Human Milk Processing and the Nutrition of the Very-Low-Birth-Weight Infant: Discussion

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A principal effect of juxtaposing presentations of in vitro biochemical experiments and clinical studies was disclosure of the gap between in vitro observation and the demonstration of a clinical effect. It is easy to argue teleologically that because a substance is present in milk it has a function; however, in most cases we have little clinical evidence that this is the case. The discussion was therefore devoted to the formulation of clinical questions about the use of human milk for feeding low-birth-weight infants and to suggestions as to how the investigation of these questions might be approached.

Dr. W A. Silverman prefaced the discussion by outlining how much neonatal feeding regimens had changed over his 40 years of clinical practice, pointing out the need for clinical trials “to challenge by design and scepticism when confronted with making the enormous step from observation to clinical practice.” He outlined the need to begin with an exact question and reiterated the serious problems of subject heterogeneity and therapeutic cointerventions in conducting such trials. Distinguishing between pragmatic and explanatory clinical trials, he made the point that cointervention is less of a problem in the former. Pragmatic trials merely compare treatments between equivalent and concurrently treated groups and are preferably collaborative, since this increases the legitimacy of
generalizing from their conclusions to make operational decisions about clinical practice. In the case of the explanatory trial, in which a more direct link between cause and effect is sought, the need to standardize the conditions other than the one being studied often makes it difficult to generalize results because of the artificiality of the trial conditions. A further point was the requirement for a prestudy prediction of the difference in outcome measure expected. This is, in itself, a difficult estimate to make without a clear appreciation of the basic patterns of early postnatal growth in very-low-birth-weight (VLBW) infants.

From these generalizations, the discussion moved to consideration of separate questions that were relevant to the subject. These were threefold:

1. Should human milk be pasteurized before it is given to VLBW babies?
2. How might the effects of feeding supplemented human milk to VLBW babies be measured?
3. By what objective tests can the physiological functions of individual milk constituents, such as secretory IgA and growth factors, be shown to be of importance to human infants?

These questions were discussed separately to illustrate some of the problems of designing clinical trials given the limited power of the experimental methods commonly employed.

SHOULD HUMAN MILK BE PASTEURIZED BEFORE IT IS GIVEN TO VLBW BABIES?

Apart from a few isolated case reports, there is little evidence to incriminate donor human milk as a vector of nosocomial infection in newborn nurseries. Indeed, in southern Sweden unpasteurized human milk has been given to babies for many years. Nevertheless, caution needs to be exercised in generalizing that because unpasteurized human milk is safely given in Sweden, the practice would be safe in all parts of the world and in all societies. On the other hand, there is some in vitro evidence that heat treatment may be deleterious to milk constituents. However, a problem in assessing
the significance of in vitro studies is that time–temperature cycles used for batch pasteurization have, in most cases, not been accurately reproduced in the laboratory. This is an important consideration, since the effects of heating are critically dependent on the time–temperature cycle that is employed. From the point of view of current clinical practice, therefore, the decision as to whether milk is to be pasteurized or not is largely one of personal opinion based on the above considerations. What is needed is a comparative clinical study between equivalent and concurrently treated groups of infants fed either pasteurized or unpasteurized donor human milk.

Two clinical questions require answering. First, does heat treatment affect nutrient absorption from donor human milk? Second, does heat treatment reduce the antimicrobial protection that we assume the infant receives from donor human milk?

The first question is of a different order from the second and could probably be answered by balance studies in small groups of infants in a single nursery, in other words, by an explanatory clinical trial. The second question is more complex because of the low incidence of proven infection in neonatal nurseries in Western countries. It would obviously require a large collaborative study for any difference in infection rates to become apparent. Furthermore, if the overall incidence of proven infection among VLBW infants receiving donor human milk is below 15%, what would we take as a substantial difference in infection rate in making the prestudy prediction? Furthermore, a sufficiently large trial in the Western countries would clearly introduce many organizational problems. For example, how would milk composition be standardized? And how would observer blindness be ensured? The latter would clearly be of great importance because of the possible bias that might be introduced if the observer had a different threshold to investigate and treat presumed infected episodes in the group receiving unpasteurized milk. Conceivably, the size of the trial could be reduced by conducting the trial in a nursery situated in a less developed country, where infection accounts for a much greater part of morbidity amongst VLBW infants.
HOW MIGHT THE EFFECTS OF FEEDING SUPPLEMENTED HUMAN MILK TO VLBW INFANTS BE MEASURED?

Again, small explanatory trials might answer some of the questions about the short-term effects of nutritional supplementation on infants' growth. However, it seems likely that, given small numbers, an effect would only be demonstrated in well infants. The reason for this is difficulty in standardizing and controlling cointerventions when studying sick VLBW infants. Such trials must also be interpreted with caution, as errors could be made in generalizing from their conclusions. Would one be justified, for instance, in extrapolating findings from well VLBW infants to sick VLBW infants? Ironically, it is studies on sick VLBW infants that are most urgently required, since, theoretically, malnutrition may compound the effects of other perinatal insults. How might such effects be measured in the long term? Professor J. Dobbing pointed out the difficulty of separating developmental effects attributable to minor differences in nutritional intake from those attributable to other environmental influences on VLBW infants. In other words, very large trials (i.e., with sufficient statistical power) might be carried out and no difference observed be attributable to problems of nutrition not because there were no such effects but because the clinical instruments were too coarse for their detection.

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BY WHAT OBJECTIVE TESTS CAN THE PHYSIOLOGICAL FUNCTIONS OF INDIVIDUAL MILK CONSTITUENTS BE SHOWN TO BE OF IMPORTANCE TO HUMAN INFANTS?

This discussion was centered on secretory immunoglobulin A as a specific milk component. Current knowledge of human milk secretory immunoglobulin A synthesis and its response to oral immunization of the mother strongly suggests that secretory immunoglobulin A has a role in passive protection of the neonatal gut. What is now needed is objective evidence of clinical advantage from such immunoglobulin A for the VLBW infant.
The prophylactic role of secretory immunoglobulin A in protecting infants from infection would require the study of either a large number of infants in developed countries or smaller numbers of infants in the less-developed countries. However, human milk resources might prove insufficient to provide the quantities of human secretory immunoglobulin A required for such a trial. As an alternative, one might be able to demonstrate an effect of supplementary secretory immunoglobulin A in a specific condition such as infantile gastroenteritis. More exploratory work is needed before a clinical trial could be mounted in order to establish what the necessary origin (and hence the bacterial specificity) of the immunoglobulin A should be and what minimum dose would be required to demonstrate an effect. Since supplies of human milk proteins are likely to be a limiting factor in mounting such trials, perhaps the effects of antimicrobial mediators from milks of other species (e.g., bovine lactoperoxidase and immunoglobulins) might be considered worthy of therapeutic trial.

Our limited understanding of the physicochemical nature of other factors in human milk, e.g., some of the growth modulators referred to by Dr. Gaull and co-workers (*this volume*), is at present an obstacle to framing the appropriate precise question that would be required before a clinical trial could be contemplated.

These questions illustrate the complexity of the problems involved in studying the nutrition of VLBW infants. It is clear that narrowing the area of uncertainty in each case will not be easy.