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Original Research Article

Prostate Gland in Human Foetuses: A Study of its Histogenesis

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ABSTRACT

Background: To study the histogenesis of the prostate gland in human foetuses. 'Prostates' is a Greek word which literally means "one who stands before", protector, guardian. It is important from a clinical point of view as it undergoes benign enlargement from the fifth decade, hence attracting the attention of males around this age and simultaneously the clinicians.

Materials and Methods: 100 foetuses of different gestational ages ranging from 14 weeks (85 mm) to 40 weeks (440 mm), products of terminated pregnancies under Medical Termination of Pregnancy, MTP Act of India, 1971 and stillbirths were collected from the Department of Obstetrics and Gynaecology, RIMS, (Regional Institute of Medical Sciences), Imphal, Manipur and utilised for the present study with permission from the Institutional Ethical Committee.

Results and Discussion: The first sign of differentiation is recognised as increased cellularity and denser mesenchymal cells. Cytoarchitecture at specific age period at different age groups are described.

Conclusion: Cytoarchitecturally, differentiation of all the three components of the prostate gland was noted as the age changes. It is inferred that of the three components of the adult tissues, the glandular component is differentiated from the epithelial lining of the urethra. This further induces the early mesenchymal tissues to differentiate into muscles and fibrous components. And at term, it has all the three components of the adult tissues although it is not as mature as in adult.

KEY WORDS: Prostate gland, human foetuses, histogenesis and cytoarchitecture.

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INTRODUCTION

"Prostates'' is a Greek word which literally means "one who stands before", "protector", "guardian". The prostate gland is the largest of the accessory sex glands found only in mammals that functions to produce a major

fraction of the seminal fluid.

The prostate is composed of approximately 70% glandular elements and 30% fibromuscular stroma. The stroma is continuous with capsule and is composed of collagen and abundant smooth muscle. The prostate gland is a composite gland made up of 30 to 50 small compound tubulo-alveolar glands that drain into the prostatic urethra by 15 to 30 small excretory ducts. The whole gland is surrounded by a thin but strong fibro-elastic capsule containing some smooth muscle fibres on its inner aspect and an extensive plexus of veins and the glandular components are embedded in an abundant dense stroma which is continuous at the periphery with the capsule. The stroma is again fibroelastic and in addition contains numerous strands of smooth muscles fibres [1].

MATERIALS AND METHODS

One hundred foetuses of different gestational ages ranging from 14 weeks (85 mm) to 40 weeks (440 mm), products of terminated pregnancies under MTP Act of India, 1971 and stillbirths were collected from the Department of Obstetrics and Gynaecology, RIMS, Imphal and utilised for the present study with permission from the Institutional Ethical Committee. Only those foetuses which were free from any gross anatomical abnormality were selected for the present study. The age of the foetuses were assessed from the obstetrical history, crown rump length (CRL) and gross features before fixation. The foetuses were preserved in 10% formalin for 10 to 15 days. The specimens were categorised into different age groups as follows for easier study and observation

GROUP I Upto 14 weeks

GROUP II 14-18 weeks

GROUP III 18-22 weeks

GROUP IV 22-26 weeks

GROUP V 26-30 weeks

GROUP VI 30-34 weeks

GROUP VII 34-40 weeks

After proper fixation (for 2 weeks) the foetuses were dissected. The abdomen was opened by a left paramedian incision. The incision was extended inferiorly to cut through the cartilage of the hip joint thus exposing urinary bladder and the prostate from the left. The prostate gland was finally removed along with the urinary bladder. Each isolated prostate gland at specific age group was processed for light microscopic study.

The stained slides of various age groups starting from 14 weeks to term were studied at low power, high power and under oil immersion in detail for panoramic view of the shapes. Study of the appearance and differentiation of various components from the early mesenchymal cells were done. Results were compiled for each group and were finally compared with the previous results of the various authors in the past and discussed thoroughly.

RESULTS AND OBSERVATIONS

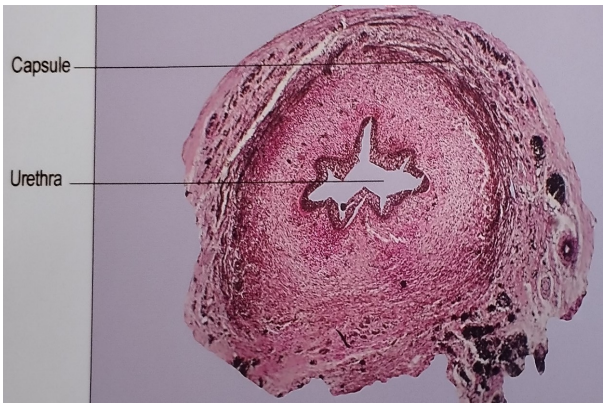

Fig. 1: Photomicrograph of 14 weeps prostate (Van Gieson's stain) showing development of capsule and homogenous undifferentiated parenchyma (5X).

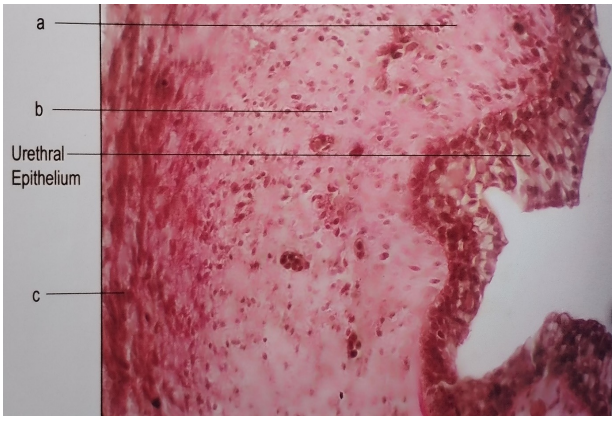

Fig. 2: Cytoarchitecture of developing prostate gland at 14 weeks (Van Gieson's stain)
Note-a. inner third-dense cellularity; b. middle lighter zone-sparse cellularity; c. outer dense more fibrous zone (10X).

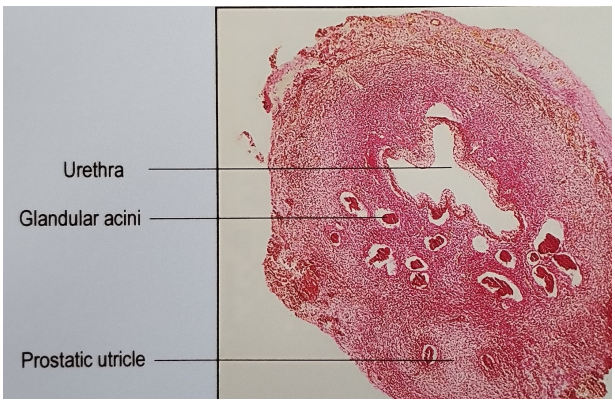

Fig. 3: Cytoarchitecture of 18 weeks old prostate (H &E) with few glandular outgrowths from its posterior urethral wall invading the mesenchymal stroma (5X).

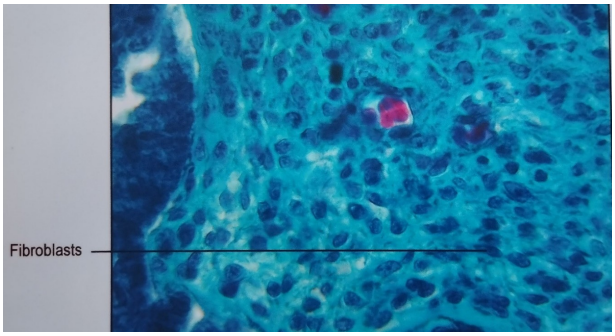

Fig. 4: Cytoarchitecture of 16 weeks old prostate (Masson's Trichrome stain) showing stromal cell with more differentiated fibroblasts (10X).

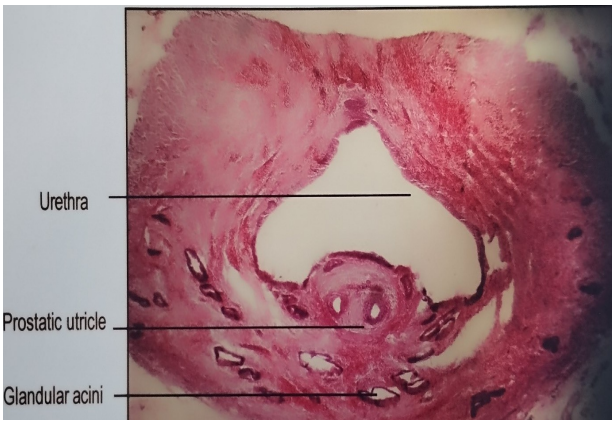

Fig. 5: panoramic view of 20 weeks prostate gland showing the increase in glandular acini along the dorsal aspect (5X).

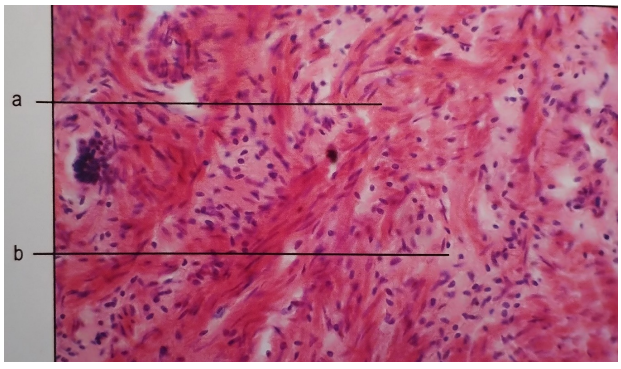

Fig. 6: cytoarchitecture of 24 weeks prostate showing (a). well-developed smooth muscle fibres predominating over the (b). collagenous fibres (40X).

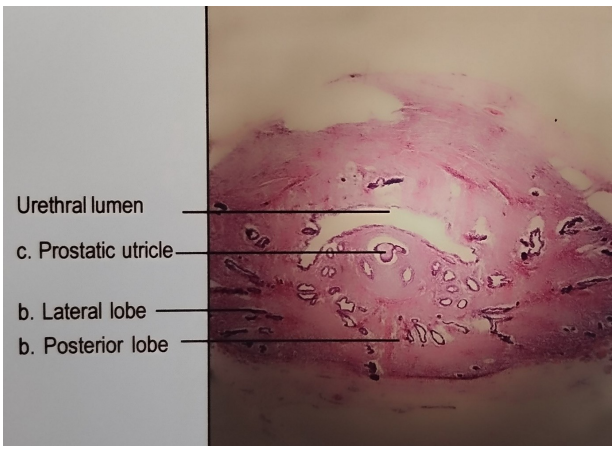

Fig. 7: Cytoarchitecture of 28 weeks prostate gland (5X).

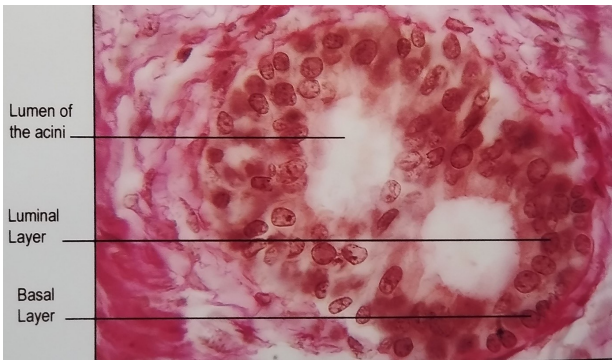

Fig. 8: Photomicrograph of the prostate gland at 28 weeks showing the two layered glandular epithelium- a luminal layer and a basal layer (40X).

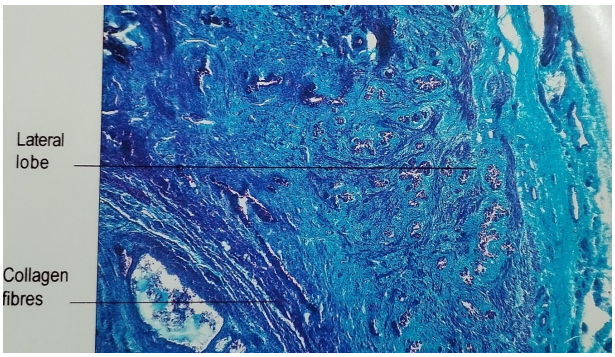

Fig. 9: Cytoarchitecture of prostate gland at 32 weeks (10X).

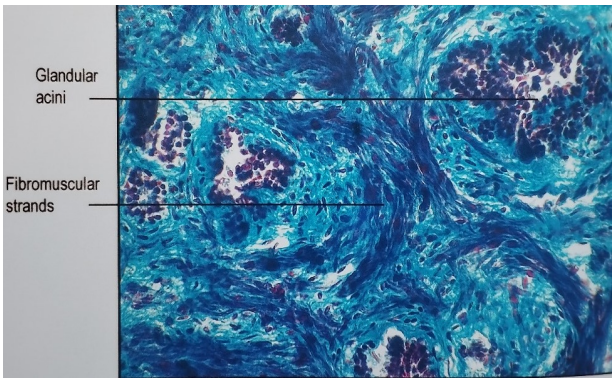

Fig. 10: Cytoarchitecture of the prostate gland at 40 weeks showing the concentric fibromuscular strands surrounding the acini forming lobules. (10X)

GROUP I: Upto 14 weeks: In the earliest age group of this series i.e., 14 weeks, in transverse section the prostate is seen as an ovoid shaped solid homogenous mesenchymal tissue without any differentiation. The urethra is centrally located and the parenchyma is characterized by homogeneous mass of immature mesenchymal tissue studded with blood vessels mostly on the ventral aspect (Fig.1). The parenchyma is divisible into 3 zones covered by a fibrous capsule. The inner 1/3rd is observed to be more vascular as compared to the outer zone. The middle 1/3rd of the parenchyma is lighter stained and consists of loosely arranged cells. The outer 1/3rd part of the parenchyma is darker stained and is denser (Fig. 2). Beneath this, the outer zone of the parenchymatous tissues is condensed and represents the true capsule and separates the prostatic tissue from the surrounding false capsule. The region just outside this zone consists of loose areolar tissues and blood vessels. At this stage no trace of glandular component is observed in the stroma throughout. Some early angiogenic tissues are visible on the anterior segment.

The urethral epithelium is lined by stratified epithelium with cuboidal to pyramidal shaped cells. The cells are pyramidal shaped in the middle region and cuboidal towards the base. The nuclei are round or ovoid and vesicular and are darkly stained and have perinuclear vacuolation. The epithelial cells towards the lumen are larger and taller. The stroma is characterised by homogenous mesenchymal tissue.

GROUP II: 14-18 Weeks: The constituent components of the adult prostate are seen differentiating from the mesenchymal tissue core. The epithelial outgrowths which are the primordia of the prostatic mucosal glands are seen invading the mesenchymal tissue more extensively on the posterior aspect.

The lateral lobes become apparent at this stage, earliest evidence of lateral lobes is represented and characterised by early prostatic glands flanking the sides of the urethra, on either side of the anterior lobe. The demarcation from the main prostatic lobe is visible by few collagen fibres at this stage. The primordium of the future middle lobe is represented as a wedge of tissue in between the posterior urethral wall and the newly developing prostatic utricle.

A few numbers of solid collections of cells having small condensed nuclei and prominent nucleoli and no clear-cut cell margin are also observed along the lateral aspect. Although some of the glandular components of the prostate gland at this stage are seen having lumina, some are still arranged as solid cords of cells. Some of the glandular sprouts on the lateral aspects which have differentiated earlier than those on the posterior aspect show central vacuolation leading to lumen formation. In between the early glandular acini and surrounding them are cells which have become larger and more elongated with larger elongated nuclei and more eosinophilic cytoplasm, the first sign of differentiation of myoblasts from the mesenchyme. (Fig. 3)

The prostatic stroma is more voluminous and denser, the constituent fibroblast cells are better differentiated and there are more collagen fibres in the parenchyma. The stroma mainly consists of mesenchymal cells which have oval nuclei. Interspersed among the mesenchymal cells, fibroblasts with elongated nuclei and tapering ends are identified.(Fig.4). Fibrous strands start appearing which is wavy in nature and arranged here and there. The cellular components are more than the fibrous components. Blood vessel formation is seen. Endothelial cells are observed.

GROUP III: 18-22 Weeks: The glandular sprouts near the utricle and along the dorsal aspect which in the previous age groups were seen as solid cords of cells have started developing lumina. The surrounding connective tissue components of the stroma invade the glandular sprouts with lumina thus giving rise to infoldings.

Under high power magnification, the glandular elements are seen lined by stratified cuboidal epithelium, the epithelial cells having spherical vesicular nuclei supported by the inter-glandular stroma which is abundant with cells and some amount of fibres.

The collagen fibres and early smooth muscle

fibres are seen just beneath the capsule as 2 to 3 distinct, thick concentric layers although the proportion of collagen fibres are predominant over the muscle fibres. (Fig. 5)

GROUP IV: 22-26 Weeks: The prostatic parenchyma at this stage is more differentiated with more elaboration of the glandular sprouts postero-laterally. A few glands have started encroaching anterolaterally. The two lateral lobes are demarcated from the anterior and posterior lobes and the central part is occupied by glandular outgrowths which are in different stages of differentiation. The middle lobe -which is a small wedge of tissue in between the dorsal urethral wall and the utricle is seen invaded by glandular outpocketings from the posterior urethral wall. On the whole, the prostatic parenchyma becomes more glandular in its posterior half as compared to the anterior half.

Under high power (x40), the fibromuscular stroma is well formed and more so in the anterior aspect where there are well developed smooth muscle fibres arranged concentrically in a semi-circular manner just beneath the true capsule at the anterior lobe. In between the smooth muscle bundles in the stroma are found the fibroblasts and collagen fibres. The smooth muscle fibres have increased and predominate over collagenous fibres. (Fig. 6). It is also observed that some of the glandular elements are seen to be composed of single layer of luminal cells and a basal layer of epithelial cells arranged horizontally.

GROUP V: 26-30 Weeks: From 26 weeks of fetal life, there is a considerable increase in the size of the prostate, due mainly to proliferation of the glandular epithelium so that there is equal proportion of the glandular acini and the fibromuscular components. The glandular sprouts are present more on the posterolateral aspect and a few glandular sprouts are also present just anterior to the urethra. On either side of the developing utricle, the two distinct lateral lobes are visualized; so also the median lobe which is present in between the posterior urethral wall and the utricle. In the posterior lobe of the developing prostate which is present behind the utricle, there is elaborate glandular tissue. The glands are organized in isolated clusters to form lobules and there are interlacing fibromuscular stroma surrounding the glandular tissues. (Fig. 7)

The anterior lobe is characterized by fibromuscular stroma consisting mostly of well-developed smooth muscles in layers and is observed to be diminished and condensed in size as compared to the previous week.

In the stroma, the smooth muscle cells are observed to predominate over the collagen fibres. In between the glandular acini and around them the smooth muscle fibres are arranged in bundles and thus form a network. Under high power (x100), the larger round pale staining cells of the glandular acini are recognizable as low columnar or cuboidal cells in 2-3 layers. The luminal or central cells have become larger and taller i.e., columnar. Vacuolation of the cytoplasm is common and is accompanied by secretion of eosinophilic granules into the lumen. The basal layer of cells still retains their condensed darkly stained look with small nuclei. It is also observed that there is increase in the size of the lumen. (Fig. 8)

GROUP VI: 30-34 weeks: All the five lobes of the gland are seen to be distinct as compared to the previous age group. The prostatic parenchyma looks more glandular due to the proliferation of the glandular components which are surrounded by a thin layer of hyaline material. They lie closer together and majority have well developed lumina. The stroma is uniformly occupied by the fibromuscular component.

The glands are directed from the posterior aspect of the urethral lumen, then directed backwards and laterally and hence change its direction towards the anterolateral aspect in a semi-circular pattern. The glands are sparse on the inner aspect of the lateral lobe and are in different stages of differentiation - simple tubular, compound branched tubule-alveolar differing in length and degree of branching. In the immediate vicinity of the glandular components, there are concentric layers of fibromuscular components. Thus the laterallobe is further subdivided into lobules

because of the circumscribed fibromuscular strands encapsulating the compound tubule-alveolar glands. This lobule character is more at the peripheral area of the lateral lobe.

Thus the prostate is seen to be made up of many compound tubule-alveolar glands in 3 concentric zones around the prostatic urethra –glands immediately around the urethra and outside of these are the middle and peripheral zones collectively forming the main glands that make up the greater part of the gland. Thus the tubule-acinar units of the gland are in different stages of differentiation- some as blind duct with lumen and some other as compound tubulo-acinar glands. Branching folds or papillae of the mucosa with a thin core of connective tissue project into the lumen. Few scattered muscle bundles are apparent in the vicinity of the prostatic glands. (Fig. 9)

GROUP VII: 34-40 weeks: In this age group, the prostatic tissue assumes more of adult character as evidenced by the presence of glands on the anterolateral aspect of the prostate.

As the total volume of the prostate increases proportionately with increase in age, the anterior lobe diminishes in size. Thus in the anterior lobe, the proportion of the smooth muscle component is quite distinct. The remaining lobes of the prostatic tissue are well developed but separated by collagen fibres. Thus at this stage, the fibromuscular components are well developed and shows great increase occupying approximately 2/3rd of the whole prostatic parenchyma. However, the muscular components still predominate over the collagen fibres. (Fig. 10). Thus near term the proportions of the components are such that the glands occupy 1/3rd of the prostatic parenchyma and the fibromuscular components occupy 2/3rd, although the muscles are more than the collagen fibres, elastic fibre is not identified till this age group in the inter-glandular stroma but it is observed in the internal elastic lamina of an arteriole.

DISCUSSION

Many authors have stated that the prostatic tissues are derived from the outgrowth of solid epithelial cords from the urogenital sinus epithelium into the surrounding mesenchyme [2,3,4]. In the present study, it is observed that the true prostatic tissue is recognizable with the elaboration of epithelial cords which are the primordia of the glandular components

The initial event in prostatic development is an outgrowth of solid epithelial cords from the urogenital sinus epithelium into the surrounding mesenchyme during 10-12 weeks of gestation [3]. However, the first indication of the formation of the prostate is an increase in cellularity of the splanchnic mesoderm surrounding the proximal part of the urethra during 10th week [5]. The present authors are also of the opinion that there is increased cellularity in the undifferentiated mesenchymal tissue in the immediate vicinity of the upper part of the urethra at 14 weeks. Simultaneously, whole early mesenchymal tissue is differentiated into three visible zones from the earliest specimen i.e., at 14 weeks.

The early outgrowths numbering 14 to 20 arise from the endoderm around the whole circumference of the proximal part of the urethra but mainly on its lateral aspects and excluding the dorsal wall above the utricular plate. They give rise to the outer glandular zone of the prostate. Later outgrowth from the dorsal wall above the mesonephric ducts arise from the epithelium of mixed urogenital, mesonephric and possibly paramesonephric origin covering the cranial end of the sinus tubercle. They produce the internal zone of glandular tissue [6]. The prostatic outgrowths initially form at least five independent groups of solid prostatic cords [7]. In the present study, in a specimen studied at 16weeks, the prostatic buds form at least 5 to 6 solid cords of cells which are arranged initially around the lateral aspects of the urethra.

The prostatic bud growth and subsequent branching morphogenesis occur in a specific spatial pattern that eventually establish lobar subdivisions of the mature prostate gland. The solid prostatic ducts are subsequently canalized from their urethral connections proceeding distally towards the ductal tips. As the solid epithelial cords canalise, the epithelium organizes itself into 2 distinct cell

types- luminal and basal cells [3]. The formation of lumen starts in foetuses of 70 mm CRL (12 weeks) [8]. In our present study, vacuolation of the central part of the solid cords i.e., future lumen is apparent from 16th weeks onwards.

The early prostatic outgrowths arise from the endoderm around the whole circumference of the tube but mainly on its lateral aspects [6]. The main prostatic tubules arise symmetrically from the lateral furrows of the urethra [9]. These opinions are in accordance to our present study where the outgrowths are initially seen arising mostly from the lateral aspects of the urethra thus flanking the sides of the urethra.

The prostatic parenchyma is divided into central zone, peripheral zone, transition zone and periurethral zone [10]. From our histological study the zones i.e., inner and outer can be identified. The glandular elements of the prostate are arranged in three concentric layers- an inner mucosal layer, an intermediate submucosal layer and a peripheral layer containing the main prostatic glands [10]. It is also observed from our study that the glandular acini of the prostate can be divided into three layers- inner mucosal layer consists of glands which lie in the mucosa and these are surrounded by the intermediate submucosal glands. The main or principal glandular elements lie peripherally and constitute the peripheral layer and constitute the bulk of the gland as per the opinion of the above author.

The lobes consisting of anterior, lateral lobes, posterior and median lobe can be identified only in foetuses before 20th week [6]. The prostate can be incompletely divided into five lobes developmentally [11,12,13]. In our present study, lobation can be identified even after 20th week of gestation. The prostate consists of 5 lobes developmentally- anterior, median, posterior and two lateral lobes. The lateral lobes are situated one on each side of the urethra and are joined together in front of the urethra by an isthmus which is devoid of glandular tissue [11,12,13]. From our present study, the earliest evidence of lateral lobes is represented and characterized by prostatic glands flanking the sides of the urethra at around 16 weeks of foetal life.

The anterior lobe develops in the 3rd month of foetal life from tubules growing from the anterior wall of the prostatic urethra although not clearly distinct anatomically [12]. But the anterior lobe persists only upto 22nd week of foetal life and thereafter disappears and its place is taken up by the fibromuscular isthmus of the gland [14]. However from our present study, the anterior lobe begins its formation in early foetal life as early as 14 weeks and is present anterior to the anterior urethral wall. It persists even beyond 22nd week of foetal life though there is gradual diminution of the size beyond 22nd week.

In a 100 mm (16 weeks) foetus, there is a condensation of the mesenchyme which also encloses the ejaculatory ducts and this condensation which separates its inclusions from the rest of the prostatic glands forms a coronally disposed shelf delineating the posterior boundary of what is usually referred as the median lobe of the prostate [8]. In our present study, the first indication of the development of the median lobe is represented as a wedge of tissue in between the urethra in front and thumb shaped tissue of hypertrophied prostatic utricle at around 16 weeks. Simultaneously, the posterior lobe begins its formation at CRL 115 mm (18 weeks) with the presence of few glandular acini behind the utricle.

The main prostatic tubules arise symmetrically from the lateral furrows of the urethra and run a curved course posteriorly, laterally and finally anteriorly into the lateral lobes. These tubules give off branches along their course [9]. The early outgrowths arise from the endoderm around the whole circumference of the proximal urethra but mainly on its lateral aspects. Later outgrowths from the dorsal wall arise [6]. Their findings are concomitant with our finding.

The muscular part of the organ develops from the surrounding mesoderm during the fourth month of intrauterine life and fuse with the glandular part [12]. From our study the appearance of myoblastic tissue starts from 18 weeks of foetal life and gradually undergoes maturation and ultimately get arranged

as randomly oriented smooth muscle bundles at term.

The capsule of the prostate gland are also described as true and false capsules [12,15]. The prostatic capsule is composed of fibrous tissue surrounding the gland which is best appreciated posteriorly and postero-laterally as a layer more fibrous than muscular between the prostatic stroma and extra prostatic fat [16] and differs from the opinions of other authors which state that the posterior lobe do not possess a capsule [9].

According to the present authors, the true capsule formation is first recognisable as a dark region of parenchymatous tissue just beneath the false capsule.

The abundant smooth muscles of the stroma encircle and invests the glands of the adult prostate and contracts during ejaculation to express prostatic secretions into the prostatic urethra [3]. In our present study, the lobules are identifiable from 30th week in the form of immature prostate gland surrounded by incomplete concentric circles of smooth muscles amidst the fibroblasts and collagen fibres.

The adult gland as a whole is composed of secretory channels (50%), smooth muscles (25%) and fibrous tissues (25%) [17]. From our histological observation, in the early stage, the glandular component is about 1/5th of the parenchyma and with further growth and differentiation, the proportion of the stromal components increases so that the acini occupy 1/3rd and the fibromuscular components occupy 2/3rd of the parenchyma. However, in the fibromuscular component, the collagen fibres and undifferentiated mesenchyme predominate till 22nd weeks and beyond 22nd week, the muscles increase and eventually predominate till term.

The histologic architecture of the adult prostate is that of a branched duct gland. Two cell layers, a luminal secretory columnar cell layer and an underlying basal cell layer line each gland or duct [18].

All the glandular elements except for those except for those arising from the posterior urethral wall acquire lumina from the stage of 100 mm CRL (16 weeks) and those glandular rudiments which occupy the middle lobe are less differentiated than the other groups within the gland and still consists of solid cords till the stage of CRL 125 mm (18 weeks) and the glands in the middle lobe start acquiring lumina from CRL 175-200 mm (weeks) [8]. From our present study, initially the solid epithelial cords are lined by 3-4 cell layers of lining epithelium which are of variable shapes. Central vacuolation of the ductular sprouts becomes apparent from 16th week onwards in some of the earlier differentiated glands as age advances. Gradually, the central vacuolation extends to the later differentiated glands too and by 26th week, the lining epithelium becomes two layered- a luminal layer and a basal layer.

The central zone which is nearly 25% of the glandular prostatic parenchyma constitutes the area surrounding the ejaculatory ducts. Nearly 75% of the glandular prostate is constituted by the peripheral zone which surrounds the central zone from behind and below. The transition zone lies around the distal part of the pre-prostatic urethra just proximal to the apex of the central zone and constitutes less than 5% of the glandular portion. The anterior fibromuscular stroma constitutes 1/3rd of the prostatic tissue within the capsule [19]. In our present study, at 16 weeks the parenchyma contains few glandular elements only. By 20th week, in the posterior part of the lateral and posterior lobes, the glandular elements are present. Overall proportion of the glandular components is about 1/3rd of the stromal elements. There is no trace of glandular elements in the anterior lobe.

The fibromuscular stroma is composed of smooth and striated muscles as well as elastin and collagen fibres [2]. From our study, the fibromuscular stroma consists of smooth muscles and collagen fibres. No striated muscles are detected and elastic fibres are present only in the internal elastic lamina of an arteriole.

It is observed that the acinar tubular epithelium in the foetal prostate remain stratified and adult type simple epithelium is not seen

during the period from 10th to 16th weeks [20]. The present authors are also of the same opinion regarding the stratified epithelium of the glands till 26th week and beyond 26th week, with the central vacuolation of the glandular elements and through the differentiation and maturation of the glands, the epithelium gets arranged into a two layered epithelium-a luminal layer and a basal layer.

The elastic tissue in the prostate is relatively scanty. It consists of fine fibrils intimately mixed with the supporting stroma [9]. In our present study, no elastic tissues can be identified in the inter-glandular area however the elastic tissues can be identified in the internal elastic lamina of an arteriole in the age group of 34-40 weeks.

It is observed that small corpora amylacea are present in many of the foetal prostates studied. In the youngest gland, they are in the terminations of the tubules near the urethra and appear to be due to accretion and inspissations of the eoninophil secretion [9].

From our present study, there is appearance of eosinophil secretions found in the lumina of the glandular acini starting from 22nd week of foetal life till term though they are not arranged as lamellar bodies as described by the above authors.

The prostate gland is an aggregation of many branched tubulo-alveolar glands. The epithelium shows a great variation in different glands and alveoli and even in a single alveolus. It is usually a simple cuboidal or columnar type and basal cells may be present. The prostatic glands show considerable infoldings of their epithelium into the lumen to accommodate the distention required during storage of prostatic fluid [2,17,21-23].

The epithelial lining may be reduced to low cuboidal or even squamous in dilated or cystic regions [9,22]. From our present study, the epithelium of the glandular acini consists of stratified cuboidal cells and with further development there is central vacuolation of the glandular elements in the central part and so the epithelium get arranged into two layers- a luminal layer consisting of large pale staining nuclei and a basal layer consisting of small cells with darkly stained nuclei. The epithelial lining of squamous cells is not observed though in a few acini, a lining epithelium of columnar cells can be observed.

CONCLUSION

It is inferred that of the three components of the adult tissues, the glandular component is differentiated from the epithelial lining of the urethra. This further induces the early mesenchymal tissues to differentiate into muscles and fibrous components. So at term, it has all the three components of adult tissues although it is not as mature as in adult.

Conflicts of Interests: None

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