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Are Breastfed Infants more Resilient?-Feeding Method and Cortisol in Infants

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Abstract

The effect of feeding method on stress hormone levels in infants is unknown. We studied infants from birth to one year, and found salivary cortisol 40% higher in breastfed infants compared with formula-fed infants. The higher cortisol levels among breastfed children may be involved in the analgesic effect of breastfeeding.

Keywords

feeding method; cortisol; interleukin-6

Cortisol, an end product of the hypothalamus-pituitary-adrenal (HPA) axis, is commonly used as a marker for stress(1). Cortisol levels are readily elevated in the newborns by minor stimulation such as undressing, weighing and measuring(2). Lack of contact comfort from the mother (such as with bottlefeeding) is a potent stressor to infants(3) and breastfeeding can have analgesic effects(4,5). Our goal was to test the hypothesis that breastfed infants would have lower concentrations of cortisol than formula-fed infants.

METHODS

We used hormone data from the Soy Estrogen and Development (SEAD) study which had a mixed cross-sectional and longitudinal design, with 6 boys and 6 girls in 31 examination age intervals (<48 hours; weekly for six months; then monthly to one year). One-third of the infants

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at each age interval were fed breast milk, cow milk formula, or soy formula. Children were eligible if they had been born at term (37–41 weeks) and with birth weight 2500–4500 g, met one of the feeding definitions and age categories, and had no major illness or birth defect. Exclusion criteria included chromosomal anomaly, major malformation, or any endocrinopathy (ambiguous genitalia, congenital hypothyroidism, etc.) Children were recruited by flyers, word of mouth including information sessions conducted by the site investigator and targeted at the clinic staff, and a computer-generated inquiry. The study was approved by the institutional review board at NIEHS (03-E-N184) and at the Children's Hospital of Philadelphia.

We recruited 166 infants whom we saw between 1 and 4 times each. Samples were collected at 382 visits: urine was collected at 381 visits, saliva at 359 visits and blood at 88 visits. The timepoints of collection did not differ between the feeding groups.

Cortisol was measured using an immunoaffinity column array.⁽⁶⁾ We looked at correlations between the cortisol values in each sample type (urine, saliva, and blood) and used salivary cortisol as our primary outcome measure. A mixed linear model, which specifically allows for multiple visits from the same individual, was used to compare the logarithmically transformed salivary cortisol concentration between feeding groups by age, adjusting for sex, race, weight, length, head circumference and BMI. Because we saw no differences in cortisol concentration between the cow-milk formula and soy formula groups ($p=0.70$), or between boys and girls ($p=0.16$), we combined the two formula groups and sexes to assess the difference in salivary cortisol between breastfed and formula-fed infants.

Interleukin 6 (IL-6), an indicator of inflammatory response, was also measured using similar analytical methods, and was used to explore whether inflammation might account for any differences in cortisol.

RESULTS

The serum cortisol level of the infants ($5.12 \mu\text{g/dL}$) was in the reference range ($3\text{--}23 \mu\text{g/dL}$) for infants less than 12 months of age.⁽⁷⁾ The cortisol concentrations in saliva correlated strongly with cortisol measures in urine and blood, with Spearman's correlation coefficients of 0.96 and 0.93, respectively (Figure 1), further supporting the validity of using salivary cortisol as a primary measure of outcome.⁽⁸⁾

The baseline-data (sex, age, birth weight and body length etc.) were balanced between breastfed and formula-fed groups. Salivary cortisol was 40% higher in breastfed infants compared with formula-fed infants ($8.66 \mu\text{g/dL}$ vs. $6.20 \mu\text{g/dL}$, geometric means adjusted by sex, age, weight, length, head circumference and BMI, $p=0.015$, Figure 2). When stratified by sex, the difference between groups was more significant in boys than in girls (57% increment vs. 32% increment).

Salivary IL-6 was about 15% higher in breastfed infants (adjusted geometric means 24 pg/ml vs. 21 pg/ml), but the difference was not statistically significant ($p = 0.37$).

DISCUSSION

In this partly longitudinal study, we found that salivary cortisol was about 40% higher in breastfed children throughout the first year of life. This finding was consistent after adjustment for infant size, sex, and race, was not accompanied by a significant difference in IL-6, and was true whether the formula-fed infants received cow-milk or soy-based formula.

Saliva is often used for biological assays in infants due to the ease of collection and now is preferred for cortisol analysis. We accounted for possible contamination such as cortisol in

maternal milk and oral blood, by taking samples at least one hour after feeding and cleaning subject's mouth with swabs. The strong correlation between concentrations in saliva and in blood or urine indicated that contamination was not a factor in this study.

Although we did not measure maternal cortisol, we considered its possible role. Previous studies showed a strong positive correlation ($p < 0.001$) between maternal and breast milk cortisol concentrations, and a fall in maternal plasma cortisol during the breast-feeding.(9) Using these data, we estimated the amount of cortisol that could be transferred to the infant, and it could account for less than 10% of the differences we observed (data not shown). Infant cortisol might also be affected by a cortisol surge at birth, but when we eliminated data from the first 48 hours of life we obtained the same results.

Our findings contradicted the hypothesis that breastfed infants would have lower levels of cortisol compared with infants in the formula-fed groups. Breast feeding, however, requires more effort on the part of the infant than does bottle-feeding due to the “hydraulics” of the process.(10) This extra effort may explain in part the higher cortisol levels seen in breastfed infants, but other explanations are possible and we have only limited data on the children in this study. We suspect that the higher cortisol concentrations may actually play a role in the analgesic effects of breast feeding. Cortisol release and blunting of pain are both associated with the stress response. Therefore, the increased cortisol levels in breastfed infants may be related to the pathway for analgesia. Future studies might include assessment of maternal cortisol levels, as well as comparison of cortisol trends in the different feeding groups with levels of inflammatory markers, such as interleukin-6, or of other stress markers, such as urinary catecholamines.

Cortisol during infancy plays an important role in the development of the HPA axis and of the stress response, a role which would have an impact throughout life.(11) The characteristics of adrenal hormone secretion change markedly during infancy. Disturbances in basal levels may produce psychological dysfunction and are associated with psychopathology in young people.(12) Although feeding method alone is unlikely to fully explain the observed difference, the results of this study that breastfed infants have higher levels of salivary cortisol than formula-fed infants, may have implications for development of the stress response and resilience later in life.

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References

1. King SL, Hegadoren KM. Stress hormones: how do they measure up? *Biol Res Nurs* 2002;4:92–103. [PubMed: 12408215]
2. Gunnar MR, Brodersen L, Nachmias M, Buss K, Rigatuso J. Stress reactivity and attachment security. *Dev Psychobiol* 1996;29:191–204. [PubMed: 8666128]
3. Harlow HF, Suomi SJ. Nature of love--simplified. *Am Psychol* 1970;25:161–8. [PubMed: 4984312]
4. Shah PS, Aliwalas LI, Shah V. Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database Syst Rev* 2006;3:CD004950. [PubMed: 16856069]
5. Carbajal R, Veerapen S, Couderc S, Jugie M, Ville Y. Analgesic effect of breast feeding in term neonates: randomised controlled trial. *Bmj* 2003;326:13. [PubMed: 12511452]
6. Phillips TM. Multi-analyte analysis of biological fluids with a recycling immunoaffinity column array. *J Biochem Biophys Methods* 2001;49:253–62. [PubMed: 11694283]
7. Degroot, LJ.; Jameson, JL. *Endocrinology*. Philadelphia: Elsevier; 2006.

8. Yao JK, Moss HB, Kirillova GP. Determination of salivary cortisol by nonisotopic immunoassay. *Clin Biochem* 1998;31:187–90. [PubMed: 9629493]
9. Patacchioli FR, Cigliana G, Cilumbriello A, Perrone G, Capri O, Alema GS, et al. Maternal plasma and milk free cortisol during the first 3 days of breast-feeding following spontaneous delivery or elective cesarean section. *Gynecol Obstet Invest* 1992;34:159–63. [PubMed: 1427417]
10. Lawrence, RA.; Lawrence, RM. *Breastfeeding: A Guide for the Medical Profession*. St Louis, Missouri: C.V. Mosby; 1999.
11. Bogdanov AI, Yarushkina NI. The role of the hormones of the hypothalamo-hypophyseal-adrenocortical system in the analgesic effect of corticotropin-releasing hormone. *Neurosci Behav Physiol* 2007;37:363–7. [PubMed: 17457531]
12. Goodyer IM, Park RJ, Netherton CM, Herbert J. Possible role of cortisol and dehydroepiandrosterone in human development and psychopathology. *Br J Psychiatry* 2001;179:243–9. [PubMed: 11532802]

Figure 1.
Correlation between Cortisol ($\mu\text{g/dL}$) Samples

Figure 2.
Salivary Cortisol in Breast-Fed and Formula-Fed Infants
*Connected points represent the same subject.