Salivary free cortisol measurement: A diagnostic approach to assess adrenal failure in symptomatic premature infants

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Background:

Adrenal failure in premature infants:

- Can be **life threatening**
- Clinical features: Mental changes, **dys-balanced electrolytes**, **haemodynamic instability** and **recurrent hypoglycaemia**
- Is **likely to be common** due **to immaturity of the hypothalamic-pituitary-adrenocortical (HPA)** axis and **sudden loss** of **placenta-derived CRH concentrations**

Why free cortisol ?

- Normally, 90% of cortisol is bound to **cortisol binding globulin (CBG)** or to albumin;
- However, **free cortisol** is the **active agent**.
- During critical illness there is a **significant decrease in CBG** and albumin leading to a **drop in total cortisol, but not in free cortisol**
- When measuring **free cortisol** an **interference with placental** or **fetal steroids** can be **excluded**

Why salivary cortisol ?

- Collection of **saliva derived cortisol**
  - is **neither painful** nor **stressful**
  - is less invasive than venipuncture
  - does propably **not alter the cortisol levels** due to collection

Aim of this prospective observational study:

- To **assess the feasibility** of **obtaining sufficient saliva samples** from preterm newborns to allow measurement of free cortisol
- To **assess the correlation**, if any, between **salivary and serum cortisol** in preterm infants between 32 + 0 and 36+6 weeks`gestational age at birth

Patients/ interventions:

Patients: 43 eutroph, preterm newborns (32+0 to 36+6 weeks gestational age), who showed clinical signs for adrenal failure (at least three of the following symptomes: hypoglycaemia, hypotension, dysbalanced electrolytes, poor temperature regulation)

Interventions: 126 paired blood and saliva samples were obtained and analyzed between 1 and 5 days of life
Serum total cortisol and salivary free cortisol was tested by liquid chromatography/ tandem mass spectrometry and immunosorbent assay

Statistical analysis: The correlation between serum and salivary cortisol was evaluatied with the linear correlation test

Table 1. Characteristics of the study population

Clinical outcome measures (N = 43)	Median and range
Female/ male n(%)	25(58)/ 18(42)
Birth weight (g)	2640 +/- 437
Gestational age	35.1 +/- 0.9
Age (hours)	1.9 (1.0 – 4.2)
Serum cortisol (µg/ dL)	7.9 +/- 5.9
Salivary cortisol (nmol/l)	35.88 +/- 17.8
Paired serum/ saliva specimen obtained n	126
Specimen with sufficient saliva volume n (%)	118 (93,5%)
Arterial hypotension n (%)	43 (100)
Recurrend hypoglycaemia n (%)	38 (88)
Dysbalanced electrolytes n (%)	32 (74)
Poor temperature regulation n (%)	36 (82)

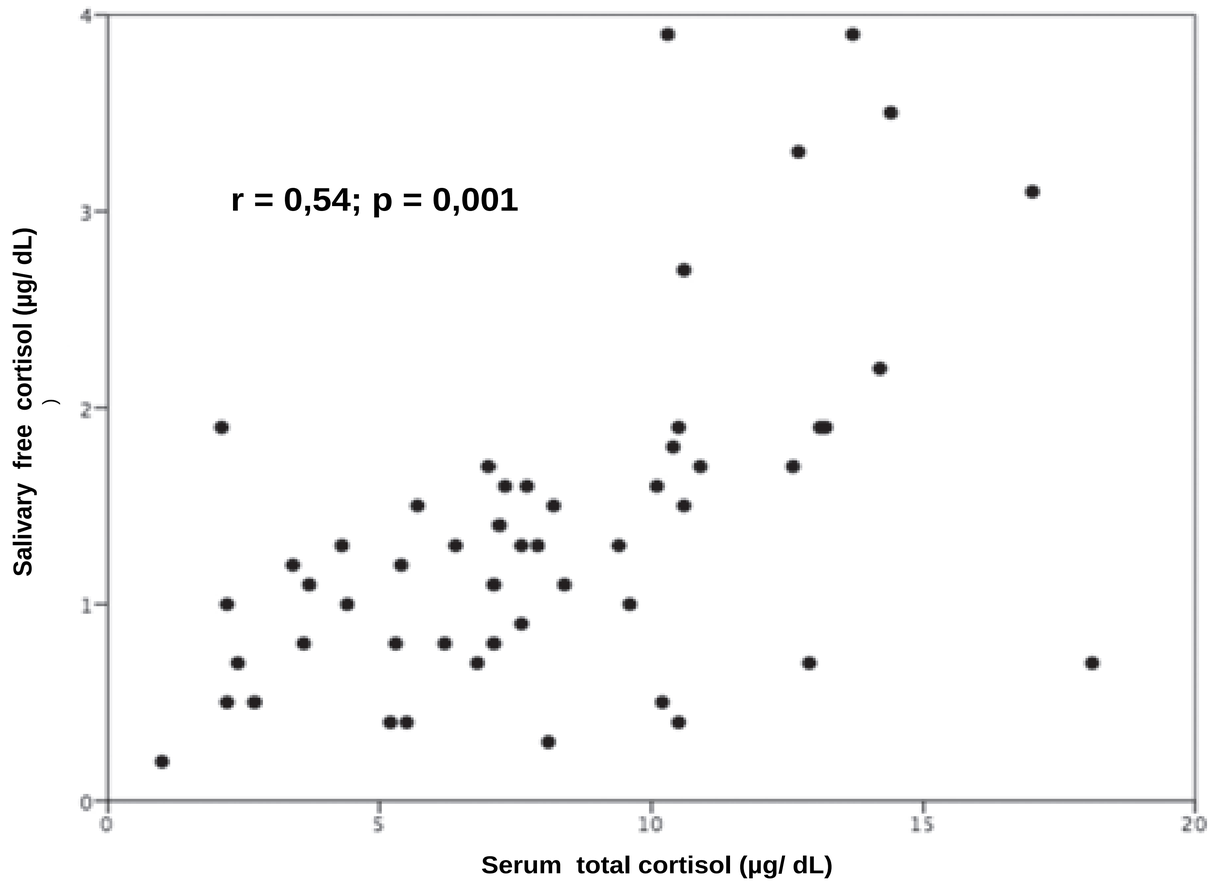

Figure 1. Correlation between serum and salivary cortisol levels in 118 paired specimens in 43 preterm newborns

Measurements and main results:

Feasability of obtaining sufficient saliva samples: **93,5 % of samples collected** had **sufficient salivary volumes** for measurement (Tab. 1)

Assesment of blood/ saliva correlation: The **total serum** and **saliva free cortisol values** from 118 paired serum/ saliva specimen had a **correlation coefficient (*r*) of 0.54** (95% CI, 0.45–0.63; $p < 0.001$). (Fig.1)

Discussion/ Conclusion:

- **Measurement of salivary free cortisol is feasible and has a low invasiveness**
- **Serum total cortisol and salivary free cortisol values correlate in preterm infants**
- **Salivary cortisol can be used as a surrogate for premature newborns, who show signs of adrenal failure**
- **Further studies must proof the observations of this study**

Literature:
(1) Gunnala V et al. Measurement of salivary cortisol level for the diagnosis of critical illness-related corticosteroid insufficiency in children. Pediatr Crit Care Med 2015; 16 (4)
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