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A Study on Morphology, Morphometry, And Histological Changes in Normal and Anomalous Human Aborted Fetal Kidney at Different Gestational Periods.

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ABSTRACT:

The human fetal kidney undergoes intricate developmental processes crucial for establishing proper renal function postnatally. Originating from the intermediate mesoderm, the kidneys undergo nephrogenesis, branching morphogenesis, and tubulogenesis to form nephrons, the functional units. Disruptions in these processes can lead to congenital renal anomalies, impacting renal function and overall health. Understanding fetal kidney development is vital, as abnormalities can predispose individuals to renal disorders later in life. Roughly 20% of fetal congenital malformations are characterized by renal anomalies, emphasizing the need for early detection and management. Elucidating normal fetal kidney development forms the basis for identifying anomalies, with investigations across gestational periods crucial for scientific understanding and clinical applications. This mini-review highlights the significance of studying fetal kidney development, providing an overview of its stages, and emphasizing the importance of recognizing normal and anomalous characteristics.

Introduction

The development of the human fetal kidney is a complex and intricate process crucial for the establishment of proper renal function postnatally (Ryan et al., 2018). The fetal kidney undergoes a series of dynamic developmental processes essential for its structural and functional maturation (Niloofar et al. 2020). During embryogenesis, the kidneys arise from the intermediate mesoderm and undergo intricate morphogenetic events, including nephrogenesis, branching morphogenesis, and tubulogenic, to form the functional units known as nephrons (Minoru Takasato & Little, 2015). Any disruption or aberration in these developmental processes can lead to congenital renal anomalies, which may manifest prenatally or postnatally, significantly impacting renal function and overall health (Stonebrook, et al. 2019). Given the critical role of the kidneys in maintaining fluid and electrolyte balance, as well as regulating blood pressure and waste excretion, understanding fetal kidney development is indispensable (Ifeanyichukwu Ogobuiro & Tuma, 2023). Moreover, abnormalities in fetal kidney development can predispose individuals

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to various renal disorders later in life, such as congenital anomalies of the kidney and urinary tract (CAKUT), renal dysplasia, and polycystic kidney disease (Stonebrook et al. 2019). Roughly 20% of all foetal congenital malformations are characterized by foetal renal anomalies, which are observed in roughly 3-4% of pregnancies (Nef et al., 2016). Therefore, elucidating the normal developmental trajectory of the fetal kidney and identifying deviations from this trajectory are essential for early detection, diagnosis, and management of renal abnormalities (Irfan, O'Hare, & Jelin, 2021). This comprehension of normal fetal kidney morphology, morphometry, and histology forms a critical basis for identifying anomalies in kidney development. Investigating these changes across gestational periods holds immense significance for scientific understanding and clinical applications. This mini-review aims to highlight the importance of studying fetal kidney development, offering an overview of its stages, and stressing the significance of grasping normal and anomalous fetal kidney characteristics.

Normal and abnormal Fetal Kidney Development

Human kidney development initiates with the pronephros (Weeks 4-5) during early embryogenesis, a rudimentary structure lacking significant functionality, which regresses before the end of the first trimester (Rosenblum, Pal, & Reidy, 2017). Mid-gestation sees the emergence of the mesonephros (Weeks 5-10), serving as the temporary kidney mainly for excretory and osmoregulatory functions during fetal life. The metanephros (Weeks 10-Birth), the definitive kidney, forms during late embryogenesis via interactions between the metanephric mesenchyme and the ureteric bud, generating the collecting duct system and nephrons (Blake & Rosenblum, 2014). Nephrogenesis persists throughout fetal life, with most nephrons forming by mid-gestation. Fetal kidney development undergoes notable morphological and morphometric changes, including alterations in size, shape, and structural organization, with kidneys experiencing rapid growth and differentiation (Mileto et al., 2018). Morphometric analyses capture dynamic changes in renal dimensions, indicating progressive development of renal structures such as nephrons, collecting ducts, and vasculature (Puelles, Combes, & Bertram, 2021). The fetal kidneys growth can be evaluated throughout pregnancy by measuring renal length and comparing it to normal charts. (As a simple rule, renal growth is 1.1 mm/ gestational week). Histological examination of normal fetal kidneys depicts characteristic features at different developmental stages. Early in development, primitive tubular structures surrounded by undifferentiated mesenchyme near the ureteric bud branches are observed. Progression reveals distinct nephron structures like renal corpuscles, tubules, and loops of Henle (Blanc et al., 2021). Concurrently, renal vasculature matures, evidenced by the development of glomerular capillaries and renal arteries (Mohamed & Luisa, 2019).

Anomalous fetal kidney development encompasses various structural abnormalities affecting different components of the renal system. Common anomalies include renal agenesis (complete absence of one or both kidneys) (Wilkinson et al. 2014), renal hypoplasia (underdevelopment) (Cain et al. 2010), renal dysplasia (abnormal tissue differentiation) (Woolf et al. 2004), polycystic kidney disease (multiple cysts in kidney parenchyma) (Ul Haque & Moatasim, 2008), and obstructive uropathies (urinary tract obstruction leading to kidney damage) (Rishor- Olney & Hinson, 2023). The etiology of these anomalies is multifactorial, involving genetic, environmental, and maternal factors (Talati, Webster, & Vora, 2019). Genetic mutations, chromosomal abnormalities, maternal drug exposure, diabetes, and intrauterine infections can disrupt normal kidney development (Goodyer et al. 2022). Abnormalities in signaling pathways like Wnt/β-catenin and Notch may also contribute (Zhou et al. 2016). Anomalous fetal kidneys exhibit variations in morphology, morphometry, and histology compared to normal kidneys. They may display reduced size, abnormal architecture, disorganized tissue, abnormal nephron formation, cysts, fibrosis, and inflammation (Goodyer et al. 2021). Morphometric analyses can identify deviations from normal renal dimensions, reflecting structural abnormalities. Histologically, anomalies show aberrant tissue organization, abnormal cell differentiation, and pathological features like cysts, fibrosis, and inflammation (Su et al., 2019).

Comparison of Normal vs. Anomalous Fetal Kidney Morphology:

During the pronephros stage, normal fetal kidneys exhibit rudimentary tubular structures as part of early kidney development (Rowe & Merguerian, 2024). These structures contribute to the transient formation of the pronephros, which regresses before the end of

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the first trimester. Anomalies during the pronephros stage may include abnormalities in tubular development, leading to structural defects or complete absence of the pronephros. Common anomalies may involve disruptions in tubular formation, contributing to renal agenesis or hypoplasia at later stages (Hernandez & Dashe, 2018).

The mesonephros emerges as the temporary kidney during mid-gestation, displaying more advanced tubular development compared to the pronephros (Mitchell, 2009). Normal fetal kidneys exhibit developing mesonephric tubules involved in excretory and osmoregulatory functions. Anomalies during the mesonephros stage may involve disruptions in tubular differentiation and organization, leading to structural abnormalities such as dysplasia or cystic changes within the mesonephric tubules (Șorop-Florea et al. 2017). These anomalies may impair kidney function and contribute to renal dysplasia or polycystic kidney disease (Ș Tudorache et al., 2016).

The metanephros represents the definitive kidney, forming during late embryogenesis through reciprocal interactions between the metanephric mesenchyme and the ureteric bud (Chaara et al. 2021). Normal fetal kidneys at this stage exhibit distinct nephron structures, including renal corpuscles, tubules, and loops of Henle, as well as developing collecting ducts and renal vasculature (Rosenblum, Pal, & Reidy, 2017). Anomalies during the metanephros stage may involve disruptions in nephron formation, leading to abnormalities in renal structure and function. Common anomalies include renal dysplasia, characterized by disorganized tissue and abnormal nephron formation, and polycystic kidney disease, marked by the formation of multiple cysts within the kidney parenchyma (Kohl et al., 2022). Additionally, anomalies in fetal kidney morphology at different gestational periods can result in structural defects, functional impairments, and abnormalities in renal development, highlighting the importance of early detection and intervention in managing congenital renal anomalies.

Differences in Morphometric Measurements Between Normal and Anomalous Fetal Kidneys

During the pronephros stage, normal fetal kidneys exhibit rudimentary tubular structures with minimal morphometric measurements. Dimensions such as kidney length, width, and volume are relatively small due to the early stage of development. The length of the fetal kidneys during this period is relatively small, typically ranging from a few millimeters to around 1 cm as pe the normal prenatal ultrasound findings (Rosenblum, Pal, & Reidy, 2017). Anomalous fetal kidneys during the pronephros stage may present with deviations in morphometric measurements, such as reduced kidney size (hypoplasia) or absence of renal structures (agenesis) (Hindryckx & De Catte, 2011). These anomalies may result in significantly smaller dimensions compared to normal fetal kidneys.

As the mesonephros emerges during mid-gestation, normal fetal kidneys exhibit more advanced morphometric measurements. Kidney dimensions such as length, width, and volume increase as tubular development progresses, reflecting the growth and maturation of the temporary kidney. The average length of the kidney is about 1 cm at 12 weeks, and 2.7 cm at 20 weeks. Researches have suggested that FKL is more accurate in estimating GA compared to the other biometric indices in the second half of pregnancy (Everistus et al. 2019). Recent study revealed a significant relationship between Foetal kidney length (FKL) and gestational age GA (Kiridi et al., 2023). Anomalous fetal kidneys during the mesonephros stage may display deviations in morphometric measurements, such as asymmetry, abnormal shape, or altered proportions. These anomalies may result in variations in kidney size and dimensions compared to normal fetal kidneys.

During late embryogenesis, normal fetal kidneys undergo significant morphometric changes as the metanephros forms. Kidney dimensions continue to increase, with marked growth in length, width, and volume, reflecting the development of nephrons, collecting ducts, and renal vasculature. By the end of the third trimester, the average length of the fetal kidneys is approximately 4-5 centimeters or more (Kiridi et al., 2023). Kidney length may vary among individual fetuses, with some exhibiting slightly smaller or larger kidneys based on genetic and environmental factors. Anomalous fetal kidneys during the metanephros stage may exhibit pronounced differences in morphometric measurements compared to normal fetal kidneys. These anomalies may include alterations in size, shape, and proportions, resulting in abnormal kidney dimensions and structural abnormalities such as cyst formation or dysplasia.

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Histological Alterations Observed in Normal vs. Anomalous Fetal Kidneys

Histological staining techniques such as Hematoxylin and Eosin (H&E), Periodic Acid-Schiff (PAS), and immunohistochemistry facilitate visualizing and characterizing these features during normal fetal kidney development (Abdulmajeed Al Drees et al. 2017). During the pronephros stage, histological examination of normal fetal kidneys reveals rudimentary tubular structures surrounded by undifferentiated mesenchyme. Primitive tubular formations with minimal differentiation are observed, reflecting the early stage of kidney development (Ahmet Kalaycioglu et al., 2010). Anomalies during the pronephros stage may result in histological alterations such as disruptions in tubular development, absence of renal structures, or abnormal tissue organization. These anomalies may manifest as structural defects or complete absence of the pronephros, leading to histological abnormalities compared to normal fetal kidneys (Ahmet Kalaycioglu et al., 2010).

As the mesonephros emerges, normal fetal kidneys exhibit more advanced histological features. Developing mesonephric tubules with increasing differentiation and organization are observed, along with primitive glomeruli and interstitial tissue. These structures contribute to the functional capacity of the temporary kidney during mid-gestation. Anomalies during the mesonephros stage may present with histological alterations such as dysplastic changes, cyst formation, or abnormal tissue differentiation within mesonephric tubules. These anomalies may impair kidney function and lead to aberrant histological features compared to normal fetal kidneys (John Curtis Seely, 2017).

During late embryogenesis, normal fetal kidneys undergo significant histological changes as the metanephros forms. Histological examination of kidney reveals distinct nephron structures, including renal corpuscles, tubules, and loops of Henle, as well as developing collecting ducts and renal vasculature (Sudha et al. 2018). These structures demonstrate progressive differentiation and maturation, contributing to the establishment of functional nephrons. Anomalies during the metanephros stage may exhibit pronounced histological alterations compared to normal fetal kidneys (Madrazo-Ibarra & Pradeep Vaitla, 2023). These alterations may include disruptions in nephron formation, dysplastic changes, cystic dilations, fibrosis, or inflammation within the renal parenchyma. These anomalies result in aberrant tissue organization and pathological features, leading to significant differences in histological characteristics compared to normal fetal kidneys.

Clinical Implications and Future Directions

Insights into fetal kidney development are crucial for prenatal diagnosis and management of kidney anomalies. Advancements in imaging techniques like ultrasound and MRI allow non- invasive visualization of fetal kidneys, facilitating early detection of structural abnormalities. Prenatal diagnosis of renal anomalies provides families with vital information, aiding in informed decision-making regarding pregnancy management and interventions.

Future research in fetal kidney development aims to address key areas. Investigating cellular and molecular mechanisms underlying nephrogenesis and renal morphogenesis is vital for understanding normal and abnormal kidney development. There's growing interest in developing novel imaging modalities and biomarkers for early detection and monitoring of fetal kidney abnormalities. Advancements in prenatal imaging and molecular diagnostics hold promise for improving prenatal diagnosis and prognostication of renal disorders.

Conclusion

In conclusion, understanding fetal kidney development has profound clinical implications for prenatal diagnosis, management, and long-term outcomes of renal disorders. Future research endeavors aimed at unraveling the complexities of kidney development and identifying innovative diagnostic and therapeutic approaches are essential for improving the care and outcomes of individuals affected by congenital renal anomalies.

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