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Original Article

Anatomy Section

Histogenesis of the Human Foetal Kidney in Mid-gestational Period: A Cross-sectional Study

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ABSTRACT

Introduction: The histological maturation of the human foetal kidney is a critical determinant of prenatal renal health and provides a primary baseline for diagnosing Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). While contemporary molecular insights have expanded current understanding of renal development, detailed morphological benchmarks for the mid-gestational period remain essential for clinical pathology and prenatal imaging.

Aim: To delineate the sequential histogenesis milestones of the human kidney during the crucial 14- to 28-week gestational period.

Materials and Methods: A cross-sectional observational histological study was conducted on 30 human foetuses (20 male, 10 female) ranging from 14 to 28 weeks of gestation at Department of Anatomy, MGM Medical College and Hospital, Chhatrapati Sambhajinagar. The study was conducted over a duration of two years, (January 2011- February 2013) to ensure the collection of adequate specimens for research. Gestational age was determined using Crown-Rump Length (CRL) and foot length. Renal specimens were fixed in 10% formalin for 24 hours, embedded in paraffin and serially sectioned at 7 µm thickness. Sections were stained with Haematoxylin and Eosin (H&E) and Masson's Trichrome. Histological sections of foetal kidneys were examined under a light microscope at 4×, 10×, 40× and 100x magnifications. Qualitative evaluation included assessment of cortical maturation, corticomedullary differentiation, nephron development and sequential stages of glomerular maturation. Quantitative morphometric analysis was performed using a calibrated ocular micrometer to measure cortical thickness at standardised sites in each specimen. All observations and measurements were documented for individual specimens and subsequently grouped according to eight gestational age categories (14-28 weeks) to evaluate the chronological progression of renal histogenesis.

Results: The Nephrogenic Zone (NZ) thinned progressively from 14 to 28 weeks. Concurrently, mean cortical thickness increased significantly from 754.68±53.40 µm to 2078.62±58.92 µm {Analysis of Variance (ANOVA), $p<0.001$}. This demonstrated a highly significant linear growth pattern ($R^2=0.992$), with the highest rate of growth occurring at 22-24 weeks (an increase of 284.63 µm). Glomerular maturation followed a centrifugal pattern, with primitive structures dominating superficially at 14-16 weeks. Proximal Convoluted Tubules (PCT) and Distal Convoluted Tubules (DCT) emerged at 18 weeks, becoming well-defined by 22 weeks. Corticomedullary differentiation began at 16-18 weeks; complete demarcation, well-organised pyramids and mature Ducts of Bellini were distinguishable by 28 weeks.

Conclusion: The present study establishes a precise morphological timeline for mid-gestational renal histogenesis. The 22-28 week window represents a phase of intense maturation characterised by significant cortical growth and marked nephron polymorphism. These findings serve as a normative anatomical baseline essential for the prenatal diagnosis of congenital anomalies and understanding the impact of preterm birth on nephron endowment.

Keywords: Congenital anomalies, Crown-rump length, Glomerulogenesis, Nephrogenic zone

INTRODUCTION

The advancement of prenatal diagnostic and therapeutic procedures in modern medical science necessitates a rigorous understanding of basic human morphology and developmental anatomy. Prenatal development represents a critical period in organogenesis and tissue maturation. Although organogenesis is largely completed during embryonic life, histogenesis continues throughout foetal life and, for several organs, extends into the postnatal period [1]. It is well-established that the functional capacity of an organ is intrinsically linked to this ongoing histological maturation.

The human kidney undergoes a complex sequence of developmental events during foetal life. Establishing normal histological milestones is essential for understanding renal morphogenesis. Precise knowledge of foetal renal histogenesis is therefore fundamental to developmental anatomy, foetal pathology and prenatal diagnosis. CAKUT constitutes one of the leading causes of chronic kidney disease in children. Accurate identification of normal developmental stages is essential for recognising deviations in renal morphogenesis that underlie these congenital disorders [2].

Normal nephrogenesis is regulated by a complex molecular network involving transcription factors such as Sine Oculis Homeobox Homolog 2 (SIX2), Odd-skipped Related Transcription Factor 1 (OSR1), Paired Box Gene 2 (PAX2) and Wilms' Tumour 1 (WT1), which coordinate nephron progenitor maintenance, differentiation and branching morphogenesis. Recent molecular studies have demonstrated that pathogenic variants of the Homeobox A11 (HOXA11) gene are associated with congenital renal malformations and impaired nephrogenesis, emphasising the close relationship between molecular regulation and structural development [3].

Understanding normal renal development is also clinically relevant in the context of preterm birth, which affects approximately 11% of newborns worldwide. Infants born during the mid-gestational window undergo postnatal nephrogenesis under extrauterine conditions. This process is frequently associated with accelerated but abnormal glomerular maturation and a reduced total nephron endowment, predisposing them to hypertension and chronic kidney disease later in life [4].

The scientific understanding of renal development has evolved substantially over the past two centuries. William Bowman first described the renal corpuscle in 1842 and Gerlach subsequently refined the understanding of glomerular development by demonstrating that growing capillaries displace capsular cells rather than perforating the capsule [5,6]. Mebane's comprehensive embryological investigations in 1924 further recognised the NZ as an important indicator of foetal renal maturation and congenital pathology [7]. Contemporary developmental biology has since established that the definitive metanephros develops through sequential stages involving the pronephros and mesonephros, reflecting the orderly progression of mammalian renal development [1].

Although classical morphologic investigations demonstrated that nephrogenesis is generally completed by 35-36 weeks of gestation, detailed histological characterisation of human renal development during the mid-gestational period (14-28 weeks) remains limited. Comprehensive chronological documentation of cortical maturation, NZ regression, glomerular differentiation and corticomedullary organisation during this critical developmental window is still lacking [8].

Therefore, the present study was undertaken to establish a chronological histological timeline of human foetal kidney development during the mid-gestational period. Such normative data may provide an anatomical reference for prenatal diagnosis of congenital renal anomalies and contribute to a better understanding of developmental arrest and disorders of nephrogenesis.

The study aimed to delineate the sequential histogenetic milestones of the human foetal kidney during the 14- to 28-week gestational period. The objectives of the study were to compare cortical thickness among different gestational age groups using morphometric analysis, to characterise the chronological stages of glomerular maturation during foetal kidney development and to evaluate the microscopic features of renal development across eight gestational age groups.

MATERIALS AND METHODS

A cross-sectional observational histological study was conducted using a convenience sample of 30 human foetuses (20 male, 10 female) obtained from medically indicated or spontaneously aborted foetuses ranging from 14 to 28 weeks of gestation. The present study was formally reviewed and approved by the Institutional Ethical Committee at MGM Medical College and Hospital, Chhatrapati Sambhajinagar, Maharashtra, India. The entire research process, encompassing sequential specimen collection, active histological processing and final statistical analysis, was conducted strictly within a two-year duration (January 2011- February 2013). The specimens were collected from the Department of Obstetrics and Gynaecology, MGM Medical College after obtaining written informed consent from the parents.

Sample Size: The sample size of (n=30) with the cohort of 20 males and 10 females foetuses were collected during the study period.

Sample size was determined by consecutive convenience sampling of all eligible specimens available during the study period rather than by an a priori statistical calculation.

Inclusion and Exclusion criteria: Specimens from parents who gave consent were included in the study. To ensure a normative morphological baseline, specimens showing visible congenital malformations or pathological defects or histological evidence of severe autolysis and maceration were excluded from the study.

Study Procedure

Gestational age determination: Gestational age was established in weeks from the Last Menstrual Period (LMP), using standardised morphometric parameters, primarily CRL and foot length, correlated with the foetal age criteria defined in Moore's clinically oriented embryology [8].

For sequential histological analysis, the specimens were stratified into eight gestational age groups: 14, 16, 18, 20, 22, 24, 26 and 28 weeks.

Histological processing and staining: Following dissection, the renal specimens were immediately fixed in 10% neutral buffered formalin for 24 hours to preserve structural integrity. The tissues underwent automated processing, including dehydration through graded ethanol, clearing in xylene and embedding in paraffin wax blocks. Serial transverse sections were obtained at a thickness of 7 µm using a rotary microtome.

General histological architecture was evaluated using H&E staining. To specifically delineate collagenous connective tissue and the presence of erythrocytes within primitive vascular networks, Masson's Trichrome staining was employed.

Two of the best-stained slides of each kidney specimen were selected and at least two fields of each slide were examined by the principal investigator. Qualitative cytological observation was conducted via light microscopy (4X, 10X, 40X, 100X) and renal maturation was assessed using specific morphological criteria mapped to progressive developmental milestones. Cortical maturation was evaluated by quantifying cortical thickness via ocular micrometry, tracking the progressive thinning of the subcapsular NZ, the presence of primitive structures (vesicles, comma and S-shaped bodies) and the emergence of PCT and DCT based on their characteristic eosinophilic and basophilic staining; medullary differentiation was assessed by the clear demarcation of the corticomedullary junction, the organisation of medullary pyramids and the structural maturation of the Ducts of Bellini into tall columnar epithelium; and glomerular staging was evaluated by identifying the six sequential stages of development (I-VI) to confirm the centrifugal pattern of maturation toward the juxtamedullary zone.

Glomerular maturation was qualitatively evaluated and classified into stages I-VI according to standardised morphological criteria described in the literature [9].

Additionally, quantitative morphometric analysis of cortical thickness was performed using micrometry under a light microscope at 4× magnification. Cortical thickness was measured by the distance between the renal capsule and the corticomedullary junction. For each gestational age group, four distinct values were measured and averaged to calculate the final mean thickness in micrometers (µm).

STATISTICAL ANALYSIS

Quantitative data for cortical thickness were summarised using descriptive statistics and expressed as mean±Standard Deviation (SD). To evaluate the statistical significance of the progressive structural increase in mean cortical thickness across the eight distinct gestational age groups, a One-way Analysis of Variance (ANOVA) was performed. Absolute mean differences between consecutive gestational groups were also calculated to assess specific periods of peak growth. Furthermore, linear regression analysis was employed to formally quantify the overall rate and trend of linear morphological growth throughout the mid-gestational period. For all statistical tests, a p-value of <0.05 was considered to indicate statistical significance.

RESULTS

The present study delineates the sequential morphometric and histological milestones of mid-gestational renal histogenesis. A total of 30 human foetuses (20 male, 10 female) were evaluated; no gross morphological differences were qualitatively observed between male and female specimens.

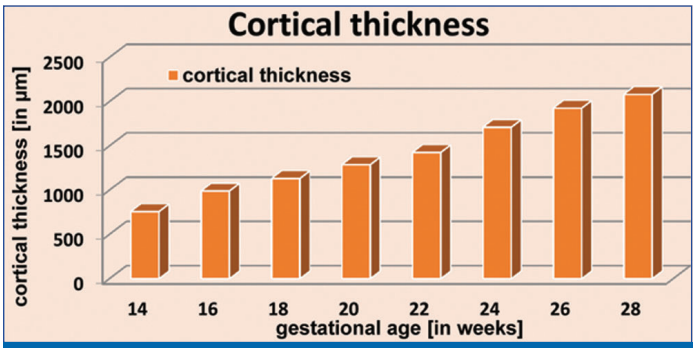
Morphometric Analysis of Cortical Thickness

To quantify the morphological growth and express the structural increase in numerical form, cortical thickness was measured using an ocular micrometer under a light microscope at 4X magnification. This

numerical quantification revealed that the mean cortical thickness increased progressively from a baseline of 754.68±53.40 µm at 14 weeks to a maximum overall thickness of 2078.62±58.92 µm by 28 weeks, as illustrated in [Table/Fig-1,2]. The highest rate of structural growth occurred between the 22nd and 24th weeks, characterised by a prominent peak increase of 284.63 µm as illustrated in [Table/Fig-1]. Minimal growth occurred between 20 and 22 weeks, with a numerically expressed difference of 138.00 µm. Statistical analysis confirmed this progressive structural increase across the gestational groups to be highly significant (ANOVA, $p<0.001$). Furthermore, linear regression analysis formally quantified this morphological increase, confirming an exceptionally strong linear growth trend throughout the mid-gestational period ($R^2=0.992$).

Gestational age (in weeks)	Mean cortical thickness±SD (in µm)	
14	754.68	53.40
16	987.56	161.43
18	1129.87	103.02
20	1285.12	76.49
22	1423.12	130.23
24	1707.75	44.54
26	1923.37	58.91
28	2078.62	58.92

[Table/Fig-1]: Relation of mean cortical thickness with gestational age.



[Table/Fig-2]: The measurement of cortical thickness (14-28 weeks).

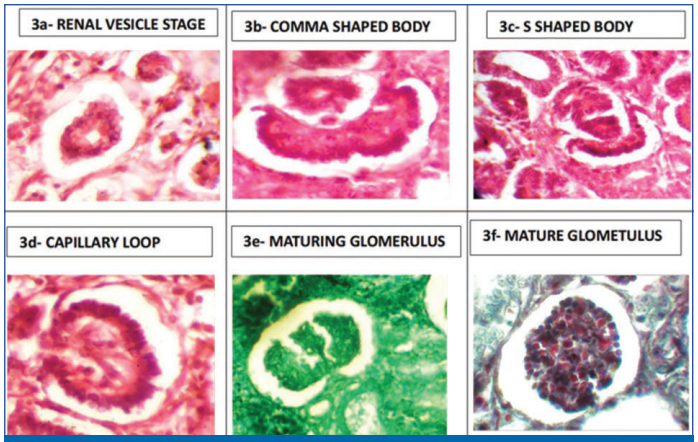
Chronological Analysis of Histogenesis

The results are presented chronologically, detailing the transformation from undifferentiated mesenchymal concentrates to well-defined renal structures.

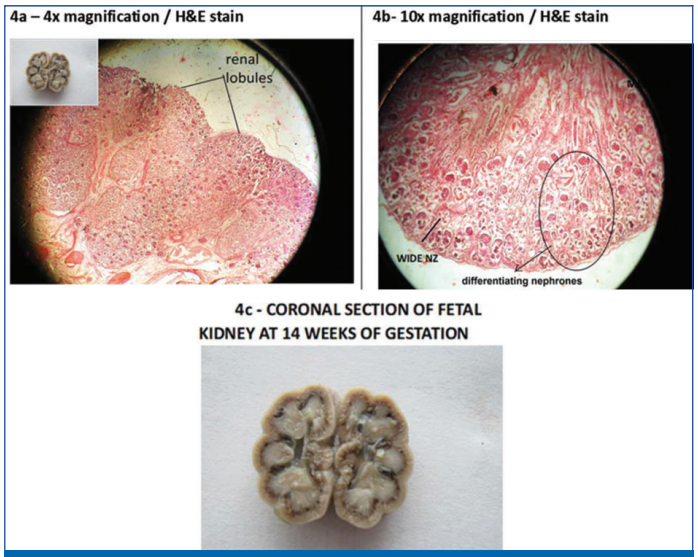
- **Glomerular maturation stages:** Histological evaluation demonstrated marked nephron polymorphism across the mid-gestational period. All six sequential stages of glomerular maturation: renal vesicle stage, comma-shaped body stage, S-shaped body stage, capillary loop stage, maturing glomerulus stage and mature glomerulus stage were successfully identified within the specimens, as illustrated in [Table/Fig-3].
- **Chronological milestones (14-28 weeks)**

Group 1 (14 Weeks): ([Table/Fig-4] 14 weeks of gestation)

Initial nephrogenic architecture at 14 weeks, the foetal kidney exhibited a distinct lobulated macroscopic structure encapsulated by a thin fibrous layer. The cortex was dominated by a wide subcapsular NZ containing densely packed, dark-staining undifferentiated mesenchymal cells possessing oval nuclei of the metanephric blastema. Active induction was evident where ureteric bud ampullae were capped by these mesenchymal concentrates. Primitive stage I, II and III structures, including nephrogenic vesicles, Comma-shaped and S-shaped bodies, were abundant in the superficial cortex, while the deeper cortex contained early immature glomeruli. Nephrogenic vesicles were identified by a central cavity lined by tall columnar cells. The medulla at this stage is composed of spindle-shaped mesenchymal cells with early grouping of collecting tubules.

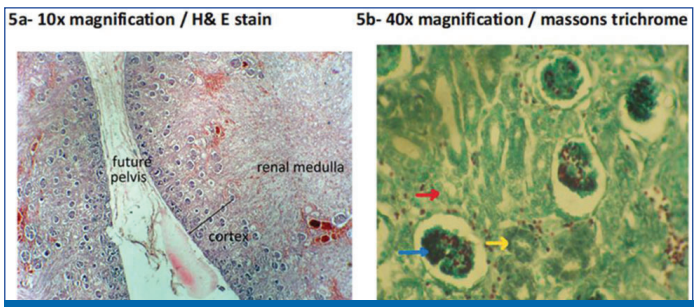


[Table/Fig-3]: Stages of maturation of glomerulus: a) stage I- Renal vesicle (40x magnification, H&E stain); b) stage II- Comma-shaped (40x magnification, H&E stain); c) stage III -S-shaped (40x magnification, H&E stain); d) stage IV Capillary loop (40x magnification, H&E stain); e) stage V Maturing glomerulus (40x magnification, Masson's Trichrome stain); f) stage VI Mature glomerulus (40x magnification, Masson's Trichrome stain).



[Table/Fig-4]: 14 weeks of Gestation. a) (4x magnification/ H&E stain) Microscopic evaluation illustrating distinct renal lobulations tightly enclosed by a thin fibrous capsule (Inset: Macroscopic section of the 14-week foetal kidney); b) (4x magnification/H&E stain) The cortex demonstrates a broad subcapsular Nephrogenic Zone (NZ) with densely packed metanephric blastema and abundant primitive stages of glomerular development (nephrogenic vesicles, comma-shaped and S-shaped bodies) in the superficial cortex; c) coronal section of foetal kidney at 14 weeks gestation showing the distinct lobulations.

Groups 2 and Group 3 (16-18 Weeks): [Table/Fig-5]: 16-18 weeks of gestation.



[Table/Fig-5]: 16-18 weeks of gestation. a) Corticomedullary differentiation clearly visible, with increased vascularity both in cortex and medulla; b) Shows juxtamedullary glomerulus with Red Blood Cell (RBC) penetration (blue arrow) PCT (yellow arrow) and DCT (red arrow).

Pivotal morphological transition: This period represented a critical phase where the NZ began to thin as the blastema was progressively consumed by active glomerulogenesis. By the 18th week, the following milestones were achieved:

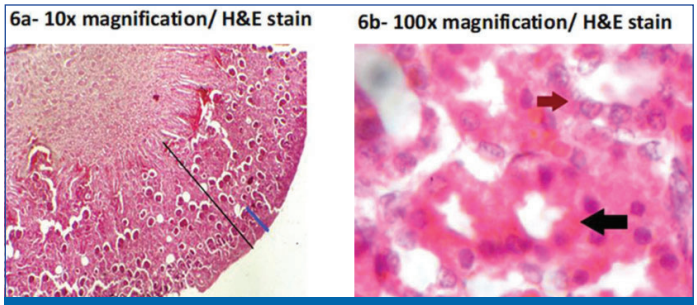
Corticomedullary differentiation: The junction between the cortex and medulla became clearly visible for the first time. Developing

glomeruli were dispersed in the parenchyma instead of limiting in subcapsular zone. Erythrocyte-filled blood vessels were readily identifiable within the cortical and medullary regions, including the glomerular capillary tufts, indicating progressive maturation of the renal vasculature.

Tubular Specification: PCT and DCT were first morphologically identifiable. PCTs were characterised by intense eosinophilic cytoplasm and a distinct brush border, whereas DCTs exhibited wider, patent lumina and pale eosinophilic cytoplasm

Medullary Progression: Loop of Henle differentiation into thick cuboidal and thin squamous segments was discernible. The renal pelvis was clearly identified.

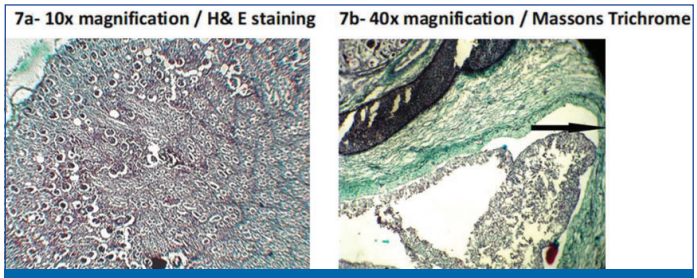
Group 4 and Group 5 (20-22 Weeks): [Table/Fig-6]: 20-22 weeks of gestation.



[Table/Fig-6]: 20-22 weeks of gestation. a) Increased thickness of cortex (black line) with reduced Nephrogenic Zone (NZ) (blue line) with large and mature juxtamedullary glomerulus; b) PCT with eosinophilic cytoplasm with microvilli (black arrow) and DCT with basophilic cytoplasm (Red arrow).

Intensive maturation and scaling: Progressive regression of the subcapsular NZ continued, occurring concurrently with an ongoing, steady increase in overall cortical thickness. Juxtamedullary glomeruli exhibited more advanced stages of maturation than superficial glomeruli, consistent with the centrifugal pattern of nephrogenesis. PCT and DCTs were well differentiated and readily distinguishable by their characteristic eosinophilic and basophilic staining patterns, respectively. In the medulla, collecting ducts demonstrated progressive organisation into an arcade-like arrangement converging toward the renal pelvis.

Group-6 and Group-7 (24 -26 Weeks): [Table/Fig-7]: 24-26 weeks of gestation.



[Table/Fig-7]: 24-26 weeks of gestation. a) Distinct corticomedullary junction with definitive renal organisation, exhibiting a centrifugal pattern of glomerular maturation and well-defined renal pyramids; b) Renal pelvis lined by distinct transitional epithelium (black arrow).

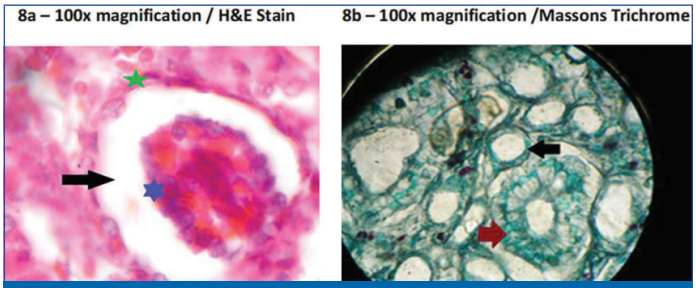
Corticomedullary differentiation became highly distinct, culminating in a well-differentiated cortex by 26 weeks with a notable absence of dispersed glomeruli. The structural thickening of the cortex was numerically quantified via ocular micrometry, demonstrating a progressive increase from 1707.75±44.54 µm at 24 weeks to 1923.37±58.91 µm at 26 weeks. Furthermore, the centrifugal pattern of glomerular maturation was structurally evidenced by the arrangement of mature Stage VI glomeruli into 3-4 distinct juxtamedullary rows, establishing definitive renal organisation as illustrated in [Table/Fig-6a]. Cortical maturation was further evidenced by an increased density of fully defined PCT and DCT, alongside a progressive reduction in undifferentiated tubules and intervening connective tissue.

The medullary region exhibited a progressive increase and elongation of collecting tubules, as well as thick and thin segments of the loops of Henle. Connective tissue was significantly thinned out. Collecting tubules in the superficial medulla were lined by simple cuboidal epithelium. In the deeper medulla, the Ducts of Bellini became well-differentiated, lined by tall columnar epithelium with basally placed round nuclei. Ampullary arcades were observed in the juxtacortical area and by 26 weeks renal pelvis was lined by transitional epithelium.

Group-8 (28 weeks): [Table/Fig-8]: 28 weeks of gestation.

By the 28th week, corticomedullary differentiation was completely demarcated, establishing mature renal architecture. The continuous structural growth of the cortex was quantitatively confirmed via ocular micrometry, reaching a maximum overall thickness of 2078.62±58.92 µm during the observed mid-gestational window. Qualitative microscopic evaluation of the cortical parenchyma revealed a significantly greater density of mature glomeruli compared to all previous developmental stages. These mature Stage VI glomeruli exhibited highly-differentiated structural features, notably a well-defined parietal and visceral layer of Bowman's capsule, as explicitly demonstrated in [Table/Fig-8a].

The medullary region exhibited advanced progressive maturation, characterised by a well-delineated medullary pyramid system and a rich network of blood capillaries. A prominent proliferation of collecting tubules was noted, alongside well-defined thick and thin segments of the loops of Henle as illustrated in [Table/Fig-8b]. In the deep medulla adjacent to the renal pelvis, mature Ducts of Bellini-distinctly lined by tall columnar epithelium, were clearly identified converging toward the excretory system. Crucially, despite this advanced state of architectural maturation, a residual band of peripheral mesenchymatous tissue persisted in the subcapsular region, providing key morphological evidence of ongoing, active nephrogenic induction.



[Table/Fig-8]: 28 weeks of gestation. a) Mature glomerulus showing a well-defined parietal layer (green star) and visceral layer (blue star) of Bowman's capsule (black arrow); b) Medulla showing a distinct thin limb of the loop of Henle (black arrow) and a collecting tubule (red arrow).

DISCUSSION

Spatiotemporal Dynamics of the Nephrogenic Zone (NZ) and Cessation

The present study confirms a distinct centrifugal pattern of renal maturation, where the most advanced nephrons occupy the juxtamedullary zone while undifferentiated mesenchymal concentrates persist in subcapsular area. While mouse models are frequently used, the present study highlights the significant human-mouse developmental divergence; human nephrogenesis is an expansive process spanning 26-28 weeks, which is known to produce approximately one million nephrons, whereas mice complete the process in 10-11 days [10].

The observed progressive thinning of the NZ with advancing gestational age is consistent with the classical observations reported by Moore KL et al., and Lizardo-Daudt HM et al., [8,11]. This progressive architectural organisation and continuous reduction of undifferentiated mesenchymal tissue strongly corroborate the recent contemporary findings by Das N et al., (2024) [12].

While the study concludes at 28 weeks with the zone still present, it is established that this zone typically disappears between the 34th and 37th week of gestation, marking the absolute cessation of de novo nephron formation bounded by the findings of Shimada K et al., and Ryan D et al., [13,14].

The overall cortical thickness was continually increased till the age of 28 weeks. Although morphometric data identified a brief interval of minimal structural growth between 20 and 22 weeks (138.00 µm), the continuous overarching growth trajectory observed throughout the entire mid-gestational period, remains highly significant ($p < 0.001$) and is firmly in concordance with Dakovic-Bjelakovic M et al., and Macdonald MS and Emery JL [15,16].

Nephron Polymorphism and Glomerular Generations

A hallmark of mid-gestational histogenesis observed in the present specimens is nephron polymorphism, the simultaneous presence of all developmental stages (Stages I-VI) within a single specimen.

These observations support a centrifugal pattern of maturation, where the oldest nephrons are located in the juxtamedullary zone and newer ones are added peripherally.

Recent quantitative research by Ryan D et al., provides a modern framework for these results, demonstrating a linear relationship between gestational age and the number of glomerular generations with approximately 10 generations completed during this developmental window [14].

Study by Pokarna DJ et al., corroborated the present findings regarding the emergence of the corticomedullary junction by 18 weeks [17].

Tubular Differentiation and Maturation

The identification of PCT and DCT by 18 weeks, becoming well-defined by 22 weeks, provides a reliable morphological benchmark for assessing functional maturation and corroborates the observations reported by Tank KC et al., and Patil S et al., [18,19]. Recent study by Pokarna DJ et al., further confirm this timeline, noting that well-differentiated tubules are formed between 19 and 23 weeks [17].

The specific staining characteristics including eosinophilic brush borders in PCTs versus basophilic patent lumina in DCTs reflect the emergence of specialised transport machinery.

Medullary Maturation and Multipapillary Organisation

The results also emphasise the multipapillary organisation of the human medulla, noting the convergence of collecting ducts into pyramids by the 28th week along with the predominant appearance of papillary (Bellini) ducts between 20 and 28 weeks.

This medullary maturation is critical, as the first 3-5 generations of ureteric bud branching are essential for renal pelvis formation, while subsequent generations form the minor calyces and papillae. These findings are in agreement with the work of Winyard PJD et al., [20]. This explains our observation of the renal pelvis appearing as early as 18-20 weeks.

Clinical and Diagnostic Significance

The 22-28 week window is the most active period of human foetal nephrogenesis. This observation is consistent with the report by Deffrennes S et al., (2024), who demonstrated that the period beginning at approximately 22 weeks is the most active for lateral branch nephrogenesis, accounting for more than 60% of the total nephron count [4].

Nephron polymorphism: A hallmark of mid-gestational histogenesis is nephron polymorphism suggest the simultaneous presence of every developmental stage (from primitive vesicles to Stage VI glomeruli) within a single specimen. This reflects the staggered, progressive nature of maturation characteristic of the foetal period. Similar observations have been reported by Patil DS et al., [19].

Clinical Relevance: Preterm Birth and Pathogenic Risks

Understanding the temporal sequence of renal histological maturation is crucial for evaluating the impact of preterm birth, which often leads to podocyte depletion and limited nephron endowment as noticed by Deffrennes S et al., [4].

Of particular pathological relevance, the blastemal-like phenotype observed in malignant transformation linked to OSR1 overexpression shows histological similarity to the densely staining, undifferentiated mesenchymal cell population identified at approximately 14 weeks of gestation. In this context, Pode-Shakked N et al., proposed that persistence or aberrant reactivation of such primitive mesenchymal elements may contribute to the pathogenesis of Wilms' tumour [21].

Collectively, these developmental correlations underscore that systematic knowledge of the chronological sequence of nephrogenesis enables clinicians to discriminate between physiological maturation and developmental arrest in foetal renal growth trajectories.

Limitation(s)

Certain methodological considerations accompany these findings. The reliance on two-dimensional histological sections and a single, unblinded observer inherently restricts the capacity for complex three-dimensional architectural quantification. Additionally, while the total sample size (n=30) yields significant developmental data, the statistical robustness of the ANOVA results is moderated by the smaller number of specimens available within each specific gestational subgroup.

CONCLUSION(S)

The present study establishes a precise morphological timeline and morphometric baseline (evaluating cortical thickness) for mid-gestational renal histogenesis during the critical 14-28-week gestational window. This study confirms a definitive centrifugal maturation pattern, characterised by the progressive thinning of the NZ, the emergence of mature tubules by 18-22 weeks and complete corticomedullary demarcation by 28 weeks. The 22-28-week window represents a phase of intense maturation, characterised by significant cortical growth. The simultaneous presence of multiple glomerular stages highlights the intense, staggered nature of mid-gestational maturation. Ultimately, these benchmarks provide a crucial normative baseline for the high-resolution prenatal diagnosis of congenital anomalies (CAKUT), identifying genetic developmental arrests (e.g., HOXA11 mutations) and assessing the long-term renal risks such as reduced nephron endowment associated with preterm birth.

Acknowledgement

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REFERENCES

[1] Sadler TW. Langman's medical embryology. 15th ed. Philadelphia (PA): Wolters Kluwer; 2023. p. 248–279.
[2] Kolvenbach CM, Shril S, Hildebrandt F. The genetics and pathogenesis of CAKUT. Nat Rev Nephrol. 2023;19(11):709-20. doi: 10.1038/s41581-023-00742-9.
[3] Saygili S, Atayar E, Canpolat N, Elicevik M, Kurugoglu S, Sever L, et al. A homozygous HOXA11 variation as a potential novel cause of autosomal recessive congenital anomalies of the kidney and urinary tract. Clin Genet. 2020;98(4):390-95. doi: 10.1111/cge.13813.
[4] Deffrennes S, Rayyan M, Fidlers T, van den Heuvel L, Levtchenko E, Arcolino FO. Impact of preterm birth on kidney health and development. Front Med (Lausanne). 2024;11:1363097. doi: 10.3389/fmed.2024.1363097. PMID: 38601116; PMCID: PMC11004308.

[5] Bowman W. On the structure and use of the Malpighian bodies of the kidney. Phil Trans R Soc. 1842;132:57-80. https://doi.org/10.1098/rstl.1842.0005.
[6] Gerlach J. Beiträge zur Strukturlehre der Niere. Contributions to the theory of structure of the kidney. Archiv für Anatomie, Physiologie und wissenschaftliche Medicin. 1845;363-86.
[7] Mebane DC. The significance of the presence of the nephrogenic zone of the kidney in the normal and the syphilitic fetus and the new-born. Am J Dis Child. 1924;28(6):668-77. doi: 10.1001/archpedi.1924.04120240011002.
[8] Moore KL, Persaud TVN, Torchia MG. The developing human: clinically oriented embryology. 11th ed. Philadelphia (PA): Elsevier; 2020. p. 69-92.
[9] O'Dowd G, Bell S, Wright S. The urinary system. In: Wheater's functional histology: a text and colour atlas. 7th ed. Philadelphia: Elsevier Health Sciences; 2023. p. 302-306.
[10] Schnell J, Achieng M, Lindström NO. Principles of human and mouse nephron development. Nat Rev Nephrol. 2022;18(10):628-42. doi: 10.1038/s41581-022-00598-5.
[11] Lizardo-Daudt HM, Edelweiss MI, Santos FT, Schumacher RD. Diagnosis of the human fetal age based on the development of the normal kidney. J Bras Patol Med Lab. 2002;38(2):135-39.
[12] Das N, Das N, Ajita R, Chongtham R. Histogenesis of human fetal kidney: a cross-sectional descriptive study in a tertiary care institution in the northeastern region. Int J Pharm Clin Res. 2024;16:01-04.
[13] Shimada K, Hosokawa S, Tohda A. Histological study of the fetal kidneys: development of the nephrons according to gestational weeks. Nihon Hinyokika Gakkai Zasshi. 1993;84(12):2091-96. Japanese. doi: 10.5980/jpnjurol1989.84.2091. PMID:8309115.
[14] Ryan D, Sutherland MR, Flores TJ, Kent AL, Dahlstrom JE, Puelles VG, et al. Development of the human fetal kidney from mid to late gestation in male and female infants. EBioMedicine. 2018;27:275-83. doi: 10.1016/j.ebiom.2017.12.016.
[15] Daković-Bjelaković M, Vlajković S, Cukuranović R, Antić S, Bjelaković G, Mitić D. Quantitative analysis of the nephron during human fetal kidney development. Vojnosanit Pregl. 2005;62(4):281-86. doi: 10.2298/vsp0504281d. PMID: 15889592.
[16] Macdonald MS, Emery JL. The late intrauterine and postnatal development of human renal glomeruli. J Anat. 1959;93(Pt 3):331-40. PMID: 14419327; PMCID: PMC1244288.
[17] Pokarna DJ, Kshitija K, Saritha S. Histogenesis of human fetal kidney from 14 weeks to 36 weeks: a study. Int J Res Med Sci. 2019;7(11):4330-34.
[18] Tank KC, Saiyad SS, Pandya AM, Akbari VJ, Dangar KP. A study of histogenesis of human fetal kidney. Int J Biol Med Res. 2012;3(1):1315-21.
[19] Patil DS, Patil DP, Mane DA. Histogenesis of human fetal kidney. Natl J Integr Res Med. 2013;3(3):118-23.
[20] Winyard PJD, Napolitano R, Sebire NJ. Normal human kidney development and congenital anomalies of the kidneys and urinary tract. In: Liapis H, ed. Pediatric Nephropathology & Childhood Kidney Tumors. Diagnostic Pediatric Pathology. Cambridge University Press; 2023:1-16.
[21] Pode-Shakked N, Cohen-Zontag O, Omer D, Harari-Steinberg O, Vax E, Pleniceanu O, et al. OSR1 and SIX2 drive divergent transcriptional programs in human kidney cells: implications for regeneration and tumorigenesis. Front Bioeng Biotechnol. 2025;13:1645499. doi: 10.3389/fbioe.2025.1645499. PMID: 41112069; PMCID: PMC12531215.

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