Infant Skin Development – The State of the Science & Future Perspectives

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Objectives

1. Infant skin development in utero and effects of vernix caseosa
2. Compare the features of premature and full term infant skin at birth
3. Discuss knowledge gaps, remaining questions and future research needs
Infant Skin Development and Vernix

How does the infant develop excellent skin while soaking in water and urine before birth?
Skin Functions at Birth

• Barrier to water loss (inside) and irritants (outside)
• Immuno surveillance and infection control
• Resilience to mechanical trauma
• Thermal regulation
• Tactile discrimination
• Acid mantle formation
• *The fully formed epidermis continually replenishes itself and repairs tissue injuries.*
Early Gestation

- Day 14
  - Ectoderm is the outermost of three primary germ layers

- Day 21
  - Ectoderm differentiates into the neuroectoderm and epidermis
Fetal Skin Development

At week 4, the basal layer with keratinocytes has formed and covered with periderm.
Fetal Skin Development

Melanocytes start appearing in the basal layer from 5-8 weeks
Fetal Skin Development

From 8-14 weeks, keratinocytes proliferate to form the spinous layer.
Fetal Skin Development

From weeks 16 – 26, the granular has formed and a few stratum corneum layers may appear.
Fetal Skin Development

From week 4, the basal layer with keratinocytes has formed and covered with periderm. Melanocytes start appearing in the basal layer from 5-8 weeks.

From weeks 8-14, keratinocytes proliferate to form the spinous layer. From weeks 16-26, the granular has formed and a few stratum corneum layers may appear.
Full Term Neonatal Skin

- Stratum corneum is well formed and an excellent barrier
- Thick epidermis
- Fully functional at birth despite being in water and amniotic fluid
Vernix Formation

- Hair follicles
- Spinous layer
- Basal layer
- Basal lamina
- Dermis
- Melanocyte
Vernix Formation

- Epidermis
- Sebaceous Gland
- Hair Follicle
- Hair Shaft
- Stem cells
- Dermis
Vernix Formation

- Sebaceous gland lipids and stem cells mix and co-extrude along the hair shaft to cover the skin surface
- Hydrophobic vernix lipids protect the skin surface from water
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Vernix Formation

- Hydrophobic vernix lipids protect the skin from water
- Stratum corneum forms under the vernix covering.
- When the lungs are mature, they secrete pulmonary surfactant that detaches vernix
Vernix: Properties

Composition:

• Water (80%)
  – much > Eucerin, Aquaphor, etc.

• Protein (10.3%)
  – From flattened cells (corneocytes) embedded in lipids
  – Water is associated with cells

• Lipids (9.7%)

Vernix Composition: Lipids

- Non-polar and polar lipids
  - triglycerides
  - sterol esters
  - wax esters
  - squalene
  - cholesterol
  - free fatty acids
  - ceramides

Vernix: Antimicrobial Properties

Lysozyme
Lactoferrin
Cytokeratin

Vernix: Functions

• **Native vernix is a multifunctional skin cream with the following properties**
  – Skin moisturizer
  – Anti-infective
  – Anti-oxidant
  – Skin cleanser
  – Skin repair and wound healing, semipermeable
  – Barrier protectant, e.g. against enzymes

• **Stay tuned…..to be continued**
Vernix functions to be added with infant skin discussions

- Dryness, erythema, hydration, pH in different graphs and relevance
- Wound healing – minor barrier repair
- Penetration of exogenous agents
Stratum Corneum: ........
A Few More Points
Stratum Corneum – Details

- 16 cell layers thick and 10 – 40 μm
- Difficult to penetrate

- Cornified envelope
- Intercellular lipid bilayers
- Corneo-desmosomes
- Natural moisturizing factor produced by filaggrin in SC
- Lamellar bodies in spinous layer
- Stratum corneum ~ 16 layers
Skin Barrier – Structure

- Cornified envelope
- Intercellular lipid bilayers
- Corneodesmosomes
- Natural moisturizing factor produced by filaggrin in SC
- Lamellar bodies in spinous layer

Stratum corneum

Desmosome
Ways to breech the mighty skin barrier

Mitragotri, Nature Reviews Immunology 2005;5:905
Innate Immunity

A. Skin Surface: sebum, sweat fatty acids

B. Stratum Corneum: barrier lipids, corneodesmosomes, antimicrobials

C. Structural proteins: architecture, physical barrier

D. Lamellar bodies make SC lipids, have human beta defensin 2 (HBD2) & catelicidin (LL37)

E. HBD, IL1β, catelicidin, wound healing

F. LCs: antigen presenting cells
Premature & Full Term Infant Skin
Transepidermal Water Loss (TEWL)

- Water of respiration normally moves through the SC from below.
- The rate of transepidermal water loss (TEWL, g/m²/hr) is a measure of skin barrier integrity.
- Faster for damaged SC
Skin Hydration

• Adequate skin hydration is essential
  – for plasticity and flexibility during movement
  – to prevent cracking
  – for desquamation of the outermost layer
• Measured noninvasively with a small probe

Full Term Infant Skin

- Image on the right shows the dermis, epidermis and stratum corneum from an histological specimen.
Full Term Infant Skin

- Low TEWL at birth, i.e., 4-6 g/m²/hr, indicates a competent skin barrier
- TEWL is lower than adult values of 6-8 g/m²/hr
- Remains low over first month of life
Full Term Skin Hydration

- Skin hydration decreases rapidly after birth.
- Dryness/scaling can be seen.
- By one month, hydration is significantly higher for the infant vs. mother.
- Changes in hydration indicate skin adaption to the new environment.

Full Term Skin pH

- Skin pH nearly neutral at birth
- Rapid decrease during first 4 days
- Lower pH for nondiaper (chest) site

Premature Infant Skin

1. Stratum corneum under developed or absent
2. Thin epidermis
3. Dermis deficient of structural proteins
Premature Infant Skin - Risks

- Increased permeability
- High water loss
- Electrolyte imbalance
- Thermal instability
- Skin compromise
- Delayed barrier maturation
- Infection

*Presently, the impact of premature birth on LC proliferation is unknown but of clinical importance in late onset sepsis.*
“Dressing” the Premature Infant
Premature Infant Skin

- Premature infant skin barrier integrity varies greatly with gestational age.
- TEWL for 24 – 25 wks gestation is very high, due to few stratum corneum layers
- At 29 wks, TEWL ~ 17 g/m²/hr

Premature SC Barrier Development

- At one month post birth, TEWL is *significantly higher* for the preterm infant than for the full term newborn.
- May lead to increased susceptibility to infection and penetration of exogenous agents.

Rate of Premature Barrier Maturation

- One study: $n = 10$ premature infants
- Premature Infants: 23-26 wks GA

Premature Skin Development

- The SC barrier forms rapidly due to the decrease from high humidity in utero to comparatively low humidity after birth.
- Surface hydration decreases over a few days.

Premature Skin Development

- The rate of barrier development is accelerated by the dry environment causing dry, scaly skin.
- Abnormal desquamation, indicative of hyperproliferation is observed after birth.

Premature Skin Maturation – Strategies??

**Humidity**

- Premature infants 23-27 wks GA in incubator at ~80% RH for first week and 75 or 50% thereafter
- SC barrier maturation was more significantly rapid at 50% vs 75% RH

Premature Skin pH

- Skin pH profile for the preterm infant varies with gestational age.
- Initial pH drop observed in both groups.
- Smaller babies have a higher pH for a longer time.

Skin pH over Time: Premature & Full Term

- SC maturation was assessed over 10 days from chest pH measurements.
- Chest pH decreased for premature and full term neonates (p < 0.05).

Visscher, Taylor, Narendran, JEADV 2013 Apr;27(4):486-93
Comparison of Premature and Full Term NICU Patients
Infant Skin Compromise

Prematurity
Fewer layers, poor barrier

Enzymes:
- Degrade SC proteins

Water, cleansers disrupt lipids

Irritants can penetrate

Tape Stripping: Removes layers

Damaged Barrier

Cincinnati Children’s
Factors Influencing Skin Integrity

- Determine the effects on SC integrity over time
  - Gestational age
  - Time from birth
  - Excretory processes
  - Nutritional status/source

Visscher, Taylor, Narendran, JEADV 2013 Apr;27(4):486-93
Subjects: Three Groups

- **Group 1**: GA < 38 & actual < 38
- **Group 2**: GA < 38 & actual ≥ 38
- **Group 3**: Both ≥ 38

• NOTE: Group 2 had a significantly longer time from birth than both Groups 1 & 3
Results: Irritant Response

- Perineal erythema differed for all 3 groups; lowest values for premature infants older than 38 wks.
- Rash scores were higher for full terms

Visscher, Taylor, Narendran, JEADV 2013 Apr;27(4):486-93
Results: TEWL

- TEWL for the perineal site was lower for both premature groups compared with full term infants ($p < 0.05$).
- TEWL was moderately correlated with erythema ($r = 0.4$)

Visscher, Taylor, Narendran, JEADV 2013 Apr;27(4):486-93
Results: Erythema

Group 1 = 31%
Group 2 = 61%
Group 3 = 30%

% with no observable erythema (score = 0)

Visscher, Taylor, Narendran, JEADV 2013 Apr;27(4):486-93
Results: Stool Exposure

- Stool exposure was higher for full term neonates than either premature group (p < 0.05).
- The number of days from birth to the first stool-skin contact was greater for premature group 2 (p < 0.05).
Conclusions & Implications

- Premature infants with early stool contact and high exposure and full term infants are at high risk for skin breakdown and may benefit from prophylactic interventions to minimize compromise.
- Low stool exposure and greater time before the first stool contact appear to be protective against skin compromise.

Visscher, Taylor, Narendran, JEADV 2013 Apr;27(4):486-93
Native vernix is a multifunctional skin cream with the following properties:

- Skin moisturizer
- Anti-infective
- Anti-oxidant
- Skin cleanser
- Skin repair and wound healing, semipermeable
- Barrier protectant, e.g. against enzymes
Low Skin Hydration

1. Transition from high to low humidity at birth may initiate epidermal changes such as the proteolysis of filaggrin to natural water binding molecules known as moisturizing factor (NMF).

2. Extensive exposure to amniotic fluid extracts water binding molecules from newborn stratum corneum.

Water Binding Free Amino Acids

- Free amino acid (FAA) levels are very low at birth and then increase significantly over the first month ($p < 0.05$).
- FAAs are substantially lower in infants at one month of age than in adults ($p < 0.05$).

Vernix & Free Amino Acids

- Vernix retained skin had significantly higher FAA levels versus infants with it removed.
- Free amino acids in vernix retained skin appear to originate from vernix itself.

Vernix Retained Skin

1. More hydrated

2. Less Red

3. Of lower skin pH

Vernix: SC Barrier Repair

- Wounds made at 25 microns of laser energy.
- Vernix and petrolatum-based cream (PBC) had greater recovery than no treatment, day 2 (p < 0.05).
- PBC had directionally faster recovery than both others on day 7 (p = 0.06).

Vernix: SC Barrier Repair

- Vernix contains a number of fatty acids, including oleic, linoleic and long chain species.
- Fatty acids, particularly linoleic, activate peroxisome proliferator-activated receptor-α (PPARα) which increases the rate of SC barrier formation.
- Linoleic acid has anti-inflammatory properties which may favorably impact SC repair or development.

Summary

1. FAA production may be initiated with high-to-low humidity transition in the neonatal period.
2. The low levels of FAA in neonatal foreskin is consistent with reports that 100% humidity blocks filaggrin proteolysis (animals).
3. Retention of FAA containing vernix appears to facilitate increased hydration and pH reduction at birth.

Clinical Relevance

- Implementation of evidence-based catheter insertion among 22-29 wk GA infants in 24 NICUs significantly reduced catheter-related bloodstream infections.
- The decrease was *less than expected*.

Clinical Relevance

• Poor skin integrity is now believed to be a major predisposing factor for neonatal sepsis.

• Prevention and mitigation of premature skin compromise are essential.
Translational Relevance

• The premature infant has a poorly formed, incompetent skin barrier that is ill-equipped to handle environmental stressors.

• A comprehensive understanding of skin barrier formation in both infant groups is expected to guide the development of effective strategies to minimize the consequences of an immature epidermis.
State of the Science: Premature Infant Skin

• Information on premature skin barrier maturation is limited.
• Data are largely descriptive, i.e., visual and instrumental quantitation of integrity, acidity, irritation, rash, etc. provide the
  – *What* but not the
  – *How*, i.e., the underlying physiology
• Interventions cannot readily be devised.
Knowledge Gaps & Future Research

- SC structure, composition, integrity, permeability, cohesiveness as a function of gestational age at birth, i.e., ontogeny
- When does the SC barrier become fully competent, i.e., comparable to full term healthy newborn at 1-3 months of life?
- Skin microflora vs. gestational age and environment
- How would variability due to gestational age influence treatment selection?
Hypothesis & Specific Aims

Specific Aims

1. Determine the ontogeny of stratum corneum barrier maturation in premature infants as a function of gestational age.
2. Compare premature skin during development to full term infants and adults

- SC ceramides, sphingoid bases, and free fatty acids will be lower in premature than full term infants & adults and will normalize over 3-4 months post birth.
Outcome Measures

• Noninvasive measures of integrity, maturity
  – Skin scores
  – TEWL
  – pH

• Genomic Analyses and Biomarkers of SC composition & response:
  – Lipid composition
  – Proteins (structural, serum albumin)
  – Biomarkers (cytokines)