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**ORIGINAL RESEARCH**

# Microanatomical study of chronological events in embryological development of human skin

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## ABSTRACT

**Background:** Literature describing chronological development of fetal skin beyond 12 weeks is scanty as there is scarcity of human fetuses for research in later stages of development due to diverse abortion laws and stringent guidelines on fetal research across the countries. Moreover, religious customs, ritual factors and sentimental issues also contribute to scarcity of fetal tissue for research. There is a great variability in the time of appearance of melanocytes and Keratinocytes, as shown by most studies. It is presumed to fall in a range from 12 to 20 weeks. Melanocytes appear in transitionally in dermis of fetal skin but there are inconsistencies in timings of appearance and disappearance. As the Medical Termination of Pregnancy Act (1971) allows abortion till 24 weeks of gestation, I have chosen this time as the upper limit of fetal age for the purposes of my study. This study will supplement existing literature on development of fetal skin beyond 12 weeks of development. **Aims and Objectives:** The current research aimed to assess the diagnostic utility of pap smear cytology and VIA as a screening test for various cervical lesions. **Materials and methods:** Determine fetal age by history and USG data. Arrange fetuses according to their gestational age by making their groups. Extract 5mmx5mmx5mm skin snips from dorsal aspect of forearm (for thin skin) and palm (for thick skin) with underlying subcutaneous tissue from fetal skin. Tissue fixation in 10% formalin followed by routine histological processing. All tissue blocks were alphanumerically coded. Tissue sections stained with H&E, Von Gieson. Observe, document and arrange findings in chronological order of embryological development. **Results:** In the initial weeks of development, only 2 to 3 layer of epidermis can be observed. In progressive weeks of development, skin appendages appear but not in well develop form. There is difference in the appearance of skin component in thin skin and thick skin. There is variability in the presence of rete pags. In some week of development, it is well defined while in higher weeks, it is not well defined in thin skin. Presence of fibroblast, melanocyte, keratin layer is less observed. Development of sweat gland begins in early stage and it is found in approximately all the sample. Presence of Rete pags shows the main difference in the thin & thick skin. Most of the data which have been collected after the observation, shows the appearance of skin appendages & component are well defined in group 4 which include fetus from 21 to 24 week of gestation. **Conclusion:** In the beginning weeks of development, epidermis is 2 to 3 layer thick in thin skin while it is 3 to 4 layer thick in thick skin. Keratinohyline present in all the group but keratin layer is not defined in any group. Rete pags create the main difference between thin & thick skin as it is observed in all the group of thick skin but in thin skin, it is not in regular basis. Carbohydrate observed in internal sheath of hair follicle. Most of the cells appears in thick skin of group 4 fetus like melanocytes, keratinocytes which can be easily observed in this group. Group 4 fetus sample shows presence of thin papillary dermis & thick reticular dermis in thick skin while it is not do defined in thin skin. Stratum spinosum begins to appears in group 4 in thin skin but it is not observed in other group.

**Keywords:** Fetus, Skin, Thin skin, Thick skin, Palm, Dorsum, Epidermis, Skin appendages, Rate pags, Group, Staining, Tissue.



## INTRODUCTION

Largest organ of our body which is skin, constitute 15% of the complete body weight. It serves a variety of purposes, including regulating temperature & protects our body from physical, chemical, and biological pathogens [1]. Skin of full-term newborns

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is histologically developed at birth, yet it is functionally immature. A range of biophysical skin factors may be used to characterize skin, allowing for non-invasive skin research. Atopic dermatitis, psoriasis, and allergic or irritating contact dermatitis all influence many parameters, including trans epidermal loss of water, hydration, and acidity of skin. It continuous with the mucous membrane which lined the body surface. It also adorns body and expresses the feeling of touch. Its shape, color, patterns, and composition helps in identifying different species. Skin and its derivative are the part of integumentary system. This system is having three layers named as Epidermis, Dermis, and Subcutaneous tissue called hypodermis [2-3]. An adult epidermis of the skin consists of different strata of cells which are arranged in deep to superficial manner: Stratum Basale, Stratum Spinosum, Stratum granulosum, Stratum Lucidum (in thick skin only), Stratum Corneum while in fetal skin only Stratum Basale is present which later gives off another layer called periderm [4]. Fetal skin may be seen as two different layers during four weeks of gestation. Periderm is an outer layer that protects basal cell layer. Keratinization occurs at nine weeks of pregnancy, and stratification into distinct layers appears at thirteen weeks [5-8]. At fourteen weeks of pregnancy, hair follicles starts to develop as epidermal buds on the surface of the epidermis. As hair follicles grow rapidly over the next two weeks, epidermal buds are accompanied with a local proliferative mesenchymal cells in relation to the epidermal bud [9-10]. In comparison to adult dermis, this dermis has larger quantities of type III collagen, chondroitin sulphate, proteoglycans, and hyaluronic acid [11]. In mammals, Epidermal development consists of several steps, including epidermal specification, commitment, stratification, terminal differentiation, and epidermal appendage growth [12-13]. Epiblast invaginates along the primitive streak, and epiblast cells proliferate and migrate downhill during gastrulation. Gastrulation culminates in the creation of three germ layers: ectoderm, mesoderm, and endoderm, each with its own cell lineage. Development of basement membrane, which is formed by the basal layer cells, coincides with establishment of embryonic basal layer. Basement membrane divides epidermis from dermis and supplies growth factors to epidermal basal cells [14]. During embryonic development, about 4-8 weeks of gestation, a layer of strongly adherent cells termed the periderm transiently overlaps the ectoderm. In the human foetus, a specialised temporary embryonic skin known as the periderm is produced. The periderm protects the developing epidermis from amniotic fluid and is lost as the epidermis stratifies. In animals, a sebaceous gland is found towards the top of the hair follicle and aids in the release of sebum to lubricate the skin and preserve the waterproof quality of hair. Around 13-14 week of gestation, sebaceous glands begin to form [15].

## AIMS AND OBJECTIVES

To describe events during development of human skin between 12 to 24 weeks of gestation.
To observe & describe development of human skin between 12-24 weeks of gestation using hematoxylin-eosin & “special stains (Von Gieson)”.
Preserve tissue blocks in Department of Anatomy for future immuno-histochemical studies on fetal skin.

## MATERIALS AND METHODS

To obtain 50 samples, palmer & dorsal surface of fetus skin were chosen for thick & thin skin sample respectively. The entire fetus were collected from the women who have undergone induced or spontaneous abortion in the department of Obstetrics and Gynecology.
Before to proceed further, examination of all the fetus done macroscopically to check for the presence of any abnormality or scratch over the skin of palm and dorsum of hand. After confirming the desirable skin condition, the entire fetus divided into four groups based on their gestational week. Alphanumeric code given to the entire sample so that confidentiality could be maintained and sample kept in department for future study. The entire sample were stained by H&E & VVG staining method.

| Group | Gestational Periods (In Week) |
|---|---|
| I | $12^{th}$, $13^{th}$, $14^{th}$ |
| II | $15^{th}$, $16^{th}$, $17^{th}$ |
| III | $18^{th}$, $19^{th}$, $20^{th}$ |
| IV | $21^{st}$, $22^{nd}$, $23^{rd}$, $24^{th}$ |


**Image 1: Alphanumeric coded block**

Informed consent was taken from parents who wanted to donate their aborted fetus to the department in English as well as in Hindi. It was assured to all parents that the data of all fetus will be completely confidential.
The IRB given their approval to carry out this study. IRB no is 468/IEC/M.Sc/2020 approved by All India Institute of Medical Sciences (AIIMS), Rishikesh & its registration no is ECR/736/Inst/UK/2015/RR-18.

## METHOD OF OBSERVATION

Excel sheet prepared for the observation in which all the component written which need to observed.

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Attached in appendices. All the prepared slide observed under the 10X & 40X magnification in which epithelial layer were focused for different layers. Arrangement of all the layer were observed in both magnifications with other cells like melanocytes and keratinocytes. In H&E stained slide, nucleus & Appearance of akin appendages and arrangement of their cells observed. In VVG stained slide, presence of collagen fibers will be recorded after the observation under the microscope. Photography done for only one tissue from each group of sample through high quality image recorder microscope in 10X & 40X magnification. All the photograph was scaled.

## RESULTS

**Group 1 which included fetus from 12, 13 & 14 week of gestation:**

In the 13 week of gestation fetus, thin skin (collected from dorsum of hand) is having 2 to 3 layer of epidermis in which single basal layer observed. Basal layer shows columnar cells with oval nucleus. Keratinohyline granules are present superior to basal layer. Sweat gland as well as sebaceous gland is present. **Rete pags are not seen**. Superficial vascular plexus is present. Hair follicle with hair shaft and inner& outer root sheath of seen. Collagen fibers are thin in superficial layer as well as deep layer which is present superior & inferior to superficial vascular plexus respectively.

In the thick skin (collected from palm of hand), there are 3 to 4 layer of epidermis present. **Rete pags are seen**. Sweat gland and its duct is present. Keratinohyline granules are present. Hair follicles are not seen.

**Group 2 which included fetus from 15, 16 & 17 week of gestation:**

In the 17 week of gestation fetus, thin skin is having 2 to 3 layer of epidermis. Single basal layer is present. Keratinohyline granules are present. **Rete pags are not seen**. Sweat gland with duct is present. Sebaceous gland is present. Superficial vascular plexus is present. Arteriole &venules are present. Hair follicle with shaft and their inner & outer root sheath is present. Lymphocytes around the blood vessels is not present. Collagen fibers are thin in superficial layer which is above the superficial vascular plexus and thick in deep layer which is present below the vascular plexus.

In thick skin, 3 to 4 layers of epidermis is present. **Rete pags are seen**. Fibroblasts are present. Sweat gland with duct is present. Keratinohyline granules are present. There is superficial vascular plexus and arteriole &venules are present. Hair follicles are absent here. **Sebaceous gland is not seen.**Collagen fibers are present in dermis.

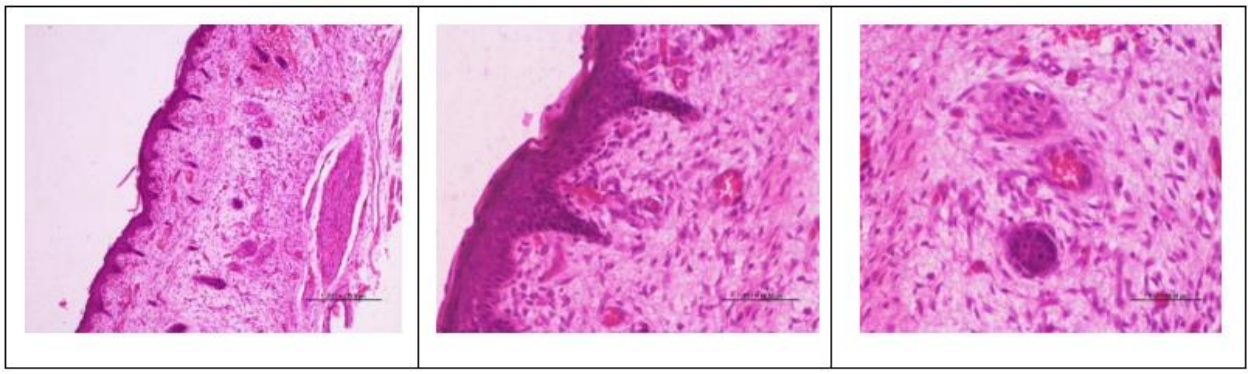

**Image: 2H&E Stained Slide Image of fetus from 17 Week of Gestation in 4X, 10X & 40 X magnifications**

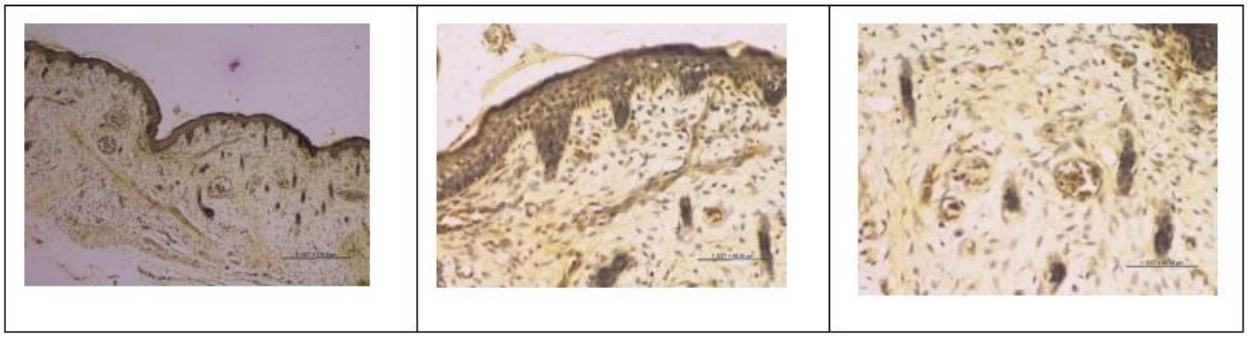

**Image: 3** VVG **Stained Slide Image of fetus from 17 Week of Gestation in 4X, 10X & 40 X magnifications**

**Group 3 which included fetus from 18, 19 & 20 week of gestation:**

In the 19 week of gestation fetus, thin skin is having 2 to 3 layers of epidermis in which single basal cell layer is present. Keratinohyline granules are present above the basal layer.**Rete pags are not seen**.**Sweat**

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**gland is not seen**. Sebaceous gland is present. Superficial vascular plexus is present. Arteriole &venules are present. Hair follicle with hair shaft & inner root sheath is present. Lymphocytes around the blood vessels are not seen. There is collagen in dermis. In the thick skin, 3 to 4 layers of epidermis is present. **Rete pags are present.** There are sweat glands with duct are present. Keratinohyline granules are present. Superficial vascular plexus is present. VVG stained collagen fibers are present in reticular & papillary dermis. In the 20 week of gestation fetus, thin skin is having 2 to 3 layers of epidermis. Keratinohyline granules are present above the basal layer. Rete pags are present. Sweat gland & its duct is present. Hair follicle with hair shaft present. **Fibroblasts are seen**. Superficial vascular plexus is present. Lymphocytes around the blood vessels are not present. Collagen is stained with VVG which is present in rete ridge. In the thick skin, epidermis is 2 to 3 layer is thick. Reticular dermis is thick while papillary dermis is thin. Sweat gland with duct are present. **Rete pags are present**. Superficial vascular plexus is present. Arterioles &venules are present. Collagen fibers are present in dermis which is stained through VVG.

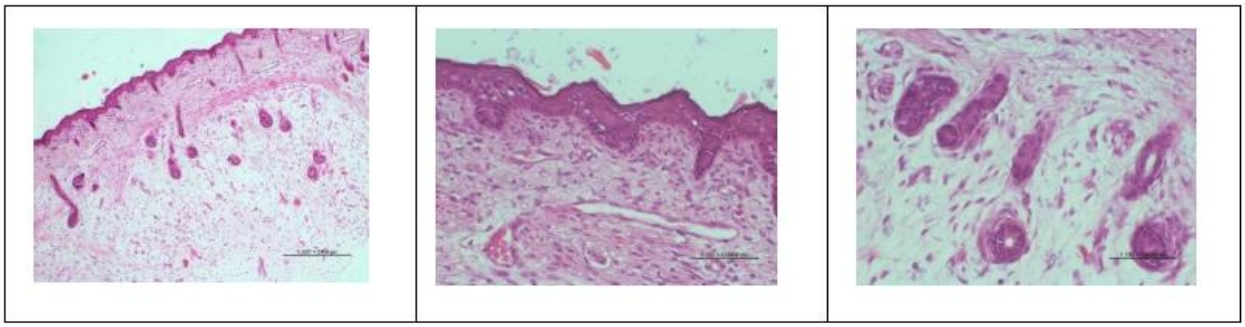

**Image: 4H&E Stained Slide Image of fetus from 21 Week of Gestation in 4X, 10X & 40 Xmagnifications**

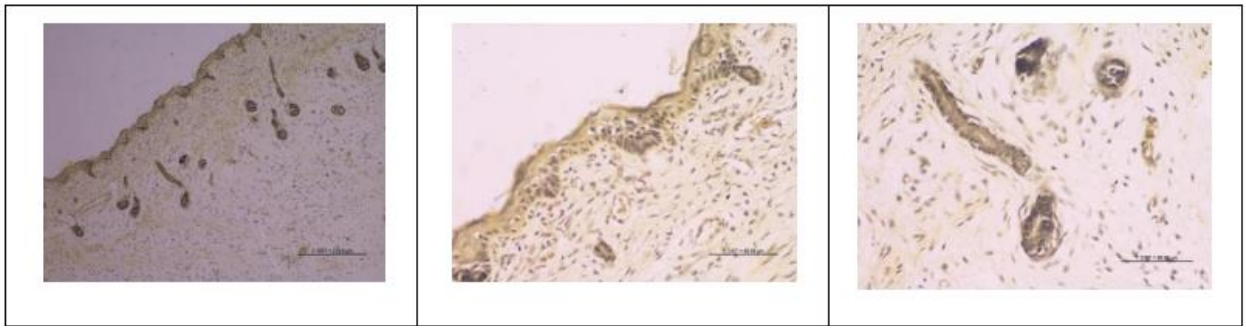

**Image: 5 VVG Stained Slide Image of fetus from 21 Week of Gestation in 4X, 10X & 40 X magnifications**

**Group 4 which included fetus from 21, 22, 23, 24 week of gestation:**

In the 21 week of gestation fetus, thin skin is having 2 to 3 layer of epidermis in which **spinosum layer is present**.Keratinohylines are present. Sweat gland with duct is present. **Sebaceous gland is not seen**. Adipose tissue is present. **Arrector pili muscle is seen**. Hair follicle is in developing stage. Hair shaft as well as inner root sheath are not present. Superficial vescular plexus is present. VVG stained collagen fibers are present in dermis.

In thick skin, there are 4 to 5 layer of epidermis. **Spinosum layer is not well defined**. Dermal papilla is present. **Melanocytes are present**. There are melanin granules are present. Sweat gland with duct is present. Keratinohyline granules are present in epidermal cells. Capillaries in dermal papilla is present. Superficial vascular plexus is present. Arteriole &venules are present. **There are nerve fibers in dermis**. VVG stained collagen fibers are present in dermis.

In the 23 week of gestation fetus, thin skin is 3 to 4 layer thick in which **stratum spinosum is seen here**. Kertinohyline granules are present above the spinosum layer. Sweat gland with duct is present. Sebaceous gland is present. **Periderm is present** in this fetal skin. dermal papilla is absent. **Rete pags are not seen**. Superficial vascular plexus is present. Arteriole &venules are present. There is germinative layer of sabacious gland. Hair follicle with hair shaft is present. Adepose tissue around the sweat gland is there. Lymphocytes around the blood vessels is not present. **Keratin layer is present.**Fibroblast are present.

In the thick skin, there are 2 to 3 layer of epidermis with **melanocytes**. Sweat gland with duct is present. **Sebaceous gland is not seen**in thick skin. keratinohyline granules are present. **Stratum lucidum is present**. Papillary dermis and rete pags are present. Capillaries in dermal papilla is present. Superficial vascular plexus is present. Arteriole and venuoles are also there. There is no germinative layer of sabacious

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gland. Hair follicle and hair shaft is absent. Lymphocytes around the blood vessels are absent. VVG stained cells are present in dermis.

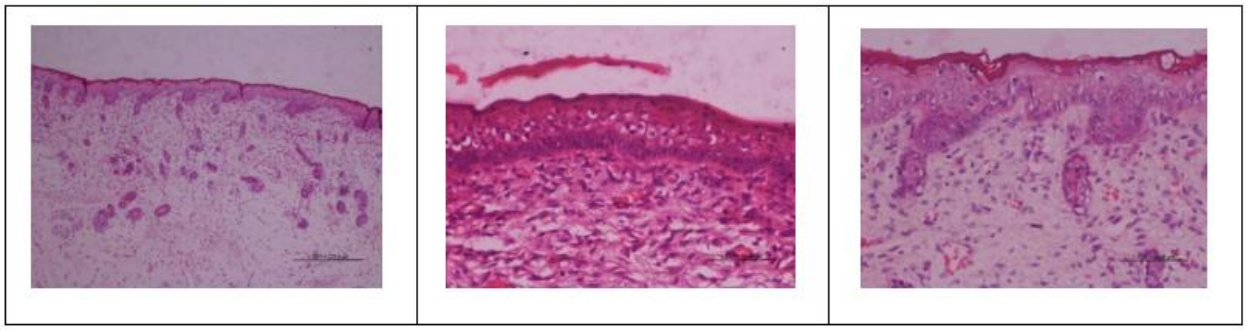

**Image: 6H&E Stained Slide Image of fetus from 23 Week of Gestation in 4X, 10X & 40 X magnifications**

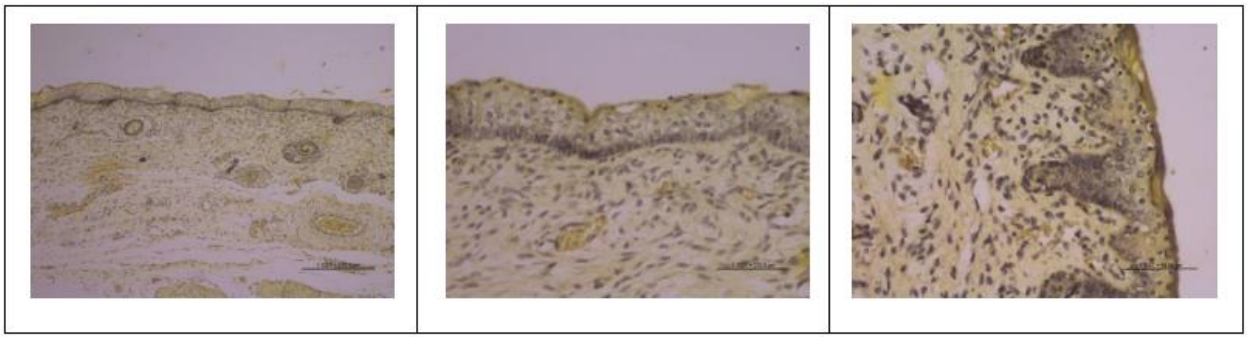

**Image: 7VVG Stained Slide Image of fetus from 23 Week of Gestation in 4X, 10X & 40 X magnifications**

## DISCUSSION

After a complete history and sufficient consent, the current study was conducted in the Department of Anatomy on 50 spontaneously and induced aborted fetuses acquired from the Department of Obstetrics and Gynecology. The gestational age of the fetuses was determined using maternal history, ultrasonography, and online gestational age calculator software and varied from 12 to 24 weeks. Fetuses were divided into four groups based on their gestational weeks: group 1 (12-14), group 2 (15-17), group 3 (18-20), and group 4 (20-24). (21-24).

In Serri study [9], Serri, et al. took 46 fetus sample belongs from 4 to 32 week by spontaneous and premature births immediately after parturition. they explainstratum intermedium or intermediate layer which is a characteristic feature of embryonic skin, develops between stratum germinativum and peridermal layer. Stratum intermedium which appears at 10th to 12th week of gestation is composed of cells that are smaller than those of basal layer, and which are abundant in glycogen from the time of their appearance, as the cells of periderm. Haematoxylin and eosin, VVG staining was done. We showed that group 1 - fetal sample is having 2 to 3 layer of epidermis with single basale layer and rete pags are absent in thin skin other component of skin like sweat gland and sebaceous gland are well defined with their duct. Duct are not appeared coiled. Superficial vascular plexus is not well developed but it shows its presence. Hair follicle with shaft starts to develop in this group. In the thick skin of this group fetus, epidermis is 3 to 4 layer thick and rete pags are developed. Sweat glands are abundant with their duct. Niemann, et. al. studied about the sebaceous gland & sweat gland in 30 fetus sample [3].They added that sebaceous glands appear during the 13th to 14th week of pregnancy, are normally placed at the top portion of the hair follicle, and aid in the release of sebum to lubricate the skin and keep hair waterproof in mammals. Sweat glands begin to form during the 13th to 14th week of pregnancy and mature by the 24th week. At different stages of development, three kinds of cells migrate into the human epidermis. Melanocytes are cells generated from the neural crest that migrate into the foetal epidermis around the 12th week of pregnancy. Our study included fetuses from 12 to 24 weeks of gestation age. Results showed that Group 2 which include fetus from 15 to 17 week of gestation, thin skin is having 2 to 3 layer of epidermis with single basal layer. Keratinohyline granules are abundant which spread above the basal layer. Rete pags are not present. Sweat gland is having cuboidal cells and well is in developing stage. Sebaceous glands are not well defined while superficial vascular plexus present between the superficial & deep layer. Arteriole &venules are developing. Hair follicle with shaft and their inner & outer root sheath is having single layer of cells in thin skin.

Collagen fibers are thin in superficial layer and thick in deep layer. In thick skin, 3 to 4 layers of epidermis is observed with rete pags. Fibroblasts are well defined in this group. Sweat gland is having cuboidal cells. Keratinohyline granules are spread above the

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basal layer. There is superficial vascular plexus and arteriole &venules are present. Sebaceous gland is not present in this. Cichorek et al. explains in 25 fetus range from 8 to 30 week of gestation thatat the end of 16thweek of gestation, epidermis acquires definitive arrangement in four layers which can be observed under microscope.Eccrine sweat gland development starts as epidermal buds in the basal layer around 20thweeks of pregnancy and continues for the following ten weeks, by elongating and coiling. We can see fully formed spinous cells with granular cells at the beginning of the 22nd week of pregnancy [5].

Our study with 50 fetus sample gestational age from 12 to 24 week, Group 3 in which 18 to 20 week of gestational fetus included shows that Thin skin of this group is having 2 to 3 layers of epidermis in which single basal cell layer in cuboidal shape present. Keratinohyline granules are present but as compare to group 2, it is less dense. Sebaceous glands are well developed around the hair follicle. Hair follicle with hair shaft & inner root sheath is well defined. Superficial vascular plexus is developing in this group of fetus. Cells in inner root sheath shows presence of carbohydrate. Collagen fiber is not well developed in dermis. In the thick skin, 3 to 4 layers of epidermis is present. Rete pags are present which clearly shows presence of 2 layer in dermis. Sebaceous glands are not developed in this. Cells present above the basal layer shows the presence of carbohydrate. Collagen fibers are present in reticular & papillary dermis. Sweat gland with duct is present but it is few. Sebaceous gland is present but it is not well defined. There is germinative layer of sabacious gland which is present around the hair follicle. Hair follicle with hair shaft is present. The main thing Adepose tissue around the sweat gland is observed in this group. Keratin layer is well defined here. Fibroblast are present. In the thick skin, there are 2 to 3 layer of epidermis with melanocytes. Sweat gland with duct is present and it abundant. Stratum lucidum is welldefined. Papillary dermis is having thick collagen fiber as compare to reticular dermis and rete pags are present. Capillaries in dermal papilla is present. Superficial vascular plexus is present. Arteriole and venuoles are also there. There is no germinative layer of sabacious gland. Hair follicle and hair shaft is absent.

## CONCLUSION

In the beginning weeks of development, epidermis is 2 to 3 layer thick in thin skin while it is 3 to 4 layer thick in thick skin. Keratinohyline present in all the group but keratin layer is not defined in any group. Keratinocytes, a kind of cell found in the epidermis, create keratin, a long, thread-like protein with a protective function. Collagen, a fibrillary structural protein, is largely found in the dermis, the intermediate layer. The dermis is found on the panniculus, which is a subcutaneous tissue that contains little lobes of fat cells called lipocytes. These layers vary substantially in thickness depending on where they are on the body's structure. Rete pags create the main difference between thin & thick skin as it is observed in all the group of thick skin but in thin skin, it is not in regular basis. Appearance of fibroblast begins from group 2 which include 15 to 17 week of gestation fetus. Carbohydrate observed in internal sheath of hair follicle. Most of the cells appears in thick skin of group 4 fetus like melanocytes, keratinocytes which can be easily observed in this group. The epidermis is made up of keratinocytes, a special type of cell that produces keratin, a long, threadlike protein with a protective function. Collagen, a fibrillar structural protein, makes up the majority of the dermis, or middle layer. The dermis is found on the panniculus, which is a subcutaneous tissue that contains little lobes of fat cells called lipocytes. These layers vary substantially in thickness depending on where they are on the body's structure. Group 4 fetus sample shows presence of thin papillary dermis & thick reticular dermis in thick skin while it is not do defined in thin skin. Stratum spinosum begins to appears in group 4 in thin skin but it is not observed in other group. Startum lucidum also observed in only group 4 fetal sample. The epidermis layer on the eyelid is the thinnest (less than 0.1 mm), while the epidermal layer on the palms and soles of the feet is the thickest (1.5 mm). The thickest dermis is found in the rear of the body, which is 30-40 times thicker than the front compare with epidermis which covers the skin. The epidermis layer on the eyelid is the thinnest (less than 0.1 mm), while the epidermal layer on the palms and soles of the feet is the thickest (1.5 mm). The thickest dermis is found at the back of the body, which is 30-40 times thicker than the front epidermis above it. With this study I intend to observe and describe various histological changes that appear in fetal skin from 12 to 24 weeks of gestation. Literature describing chronological development of fetal skin beyond 12 weeks is scanty as there is scarcity of human fetuses for research in later stages of development due to diverse abortion laws and stringent guidelines on fetal research across the countries. Moreover, religious customs, ritual factors and sentimental issues also contribute to scarcity of fetal tissue for research.

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