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Original Research Article

MICRO-MORPHOMETRIC STUDY OF SKIN IN DEVELOPING HUMAN FETUSES AND ITS CLINICAL RELEVANCE

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ABSTRACT

Studies on the human skin microanatomy are few and contradictory. Using fetal skin of different age group, doing H & E staining followed by correlative light microscopy of serial tissue sections, and comparing it at different fetal age, we studied the topographic microanatomy of the skin of human fetuses. Histomorphology was compared from 8 weeks of gestation upto 30 weeks from last menstrual period (LMP). We found that epidermal differentiation begins at 8 weeks of gestation. A single layer of epidermal cells covers embryos up to 9 weeks of gestation after the LMP. At 9 weeks, periderm is also visible and it's called as a double layer stage. It is followed by appearance of intermediate layer at 13 weeks. Budding cells are found only at 14 weeks. Hair follicles are visible at 16 weeks, whereas eccrine sweat glands appear at 20 weeks. Eccrine ducts are elongated and visible at 23 weeks. Coiling of the duct starts at 29th week. Thus, fetal age can be determined by studying the features of developing skin. Also many skin diseases show morphological changes in early fetal life. Congenital skin diseases can be predicted by the knowledge of normal fetal skin development.

KEY WORDS: Fetal Skin, Development, Histology (Microanatomy), Congenital, Skin diseases.

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INTRODUCTION

The objective of the study was to evaluate the histological changes of fetal skin development at different stages of fetal development. Human skin consists of a stratified cellular epidermis and an underlying dermis of connective tissue [1,2].

Knowledge of the development of organs facilitates the study of its adult anatomy; it also helps to understand the developmental defects and structural malformation. Beginning at 10th weeks and continuing until 30th weeks, the development of skin appendages is a sequence of easily recognizable histological patterns within the skin of the foetus [3–5]. Identification of these age-related morphologic patterns allows a definition of fetal age and offers background information for detecting congenital skin diseases, such as ectodermal dysplasias, blistering diseases, and ichthyosis [6-8].

Skin is a complex organ system in adult, acts as protective barrier/ protective membrane of the body, body temperature regulation, sensation, excretion, immunity, a blood reservoir, and synthesis of vitamin D [9]. There are two types of human skin, glabrous skin (non-hairy skin) and hair-bearing skin. Glabrous skin found on the palms and soles, is grooved on its surface by

continuously alternating ridges and sulci, in individually unique configurations known as dermatoglyphics. It is characterized by a thick epidermis divided into several well-marked layers including a compact stratum corneum, by the presence of encapsulated sense organs within the dermis, and by a lack of hair follicles and sebaceous glands. Hair-bearing skin (Fig. 3.1), on the other hand, has both hair follicles and sebaceous glands but lacks encapsulated sense organs. Skin consists of two layers derived from two germ layers: ectoderm and mesoderm. The prospective epidermis, which originates from a surface area of the early gastrula, and the prospective mesoderm, which is brought into contact with the inner surface of the epidermis during gastrulation [10, 11].

The mesoderm not only provides the dermis but is essential for inducing differentiation of the epidermal structures, such as the hair follicle in mammals [12]. The embryonic mesenchyme that forms the connective tissue of the dermis. Sebaceous glands are first visible from the 13th to the 16th week of fetal development, as bulging off hair follicles. Sebaceous glands develop from the same tissue that gives rise to the epidermis of the skin. The sebaceous glands of a human fetus secrete a substance called vernix caseosa, a waxy, translucent white substance coating the skin of newborns. After birth, activity of the glands decreases until there is almost no activity during ages 2–6 years, and then increases to a peak of activity during puberty, due to heightened levels of androgens. The neural crest also makes the pigment cells to the skin. During the newborn period a large number of pathological conditions can cause vesicles (small blisters), bullae (big blisters) pustules (yellow blisters), erosions (sores) and ulcerations. Erythema toxicum neonatorum and malaria are the most common skin conditions of newborn.

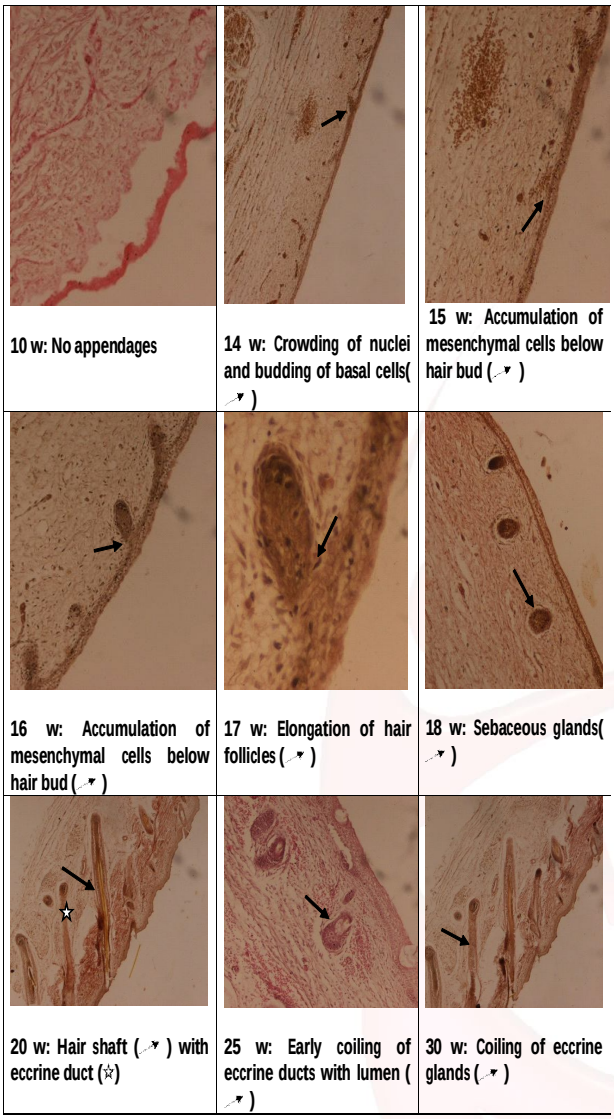
MATERIALS AND METHODS

Twenty-four human fetuses with known gestational ages of 10-30 weeks were examined at autopsy. Gestational age derived from the last menstrual period (LMP) coincided with early ultrasound measurements and developmental indices (especially crown-rump length & foot length) at postmortem examination. The causes of abortion or fetal death included intradecidual hemorrhage with abruptio placentae, premature rupture of membranes with chorioamnionitis, and pregnancy termination for localized fetal malformations. Skin from gluteal regions were taken for histology/ micro-morphometric study. Fetuses were collected from the department fetal lab. After measurement of the crown-rump (CR) for determining the age of fetuses, tissue specimens were collected and fixed in 10% buffer formal saline, processed and sectioned into 5–7 µm thick layers. The sections were stained with H&E method and observed by graduated objective lens. To study the reticular, elastic and collagen fibers and mast cells, appropriate staining methods such as PAS, Verhoeff, Van Giesson and toluidine blue were used, respectively. These tissue samples were studied to establish the histological changes from the development of skin appendages, hair and apocrine & eccrine glands. Skin from other parts of the body differs in the quantity of skin appendages and the time sequence of developmental events. Stages of skin development would be 1–2 weeks ahead of schedule if skin from the neck was examined and 2 weeks behind if skin from the thigh were used. This phenomenon reflects the overall development of mammalian embryos, which proceeds from the head pole to the caudal pole.

RESULTS

Assessment of skin samples allowed details of those features that are suddenly noticed and understood and can be used to determine the gestational age. This study showed that the differentiation of epidermis begins from the end of the second month. Based on the histologic sections, the stages of the gradual development of epidermis and skin appendages are illustrated to clarify the structures and their nomenclature (Figure 2).

Patterns of skin development are very easy to identify as soon as one recognizes the morphologic differences between budding of basal cells leading to hair follicles and budding leading to eccrine glands. The latter process is characterized by slightly different cell morphology within the buds and the lack of mesenchymal



10 w: No appendages | 14 w: Crowding of nuclei and budding of basal cells( ) | 15 w: Accumulation of mesenchymal cells below hair bud ( )

16 w: Accumulation of mesenchymal cells below hair bud ( ) | 17 w: Elongation of hair follicles ( ) | 18 w: Sebaceous glands( )

20 w: Hair shaft ( ) with eccrine duct (☆) | 25 w: Early coiling of eccrine ducts with lumen ( ) | 30 w: Coiling of eccrine glands ( )

condensation below the buds. A single layer of epidermal cells covers embryos up to 9 weeks of gestation (after the LMP). From 9 to 13 weeks, two-layered skin is seen with a second, superficial layer called periderm. From 13 weeks on, an intermediate layer is added and fetal skin is stratified, but still does not show appendages. Starting at 14 weeks, the developing skin shows budding of cells of the basal layer into the underlying mesenchyme. At 16 weeks, a corresponding proliferation of mesenchymal cells is seen just below the epidermal cell bud. Hair follicles grow rapidly, and second and third generations of buds arise from the basal skin layers. In the 18th week, hair shafts become clearly visible and sebaceous glands are recognizable.

Fetal skin at 20 weeks is characterized again by budding of cells from the basal cell layer, resulting in the anlage of eccrine sweat glands. In contrast to the budding hair follicles, cells of the eccrine sweat glands are more eosinophilic, cylindrical, and budding is not accompanied by a corresponding proliferation and condensation of the underlying mesenchymal tissue. At 23 weeks, the eccrine gland ducts have elongated and reached the level of transition of dermis to fatty tissue, and a lumen is hardly visible. At 24 weeks, enlargement and kinking of the duct end occur within the depth of the dermis, with the duct ends beginning to coil at 25 weeks. At 29 or 30 weeks, eccrine sweat glands are coiled to such an extent that multiple transverse sections can be seen within the depth of the dermis melanocytes were appeared in 61–65 days of fetal period in epidermis. The hair follicles were seen as cell accumulations in epidermis that protruded toward dermis in the first half of the third month. The hair follicles growth, sebaceous and sweat glands were appeared from the second half of the third month. They were quickly increased in the first half of the fourth month in all. The relationship between thickness of epidermis and its cell layer numbers in all areas were significant ($P<0.05$) and their correlation coefficient?

DISCUSSION

Present study was carried out to see the epidermal development in 1st & 2nd trimester human fetuses. Analysis of epidermal development in 2nd trimester shows the substantial development of hair follicle, separate the epidermis into follicular and interfollicular region. In past few years, the use of fetal skin biopsies for prenatal diagnosis of severe inherited skin diseases has shown the importance of the structural knowledge of normal human fetal skin. During the first 10 weeks of gestation, the basic structure of epidermis is built up. In the first 18 weeks of gestation the most of the structural part and antigenic markers of epidermis are fully formed, both these are used for prenatal diagnosis for which fetal skin biopsy is usually carried. Epidermolysis bullosa lethalis and ichthyotic erythroderma have been diagnosed on fetal skin samples at 16th to 20th week of gestation. Identification of structural abnormalities through fetal skin biopsy in prenatal diagnosis is a feasible alternative to time consuming biochemical analysis. In ichthyotic erythroderma, biopsy

of fetal skin may be done to assess the histologic characteristics of the cells. Histological results usually reveal hyperkeratotic skin cells, which ultimately give rise to a thick and hard skin layer. The developing fetus has the ability to heal wounds by regenerating normal epidermis and dermis with restoration of the extracellular matrix (ECM) architecture, strength, and function. In contrast, adult wounds heal with fibrosis and scar.

Scar tissue remains weaker than normal skin with an altered ECM composition. Despite extensive investigation, the mechanism of fetal wound healing remains largely unknown. As a result of research in past, we do know that early in gestation, fetal skin is developing at a rapid pace and the ECM is a loose network facilitating cellular migration. Wounding in this unique environment triggers a complex cascade of tightly controlled events culminating in a scarless wound phenotype of fine reticular collagen and abundant hyaluronic acid. Comparison between postnatal and fetal wound healing has revealed differences in inflammatory response, cellular mediators, cytokines, growth factors, and ECM modulators. Investigation into cell signaling pathways and transcription factors has demonstrated differences in secondary messenger phosphorylation patterns and homeobox gene expression. Further research may reveal novel genes essential to scar less repair that can be manipulated in the adult wound and thus ameliorate scar. The differences were found to be small but consistent with the ages of the fetuses.

CONCLUSION

Skin development is continuous process but some noticeable and discrete patterns are strongly related to fetal age and are easy to recognize congenital primary skin diseases have a great impact on developing skin morphology [13-15]; conditions such as restrictive dermopathy, ectodermal dysplasia, and different forms of epidermolysis bullosa show abnormalities already in the early stages of fetal development. Recognition of the early manifestations of congenital skin diseases is possible only with exact knowledge of normal histology. In postmortem examination the clinician usually gives gestational age of a fetus. However, in many cases, this information is not given or the accuracy of the age given is doubtful because of severe growth, retardation or organ hypoplasia then assessing gestation age from histology of fetal skin is done. This data have potential relevance to prenatal diagnosis of inherited skin disease. From amniocentesis and/or fetal biopsy specimens; the present study of fetal epidermal surface will allow one to predict the types of skin-derived cells that should be present in the amniotic fluid at a given age, and to evaluate a fetal biopsy from skin and be confident that it is an accurate index of fetal skin development, age and status in general.

Conflicts of Interests: None

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