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Histogenic Study of Human Foetal Endocrine Pancreas

Dr. Ramani T.V,[*] Dr. D. Nagajyothi[*], Dr S. Saritha[**], Dr. Gayathri. P[*],
Dr. M. Yesender,[***] Mrs. AsraAnjum[****].
Assistant professor, Professor and H.O.D. Department of Anatomy[**], Associate Professor[***], Lecturer[****].*
KAMS& RC , LB. Nagar, Hyderabad.
Corresponding author: Dr. T.V. Ramani.

Abstract: *The pancreas is an important organ from the point of view in human medicine, because it involves two important diseases Diabetes mellitus and pancreatic cancer. Pancreas has two distinct population of cells. Endocrine cells, Islets of Langerhans that secrete hormones. The exocrine cells, pancreatic acini secrete range of enzymes which together play an important role in metabolisms. Endocrine disease causes diabetes which affects at least 200 million people worldwide, and this number is expected to be doubled by the year 2025.[1]The exocrine part leads to pancreatic cancer causing about 65,000deaths in European countries which is virtually incurable.[2] The study was conducted on the histogenesis of Pancreatic Islets in 50 fresh human aborted foetuses without gross abnormality and were analysed in detail. The foetuses were from 12 to 40 weeks of gestational age of both the sexes and were preserved in formalin. These foetuses were collected from the Department of Obstetrics and Gynaecology, KIMS Narkatpally, Nalgonda (Dist.), Telangana, (INDIA).*
Human foetal pancreases were studied under five stages of development of Pancreatic Islets and were screened by Haematoxylin and Eosin staining.The specimens were observed under light microscope and discussed with the findings from the available literature. The research of foetal pancreas has great implication in clinical practice and treatment protocol, as it is an optimal stage and a suitable organ for transplantation in patients of insulin dependent Diabetes mellitus as complete cell replacement therapy.
Key words: *Histogenesis, Pancreas, Islets of Langerhans, Gestationalweeks (GW)*

I. Introduction

The name Pancreas derives from the Greek roots 'pan meaning all' and 'creas meaning flesh'. Functionally Pancreas is a both exocrine and endocrine gland, soft lobulated retroperitoneal organ, retort flask shape, occupying epigastrium and left hypochondrium, measures about 12 to 15 cm long and weighs 80 to 90 grams.It has two ducts, main duct and an accessory pancreatic duct.**[3]**

It develops at the foregut/ midgut junction by two pancreatic buds (dorsal and ventral endodermal buds) which will fuse to form single pancreas at around 7th week IUL. Main and accessory pancreatic ducts develop at around 6th week. Pancreatic acini and Islets of Langerhans start developing from 12th week of foetal life[4, 5] and Islets of Langerhans are proportionately more numerous in foetuses and infants than in older individuals. Many studies inferred that transition from Islets to acini or vice- versa can occur and developmentally they are not independent structures**[6]**

The acinar cells or the duct system give rise to endocrine part, Islets of Langerhans which later gets detached and forms independent colonies.**[6, 7, 8]** In the foetus the Islets of Pancreas are arranged in single or small groups and has structural organisation of 4 cell types with functional significance.The beta cell occupy the central core of Islet and other cells Alpha, Delta, PP cells are located at peripheral region.**[9]**

The present study was undertaken in an attempt to describe the sequential development of Islets of Langerhans in human foetal pancreas employing H&E techniques, as this has relevance in foetal tissue transplants.

II. Materials And Methods

The material consists of 50 aborted human foetuses of gestational age between 12 to 40 weeks were obtained from the Department of Obstetrics and Gynaecology KIMS, Narkatpally. Permission was obtained from institutional ethical committee.

The age of the foetuses was calculated by crown- rump length, bi-parietal diameter, head circumference and abdominal circumference. Foetuses were arranged in five gestational groups of 6 weeks interval. After opening of the abdomen, pancreas was dissected out from the foetuses and fixed in 10% formalin. The tissues were subjected to routine histological preparation and paraffin blocks were prepared. Sections of 3-5 microns thickness were cut and stained with Haematoxylin and Eosin.

Microphotography of sections were studied under the trinocular microscope having close circuit camera and an adaptor.

The recent study of foetal Islet of pancreas were divided in to 3 stages of development[10]
(a) Single cells (b) Inselfield (c) Mantellinsel

Group	Gestational Age (weeks)
Group – 1	12 – 18
Group – 2	> 18 – 24
Group – 3	> 24 – 30
Group – 4	> 30 – 36
Group – 5	> 36 - term

Histological Observations:
Group 1 (12 to 18weeks) Figure 1a & 1b
1. Mesenchymal tissue showed branched tubules with wide lumen.
2. Budding was observed at the end of the tubules forming primitive acini.
3. Undifferentiated cells were also seen within the mesenchyme.
4. Single ***Small islet cells having an ill-defined capsule from terminal process of duct system without capillaries were seen.(Stage 1 – single cell stage)***
5. Parenchyma begun to organise into lobes and lobules

Group 2 (18 to 24 weeks) Figure 2a & 2b
1. Mesenchymal tissue was reduced and proliferation of acinar cells
2. Establishment of small lobes and lobules.
3. Intra lobular ducts lined by cuboidal cells.
4. ***Increase in size of the islet arranged in small groups, entrapped within the acinar cells.(Stage 2 – Inselfield)***

Group 3 (24 to 30 weeks) Figure 3
1. Well-formed lobes and lobules with packed pancreatic acini
2. ***Clumps of undifferentiated cells (Islet of Langerhans) from the intra lobular duct lined by Cuboidal epithelium was also observed.(Stage 3 - Mantel field)***

Group 4 (30 to 36 weeks) Figure 4
1. Well differentiated groups of Islets of Langerhans with a thin capsule with capillaries were observed.(Stage 3 – Mantel field)
2. Lobes and lobules packed with serous acini.
3. Well-developed duct system with thick Interlobular septa was seen.

Group 5 (Full term) Figure 5a & 5b
1. The adult format of the microscopic appearance of pancreas was seen at 40th weekwith distinct Lobes and lobules.
2. ***Large, vascular islets with thin septa among mature acini were seen. (Stage 3 – Mantel field)***
This grouping was done in order to facilitate the description correlating with developmental sequence.

III. Discussion

Mammals, birds, reptiles and amphibians have a pancreas with similar histology and mode of development, while in some fish, the Islet cells are segregated as Brock Mann bodies. Invertebrates do not have a pancreas, but comparable endocrine cells may be found in the gut or in the brain [2] Development includes three fundamental processes, the growth, the differentiation and the metabolism. Growth is increase in spatial dimensions and in weight. Differentiation is increase in complexity and organisation and it is known as 'Histogenesis'[11]

The developmental knowledge of normal pancreatic growth and differentiation will also inform ongoing studies of pancreatic regeneration following surgical pancreatectomy[1]

The Pancreas plays a key role in the treatment and pathogenesis of Diabetes mellitus.

The diabetes mellitus occurs following total pancreatectomy in the dog was discovered by Mering and Minkowski which marked the beginning of 'pancreatic era'[12]

Pancreatic extract was prepared by Banting and Best in 1922 and was used for the treatment of diabetes mellitus. Recently clinicians are making an attempt to treat the patients of insulin dependent diabetes mellitus by transplantation of foetal pancreas and it forms paramount importance for the successful cell replacement therapies.[12]

The initial study of pancreatic islet formation in the human foetus was reported byPearce (1903). The origin of pancreatic endocrine cells is controversial, suggested that they arise from neural crest cells or from cells in bone marrow or from the epithelial cells of pancreatic ducts.[13, 14]

The present study provides a detail characterisation of foetal pancreatic Islets in various gestational stages as Islets are extremely difficult to isolate from adult human pancreas.

As noted by the previous investigators both acinar and islet epithelia develop from primitive pancreatic tubules. These tubules branch repeatedly and give rise to an arborescent duct system from which small groups of cells proliferate to form islet and acinar cell buds.

In the present studythe earliest foetus procured was of 12 weeks of gestation.Its parenchyma appeared as collection of branched tubules lined by cuboidal epithelial cells.Groups of cells proliferated from these branched tubules and form primitive islets and ducts around 8 – 10 weeks,primitive acini by 12 weeks. Parenchyma begun to organise into lobes, lobules and intra lobular ducts by the end of 18 weeks. Adult architecture of human foetal pancreas was observed by 24 – 30 weeks.

These observations were supported by J.Conklin, Gupta. V etal, P. Robb and Achaya Anand [9,12,15,16]
During our investigation we obtained mainly ducts (intra and interlobular) as compared with few acini and Islets in micro architecture of the foetal pancreas. This is in agreement with studies of Dietrich Grube[17]
Cytogenesis of human foetal pancreas was studied in detail by James L. Conklin[9].The tissues employed in his study consisted from 54 human foetuses subjected for Haematoxylin and Eosin method. My observations were similar to his findings as arranged in the group wise stages of development.

Gupta Renu et al studied electron microscopically 12 human foetal pancreases. In their study pancreatic acini were well formed by 12 weeks of gestation and isolated endocrine cells by 14weeks of gestation and very close proximity with the acini. According to them it was suggested that both exocrine and endocrine part arise from common source i.e. from the ductal epithelium. This observation was also seen in our present study.
Ferner and Stoeckenieus1950 studied 12 foetal pancreas and found islet buds by 10^{th} week of development. He used Gomori's method to recognise the alpha and beta cells in the human pancreatic islets as early as 10 – 13 weeks. In their study, foetal Islet of pancreas were divided in to 3 stages of development, i.e. Single cell,Inselfield and Mantellinsel[10].

In the current study, no special stains were used to identify the alpha and beta cells , however the 3 stages of development was observed during 12 – 18 weeks, 18 – 24 weeks and stage three was present from 25 weeks onwards.

Hahnvon Dorsche H etal investigated 41 human pancreata from 14 – 26 weeks of development. He divided them into 3 phases of development. Phase 1, 14 – 16 weeks characterised by Islet buds which originated from the ducts. Phase 2, from 17 – 20 weeks showed islets were detached from the ducts and form mantle field islets.Phase 3 from21 – 26 weeks showed islet cytology approximately similar to the adult human islets.
The present study was taken into account with the islets having the similar architecture of Hahnvon[18]
Another interesting observation was islet cell aggregation which isheterogeneous within the development of pancreas. Initially it develops in the centre of the tissue and then spreads towards the periphery of the organ where they start forming clusters continuously generating from the progenitor cells present in the expanding ductal epithelium.[19]

The appearance of first Islet cell groups was well defined **in this work** around 18 – 24 weeks of gestation in the centre of the pancreatic tissue. The cell buds destined to form Islets were seen enclosed in groups of capillaries around 30^{th} – 40^{th} week. This present investigation of regional distribution of Islets of Pancreas was significantly seen in the region of tail of pancreas as compared to body and neck.
Brown etal[20]1980 reported human foetal pancreas between 20- 24 weeks may be a suitable donor material.

IV. Conclusion

Human foetal pancreas at an optimal stage of its development is a suitable organ for transplantation in patients with insulin dependent Diabetes mellitus. The success of pancreatic transplant requires the knowledge of development, morphology and islet genesis for cell replacement therapies.

The data presented in our study of Histogenesis of Islets may contribute for better understanding and should benefit greatly with the rapid progress over the next few years.

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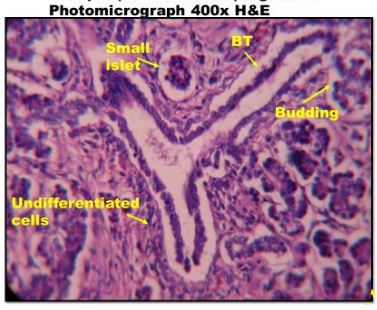
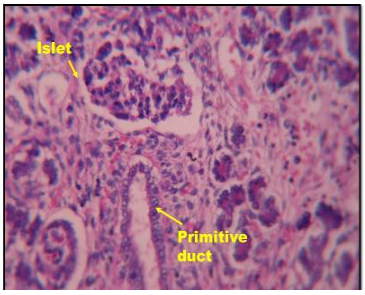
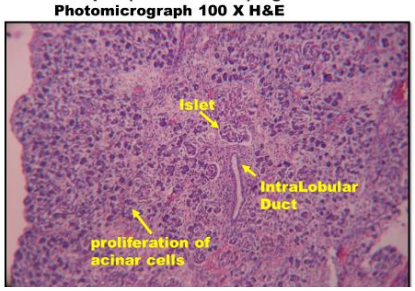
Group 1 (12 – 18 weeks) Figure 1a
Photomicrograph 400x H&E



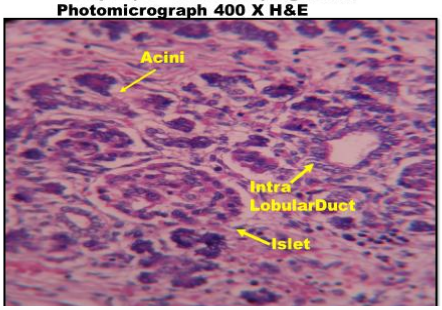
Group 1 (12 – 18 weeks) Figure 1b
Photomicrograph 400 X H&E



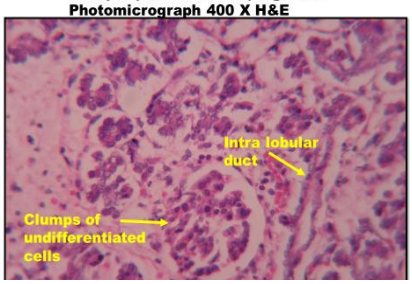
Group 2 (18 – 24 weeks) Figure 2 a
Photomicrograph 100 X H&E



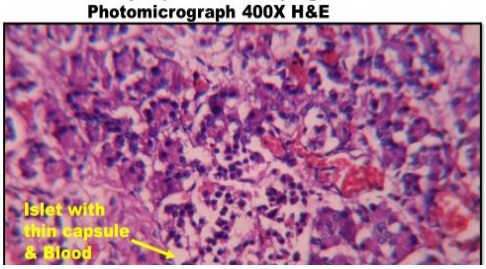
Group 2 (18 – 24 weeks) Figure2b.
Photomicrograph 400 X H&E



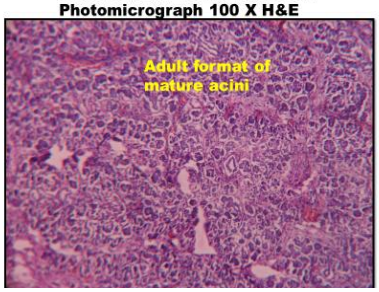
Group 3 (18 – 24 weeks) Figure 3.
Photomicrograph 400 X H&E



Group 4 (30- 36 weeks) Figure 4.
Photomicrograph 400X H&E



Group 5 (Full Term) Figure 5a.
Photomicrograph 100 X H&E



Group 5 (Full Term) Figure 5b.
Photomicrograph 400 X H&E