

Skin Evolution in the First Years of Life: Implications for Barrier Protection and Moisture Homeostasis



Lawrence Eichenfield, MD

Chief of Pediatric and Adolescent Dermatology, Rady Children's Hospital—San Diego; Vice Chair, Professor of Dermatology and Pediatrics, University of California, San Diego (UCSD) School of Medicine

It has long been suspected that the skin of neonates and young babies is in some way different than adult skin. Previous studies have shown that transepidermal water loss (TEWL) is greater in premature neonates, indicating incomplete barrier function; the implications of this finding are evidenced in higher rates of infection and skin disease among infants born prematurely, most likely due to increased percutaneous absorption of microbes and other chemical substances, as well as their relative immunosuppression. One remaining question is whether the skin of full-term neonates is also morphologically different than that of adults, and whether these differences have any clinical or functional consequences.

Indeed, a growing body of evidence seems to suggest that there are structural differences in the skin of full-term neonates compared with adults (e.g., thinner stratum corneum [SC] and papillary dermis). More evidence is needed, however, to bridge the gap between our growing understanding of the evolving structure of the skin in the first years of life and what implications this post-natal development has for basal skin functions.

Two recent studies,^{1,2} supported by Laboratoires Expanscience, are welcome additions to the literature, as they provide additional evidence that evolution of the integument continues after birth, with the most critical period being the first 2 years of life. The data derived from these studies are both clinically and scientifically interesting. In addition, they leave us with a provocative question: Now that we have additional evidence that the skin undergoes continued evolution in the first years of life, is there a potential role for treatments that rebalance the skin and provide the mechanisms for improved barrier function and water homeostasis?

NEONATAL SKIN IN THE EXTRA-UTERINE ENVIRONMENT: EVIDENCE OF EVOLUTION

The first months of life are important for developing, among

other things, motor skills, functional senses, and the precursors for communication skills. It is not entirely surprising, then, that the skin is also undergoing extensive physical changes, especially as the neonate has moved from the aqueous fetal environment to the relatively dry natural world full of desiccating stresses.

To study the effects of transitioning to the extra-uterine environment on skin development, Fluhr and colleagues compared the molecular composition of the SC in 108 subjects with presumably healthy skin across six age groups: (1) full-term newborns (1-15 days); (2) babies aged 5-6 weeks; (3) babies aged 6 ± 1 months; (4) children aged 1-2 years; (5) children aged 4-5 years; and (6) adults aged 20-35 years.¹ Measurements included TEWL, pH of the skin surface, and several assessments of SC hydration.

Measurement of TEWL is generally accepted as a reliable tool to assess objectively the epidermal barrier function. In the present study, there were no differences in TEWL between the groups, suggesting that the skin of newborns is fully competent with respect to water homeostasis. Based on previous studies demonstrating higher permeability and water sorption/desorption rate in infants compared with adults, one might expect to see greater water loss. Yet, the study authors noted that “in infants the fully developed, albeit thinner, SC [sic] assures competent skin barrier function.” However, a trend was noted toward higher TEWL in the 1-2 year old group, perhaps indicating continuing adaptation at that time to the gaseous extra-uterine environment.

The study also looked at levels of natural moisturizing factor (NMF) at various skin depths. Not surprisingly, NMF levels were highest in all age groups at 5-15 μ m below the skin surface, a distance that correlates with the approximate location of NMF production. At all depths studied—0-5 μ m, 5-15 μ m, and 15-25 μ m—NMF levels were highest among infants and babies through 6 weeks of life, trended downward among those in the 6 month group, and then returned to a level that was consistent among the 1-2 year old, 4-5 year old, and 20-35 year old groups.

These data are more meaningful given that skin of 1-15 day old neonates was more alkaline (pH = 6.0) compared with all other groups (range, 4.9 to 5.5), and also less hydrated (mean 17.4 a.u. compared to 28 to 41.5 a.u. for other age groups). Thus, while a

fully realized, albeit thinner SC may provide an adequate barrier against uncontrolled water loss, other mechanisms important for skin hydration are still developing after birth. Increased MNF production during the immediate postnatal period may serve to rebalance pH and increase hydration using “adaptation processes and increased compensatory mechanisms.” “It takes about a year for the complete adaptation to the dry gaseous environment, witnessed by the lowers NMF profile in babies aged 6 ± 1 months and then the relatively similar levels in the older age groups. This is likely to influence the water-handling properties of the skin and to impact its water barrier function and competence.”

Meanwhile, the higher pH of infant skin has important implications for local skin cell biology. For example, enzymes that play a crucial role in processing lipids for construction of the hydrophobic extracellular matrix of the SC are denatured (and, thus, dysfunctional) outside their optimal pH. In turn, incomplete SC development may potentiate development of inflammatory dermatoses (ie, atopic dermatitis, seborrhoeic dermatitis); the less acidic environment may favor microbial colonization.

TOWARDS A SEMI-QUANTITATIVE SKIN SCORE

Study findings noted above support the theory that local skin morphology continues to evolve in the post-natal period. To further demonstrate relevant post-natal skin changes, the same group of investigators conducted a biphasic study aimed at (1) developing a quantitative grading scale for measuring skin maturation using scanning electron microscopy (SEM) to analyze morphological features of the superficial SC, and (2) validating and refining the method with a combined corneodesmosome analysis (factor influencing SC cohesion and desquamation).²

For the first part of the study, investigators recruited six subjects into each of the same age groups used in the previous study. Using SEM images of skin samples acquired from the participants, independent and blinded dermatologists generated an electron microscopy isotropy (EMI) score using four criteria: density of corneocytes, formation of cell clusters and regularity of their appearance, cell shape and symmetry, and resolution of cells. Overall, a lower EMI value represented a more disorganized SC surface morphology (i.e., low isotropy).

Two distinct patterns in the EMI score are notable. First, EMI scores were lowest in the neonate group and increased with age. The EMI score for neonates was significantly lower than all older groups (except for 5-6 week old babies); as well, the EMI score among 5-6 week old babies was significantly lower than older groups, and the same pattern was present among the 4-5 year old group compared with adults. The consistency of lower EMI scores in younger versus older age groups suggests the validity of the findings and supports the hypothesis that the SC is relatively disorganized in early life, progressively organizing itself over time.

Second, the rate of change in EMI score between age groups reinforces that there are discernable differences in the skin in

the early period of life and suggests a timeline for normalization of the SC. According to the study authors, there was a “very rapid” increase in EMI score under 2 years, which slowed thereafter. This finding indicates “a high maturation rate from birth to the age of 2 years, apparently leading to the state of maturity of the skin surface, followed by a clearly slower rate of EMI score evolution from 2 years old to adults. The EMI score is thus indicative of skin surface maturation and can be used for semiquantitative evaluation of its micromorphology.”

In the second phase of the study, immunocytochemical corneocyte labeling was used in conjunction with SEM to assess the distribution of corneodesmosome remnants. The percentage of corneocytes displaying central corneodesmosome labeling was lowest in the 5-6 week old group ($1.4\% \pm 0.08$)—with a low percentage being perhaps “suggestive of a poorly controlled process of keratinization and desquamation.” By 1 year of life, the percentage rose to $8.9\% \pm 1.78$, which was not statistically different compared with 4-5 year olds ($8.4\% \pm 0.74$) or 20–35 years ($7.3\% \pm 0.93$; there was no neonate group in this phase of the study). Similarly, the projected area of individual corneocytes showed a progressive age-dependent increase.

Overall, both analyses revealed a correlation between EMI score and increasing age; both parts of the study combined demonstrate, “the relative immaturity of the epidermal barrier from birth to 1–2 years that may contribute to explain the fragility of the skin of children, its susceptibility to chemical, physical and microbial aggression and also its well-known relative permeability.”

CONCLUSION

The continually developing integument of babies is not surprising given the enormous amount of postpartum development that occurs in infants and into childhood. Nevertheless, it is reassuring to have quantitative data to support this perspective. More studies elucidating the myriad changes occurring at the various levels of the skin in the first few years of life—and how those changes affect function—would certainly be welcomed.

In addition, findings like the ones noted above may inspire dermatologists to rethink the treatment versus prevention paradigm. If the skin of neonates and young babies is less than optimal with regard to moisture retention and hydration (as these data suggest), then there may be a role for skin applications to provide additional protection. It is reasonable to consider that greater emphasis on preventive strategies would lower the incidence of skin disorders either manifested or exacerbated by desiccating stress. Although the skin of infants is demonstrably different than that of adults, the concept that “an ounce of prevention is worth its weight in gold” holds true for the skin at any age. ■

1. Fluhr JW, Darlenski R, Lachmann N, et al. Infant epidermal skin physiology: adaptation after birth. *Br J Dermatol* 2012;166:483–490.

2. Fluhr JW, Lachmann N, et al. Development and organization of human stratum corneum after birth: electron microscopy isotropy score and immunocytochemical corneocyte labelling as epidermal maturation's markers in infancy. *Br J Dermatol* 2014;171(5):978–986.