J Pediatr (Rio J). 2013;89(4):327–329

Jornal de Pediatria
www.jped.com.br

EDITORIAL

Breastfeeding and cognitive development: is there an association?☆,☆☆

Amamentação e desenvolvimento cognitivo: existe uma associação?

Arthur I. Eidelman

MD. Shaare Zedek Medical Center, Department of Pediatrics, Hebrew University School of Medicine, Jerusalem, Israel

The holy grail of pediatric medicine has been to design the definitive study that will ultimately resolve the question of the relationship between breastfeeding and cognitive development in otherwise healthy term infants. Unfortunately, by definition such a quest is doomed to fail, as a grail is something very much wanted, but very hard or impossible to achieve. A corollary is that, despite the inevitability of failure, continuing with the quest *per se* is encouraged, as there is secondary value in the process itself.

As such, one should welcome, despite all its limitations, the publication of the study by Fonseca et al.[1] in this issue of the journal. The authors attempted to measure the impact of breastfeeding on the ultimate intelligence of children. In assessing the quality of such a study, one is best guided by the monumental publication by the Agency for Health Care Research and Quality (AHRQ) of the United States Department of Health and Human Services entitled ''Breastfeeding and maternal and infant health outcomes in developed countries''.[2] This report provided both detailed discussion of the methodological issues involved in assessing the published studies on this subject and a series of conclusions based on meta-analyses using appropriate statistical techniques, and should thus be utilized as a reference point for any future discussion.

What are the methodological issues in studying the effect of breastfeeding on any health outcome and what are the specific and additional limitations when one wants to investigate the impact on cognitive development? It is clear that the overriding concern regarding the quality of any breastfeeding research program is the inability, due to ethical considerations, to perform a truly randomized controlled study. Thus, all studies that attempt to compare breastfed infants with non-breastfed infants suffer from a basic maternal selection bias, and the concern (most likely justified) that the mothers who have chosen to breastfeed are different from those who choose to bottle-feed. In turn, these differences may have measurable impact on health outcomes. In an attempt to overcome such concerns regarding observational studies, cohorts and case-controlled study designs have been employed using the duration and degree of exclusivity of breastfeeding adjusted for measurable confounders as the endpoints. Conventional confounders that have been corrected for (unfortunately not uniformly) include maternal/parental socioeconomic class, household income, maternal education, parental age, and race. Specific confounders that have been additionally adjusted for in studies of intelligence include birth weight, gestational age, birth order, home environment, marital status, number of siblings, and maternal and paternal intelligence.

Questions have been raised as to what should be the end point for cognition assessment (which tests) and at what age should the child be assessed. For example, the Bayley exam is not predictive of ultimate intelligence, even at age 2 years, and should thus be used sparingly in these studies.

DOI of refers to article:
http://dx.doi.org/10.1016/j.jped.2012.12.010

☆ Please cite this article as: Eidelman AI. Breastfeeding and cognitive development: is there an association? J Pediatr (Rio J). 2013;89:327–9.

☆☆ See paper by Fonseca AL et al. in pages 346–53.

E-mail: arthur.eidelman@gmail.com

http://dx.doi.org/10.1016/j.jped.2013.05.002

The acknowledgement that the accurate assessment of cognition in children should not happen before the age of 5 years creates an almost inevitable situation of significant loss to follow-up over the years, and thus reintroduces the combination of selection and residual bias. It is particularly concerning that in most studies the specific measurement of maternal intelligence (the major variable that correlates with the child's intelligence) has not been measured, and markers such as socioeconomic status and educational achievement (number of grades completed) have been used instead. In fact, when maternal IQ is specifically included in an analysis, there is little if any evidence for an association between breastfeeding and cognitive performance. Sibling studies, wherein the maternal IQ is by definition the same, likewise do not substantiate any advantage to breastfeeding.[3] The study by Zhou et al.,[4] which substantiates that the critical variable impacting on the child's cognitive development is the home environment, further emphasizes the complexity of executing studies that control for all the critical variables that interplay in matters of child development.

Not surprisingly, the AHRQ comprehensive analysis published in 2007 included a review of studies published until 2006 and concluded that, given the at best variable quality of the then existing studies (*e.g.* increased loss to follow up, assessment only up to 2 years of age, small sample size, *etc.*) there was a serious question whether one can make conclusions regarding the validity of the thesis that breastfeeding *per se* in term infants is associated with an improvement in the intellectual function.

Given these data limitations, what can we learn from more recently published studies? Of greatest interest is the monumental project of Kramer et al., who addressed the question of breastfeeding impact on health outcomes in an indirect fashion, with results that paradoxically may have provided the most direct answer to the effect of breastfeeding on cognitive development. The results of the Kramer's 22 publications (the PROBIT Study) were recently succinctly reviewed by Martens.[5] In order to appreciate the quality of the study and the relevance of the PROBIT results, the study design must be clearly described.

Confronted by the same ethical dilemma that forbids randomization of breastfeeding and bottle-feeding, Kramer choose to study only mothers who initiated breastfeeding in the immediate postpartum period. Then, a ''cluster randomization'' was performed, *i.e.* randomly assigning a matched hospital to receive or not receive a structured intervention consisting of an intensive lactation management program for both the hospital postpartum period and for the community clinics. The specific aim was to examine the effect of the intervention on breastfeeding duration and exclusivity. Over 17,000 mother-infant dyads from either the 16 hospitals that received the intervention or the 15 control sites (all in Belarus) were studied. The analyses were basically of two types: comparing infants born in hospitals that received intervention as opposed to no intervention, and alternatively, combining the entire data set and analyzing it as one observational cohort study, focusing on the effect of breastfeeding duration and exclusivity.

The most striking result was the percentage of mothers exclusively breastfeeding in the intervention group, as opposed to the nonintervention group (43.3% *vs.* 6.4% at three months and 7.9% *vs.* 0.6% at six months). Thus, as a group, infants born at an intervention site had a variety of increased health benefits, including cognitive development and academic achievement. Most importantly, when studying the entire cohort regardless of place of birth, the investigators observed that exclusively breastfeeding for at least three months and continuing some breastfeeding for at least until six months conferred an increase in the verbal IQ by 4.7 points, and in the overall IQ by 3.3, as opposed to those infants who were exclusively breastfed for less than three months.[6] The fact that all mothers initiated breastfeeding (thus minimizing selection bias) and that these comparisons were appropriately adjusted for most standard confounders strengthened the conclusion that this dose relationship confirms the specific value of breastfeeding on cognitive development. Of interest, no statistically significant additional benefit was attained when exclusive breastfeeding exceeded six months, as compared to the less than six months, although the trend was in that direction (verbal IQ increased by 5.2 points, and overall IQ by 4.2).

What is the basis for this positive effect of breastfeeding, and to what degree does breastfeeding enhance the maternal-infant attachment process facilitated by the maternal secretion of oxytocin secondary to the infant's suckling?[7] Alternatively, it may be the variety of critical nutritional and neurotrophic agents that are in breast milk and not in any human milk substitute that is the critical factor. Observing the list of substances that have been detected in fresh human milk, one should not be surprised regarding breastmilk's added value in facilitating maximum infant neurodevelopment.

- Fat: cholesterol (myelin), LCPUFA (membranes)
- Amino sugars: N-acetyl glucosamine (brain gangliosides), N-acetylneuraminic acid
- Peptides: EGF, insulin, IGF-1, NGF, delta sleep inducing peptide
- Amino acids: taurine, glutamine, carnitine
- Hormones: thyroxine (TRH TSH) cortisol, prolactin,

The current study by Fonseca et al.[1] did not compare the effect of three months *versus* six months of feeding, and thus cannot be compared to the PROBIT Study. Likewise, the use of Raven's Colored Progressive Matrix precluded presenting data as an IQ score, as is done with the conventional tests (such as WISC Picture Vocabulary or Wechsler), again precluding full comparison. Also, the statistically significant higher score in the breastfed group was of a magnitude that may have little, if any, clinical significance. Breastfeeding was not clearly quantitated, and to what degree there was supplementary or complementary feeding is unclear. The loss of almost half the cohort group during the eight-year follow-up raises a serious question as to selection bias. However, despite all these issues, this study adds another data set that points in the direction of the conclusion that other studies have made, *i.e.* breastfeeding is associated with enhanced cognitive development and as such should be supported by the medical profession as a critical public health measure.

Conflicts of interest

The author declares no conflicts of interest.

References

1. Fonseca AL, Albernaz EP, Kaufmann CC, Neves IH, de Figueiredo VL. Impact of breastfeeding on the intelligence quotient of eight-year old children. J Pediatr (Rio J). 2013;89:346–53.
2. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, et al. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess (Full Rep). 2007;153:1–186.
3. Der G, Batty GD, Deary IJ. Effect of breastfeeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis. BMJ. 2006;333:945.
4. Zhou SJ, Baghurst P, Gibson RA, Makrides M. Home environment, not duration of breast-feeding, predicts intelligence quotient of children at four years. Nutrition. 2007;23:236–41.
5. Martens PJ. What do Kramer's Baby-Friendly Hospital Initiative PROBIT studies tell us? A review of a decade of research. J Hum Lact. 2012;28:335–42.
6. Kramer MS, Aboud F, Mironova E, Vanilovich I, Platt RW, Matush L, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry. 2008;65:578–84.
7. Feldman R, Eidelman AI. Direct and indirect effects of breast milk on the neurobehavioral and cognitive development of premature infants. Dev Psychobiol. 2003;43:109–19.