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Analysis of fetal renal cortex development: cortical maturation index as a new potential guide in fetal renal cortex assessment

Analiza razvoja bubrežne kore fetusa: indeks maturacije korteksa kao novi potencijalni vodič u proceni razvoja fetalne kore bubrega

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Abstract

Background/Aim. To date, most of the scientific attention has been aimed at the morphometric analysis of the nephrogenic zone (NZ) of the fetal renal cortex, while the quantification and analysis of the maturation zone (MZ) and other indicators of renal maturity were missing. The aim of the study was to examine the characteristics of fetal kidney cortex maturation, as well as to propose the development of a new cortical maturity index (CMI). **Methods.** The study included 42 paraffin molds of the fetal kidney, divided into three groups according to gestational age (GA). After hematoxylin and eosin staining, tissue sections were analyzed through the following parameters: the thickness of the NZ and MZ, the renal corpuscles area (RCa) and the glomerular capillary tuft area (GCTa), and the maturation stages of the glomeruli. In addition, a new parameter, CMI, was formed as a ratio of NZ and MZ thickness. The collected data were statistically processed. **Results.** Changes in NZ and MZ thickness were statistically significant, and they correlated with GA. A value of CMI higher than 0.2 was recorded in the kidney samples of fetuses younger than the 20th gestational week (GW), while a value lower than 0.1 was recorded in the samples older than the 30th GW. With an increase in GA in all zones of the renal cortex, RCa and GCTa decreased. A statistically significant reduction of GCTa was observed in the oldest group in the juxtamedullary and intermediate zones of the cortex ($p < 0.01$). Glomeruli located in the deeper parts of the cortex were more mature than the superficial ones. **Conclusion.** The measured parameters can serve as a starting point for future studies that would analyze the histomorphological characteristics of the fetal kidney cortex. In the absence of clinical data, a newly formed parameter CMI can represent assistance with the determination of GA, as it significantly correlates with GA ($p < 0.01$).

Key words:
fetal development; fetus; histological techniques; kidney cortex.

Apstrakt

Uvod/Cilj. Do sada, pažnja naučne javnosti bila je većinski usmerena ka morfometrijskoj analizi nefrogene zone (NZ) bubrežne kore fetusa, dok su izostali kvantifikacija i analiza maturacione zone (MZ) i drugih indikatora zrelosti bubrega. Cilj rada bio je da se ispitaju karakteristike sazrevanja korteksa bubrega fetusa, kao i da se predloži formiranje novog indeksa maturacije korteksa (IMK). **Metode.** U studiju su bila uključena 42 parafinska kalupa fetalnih bubrega, podeljeni prema gestacijskoj starosti (GS) u tri grupe. Posle bojenja uzoraka hematoksilinom i eozinom, analizirani su sledeći parametri: debljina NZ i MZ, površina bubrežnog telašca (BTp) i glomerularnog klupčeta (GKp), kao i maturacioni stadijumi glomerula. Dodatno, formiran je novi parametar, IMK, kao odnos između debljine NZ i MZ. Sakupljeni podaci su statistički obrađeni. **Rezultati.** Promene u debljini NZ i MZ bile su statistički značajne i u korelaciji sa GS. Vrednost IMK viša od 0,2 zabeležena je u uzorcima bubrega fetusa mlađih od 20. gestacijske nedelje (GN), dok je vrednost niža od 0,1 zabeležena u uzorcima bubrega fetusa starijih od 30. GN. Sa porastom GS u svim zonama bubrežnog korteksa

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smanjile su se vrednosti BTp i GKp. Statistički značajna redukcija GKp primećena je u najstarijoj grupi u jukstamedularnoj i intermedijarnoj zoni kore ($p < 0,01$). Glomeruli locirani u dubljim delovima kore pokazivali su veći stepen zrelosti od onih koji su bili locirani površnije. **Zaključak.** Izmereni parametri mogu poslužiti kao početna tačka za buduće studije koje bi analizirale histomorfološke karakteristike korteksa bubrega fetusa. U nedostatku kliničkih podataka, novoformirani parametar IMK može pomoći pri određivanju GS, s obzirom na to da značajno koreliše sa GS ($p < 0,01$).

Ključne reči:
fetus, razvoj; fetus; histološke tehnike; bubreg, kora.

Introduction

The majority of people are aware of the kidneys' primary excretory function – to eliminate harmful substances from the human body. Furthermore, kidneys have many other homeostatic functions, such as water and electrolyte regulation, osmoregulation, arterial blood pressure regulation, acid-base regulation, hormone secretion, and the ability to perform gluconeogenesis [1]. As part of the urogenital system, kidneys are developed by a process of differentiation of the intermediate mesoderm, which forms urogenital folds and later a nephrogenic cord [2], so that three developmental forms can be obtained. The first one is the pronephros, which is rudimentary and nonfunctional in humans, the second one is the mesonephros, which functions for a short period, and the third is metanephros [3], referred to as the primordium of the definitive kidney [4–6]. During the development of the kidney cortex, two zones are observed. In the superficial parts of the cortex, beneath the capsule, the nephrogenic zone (NZ) is described as a zone of undifferentiated mesenchyme with developmental forms of glomeruli [7]. The subjacent, inner zone of the cortex is described as a maturation zone (MZ), spreading to the kidney's medulla. MZ is a place of differentiation and maturation of glomeruli and specific nephron segments. As a result, it contains various stages of maturing glomeruli, which are more or less immature in terms of histological appearance as well as function [8].

Active glomerulogenesis in NZ is a result of a complex interplay between ureteric bud branches and metanephric mesenchyme (blastema). Cells of the metanephric blastema condense under the influence of the ureteric bud epithelium, forming the following developmental forms of glomeruli: cap, renal vesicle, comma-shaped form, and S-shaped form [3]. Bowman's capsule (BC) is developed from the inferior part of the S-shaped form. Renal corpuscles (RC) are formed by the ingrowth of capillaries of adjacent mesenchyme into BC [2]. Those capillaries inside the RC are called a glomerulus, also known as the glomerular capillary tuft (GCT) [9]. Glomerulogenesis is a complex process during which cell differentiation occurs as a consequence of numerous intercellular and cell-matrix interactions [10]. Defects in this intricate process are known as impaired glomerulogenesis, providing a fundamental basis for understanding disorders such as glomerulocystic disease and for linking adult-onset conditions like chronic kidney disease (CKD) and hypertension to inadequate fetal development [11, 12]. Prematurity is one of the most common risk factors associated with impaired glomerulogenesis and is closely linked with oligonephropathy [13].

Analyzing the importance of the kidneys through their numerous functions, particularly in light of the rising prevalence of premature births [14], it becomes clear why their prenatal development and maturation should be studied further in the future. So far, most of the scientific attention has been aimed at the morphometric analysis of the NZ. In contrast, extensive and detailed morphometric studies of the MZ, as well as defining indicators of cortical maturity, are quite rare. Therefore, we aimed our research in that direction, believing that not only can this type of data be implemented into clinical and experimental research, but it can also provide important information about kidney maturity that neonatologists can expect in premature fetuses of the appropriate gestational age (GA).

Methods

This retrospective study was approved by the Ethics Committee of the University Clinical Center of Vojvodina, Novi Sad, Serbia (No. 00-1160, from December 16, 2019) since we used paraffin molds of autopsied fetal kidney tissue obtained from the archive of the Center for Pathology and Histology of the aforementioned Clinical Center.

The study included 42 specimens over a two-year period (January 1, 2019, until October 1, 2020), selected based on the inclusion criteria.

The inclusion criteria were the following: absence of malformations of the urinary system noted during the autopsy; clinical evidence indicating the absence of chromosomal abnormalities; absence of maceration and autolysis of the kidney tissue; presence of the capsule on the kidney surface. The chosen specimens were then classified into three groups, based on their fetal GA as determined by clinicians: G1 – kidney tissue samples from fetuses younger than the 19th gestational week (GW) (n = 18), G2 – kidney tissue samples from fetuses between the 20th and 24th GW (n = 10), and G3 – kidney tissue samples from fetuses older than the 25th GW (n = 14).

Histological staining

Sectioning and staining with hematoxylin and eosin was conducted at the Department of Histology and Embryology, Faculty of Medicine of the University of Novi Sad, during a noted period.

Morphometric analysis

Stained tissue slides were analyzed by a digital microscope, VisionTekTMSakura (Japan), under a magnification of x20. Measurement was done by the software VisionTek

Live 2.6 (Sakura, Japan). The kidney cortex was measured at five points in every specimen (option Ruler). The NZ thickness was measured from the capsule to the distal end of the S-shaped form, following the methodology of the previous study [15]. MZ thickness was measured from the inner border of NZ (distal end of the S-shaped form) to the medulla. The results were presented in micrometers (μm). Based on these values, we established a new parameter called the cortical maturity index (CMI), defined as the NZ/MZ ratio (presented as an absolute value).

At five randomly selected visual fields, an area of 2 mm^2 of the renal cortex was analyzed. The visualized glomeruli were classified into three groups, based on their localization within the cortex: (I) juxtamedullary (JM) glomeruli included a single row of glomeruli located closest to the medulla, (II) superficial glomeruli including a single row of glomeruli that were closest to the NZ, and (III) intermediate group which consisted of all glomeruli between the two previously described groups. At each visual field, five representative glomeruli were chosen in each cortical zone (superficial, intermediate, and JM), and the area of RC and glomeruli was measured (option free form area). The results were presented in μm^2.

Glomerular maturity assessment

The maturation stages of glomeruli were examined on all the glomeruli captured on the slides. The assessment was done by a modified classification proposed by Macdonald and Emery [16], which is given in the following text. First stage – glomerular bud is recognizable. It is fungi-shaped, and the real vascular pole cannot be obtained. The parietal layer of BC is made of cubic epithelium (Figure 1A). Second stage – the vascular pole of the glomerular bud can be obtained. The glomerulus is not lobulated, and it is covered by an uninterrupted visceral layer of BC. The parietal layer of BC is still built of the cubic epithelium (Figure 1B). Third stage – glomerular bud is distended and lobulated, but the uninterrupted visceral layer of BC is still present. BC epithelium of the parietal layer becomes thinner (Figure 1C). Fourth stage – glomerular buds continue to grow. The visceral layer of BC becomes fragmented, while the parietal layer is built of simple squamous epithelium. Capillary spaces are visible (Figure 1D).

Statistical analysis

For statistical analysis, we used Excel for Microsoft 365. A Kruskal-Wallis test was used to determine whether there was statistical evidence that the analyzed groups' means were significantly different. To analyze the correlation, we used Spearman's rank correlation test. Significant values were obtained at $p < 0.05$ and $p < 0.01$.

Results

NZ thickness decreased with increasing GA, with the highest values in the G1 (Figure 2). Statistical significance both in the reduction of the NZ thickness ($p < 0.05$) and the NZ thickness correlation with GA was noted ($p < 0.01$), and it showed a negative trend in the older specimens. On the other hand, MZ thickness increased with GA (Figure 3) and showed a positive trend of correlation with GA. Statistical significance was noted in both analyses ($p < 0.01$).

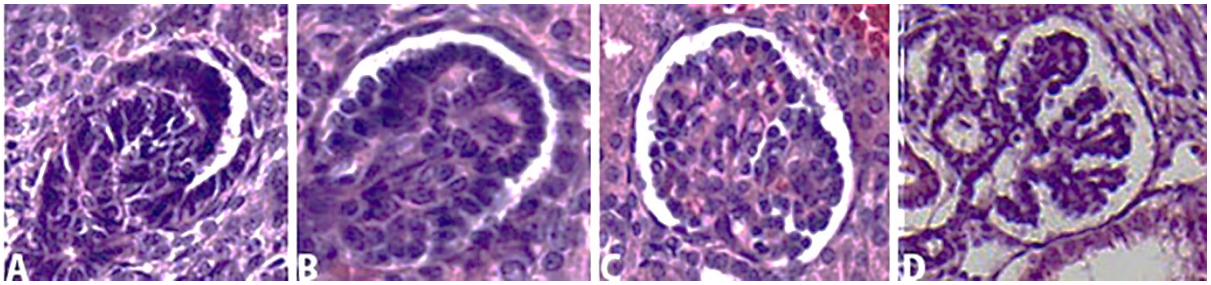

Fig. 1 – Micrographs showing maturation stages of glomeruli (hematoxylin and eosin staining × 630); A) 1st stage; B) 2nd stage; C) 3rd stage; D) 4th stage.

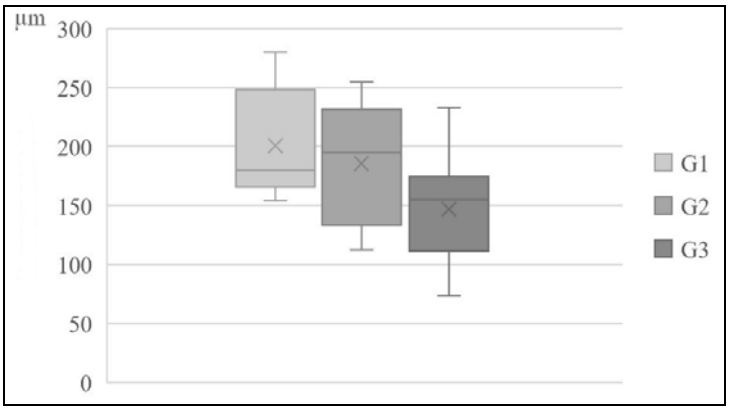

Fig. 2 – Distribution of the nephrogenic zone thickness. For abbreviations, see Table 1.

CMI decreased with the increase of GA within the analyzed groups, with statistical significance ($p < 0.01$) (Figure 4). A value of CMI that was higher than 0.2 was noted in the kidneys of fetuses younger than the 20th GW and a value lower than 0.1 in those older than the 30th GW. Correlation analysis showed a negative relationship between analyzed parameters, with statistical significance ($p < 0.01$).

RC area decreased in all three zones of the renal cortex with an increase in GA. GCT area also decreased in analyzed zones. Statistical significance in the reduction of GCT area was noticed in the third group ($p < 0.01$) in both JM and intermediate zones of the cortex (Table 1).

In the superficial zone of the renal cortex, in younger fetuses (G1 and G2), the first stage of glomerular maturation predominates. In fetuses older than 25 weeks, the second stage of glomerular maturation prevails. The third stage is slightly more frequent in older fetuses, and the fourth developmental stage was not present in the superficial zone of the cortex, regardless of GA. The intermediate cortical zone was predominantly populated by glomeruli in the third maturation

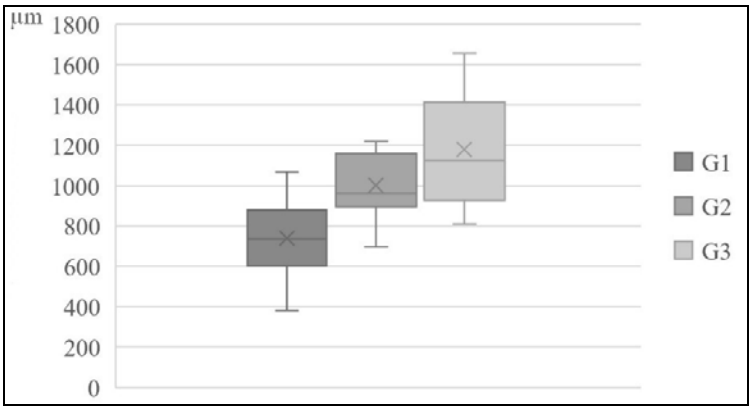

Fig. 3 – Distribution of the maturation zone thickness. For abbreviations, see Table 1.

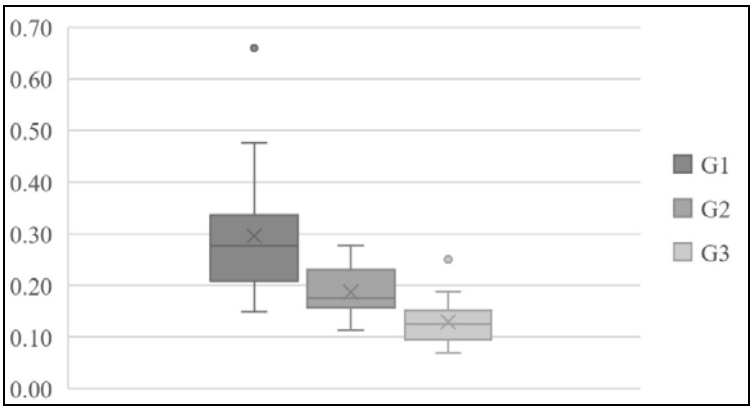

Fig. 4 – Distribution of the cortical maturity index. For abbreviations, see Table 1.

Table 1

Renal corpuscle area (RCa) and glomerular capillary tuft area (GCTa) in all three zones according to gestational ages

Zone	G1	G2	G3
Superficial			
RCa	5,350 ± 1,372	5,637 ± 855	5,101 ± 1,067
GCTa	2,719 ± 884	3,083 ± 805	3,014 ± 818
Intermediate			
RCa	9,494 ± 1,385	9,096 ± 1,360	6,507 ± 1,511
GCTa	5,443 ± 1,575	5,601 ± 1,624	3,744 ± 932*
Juxtamedullary			
RCa	16,669 ± 2,235	15,176 ± 2,597	11,916 ± 2,105
GCTa	9,266 ± 2,817	9,081 ± 2,070	6,428 ± 1,830*

Kidney tissue samples from fetuses: G1 – younger than 19th gestational week (GW) (n = 18); G2 – between the 20th and 24th GW (n = 10); G3 – older than the 25th GW (n = 14).

All values are given as mean ± standard deviation; all units of measurements are given as µm^2. *Statistical significance ($p < 0.01$).

Table 2

Distribution of the glomerular maturation stages

Group	Maturation stages of glomeruli (%)											
	superficial zone				intermediate zone				juxtamedullary zone			
	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th
G1	48.6	40	11.4	0	0	3.2	95.2	1.6	0	0	83.3	16.7
G2	55.2	37.9	6.9	0	0	6.4	92.7	0.9	0	0	80	20
G3	32.1	49.1	18.8	0	0	10.1	76.9	13	0	0	34.1*	65.9*

For abbreviations, see Table 1; 1st, 2nd, 3rd, and 4th are different glomerular stages – see Figure 1.
***Statistical significance $p < 0.01$.**

stage, while the first stage was not recorded in any GA. In addition, statistical significance was not observed (Table 2).

In the JM cortical zone, the predominant form in G1 and G2 was the third maturation stage, but in G3, the oldest group, the fourth maturation stage was predominant. A statistically significant reduction of the third and increase of the fourth maturation stages was observed in fetuses with the highest GA ($p < 0.01$) (Table 2).

Discussion

The tendency to realize and understand complex processes, such as organ development, is getting more attention in modern science. About 20 years ago, David Barker [17] set up the fetal origin hypothesis and correlated low birth weight with a higher risk for the later development of numerous chronic diseases. Furthermore, Maringhini et al. [18] found that low birth weight is a significant risk factor for developing CKD. Knowing that congenital malformations are one of the most common causes of acute kidney injury and CKD [19, 20], the need to explore kidney development comes by itself.

The findings of our study showed that the thickness of NZ decreased with the increasing GA of the fetus and that it strongly correlated with GA, which is concordant with the results of previous studies that have analyzed kidney embryological development [7, 15, 21, 22]. A statistically significant decrease in NZ thickness was observed in the oldest group, similar to the results described by Ryan et al. [15]. By morphometric analysis of the kidney cortex, they recorded that the thickness of the NZ in the kidneys of fetuses younger than 20 GWs was around 200 μm, and while decreasing, NZ was still present in some of the specimens of the oldest group (37th GW). On the contrary, Tank et al. [23] stated in their study, conducted on 20 fetal kidney tissue specimens, that NZ could not be observed in the tissue material of fetuses older than 36th GW, and this variability about NZ still represents a kind of enigma. The oldest specimen in our study was 36 weeks old, and NZ was still present, indicating: a) variability in the disappearance of NZ and b) the possibility of postnatal glomerulogenesis. The presence of the NZ in the late periods of pregnancy points out that prematurely born neonates are exposed to a higher risk for two reasons. The first one is the fact that a higher percentage of glomeruli in less mature stages in younger fetuses indicates more immature kidneys with lower functional performances. Second, premature birth would stop, delay, or alter the development of new glomeruli in NZ, which implies that premature children would be born with fewer glomeruli compared to term children. Nephrogenesis and the morphogenetic activity in the renal cortex are down-regulated by unknown signals with the start of the perinatal period [8], and data suggest that the number of nephrons at birth is permanent during life [24]. Although some data suggest that nephrogenesis in the kidneys of preterm-born neonates continues and leads to a significant increase in the number of glomeruli and nephrons within the kidney after birth [25], this point of view is debatable, knowing that preterm and low-birth-weight neonates frequently suffer from oligonephropathy with lifelong disease risk. This is the reason some researchers are analyzing mechanisms by which nephrogenesis could be prolonged even after birth [26]. Similar to the disappearance of the NZ and the termination of glomerulogenesis, postnatal glomerular development is also not precisely determined and brings up disagreement and uncertainty.

While NZ represents a real area of interest for researchers, data about MZ is severely lacking, and it is important to understand the significance of this developmental zone. In our study, MZ increased within older specimens, and the exact values were collected. In this zone, maturating glomeruli, tubules, and blood vessels, such as cortical radiate arteries, can be obtained [27]. While the nephrons are maturing in the MZ, they are being formed in the NZ, and their following apposition to the MZ results in a radial extension of the renal parenchyma. During their development, RC located in NZ did not have established vessels or perfusion, and it is believed that these events happened later, after their relocation to the MZ. Vascular supply, including perfusion with erythrocytes, is in part developed in the MZ, so the initial perfusion of the GCT occurs here and not in the NZ, where vasculature is incomplete. It was believed that impaired nephrogenesis is caused by noxae altering the MZ and maturating glomeruli. However, actual data points out the significance of the primary and secondary steps of the nephrogenesis that are happening in the NZ [8]. Consequently, the last generation of maturating nephrons that are located in the MZ, as well as developing forms located in the NZ, are the targets of described noxae [28]. The functions of the MZ, other than maturation and vascularization of renal corpuscles, are not certain, and they represent a real field of possibilities for future research.

CMI, the ratio between NZ and MZ, decreased with the higher GA, which correlates with the decrease in the NZ thickness and the increase in the thickness of MZ. This index

showed a high statistically significant correlation ($p < 0.01$) with the decrease in fetal GA, which suggests that it could be used as a precise marker of this change. It can provide an estimate of the fetal GA and kidney maturity if other information is not available. In our research, a value of CMI higher than 0.2 was noted in the kidneys of fetuses younger than the 20th GW, while a value lower than 0.1 corresponded with the kidney tissue material of fetuses older than the 30th GW. Although this parameter showed a strong correlation with GA, these new findings need to be verified through future studies by expanding the number of specimens and their clinical implementation.

RC area analysis has shown that the value of this parameter decreased in all three cortical zones with the increase in GA. However, statistical significance was not noticed. Similarly, GCT area also decreased, and statistical significance in the reduction was noticed in the G3 ($p < 0.01$) in both JM and intermediate zones of the cortex. The presence of "abortive forms" of the glomeruli in the deeper parts of the renal cortex, which are thought to be direct arterio-venous anastomoses [7], could explain these findings. Crobe et al. [29] pointed out that with the increased GA, podocyte number decreases. This fact could correlate with the decrease of the GCT area, knowing that podocytes form the visceral layer of the BC and that their presence leads to glomerular hypercellularity in the early developmental stages of the GCT. Glomeruli of the superficial cortical zone contains fewer podocytes, and their GCT area are consequently lower compared to the GCT area of some more deeply placed glomeruli. In addition, Schell et al. [27] described changes in the shape of podocytes that occur during glomerular maturation. In the beginning, podocytes can be described as classic columnar epithelium, and later, they get thinner, which can additionally influence the GCT area values.

By analyzing the maturation stages of glomeruli, a common pattern of renal cortex maturation could have been observed, meaning that in each of the observed gestational periods, glomeruli located in the deeper parts of the cortex were more mature. The superficial zone of the renal cortex contained less mature glomeruli compared to the intermediate and, even deeper, JM zone. Furthermore, while the superficial zone did not contain glomeruli of the fourth stage of maturity, the JM zone did not contain glomeruli of the first and second stages of development. This finding is concordant with the previous studies, and it is a significant sign of cortical maturation [16].

Conclusion

This study has quantified and more thoroughly analyzed the developing renal cortex. The results have shown and numerically expressed the parameters of renal maturation, such as the thickness of the nephrogenic zone and maturation zone, as well as the glomerular maturation stages. In addition, a newly formed parameter, the cortical maturity index, can help with the estimation of gestational age as it significantly correlates with gestational age.

Obtained data are the basis for future research in the domain of histomorphology and ontogenesis of the kidney, which, we hope, will lead to an enhancement in prenatal, perinatal, and postnatal care.

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