

# Original Research Article

## SONOGRAPHIC EVALUATION OF RENAL DIMENSIONS AND VOLUME IN NORMAL PREGNANCY IN BAYELSA STATE, SOUTH-SOUTH, NIGERIA

### ABSTRACT

**Background:** Physiological changes in the renal system lead to important modifications in electrolyte, acid-base balance and renal function. Some of these changes occur in the renal dimensions and volume, and to adequately interpret these changes, physiological changes in pregnancy should be well understood.

**Objective:** To evaluate the renal dimensions and volume, and correlate them with age, parity and trimesters in normal pregnancy in Bayelsa State, Nigeria.

**Study design:** Prospective, descriptive, cross-sectional study.

**Place and Duration of Study:** Departments of Obstetrics and Gynaecology, and Radiology of the two tertiary hospitals in Bayelsa State, Nigeria, from July to December, 2021.

**Materials and Methods:** Sonographic assessments of the renal dimensions and volume in randomly selected 400 normal pregnant women in both tertiary health institutions were done, after obtaining written informed consent from them. Data were entered into a pre-designed proforma, and analysed using Statistical Product and Service Solutions for windows® version 25, SPSS Inc.; Chicago, USA). Results were presented in frequencies and percentages for categorical variables; mean and standard deviation for continuous variables; Student's t-test to compare sample means; and Chi-square for associations.

**Results:** A total of 400 pregnant women were scanned. The mean renal bipolar length, mean antero-posterior diameter and mean renal width were  $10.9 \pm 1.0$  cm,  $4.7 \pm 0.6$  cm and  $6.4 \pm 0.7$  cm respectively. Mean renal volume was  $174.2 \pm 44.8$  cm. Renal volume was highest in the left kidney of women > 35 years ( $186.8 \pm 47.3$  cm<sup>3</sup>), and was lowest ( $162.8 \pm 33.6$  cm<sup>3</sup>) in the right kidney of women < 20 years. The mean values of the renal dimensions and volume increased with parity of the women and trimester of pregnancy.

**Conclusion:** This study produced a mean renal volume in pregnancy for our locality. It was revealed that the renal volume and dimensions were lowest in younger women and highest in older women. The renal volume increased as pregnancy advanced; and with increasing parity.

**Keywords:** Physiological changes, Renal dimensions, Renal Volume, Kidney, Age, Parity, Trimesters.

### 1. INTRODUCTION

Pregnancy is associated with many physiological changes, and the renal system is not left out. These physiological changes in the renal system lead to important modifications in electrolyte, acid-base balance and renal function.[1] The changes in the renal system occur in the kidneys, renal calyces, ureter, urinary bladder and the urethra. To adequately interpret patients' investigation results, these physiological changes in pregnancy should be well understood.

The size of the kidneys increases by 1 – 1.5 cm.[1] This is due to the smooth muscle-relaxing effect of progesterone and relaxin.[1,2] This change may be present till 12 weeks postpartum, and should not be misdiagnosed as hydronephrosis on ultrasound scan.

From early pregnancy, the glomerular filtration rate starts increasing, and increases to about 50% in the second trimester and then reduces to about 20% before term.[1] Renal plasma flow increases to as high as 85% in the second trimester as a result of increase in cardiac output and increased renal vasodilation.[1] These changes should not be misdiagnosed as renal disease in pregnancy. The renal volume increases by about 30% due to increase in renal vascular and interstitial volume, and not as a result of increase in the number of nephrons.[1,2] The various physiological changes in pregnancy return to normal at different times in the puerperium.

During pregnancy, ultrasound measurement of renal dimensions and volume is crucial for routine evaluation, and for follow-up of those with renal disease in pregnancy. This investigative modality is non-invasive, cheap, reliable, easy and safe in pregnancy. Ultrasonography uses sound energy, and has an advantage of not using ionizing radiation, like computed tomographic scan.[2] Therefore, the objective of this study is to evaluate the renal dimensions and volume, and correlate them with age, parity and trimester in normal pregnancy in Bayelsa State, Nigeria.

## **2. MATERIALS AND METHODS**

### **Study area/setting**

This study was conducted at the Departments of Obstetrics and Gynaecology, and Radiology of the two tertiary hospitals in Bayelsa State, Nigeria, over a six-month period, from July to December, 2021. The hospitals are the Federal Medical Centre, Yenagoa and Niger Delta University Teaching Hospital, Okolobiri. The core mandate of these tertiary health institutions revolves around service, training and research, and serve as referral centres for hospitals in Bayelsa State and neighbouring Delta and Rivers States.

### **Study design**

This was a prospective, descriptive, cross-sectional study.

### **Study population**

Pregnant women that presented to the antenatal clinic for their routine antenatal care, and being referred to the Radiology department for their routine obstetric ultrasound scan.

### **Sample size determination**

The sample size for this study was calculated using the formula:

$$n = z^2 pq/d^2 \quad [3]$$

**Where:**

n = minimum sample size

z = normal standard deviation set at 95% confidence limit = 1.96

p = proportion of women in the target population which was 50% (0.5) from a previous study.[4]

q = 1 – p (complementary probability).

d = margin of error = 5% = 0.05

**Calculation:**

$$n = (1.96)^2 \times 0.5 \times 0.5 / (0.05)^2$$

$$n = 3.8416 \times 0.5 \times 0.5 / 0.0025$$

$$n = 0.9604 / 0.0025$$

$$n = 384.16$$

After considering attrition, 'n' was adjusted to 400

**Sampling**

Therefore, 400 normal pregnant women were randomly selected for this study from the antenatal clinic. These participants were recruited consecutively until the sample size was complete. Sonographic assessments of the renal dimensions and volume in these normal pregnant women in both tertiary health institutions were done.

**Selection criteria**

Pregnant women without any known renal or cardiovascular diseases were included in the study. Women with known renal pathologies or medical condition(s) in pregnancy were excluded from the study.

**Data collection**

After a written informed consent, pregnant women that met the inclusion criteria were referred to the Radiology Department for routine obstetric ultrasound scan. The age of the women, parity, gestational age, and blood pressure were obtained and documented. To rule out proteinuria and glycosuria prior to ultrasound scan evaluation, urinalysis was done with the use of dipstick.

A real time, grey scale, ultrasound examination was carried out with the use of the 2012 Philips HD11 machine fitted with a 3.5 MHz curvilinear transducer, with electronic calipers to measure the length, width and thickness of each of the kidneys. The accuracy of the device used was maintained by always adjusting the 'gain' and applying adequate ultrasound gel. This helps to get the best image quality and resolution possible. Sonography was performed in the semi prone/lateral decubitus position in order not to put pressure on the pregnant uterus, and optimise the image quality of the kidneys in the pregnant women. All patients were required to empty their urinary bladder prior to scanning.

All scans were performed posteriorly through the back. The real time grey scale images were frozen following clear identification of the inferior and superior renal poles in the longitudinal plain. The renal

length (L) was taken as the longest distance between the poles using an electronic caliper while the antero-posterior (AP) diameter (thickness) was measured from anterior wall to the posterior wall of the kidney at its mid portion. The renal width (W) was measured on transverse scan and the maximum transverse diameter was taken at the level of the hilum as the renal width. The unit of measurement was centimeter (cm). Using the formula, volume = length x width x breadth x 0.523, the renal volume was calculated.

### **Data Analysis**

Data were entered into a pre-designed proforma, and were analysed using Statistical Package for Social Sciences version 25.0. Results were presented in frequencies and percentages for categorical variables and mean and standard deviation for continuous variables. P-value less than 0.05 was taken as being statistically significant.

### **Ethical consideration**

Ethical approval for this study was duly obtained from the Hospital's Research and Ethics Committee (FMCY/REC/EAF/02/22/564-1153). Written informed consent was obtained from every participant.

Privacy was given to respondents and all information supplied were handled confidentially. In order to ensure confidentiality of the respondents, the hospital case note numbers and study code numbers rather than names were used to identify the participants. Participants were informed that they had the right to decline participation or to withdraw from the study at any time they wished. They were also informed that there were no penalties or loss of benefits for refusal to participate in the study or withdrawal from it.

The ethical considerations in this study were based on the general ethical principles:[5] Respect for persons, beneficence, non-maleficence and justice.

Respect for persons: patients were recruited into the study after adequate information were provided and informed consent obtained. Their rights to participate or to withdraw from the study were respected.

Beneficence: Ethical obligation to maximize benefits and minimize harm or wrong was taken into consideration.

Non-maleficence: No harm was done to any patient.

Justice: All patients were treated equally. Refusal to participate in the study did not alter the management of patients. Data was not manipulated to suit presumed results.

## **3. RESULTS**

### **Demographic and obstetric characteristics**

A total of 400 pregnant women were scanned, their mean age was 28.7 years with a standard deviation of 6.1 years. The modal (30%) age group was 25 – 29 years. Most (39%) of the women were nulliparous women. Parity ranged between 0 and 6 with a median of 1. Above half (56%) of the women were in the second trimester of pregnancy (Table 1).

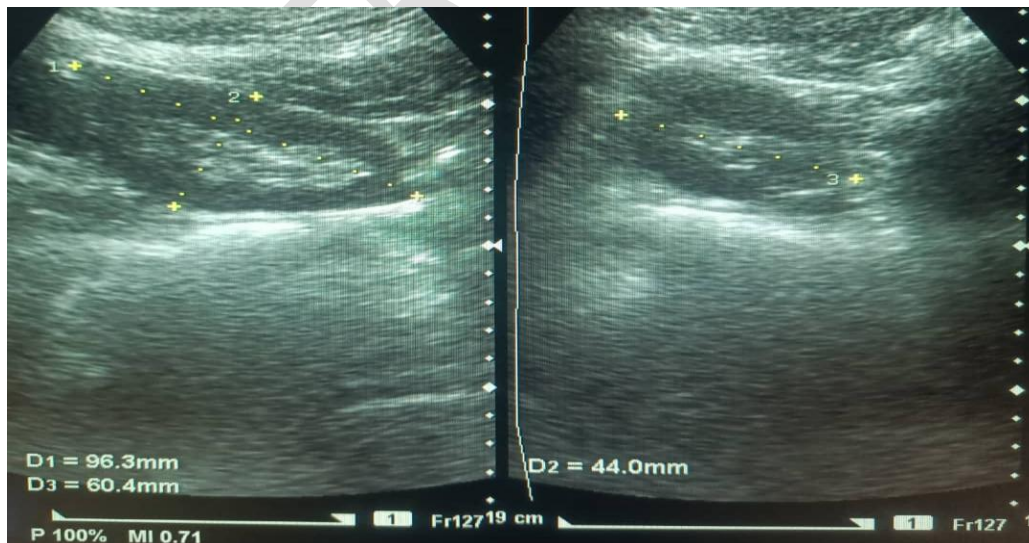
**Table 1: Demographic and obstetric features of the participants**

Characteristics	Frequency N = 400	Percent
<b>Age (years)</b>		
> 20	28	7.0
20 – 24	76	19.0
25 – 29	120	30.0
30 – 34	100	25.0
> 35	76	19.0
<b>Mean Age ± SD in years</b>		28.7 ± 6.1
<b>Parity</b>		
Nulliparous	156	39.0
Primiparous	92	23.0
Multiparous	132	33.0
Grand multiparous	20	5.0
Median Parity	1 (0 – 6)	
<b>Trimester of Pregnancy</b>		
First trimester	28	7.0
Second trimester	224	56.0
Third trimester	148	37.0

**Renal dimensions and volume in Pregnancy**

The mean ± SD renal bipolar length, mean antero-posterior diameter and mean renal width were 10.9 ± 1.0 cm, 4.7 ± 0.6 cm and 6.4 ± 0.7 cm respectively (Figure 1, Table 2). Mean renal volume was 174.2 ± 44.8 cm.

The right and left kidneys were averagely of the same dimension with very minimal difference in variations. The student's t-test that explored the differences between the dimensions of the right and left kidneys showed no significant difference ( $p > 0.05$ ).



**Figure 1: Sonogram showing renal dimensions.**

**Table 2: Comparing dimensions and volume of the right and left kidneys in the pregnant women**

Renal parameter	Renal Dimensions – Mean ± SD* (cm)			T-test	p-Value
	Both Kidneys	Right Kidney	Left Kidney		
Renal Bipolar length	10.9 ± 1.0	10.9 ± 1.0	10.9 ± 1.1	0.14	0.887
AP <sup>†</sup> Diameter	4.7 ± 0.6	4.7 ± 0.6	4.7 ± 0.5	1.08	0.282
Renal Width	6.4 ± 0.7	6.5 ± 0.7	6.3 ± 0.7	1.17	0.243
Renal Volume	174.2 ± 44.8	174.4 ± 46.9	174.0 ± 42.9	0.05	0.956

\*SD – Standard deviation; <sup>†</sup>AP – Anterio-posterior.

### Relationship between age of respondents, and renal dimensions and volume

The mean renal bipolar length in the right kidney was lowest (10.7 ± 0.9 cm) among participants who were aged 20 – 24 years and highest (11.1 ± 1.1 cm) among pregnant women aged > 35 years. For the left kidney, a similar trend was noticed, participants aged 20 – 24 years also had the lowest dimensions (10.8 ± 0.7 cm) while those aged > 35 years had mean renal bipolar length of 11.1 ± 1.1 cm (Table 3).

Mean renal antero-posterior diameter for the right and left kidneys was 4.5 cm for women aged > 35 and < 20 years respectively. Women aged 20 – 24 years had the highest renal antero-posterior diameter in the right kidney (4.7 ± 0.5 cm) and left kidney (4.9 ± 0.5 cm) (Table 3).

Renal volume was highest in the left kidney of women > 35 years (186.8 ± 47.3 cm<sup>3</sup>), and was lowest (162.8 ± 33.6 cm<sup>3</sup>) in the right kidney of women < 20 years. All the renal dimensions measured were not significantly different (p > 0.05) in relation to the age of the participants (Table 3).

**Table 3: Relationship between renal dimensions and volume, and the age of pregnant women**

Renal Parameter	Frequency N = 400 (%)	Right Kidney		Left Kidney	
		Mean ± SD (cm)	F-Statistic (p-Value)	Mean ± SD (cm)	F-Statistic (p-Value)
<b>Renal bipolar length</b>					
> 20 years	28 (7.0)	10.9 ± 1.0	0.32 (0.865)	11.0 ± 0.8	0.53 (0.713)
20 - 24 years	76 (19.0)	10.7 ± 0.9			
25 - 29 years	120 (30.0)	11.0 ± 0.9			
30 - 34 years	100 (25.0)	10.9 ± 1.1			
> 35 years	76 (19.0)	11.1 ± 1.2			
<b>Renal antero-posterior diameter</b>					
< 20 years	28 (7.0)	4.6 ± 0.4	0.33 (0.855)	4.5 ± 0.4	1.32 (0.267)
20 - 24 years	76 (19.0)	4.7 ± 0.5			
25 - 29 years	120 (30.0)	4.7 ± 0.6			
30 - 34 years	100 (25.0)	4.6 ± 0.7			
> 35 years	76 (19.0)	4.5 ± 0.7			
<b>Renal width</b>					
< 20 years	28 (7.0)	6.3 ± 0.7	0.60	6.4 ± 0.8	1.04

20 - 24 years	76 (19.0)	6.6 ± 0.6	(0.664)	6.4 ± 0.6	(0.389)
25 - 29 years	120 (30.0)	6.5 ± 0.7		6.2 ± 0.7	
30 - 34 years	100 (25.0)	6.5 ± 0.8		6.3 ± 0.6	
> 35 years	76 (19.0)	6.3 ± 0.8		6.3 ± 0.7	
<b>Renal volume</b>					
< 20 years	28 (7.0)	162.8 ± 33.6	0.22	164.8 ± 36.5	1.01
20 - 24 years	76 (19.0)	174.6 ± 37.7	(0.929)	177.8 ± 27.7	(0.406)
25 - 29 years	120 (30.0)	177.4 ± 37.1		163.5 ± 36.6	
30 - 34 years	100 (25.0)	177.7 ± 59.7		176.6 ± 55.3	
> 35 years	76 (19.0)	174.4 ± 46.9		186.8 ± 47.3	

### Relationship between renal dimensions and volume, and obstetric features

#### Parity of respondents and renal dimensions and volume

The mean renal bipolar length, antero-posterior diameter and width increased gradually from the primiparous to grand multiparous women in both the right and left kidneys. This gradual change in renal dimensions as parity changes was however not statistically significant ( $p > 0.05$ ). The mean values for all the renal dimensions were highest in grand multiparous women in both the left and right kidneys. The mean ± SD bipolar length was  $11.3 \pm 1.3$  cm and  $11.7 \pm 1.2$  cm; mean antero-posterior diameter was  $4.7 \pm 0.3$  cm and  $5.0 \pm 0.4$  cm; mean renal width was  $6.8 \pm 0.8$  and  $6.9 \pm 0.8$ , and mean renal volume was  $188.7 \pm 42.0$  cm<sup>3</sup> and  $208.5 \pm 35.2$  cm<sup>3</sup> for right and left kidney respectively (Table 4).

**Table 4: Relationship between renal dimensions and volume, and the parity of pregnant women**

Renal parameter	Frequency N = 400 (%)	Right Kidney		Left Kidney	
		Mean ± SD (cm)	F-Statistic (p-Value)	Mean ± SD (cm)	F-Statistic (p- Value)
<b>Renal bipolar length</b>					
Nulliparous	156 (39.0)	10.9 ± 0.9	0.44 (0.728)	10.9 ± 0.9	1.31 (0.275)
Primiparous	92 (23.0)	10.8 ± 1.0		10.8 ± 1.2	
Multiparous	132 (33.0)	11.0 ± 1.1		11.0 ± 1.0	
Grand multiparous	20 (5.0)	11.3 ± 1.3		11.7 ± 1.2	
<b>Renal antero-posterior diameter</b>					
Nulliparous	156 (39.0)	4.5 ± 0.5	0.40 (0.752)	4.6 ± 0.5	0.59 (0.619)
Primiparous	92 (23.0)	4.6 ± 0.7		4.7 ± 0.7	
Multiparous	132 (33.0)	4.7 ± 0.7		4.8 ± 0.6	
Grand multiparous	20 (5.0)	4.7 ± 0.3		5.0 ± 0.4	
<b>Renal width</b>					
Nulliparous	156 (39.0)	6.3 ± 0.6	1.09 (0.356)	6.3 ± 0.8	1.99 (0.120)
Primiparous	92 (23.0)	6.4 ± 0.8		6.1 ± 0.8	
Multiparous	132 (33.0)	6.6 ± 0.7		6.5 ± 0.5	
Grand multiparous	20 (5.0)	6.8 ± 0.8		6.9 ± 0.8	
<b>Renal volume</b>					

Nulliparous	156 (39.0)	166.6 ± 39.4	0.89 (0.467)	168.5 ± 40.9	1.63 (0.187)
Primiparous	92 (23.0)	172.7 ± 49.9		168.1 ± 52.8	
Multiparous	132 (33.0)	182.6 ± 53.5		179.3 ± 36.7	
Grand multiparous	20 (5.0)	188.7 ± 42.0		208.5 ± 35.2	

### Trimester of pregnancy, and renal dimensions and volume

The mean values of the renal dimensions and volume measured in relation to the trimesters of pregnancy followed the same trend as parity of the women. The renal dimensions increased from the first trimester to the third trimester of pregnancy, with the mean values highest in the third trimester of pregnancy in both the right and left kidneys.

The mean renal bipolar length in the first trimester of pregnancy for the right and left kidneys was 10.2 ± 0.6 cm and 10.3 ± 0.8 cm respectively, while in the third trimester of pregnancy the mean bipolar length was 11.3 cm ± 1.1 cm and 11.1 ± 0.2 cm respectively (Table 5). Mean renal volume of the right kidney was 136.9 ± 24.7 cm<sup>3</sup>, 168.5 ± 41.1 cm<sup>3</sup> and 190.3 ± 52.8 cm<sup>3</sup> in the first, second and third trimesters respectively and the renal volume of the left kidney was 146.8 ± 25.0 cm, 172.6 ± 40.3 cm and 181.2 ± 47.7 cm respectively (Table 5).

The mean difference in the values of the dimensions of the left kidney had no statistically significant difference ( $p > 0.05$ ), but the differences observed in the dimensions were significant statistically in the renal bipolar length (f-test=4.29;p-0.016), renal antero-posterior diameter (f-test=3.33;0.040) and renal volume (f-test=5.19;p-0.007). A Post-hoc test done revealed that third trimester values of renal bipolar length and renal volume in the right kidney were significantly different from the values of these measurements in pregnant women in the first and second trimesters, whereas in the left kidney, significant difference exists between the first and the third trimester for only the renal antero-posterior diameter (Table 5).

**Table 5: Relationship between renal dimensions and volume, and the trimester of pregnancy**

Renal Parameter	Frequency N = 400 (%)	Right Kidney		Left Kidney	
		Mean ± SD	F-Statistic (p-Value)	Mean ± SD	F-Statistic (p-Value)
<b>Renal bipolar length<sup>a</sup></b>					
First Trimester	28 (7.0)	10.2 ± 0.6	4.29 (0.016)	10.3 ± 0.8	1.73 (0.182)
Second Trimester	224 (56.0)	10.8 ± 0.9		10.9 ± 1.0	
Third Trimester	148 (37.0)	11.3 ± 1.1		11.1 ± 0.2	
<b>Renal antero-posterior diameter<sup>b</sup></b>					
First Trimester	28 (7.0)	4.2 ± 0.5	3.33 (0.040)	4.5 ± 0.3	1.19 (0.310)
Second Trimester	224 (56.0)	4.6 ± 0.6		4.7 ± 0.5	
Third Trimester	148 (37.0)	4.8 ± 0.6		4.8 ± 0.6	

<b>Renal width</b>					
First Trimester	28 (7.0)	6.2 ± 0.4	2.36 (0.099)	6.1 ± 0.4	0.79 (0.453)
Second Trimester	224 (56.0)	6.4 ± 0.6		6.3 ± 0.7	
Third Trimester	148 (37.0)	6.7 ± 0.8		6.4 ± 0.8	
<b>Renal volume<sup>a</sup></b>					
First Trimester	28 (7.0)	136.9 ± 24.7	5.19 (0.007)	146.8 ± 25.0	2.01 (0.140)
Second Trimester	224 (56.0)	168.5 ± 41.1		172.6 ± 40.3	
Third Trimester	148 (37.0)	190.3 ± 52.8		181.2 ± 47.7	

<sup>a</sup>Post-hoc test revealed a significant difference in between the first, second and third trimester values.

<sup>b</sup>Post-hoc test revealed a significant difference only between the first and third trimester values.

#### 4. DISCUSSION

Physiological changes in pregnancy lead to changes in the function of the kidneys, which include, and not limited to increase in the glomerular filtration rate, renal dimensions and renal volume. These changes therefore, return to their pre-pregnancy states after a normal pregnancy. Being able to understand and interpret these changes are key in the successful management of pregnant women.

Our study revealed a mean renal volume in pregnancy of 174.4 ± 46.9 for the right kidney and 174.0 ± 42.9 for the left kidney, with an average of 174.2 ± 44.8 for both kidneys. These were not statistically significant. Our values are higher than the 141.85 ± 41.08 (right kidney); 163.44 ± 51.33 (left kidney) reported by Ugboma et al., [2] in South-South, Nigeria, the 147.75 ± 1.87 (right kidney); 172.53 ± 2.13 (left kidney) reported by Ugochinyere et al., [6] in Enugu, South-East Nigeria, and the 105.77 ± 27.29 (right kidney); 104.23 ± 28.18 (left kidney) reported by Kamble et al., [7] in Central India. Maternal renal volume has been associated with the size of babies.[8] As the maternal renal volume increases, the size of the baby also increases.[8] The presence of big baby may be associated with difficult delivery, laceration of the genital tract, need for Caesarean section, and longer postpartum stay in hospital.

Our study revealed that the renal volume and dimensions were lowest in younger women and highest in older women. However, this difference was not statistically significant. In non-pregnant women, the renal volume and dimensions decrease with age. [8–10] This is due to parenchymal reduction as one advances in age.

In this study, the renal volume and dimensions increased as parity increased. Various studies are in tandem with this finding. [2,7,11,12] This increase in our study was however, not statistically significant ( $p > 0.05$ ). This agrees with the findings from previous studies, where there was no statistical correlation between renal dimensions and increase in parity. [2,7,11,12] The reason for this is that the renal volume

and dimensions return to normal after every pregnancy, and there is therefore, no additional increase in the size of the kidneys in subsequent pregnancies.

Renal volume gradually increased from the first trimester to the third trimester. This finding is in line with the reports of previous studies, [2,6,7] and it results from the steady increase in glomerular filtration rate, renal plasma flow and hyperfiltration that occurs as pregnancy advances, which is maximal in the third trimester. Our study revealed no significant difference between the renal volume of the right and left kidneys. This finding is in consonance with the report of Okoye et al., [13] in non-pregnant patients in Enugu, South-East Nigeria, but different from the reports of Ogunmoroti et al., [14] in Ile-Ife, South-West Nigeria, Kolade-Yunusa et al., [15] in Abuja, North-Central Nigeria and Emamian et al., [9] in Denmark, where the volume of the left kidney was more than that of the right kidney.

In our study, the antero-posterior diameter, renal length and width increased as pregnancy advanced. These dimensions also increased as the parity of the women increased. This is expected, because as the renal volume increases, the renal dimensions are also expected to increase. Our finding is in agreement with the report by Edevbie et al., [4] in Benin, South-South Nigeria. The size of the left kidney is slightly bigger (about 1.5 cm longer) than the right. [1] This may be related to the fact that the left renal artery is shorter and straighter than the right renal artery. Therefore, there is increased blood supply to the left kidney which increases its volume, and consequently, its size. Another plausible reason for the slightly bigger left kidney is that the spleen (smaller than the liver) lies superior to the left kidney, while the liver lies superior to the right kidney. Therefore, this relationship of the spleen to the left kidney gives it relatively more space to grow. Our study however, did not show any significant difference in the dimensions of the right and left kidneys. This corresponds to the report of Okoye et al. [13]

#### **STRENGTH AND LIMITATION**

The strength of this study lies in the fact that it is a prospective study where women with normal pregnancies were recruited. This removed confounding variables, like medical conditions in pregnancy, which would have affected the measurements of renal volume and dimensions.

This study is limited by the fact that it is a hospital-based study. Therefore, it may not reflect what is obtainable in the general population of pregnant women.

#### **CONCLUSION**

This study produced a mean renal volume in pregnancy for our locality. It was revealed that the renal volume and dimensions were lowest in younger women and highest in older women. The renal volume increased as pregnancy advanced; and with increasing parity.

## ETHICAL APPROVAL

The research work was examined and approved by the Hospitals' Research and Ethics Committee.

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