated cortisol measurements at a tertiary neonatal department in the UK over a seven-year period (June 2014 to July 2021). Demographic, clinical and outcome data were collected. Serum cortisol samples were analysed using the Roche Elecsys Cortisol-2 assay. A pass was defined as a peak cortisol >430nmol/L. Prior to 2016, the first-generation Roche Cobas cortisol assay was used in which a pass was defined as a peak cortisol >500nmol/L.

Results: In total, 443 neonates had serum cortisol concentrations measured during the study period. Of these, 119 (72M, 47F; 40% preterm, 60% term; gestational age (GA) range 22+5 to 41+3 weeks; 21% ELBW, 10% VLBW, 19% LBW) underwent stimulation testing with a Short Synacthen Test (SST); 92 (77%) following one or more unstimulated cortisol measurements and 27 (23%) had only an SST. The most common indications for SST were maternal antenatal steroid use (29%) and conjugated hyperbilirubinemia (24%). Overall, 89 (75%) demonstrated a normal SST response, 30 (25%) had a suboptimal response of whom two received a diagnosis of permanent AI, one died before repeat SST and four were lost to follow-up after being transferred back to their local unit. The remaining 23 (14M; 20 preterm; mean GA 29+4; 61% ELBW, 13% VLBW, 17% LBW) subsequently passed on repeat SST. There was a positive correlation between GA and peak cortisol on SST ($r=0.490$, $p=<0.001$) and peak cortisol on SST and birth weight z-score ($r=0.216$, $p=0.020$).

Discussion: In our experience, very few neonates who undergo HPA-axis testing are diagnosed with permanent AI (2/443, 0.45%) and the majority who have a suboptimal response subsequently pass their SST. The clinical relevance of this "transient AI" is unknown and may be due to the lack of neonatal specific reference data leading to false positive results. Our data indicate that prematurity and low birth weight are associated with lower peak cortisol on SST response supporting the need to establish normative neonatal adrenal function data.