Skin

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ABSTRACT. Human skin provides a barrier between the host and the physical, chemical, and biological environment. It is also a potential portal of entry for hazardous or infectious agents and a potential target of environmental toxins. Cutaneous vulnerability may take on many forms in the embryo, infant, child, and adolescent. Teratogenic agents may occasionally target skin, as appreciated in the proposed association of the antithyroid medication methimazole, with the congenital malformation known as aplasia cutis congenita. Percutaneous absorption of topicaly applied substances and the potential for resultant drug toxicities are important considerations in the child. Many topical agents have been associated with systemic toxicity, including alcohol, hexachlorophene, iodine-containing compounds, eutectic mixture of local anesthetics, and lindane. Percutaneous toxicity is of greatest concern in the premature infant, in whom immaturity of the epidermal permeability barrier results in disproportionately increased absorption. Immature drug metabolism capabilities may further contribute to the increased risk in this population. Ultraviolet (UV) radiation exposure, which increases an individual’s risk of cutaneous carcinogenesis, may be a particularly significant risk factor when it occurs during childhood. The “critical period hypothesis” suggests that UV exposure early in life increases the risk of eventual development of malignant melanoma. Other risk factors for malignant melanoma may include severe sunburns during childhood, intense intermittent UV exposure, and increased susceptibility of pediatric melanocytes to UV-induced DNA damage. Last, percutaneous exposure to environmental toxins and chemicals, such as insecticides and polychlorinated biphenyls, may differ between children and adults for several reasons, including behavioral patterns, anatomic and physiologic variations, and developmental differences of vital organs. Pediatrics 2004;113:1114–1119; skin, vulnerability, teratogen, percutaneous, ultraviolet light, toxin.

ABBRVIATIONS. UV, ultraviolet; EGA, estimated gestational age; MMI, methimazole; PTU, propylthiouracil; ACC, aplasia cutis congenita; MM, malignant melanoma.

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uman skin has the important function of providing a barrier between the host and the physical, chemical, and biological environment. As such, it is also a potential portal of entry for hazardous or infectious agents and a vulnerable target of environmental toxins. During the past several decades, we have witnessed important strides in our understanding of skin vulnerability, the cutaneous susceptibility to potentially noxious stimuli. Although the differing vulnerabilities of the skin of the embryo, infant, child, and adolescent still are not completely understood, much has been learned based on current knowledge of cutaneous embryogenesis, epidermal barrier formation and function, and the cumulative effects of ultraviolet (UV) radiation on photocarcinogenesis. These cutaneous vulnerabilities are the focus of this section.

SKIN DEVELOPMENT

Skin is a complex tissue derived from both embryonic mesoderm and ectoderm. Its presence is vital for the functions of mechanical protection, thermoregulation, immunosurveillance, and maintenance of a barrier that prevents insensible loss of body fluids. The development and growth of human fetal skin is marked by a series of sequential, patterned steps that are tightly controlled and dependent on a variety of interactions of the numerous cell types that compose the organ. As early as 6 weeks’ estimated gestational age (EGA), the human embryo has a covering of surface ectoderm that includes a basal layer and a more superficial layer termed the “periderm.” At approximately 8 weeks, stratification of the developing epidermis begins, with a resulting increase in its thickness. The periderm is a transient embryonal layer that is shed approximately at the end of the second trimester, the cells of which become a component of the vernix caseosa. Also around this time, additional stratification and maturation of the epidermal cell layers is occurring, and it is at this stage that the fetal epidermis begins to function as a barrier to the external environment. Keratinization, which is a marker for terminal differentiation of epidermal cells, starts in a “follicular” (surrounding hair follicles) pattern at 11 to 15 weeks’ EGA but does not start to occur in the remainder of the epidermis (“interfollicular keratinization”) until 22 to 24 weeks’ EGA. The keratinized (or “cornified”) cell layers continue to increase in number during the third trimester.

The most superficial layer of skin, the stratum corneum, is the foundation of the epidermal permeability barrier in terrestrials. The stratum corneum of premature infants is thinner and markedly less effective than that of full-term infants or adults. These (premature) infants therefore have a dysfunctional epidermal barrier and experience resultant difficul-
ties with fluid homeostasis, thermoregulation, and infection control. They are also at a disproportionately increased risk of systemic toxicity related to topically applied substances. Transepidermal water loss, which increases proportionate with immaturity of the epidermal permeability barrier, is 10-fold greater in a 24-week premature infant compared with a term neonate. In surviving premature infants, the cutaneous barrier usually matures rapidly, over 2 to 4 weeks, although in ultra low birth weight infants, it may take significantly longer.

CUTANEOUS VULNERABILITY OF THE EMBRYO, INFANT, CHILD, AND ADOLESCENT

There are remarkably few prospective scientific data on skin vulnerability in the pediatric population, especially with regard to the differing sensitivities between adults and children. Many of the published reports are based on anecdotal case observations. Ethical considerations impose a certain degree of limitation on the design of prospective studies, and extrapolation from adult data is of uncertain validity (excluding the case of premature infants, in which the differences in epidermal barrier function make any such extrapolation meaningless). Wester et al elegantly described an animal model for human percutaneous absorption, finding the isolated perfused porcine skin flap system to be a good model for predicting such absorption relative to humans. This system, however, was compared with adult volunteers; therefore, the applicability to children is uncertain. Percutaneous absorption characteristics of the newborn rhesus monkey have also been studied, but the relevance of this model to the human newborn (especially premature) remains unclear.

Teratogenic Agents

Teratogenic risks as they relate to skin have most frequently centered on antithyroid drugs, most notably methimazole (MMI). This agent and propylthiouracil (PTU), both members of the thioamide class of drugs, are the primary treatment of choice of gestational hyperthyroidism (with PTU being the more commonly used drug in the United States). The association between MMI and a specific congenital cutaneous malformation (aplasia cutis congenita [ACC]) has long been hypothesized. Patients with ACC are born with focal defects in skin, most commonly involving the scalp, and may present with an ulcer, blister, scar, or glistening membrane that lacks hair (Fig 1). In some instances, the defect may extend to the subcutaneous tissues or, rarely, to bone and dura. Although the majority of cases of ACC are idiopathic, there are multiple reports of affected infants who were born to mothers who were treated with MMI during pregnancy, both as a sole manifestation or as part of “MMI embryopathy” (dysmorphism, choanal and/or esophageal atresia, developmental delay, and growth retardation). The exact exposure period of risk is unclear, although the greatest risk for the gastrointestinal malformations seems to be between 3 and 7 weeks’ EGA. Although the association between MMI and ACC remains unproven, several authors now recommend PTU (which has not been reported in association with ACC) as a first-line agent in the management of hyperthyroidism during pregnancy.

Percutaneous Toxicity From Topical Agents

Percutaneous absorption of topically applied substances and the potential for resultant systemic toxicity are important considerations in the child. Absorption of drugs via the skin is influenced by both physical and chemical characteristics of the drug and the barrier properties of the skin. The majority of cases of percutaneous drug toxicity have been reported in newborns, although cases in infants and young children have also been noted. The direct correlation between risk and younger age is related to the higher surface area-to-weight ratio in infants. Other susceptibility factors include immature drug metabolism systems and, in the case of the premature infant, immaturity of the epidermal barrier (as discussed above). Table 1 lists several of the reported

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Fig 1. ACC—a localized, hairless plaque with scarring on the occipital scalp. Although most cases are idiopathic, the condition is occasionally ascribed to in utero exposure to thioamide antithyroid drugs.
TABLE 1. Some Percutaneous Toxicities Reported in Infants and Children

<table>
<thead>
<tr>
<th>Agent (Vehicle/Use)</th>
<th>Toxicity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (topical antiseptic)</td>
<td>Hemorrhagic necrosis</td>
<td>Primarily a risk on occluded skin</td>
</tr>
<tr>
<td>Aniline (diaper dye)</td>
<td>Methemoglobinemia</td>
<td>Dye stamps from freshly labeled diapers</td>
</tr>
<tr>
<td>Boric acid (diaper powder)</td>
<td>Vomiting, diarrhea, severe dermatisis, death</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids (topical anti-inflammatory agents)</td>
<td>Adrenal suppression</td>
<td>Dermatitis markedly increases risk</td>
</tr>
<tr>
<td>Hexachlorophene (antiseptic cleanser)</td>
<td>Neurotoxicity</td>
<td>Encephalopathy, seizures</td>
</tr>
<tr>
<td>Lidocaine-prilocaine cream (EMLA, local anesthetic cream)</td>
<td>Methemoglobinemia, seizures, petechial reactions</td>
<td>Seizures from lidocaine, methemoglobinemia from prilocaine</td>
</tr>
<tr>
<td>Lindane (scabicide lotion)</td>
<td>Neurotoxicity</td>
<td>Seizures</td>
</tr>
<tr>
<td>Mercuric chloride (diaper rinses)</td>
<td>Acrodermatitis</td>
<td>Also linked to mercury in tinctures, teething powders</td>
</tr>
<tr>
<td>N,N-dimethyl-meta-toluamide (DEET, insect repellant)</td>
<td>Neurotoxicity</td>
<td>Seizures, encephalopathy; risk limited to incorrect use or high concentration</td>
</tr>
<tr>
<td>Neomycin (topical antibiotic)</td>
<td>Ototoxicity, deafness</td>
<td>Premature infants</td>
</tr>
<tr>
<td>Pentachlorophenol (laundry detergent)</td>
<td>Sweating, tachycardia, metabolic acidosis</td>
<td></td>
</tr>
<tr>
<td>Povidone-iodine (topical antiseptic)</td>
<td>Hypothyroxinemia, goiter</td>
<td>Especially premature infants</td>
</tr>
<tr>
<td>Salicylates (keratolytic ointment)</td>
<td>Salicylism, encephalopathy, metabolic acidosis</td>
<td>In patients with defective epidermal barrier, ie, ichthyosis</td>
</tr>
<tr>
<td>Silver sulfadiazine (topical antibiotic)</td>
<td>Kornicetar, agranulocytosis</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus (Protopic, topical anti-inflammatory ointment)</td>
<td>Elevated serum tacrolimus level</td>
<td>Patients had barrier dysfunction as a result of Netherton syndrome</td>
</tr>
</tbody>
</table>

Adapted from references 8, 17, 21, 25, 38–44.

EMLA indicates eutectic mixture of local anesthetics.

causes of percutaneous toxicity in infants and children. A few of these are discussed in more detail.

One of the earliest observations of infantile percutaneous toxicity occurred in the late 1800s, when several infants were noted to have a mysterious cyanosis. It was subsequently discovered that 1 of the affected children had the imprint of a dye stamp on her perineum and buttocks, which turned out to be aniline that was a component of the dye used at the time for labeling diapers. The resultant aniline dye-induced methemoglobinemia that occurred led to some deaths in this infant population. Nearly one quarter of the affected infants were noted to be premature.8

Alcohol is another agent that poses a risk of percutaneous toxicity in the newborn. Although mature skin is relatively impermeable to alcohol, exposure of immature skin (especially under occlusion) may lead to significant local reactions and systemic toxicity. Hemorrhagic skin necrosis has been observed in a premature infant after alcohol prepping for umbilical arterial catheterization, occurring on the back and gluteal regions where alcohol had pooled and was occluded.9 In this report, the 27-week gestation twin girl had her skin cleansed with industrial methylated spirits (95% ethanol and 5% wood naphtha, which is at least 60% methanol) before catheter placement. In addition to the skin findings, dangerously elevated levels of blood alcohol were observed. Elevated blood alcohol levels were also reported in a 1-month-old child who was treated with gauze pads soaked in industrial methylated alcohol (95% ethanol, 5% methanol) for the purpose of promoting umbilical stump detachment.10

Iodine-containing compounds such as povidone-iodine have long been used for topical antisepsis, and it has been suggested that they may carry a significant risk to infants, especially those who are premature. Elevations of both plasma and urinary iodine have been documented in premature infants who were exposed to these agents.11,12 The potential for transient hypothyroxinemia and hypothyroidism has been a concern of many clinicians and investigators. This concern stems from the known risks of abnormal thyroid function in the infant, including growth and motor retardation, cognitive delay, and intraventricular hemorrhage. Linder et al11 compared premature infants who were treated with iodinated antiseptic agents with those who were treated with chlorhexidine-containing antiseptics, measuring thyroxine and thyrotropin levels. Although both groups of infants had normal thyroxine levels, thyrotropin elevations were documented in 13.7% of iodine-exposed infants versus none in the chlorhexidine-treated group. The surface area of treated skin seems to correlate directly with the risk, as demonstrated in full-term infants who undergo topical povidone-iodine antisepsis before cardiac operation.13 Conversely, several groups have demonstrated no increased risk of transient hypothyroidism (despite elevated urinary iodine) in premature newborns who receive routine skin cleansing with iodine-containing products.14,15 Chlorhexidine gluconate is an effective topical antiseptic agent that, despite reports of variable percutaneous absorption in premature neonates, seems to be a safer alternative without known percutaneous toxicity. Recently, its effectiveness (in the form of a chlorhexidine-impregnated dressing) in the prevention of central venous catheter infections in neonates was demonstrated in a large prospective study.16

Although many reports of percutaneous toxicity highlight the disproportionate risk in premature infants, full-term newborns and older infants and children are also at risk in certain situations. Eutectic mixture of local anesthetics cream is a mixture of 2.5% lidocaine and 2.5% prilocaine that is used for topical anesthesia before procedures. The best recog-
nized percutaneous toxicity related to the prilocaine component of this cream is cyanosis related to methemoglobinemia, which has been observed in both premature and full-term infants and children.\textsuperscript{17–20} Recently, a 21-month-old girl was reported to have developed generalized tonic/clonic seizures after overapplication of eutectic mixture of local anesthetics cream for curettage of molluscum contagiosum.\textsuperscript{21} Lidocaine toxicity was believed to be the cause of the seizures in this child, who also had methemoglobinemia resulting from the prilocaine component. This report underscores the increased cutaneous susceptibility of young children related to the increased skin surface area-to-body weight ratio and the importance of avoiding the indiscriminate use of topical preparations.

Lindane (\textit{\textalpha} benzene hexachloride) lotion was considered first-line therapy for scabies infestation until reports began to surface in the 1970s about its potential for neurotoxicity.\textsuperscript{22–24} Although many of the reported cases of seizures and abnormal neurologic function were reported after incorrect (over)use or ingestion of the lotion, infants and young children who were treated according to the product label were also noted occasionally to experience percutaneous toxicity, suggesting the unpredictability of absorption. Franz et al\textsuperscript{25} in 1996 used the finite dose technique to measure in vitro percutaneous absorption of 1\% lindane lotion compared with 5\% permethrin in human and guinea pig skin after a single application. They also measured in vivo blood and brain levels of the drugs after 3 daily applications. Their results revealed similar in vitro percutaneous absorption in guinea pig skin but a 20-fold increased permeability to lindane in human skin. In addition, blood and brain levels of lindane were 4-fold greater for lindane than for permethrin. These studies documented the far greater absorption of lindane through human skin and suggested slower metabolism and/or excretion from the brain and blood when compared with permethrin. This greater margin of safety has resulted in the evolution of permethrin as the standard of care for scabies.

\textbf{UV Light}

UV light exposure results in a variety of responses in the skin, the most concerning of which is cutaneous carcinogenesis. UV light is divided into UVA (320–400 nm) and UVB (290–320 nm), which has a greater penetration of the skin. UVC, which corresponds to a wavelength <290 nm, is not present in terrestrial sunlight. UVB constitutes the minority (<0.5\%) of sunlight that reaches the earth’s surface but is responsible for the majority of both acute and chronic actinic skin damage. UV exposure can result in nonmelanoma skin cancers (squamous cell carcinoma and basal cell carcinoma) and the most serious form of skin cancer, malignant melanoma (MM). The incidence of MM in the United States has risen more rapidly than any other cancer except for lung cancer in women.\textsuperscript{26}

Although MM is fairly rare in children, childhood exposure to UV light before the age of 10 years, along with severe sunburns and intense intermittent exposure, are believed to be the most critical factors to its eventual development. Migration studies have documented that increased exposure to UV light in childhood is related to a higher risk of MM in adulthood. Studies of the “critical period hypothesis,” which attempt to pinpoint the age range of greatest risk for exposure, have revealed the highest risks of MM in those who were exposed to sunlight early in life, even if the period of exposure was relatively brief.\textsuperscript{27} However, additional studies are necessary to assess the exact effects of sun exposure at different ages or windows of time.

It has been hypothesized that the melanocytes in children may be more susceptible to UV-induced DNA damage, thus initiating carcinogenesis early in life. In a recent study, a genetically engineered mouse model was used to test the relationship between a single dose of burning UV radiation in neonates versus adults and the ability to induce melanoma-like skin tumors.\textsuperscript{28} Transgenic mice that overexpress hepatocyte growth factor/scatter factor are noted to develop sporadic melanoma with metastases with aging. In this study, albinohepatocyte growth factor/scatter factor–transgenic mice were subjected to UV irradiation at 3.5 days of age, 6 weeks of age, or both, and the findings revealed that a single neonatal dose (at 3.5 days) was sufficient to induce melanoma after a short latent period.\textsuperscript{28} Melanomas were not seen in the group that received a single dose at 6 weeks or those that were untreated. However, UV exposure subsequent to 3.5 days of age increased the number of melanocytic lesions as well as the incidence of nonmelanoma skin cancers. The UV dose administered in these experiments corresponded roughly to a sunburning dose of natural sunlight at mid-latitudes in midsummer. Although the applicability of these results to children is unclear—for instance, there are differences in skin thickness between species, and the human age equivalents of the transgenic mice cannot be calculated precisely—they are suggestive of a heightened sensitivity of young melanocytes to UV radiation and support a possible correlation between childhood sunburn and the later development of melanocytic neoplasms.

Accurate assessment of UV-related health risks for children and adolescents relies on having access to precise data on UV doses received by these individuals. Godar\textsuperscript{29} calculated these figures using the National Human Activity Pattern Survey to record daily minute-by-minute activities of approximately 2000 young Americans (0–19 years) over the course of 2 years. These data were stratified by season and age to find the amount of time that American children and adolescents spend outdoors. In addition to identifying UV doses for the different age groups, it was found that American children and adolescents now get approximately the same annual UV doses as adults, a stray from past data suggesting that an individual receives a majority of their lifetime cumulative dose by the age of 20 years.\textsuperscript{30,31} These findings are likely related to technologic advancement and the resultant “attraction” of more indoors-oriented activities. However, such data should not translate
into a “laissez faire” attitude with regard to children and sun exposure, especially given the continued worldwide rise in incidence and mortality rates of MM. Several recent studies highlight the ongoing inadequacy of sun protection practices in the United States, including inconsistency in protective behaviors among youth aged 11 to 18 years, a high incidence of sunburn among children aged 6 months to 11 years, and the need for improvement in parental behaviors and attitudes.

Environmental Toxins and Chemicals

Risks from cutaneous exposure to environmental toxins and chemicals may differ between children and adults for a variety of reasons, including differing behavior patterns, anatomic and physiologic differences in absorption and metabolism, and developmental differences of vital organs such as the brain, which may result in different end organ effects. Toxicity from chemicals has a bimodal age distribution in childhood, the first peak being between 9 months and 3 years (a risk mainly for oral exposures as a result of increasing oral exploration) and a second peak in late childhood and adolescence. Percutaneous risks include agents such as insecticides, polychlorinated biphenyls, and pesticides (eg, in children of crop pickers, who crawl in recently sprayed fields). Pediatric poisonings as a result of cleansing agents (dishwashing liquids, degreasers, bleach, glass cleaners, furniture cleaners, oven cleaners, etc) are usually as a result of ingestion, although absorption from the skin or conjunctiva is also possible, albeit significantly less common. The differential vulnerabilities of pediatric skin exposure to such environmental toxins and chemicals is difficult to quantify and in most cases are probably related to inherent developmental differences as listed above.

CONCLUSION

This review of what is known about the differing vulnerabilities of skin at various developmental stages during childhood underscores several important points: 1) the skin can be an isolated target for teratogenic insults, as observed occasionally with the use of thioamides antithyroid drugs during pregnancy; 2) the risks of percutaneous toxicity must always be considered in children, especially in premature neonates, in whom the epidermal permeability barrier is frequently incompetent; 3) there seems to be a disproportionate toxicity of UV radiation to the skin of young children, highlighting the importance of efforts to better educate parents and children about the dangers of unprotected sun exposure; 4) the disparity between adults and children in their risks from cutaneous exposure to environmental toxins or chemicals often relates to behavioral and developmental differences; and 5) the applicability of skin toxicity studies from adult humans or animals to children is unclear, and the continued development and validity testing of adequate scientific models is desirable.

REFERENCES

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http://pediatrics.aappublications.org/content/113/Supplement_3/1114