"ROLE OF TRANSABDOMINAL ULTRASONOGRAPHY IN THE EVALUATION OF ADRENAL GLAND SIZE IN NEONATES- A ONE YEAR HOSPITAL BASED COMPARATIVE STUDY"

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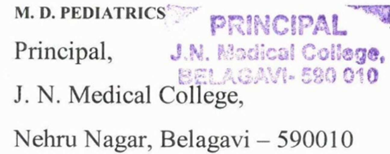

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LIST OF ABBREVIATIONS

NICU	NEONATAL INTENSIVE CARE UNIT
IVC	INFERIOR VENA CAVA
ACTH	ADRENO CORTICOTROPHIC HORMONE
HPA	HYPOTHALAMIC PITUITARY AXIS
CRH	CORTICOTROPIN RELEASING HORMONE
ACE	ANGIOTENSIN CONVERTING ENZYME
AT II	ANGIOTENSINOGEN II
ENaC	EPITHELIAL SODIUM CHANNELS
DHEA	DEHYDROEPIANDROSTERONE
CT	COMPUTED TOMOGRAPHY
CEUS	CONTRAST ENHANCED ULTRASOUND
MRI	MAGNETIC RESONANCE IMAGING
APW	ABSOLUTE PERCENTAGE WASHOUT
RPW	RELATIVE PERCENTAGE WASHOUT
PET-CT	POSITRON EMISSION TOMOGRAPHY- COMPUTED TOMOGRAPHY
HU	HOUNSEFIELD UNIT

ABSTRACT

BACKGROUND AND OBJECTIVES:

Adrenal glands are small paired structures situated superior to the kidneys on both sides, hence are also termed as suprarenal glands. They are responsible for the production and synthesis of various important hormones like cortisol, mineralocorticoids and sex steroids. These hormones have a very important role to play for the proper functioning of the adult human body. In fetal life and in neonates, these hormones are responsible for the proper and adequate growth and development of the neonates.

Limited number of studies are available which establish a normal size range of the adrenal glands in neonates and how various comorbidities affect the size of the adrenal gland. Adrenal gland size can be used as a predictor in fetal and neonatal life to predict various complications that a baby might face later in life.

The study was conducted with the objective of studying the size of adrenal glands using transabdominal sonography in various stressed and non-stressed neonates and establish normal range of adrenal gland sizes in both groups and also to establish a relationship between various stressors that the neonate might have during fetal life with its effect on adrenal gland size.

MATERIALS AND METHODS:

One year comparative study was conducted in the Department of Radiodiagnosis at KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi.

102 babies were included in the study, 51 normal healthy neonates and 51 neonates with various maternal and fetal comorbidities. These included babies present in the NICU and babies visiting the Department of Radiodiagnosis for various purposes.

After taking written informed consent from the parents, the babies underwent transabdominal sonography for evaluation of adrenal gland size.

The size of the adrenal glands were then used to establish a normal range of adrenal gland size amongst stressed and non-stressed neonates. Correlation between the stressors and the adrenal gland size was also studied.

RESULTS

In the present study, 52 cases were males and 50 cases were females. Right adrenal gland was visualized using transabdominal ultrasonography in all the neonates, however the left adrenal gland could be visualized in only 23.5 % babies with the mean volume of right adrenal gland being 1269.27 +/- 530.97 mm^3 and the mean volume of left adrenal gland being 800.71 +/- 176.17 mm^3. In this study, 51 neonates with comorbidities were studied and the volume of the adrenal gland in these neonates was compared with the adrenal gland volume of normal healthy neonates. The adrenal gland volume in preterm neonates (p value 0.001) , low birth weight neonates (p value 0.026) , small for gestational age neonates (p value 0.04), neonates whose mothers had pre eclampsia (p value 0.001), neonates with perinatal asphyxia (p value 0.015) and neonates with meconium stained liquor (p value 0.001) had a significantly higher adrenal gland volume as compared to normal healthy neonates.

Amongst stressed neonates, babies with a single stressor had a lesser adrenal gland volume as compared to neonates with progressively increasing number of stressors with the mean adrenal gland volume in a neonate with a single stressor being 1345.82 +/- 624.287 mm^3 while the adrenal gland volume in neonates with four stressors was found to be 2532.00 mm^3.

INTERPRETATION AND CONCLUSION:

Adrenal gland size can be easily evaluated using transabdominal ultrasonography in neonates owing to the reduced amount of abdominal fat in these children making visualization of adrenal gland easier. The size of adrenal gland varies significantly between normal healthy neonates and neonates with fetal or maternal comorbidities with the volume being higher in stressed neonates.

Volume of right adrenal gland was found to be higher than that of the left adrenal gland. The adrenal gland volume in stressed neonates was also found to be higher as compared to non-stressed neonates.

Amongst stressed neonates, low birth weight neonates, small for gestational age neonates, preterm neonates, neonates with perinatal asphyxia, neonates with meconium stained liquor and neonates whose mothers had pre eclampsia had a significantly higher adrenal gland volume. The volume of the adrenal gland also increased significantly depending upon the number of stressor the babies were exposed to.

Keywords: Transabdominal ultrasonography, suprarenal glands, stressed neonates, adrenal gland volume

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INTRODUCTION

The adrenal glands (also known as suprarenal glands) are small glands located on the top of both kidneys and are responsible for the production of few important hormones- aldosterone, corticosteroids and sex steroids. They play a very important role in the development and growth of the fetus and the survival of the infant after birth, apart from other important functions.

Adrenal gland is composed of adrenal cortex and adrenal medulla, with the cortex being responsible for the production of steroid hormones and the medulla being responsible for the production of catecholamines, epinephrine and norepinephrine. The adrenal gland of a neonate is composed of a fetal zone and a definitive zone, in which the fetal zone constitutes the majority portion of the adrenal cortex at birth[1]. There have been various studies which have shown that the fetal zone undergoes involution whereas there is development of the definitive zone immediately post natally.[2,3] These changes start during the fetal life and can be influenced by a variety of feto-maternal factors.[4] Since the fetal zone is responsible for the production of adrenal androgens, its involution results in a quick reduction in the levels of androgens.[5,6,7,8]

The decrease in the postnatal weight and size of the adrenal gland can be divided into two phases: rapid phase which starts from birth & ends at second week of life and followed by a slower phase. The decrease in the weight correlates with the decrease in the volume of fetal zone and the number of cells in it.[9]

The adrenal gland volume significantly decreases during the first two weeks of life following which it remains fairly constant. The changes occurring during the fetal life as well as post natally help in determining the functioning of the adrenal gland.[10]

In spite of various advances in the field of neonatology and ultrasonography, the diagnosis and treatment of various pathologies of the adrenal gland as well as checking for its optimal functioning poses a major challenge.

There is a lack of radiological data in terms of the various changes in the size and shape of the suprarenal glands immediately post natally and if these factors play a significant role in predicting the outcome of the neonate.

AIM OF THE STUDY:

- To measure adrenal gland size of neonates using high resolution 2D ultrasound and compare the sizes between neonates with comorbidities and normal healthy neonates.

OBJECTIVES OF THE STUDY:

- To establish the volume range of adrenal glands in neonates with no known maternal or fetal comorbidities
- To establish a volume range of adrenal glands in neonates with maternal or fetal or both comorbidities
- To establish a correlation between the volume of adrenal gland in neonates and presence or absence of comorbidities
- To establish a correlation between adrenal gland volume and the number of comorbidities in the neonate

REVIEW OF LITERATURE

Adrenal glands, also known as suprarenal glands form a part of the endocrine system. They are paired organs and are usually asymmetrical.

GROSS ANATOMY:

The adrenal glands are located in the lateral retroperitoneum, above the superior pole of the kidneys. They are surrounded by the perirenal fascia of the corresponding sides.

The right adrenal gland is triangular in shape while the left adrenal gland is crescent shaped. On cross section, the right adrenal gland can be either linear, comma or V shaped while the left adrenal gland can be triangular or Y shaped. The right adrenal gland is located slightly lower as compared to the left adrenal gland and is more medial to the spine as compared to the left.

The adrenal glands are located in the middle of the abdominal cavity, being situated in front of the 12th rib on right side and in front of 11th and 12th ribs on left side.

Each gland has a body and two limbs: medial and lateral limbs and consist of two portions: outer cortex and inner medulla. The cortex is dark yellow in colour with a fine granular surface and is firm in consistency. The medulla appears as a friable mass and is dark red in colour.

The size of adrenal gland is larger in neonates and infants, as compared to adults, being 1/3rd the size of the kidneys. The maximum width of the right adrenal gland is 6.0 mm while the maximum width of the left adrenal gland is 8.0 mm. Each

adrenal gland has an approximate weight of 6.0 gm. The average dimensions of the adrenal gland in adults is approximately 5.0 x 3.0 x 0.6 cm.

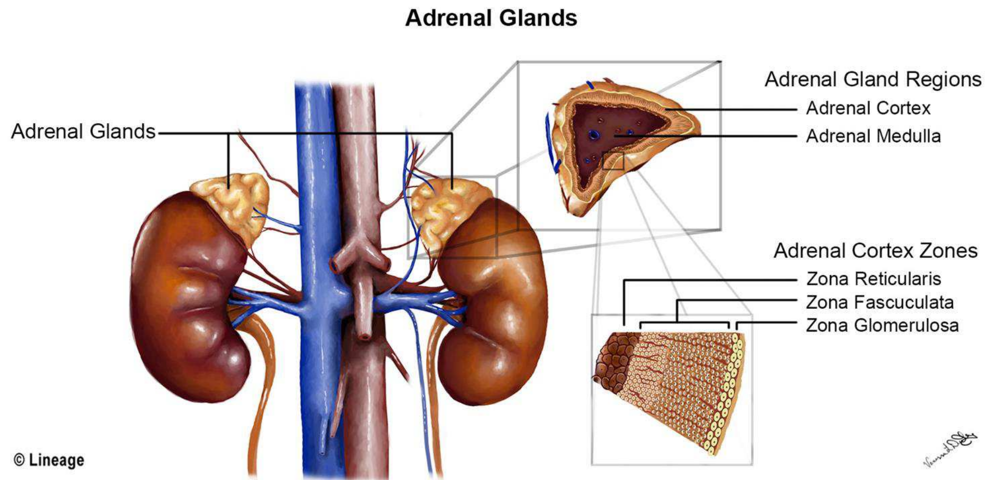


Figure 1: Anatomy of adrenal glands

RELATIONS

The relations of adrenal glands are important from a surgical point of view and helps in deciding the approach to a procedure and the important structures that a surgeon might encounter while performing the planned procedure.

For each adrenal gland, the dorsal and lateral relations are almost similar.

Dorsal and lateral relationships

The adrenal glands are in contact with the superior part of posterior abdominal wall via the perirenal fat and pararenal fascia and lie in close proximity with the crus of diaphragm on both sides. These separate the glands from the pleural reflections and 11th & 12th ribs.

Ventral relations

The right adrenal gland on its ventral and lateral aspect is overlapped by the peritoneum between liver, kidney and hepatic flexure of colon. Therefore the right adrenal gland can be adequately exposed surgically by dissecting this peritoneal layer. [11]Ventrally and medially, the right adrenal gland is situated behind the IVC which separates it from the epiploic foramen superiorly and from the duodenum & head of pancreas inferiorly.

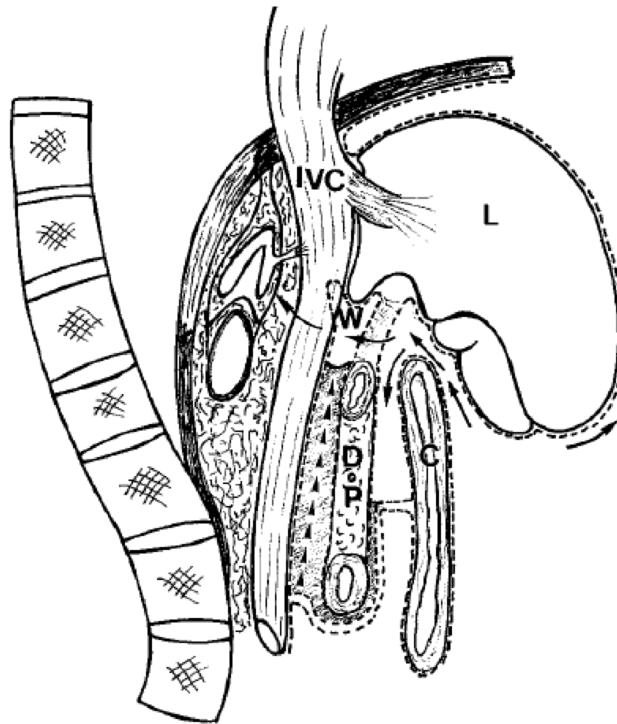


Figure 2: Ventral relations of right adrenal gland

It is difficult to surgically approach the left adrenal gland as compared to the right from the ventral aspect as it is attached to the viscera of the dorsal mesogastrium by the spleen and body of pancreas. The pancreatic body separates the gland from the lesser sac and the stomach.

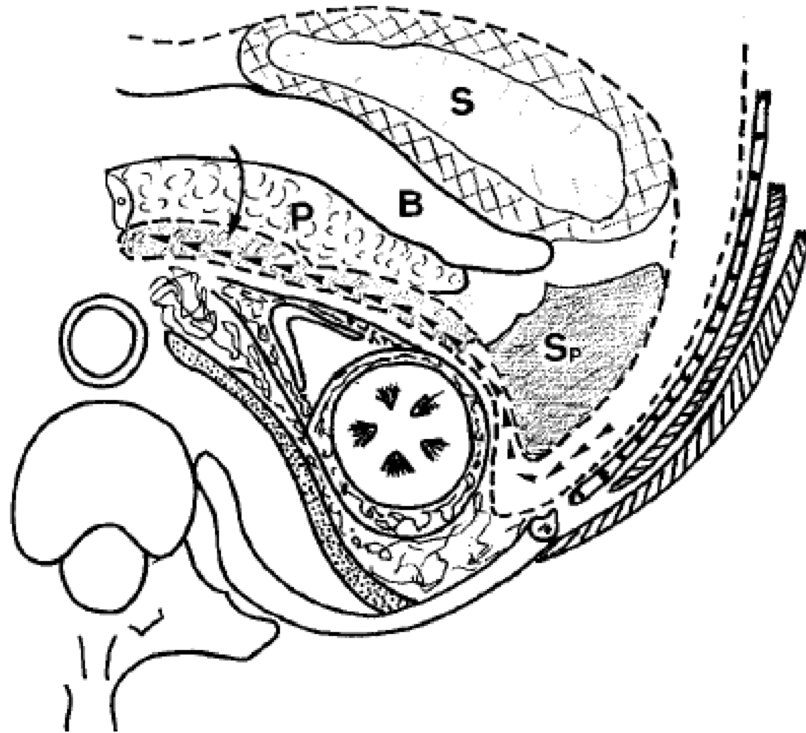


Figure 3: Ventral relations of left adrenal gland

Medial relationships

The right adrenal gland lies posterior to the IVC while the left adrenal gland lies anterior to the origin of the celiac trunk, being separated from the aorta by a distance of 7.0 mm. The left adrenal gland also lies in close proximity to the left renal vessels.[12]

ARTERIAL SUPPLY

The adrenal glands receive arterial supply from three sources:

1. Superiorly, arising from the inferior phrenic artery
2. Medially, arising as a branch of abdominal aorta
3. Inferiorly, via branches of renal artery

The cortex and medulla are supplied by the capillary network. As a result, steroid hormones present in the blood, pass through the medulla which might be favorable in the transformation of norepinephrine to epinephrine.

VENOUS DRAINAGE

The adrenal veins arise from the hilum and drain into the IVC on right side and into the left renal vein on left side after joining with the left inferior phrenic vein.

During surgical procedures, vascular control of the adrenal vein is easier on the left side as compared to the right because the adrenal vein on the left side is longer (approximately measuring 30.0 mm), joins with the left inferior phrenic vein and courses obliquely downwards to enter the left renal vein. The right adrenal vein is shorter in length (approximately measuring 6.0 mm) and directly enters the posterior aspect of IVC, thus increasing the risk of vascular complications.

Double adrenal veins can also be seen in few cases.[13]

LYMPHATIC DRAINAGE

The lymphatic vessels of both adrenal glands follow three main pathways of drainage:

1. Ending in the lateral aortic nodes (right or left) , anterior to the diaphragmatic crura and proximal to the celiac trunk
2. Ending in the lateral aortic nodes (right or left) proximal to the junction of IVC and left renal vein
3. Ending in the thoracic duct or lymph nodes in the posterior mediastinum by piercing through the diaphragmatic crura.

Only the cortex of the adrenal gland is drained by the lymphatic vessels, not the medulla. Thus, corticoids may be found in the thoracic duct.

INNERVATION

The presynaptic sympathetic fibers arising from the thoracic splanchnic nerves synapse directly with chromaffin cells.

The post synaptic fibers arising from the celiac, aorticorenal and renal ganglia innervate the surrounding vessels.

EMBRYOLOGY

Fetal pituitary gland secretes ACTH which is the prime regulator of the growth, functioning and development of the adrenal gland during fetal life.[14]

The cortex of the adrenal gland develops from the coelomic mesoderm of the urogenital ridge while the medulla develops from neural crest tissue.[15]

During fetal development, around 5th week, mesothelial cells from the posterior abdominal wall, lying between the root of mesentery of bowel and developing urogenital ridge proliferate and form the primitive adrenal cortex. [16]During the 6th week, mesothelial cells further surround the adrenal cortex resulting in the formation of adult or definitive cortex.[17] During 8th week of fetal development, there is separation of the cortical mass from the remainder mesothelial cells and it gets surrounded by connective tissue.[18]

The medulla of the adrenal gland develops from the neural crest tissue (also known as chromaffin cells) in the sympathetic ganglion at the celiac plexus level. There is seen migration of these chromaffin cells towards the adrenal cortex during 7th

week of fetal development. With time, they cause invasion of the medial aspect of the cortex along the central vein to reach its central position.

Medulla does not get completely encapsulated till later stages of fetal development. The differentiation of the adrenal cortex into the three zones occurs by 3 years of age. At birth, the neonate has only zona glomerulosa and zona fasciculata. The development of zona reticularis takes place later during the neonatal period.

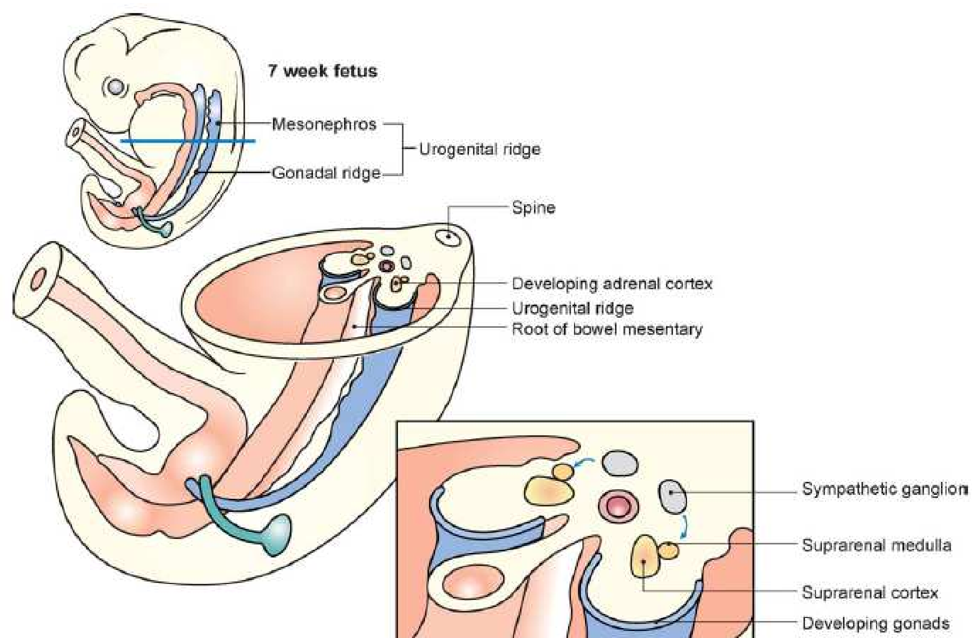


Figure 3: Embryological development of 7 week fetus

HISTOLOGY

Histologically, the adrenal cortex is divided into three zones which also have different physiological functions.[19]

1. Zona glomerulosa- outer, thin zone
2. Zona fasciculata- thick, middle zone
3. Zona reticularis- thin, innermost zone

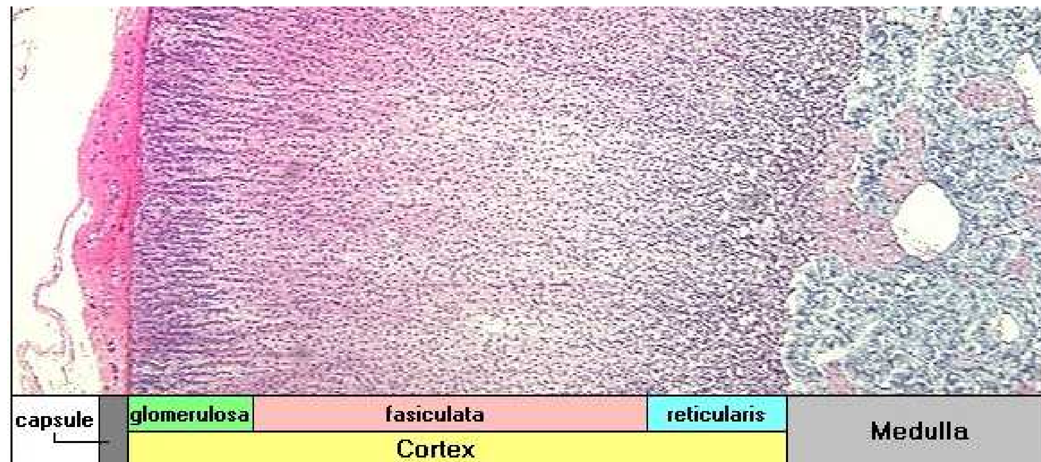


Figure 5: Histology of adrenal gland

Adrenal cortex

Cells in zona glomerulosa appear columnar in shape arranged in the form of irregular cords.

Cells in zona fasciculata (spongiocytes) are polyhedral in shape with a foamy appearance due to presence of abundant lipid droplets within them.[20] They are arranged in straight cords radiating towards the medulla. This layer also contains prominent cortical capillaries.

In zona reticularis, cells are arranged in cords projecting in different directions and anastomosing with each other.

Adrenal medulla

Chromaffin cells are the most abundant cells in the adrenal medulla. These basophilic cells are columnar in shape and have granular cytoplasm due to hormone containing granules. They are centered around the medullary veins. The medulla contains significant number of preganglionic sympathetic fibers and sympathetic ganglion cells.

PHYSIOLOGY

The adrenal cortex is responsible for the production of steroid hormones like glucocorticoids, mineralocorticoids and adrenal androgens while the medulla is responsible for the production of catecholamines, epinephrine and norepinephrine.

Every layer in the cortex produces steroid hormones using cholesterol as the precursor with CYP11A1 catalyzing the rate limiting step.[21] Zona glomerulosa produces mineralocorticoids, zona fasciculata glucocorticoids and adrenal androgens are produced by zona reticularis.

Hypothalamic-Pituitary-Adrenal (HPA) axis:

HPA axis helps in the production of glucocorticoids and adrenal androgens from zona fasciculata and zona reticularis.

The paraventricular neurons of hypothalamus, in response to circadian rhythm or stress, result in secretion of Corticotropin releasing hormone (CRH).[22] CRH leads to synthesis and release of ACTH from the anterior pituitary gland by binding to its receptors. ACTH is responsible for the synthesis of glucocorticoids.

Renin-Angiotensin-Aldosterone System:

There are two primary regulators of aldosterone production:

1. Renin-Angiotensin-Aldosterone system
2. Potassium levels

In response to reduced renal perfusion as sensed by the juxtaglomerular apparatus, there is seen production and release of renin which results in conversion of

angiotensinogen to angiotensin I which is further converted to angiotensin II by angiotensin converting enzyme (ACE) in the lungs. AT II results in synthesis of aldosterone in zona glomerulosa.[23]

Adrenal medulla and sympathetic nervous system:

Secretion of epinephrine and norepinephrine from the adrenal medulla is controlled by the sympathetic nervous system.

Function:

1. **Mineralocorticoids**

   Mineralocorticoids i.e. corticosterone, 11- deoxy corticosterone and aldosterone increase reabsorption of sodium and excretion of potassium by acting on the kidneys. Sodium reabsorption in turn results in increased water reabsorption causing increase in the blood pressure due to raised effective circulating volume. This is achieved via an increase in the synthesis of epithelial sodium channels (ENaC) and sodium-potassium ATPase in the distal nephron on the principal cells.[24]

   Mineralocorticoids also cause excretion of hydrogen ions at the intercalated cells.

2. **Glucocorticoids**

   Cortisol activates the HPA axis and its level increases in response to stress. It causes increased expression of genes that help in regulating the immune system, metabolism, cardiovascular function, reproduction and growth. It increases the sensitivity of vascular smooth muscle cells for vasoconstrictors like catecholamines and inhibits the release of vasodilators like nitrous oxide,

thus helping in maintaining blood pressure. It also causes suppression of the immune system. Cortisol is also responsible for increasing gluconeogenesis and reducing peripheral glucose uptake, thus counteracting the effect of insulin.

3. **Androgens**

In the gonads and peripheral tissue, the adrenal androgens, predominantly DHEA gets converted to active sex steroids. Circulating DHEA-sulfate is the best for measuring excess of adrenal androgens. They play an important role in puberty in both men and women and are also the major source of testosterone in females. Increase in the amount of adrenal gland androgen synthesis is responsible for adrenarche.[25] Adrenal androgens do not have a significant role in adult males as the testes are the main source of testosterone in them.

4. **Catecholamines**

Epinephrine and norepinephrine help in executing the fight-or-flight response of sympathetic nervous system. They act on the alpha-1 receptors on the vascular smooth muscles causing an increase in the blood pressure. They cause an increase in the serum glucose levels by activation of glycogenolysis and causing increased secretion of glucagon through beta-2 receptors and reduced secretion of insulin using alpha-2 receptors.

VARIANT ANATOMY

1. Lying down adrenal sign:

It is an imaging sign indicating renal agenesis or ectopia where the ipsilateral adrenal gland appears as if it was lying down on the psoas muscle posteriorly.[26] Because of its linear configuration, it is also called as discoid, straight, elongated or pancake adrenal gland.

It is an important sign for confirmation of renal agenesis where the kidney is not visualized during antenatal ultrasound. It is also useful during post natal scans to differentiate it from post nephrectomy status.

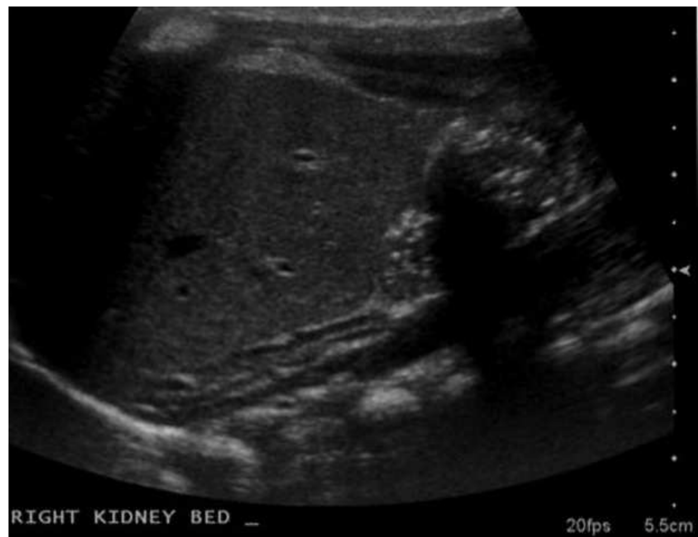


Figure 6: Lying down adrenal gland

2. Horseshoe adrenal gland:

It is also called as butterfly, fused or midline adrenal gland and is a very rare anomaly. In this case, there is a single adrenal gland which is present in the midline with the fused portion either passing between aorta and IVC or behind the aorta.[27]

It is associated with Ivemark syndrome or asplenia syndrome, neural tube defects, renal anomalies, diaphragmatic defects and vertebral anomalies.

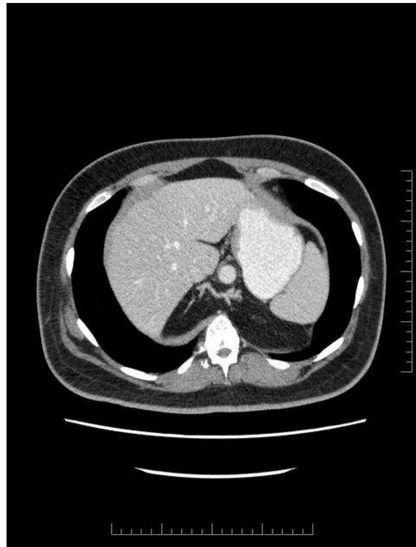


Figure 7: Horseshoe adrenal gland

ADRENAL IMAGING

Radiology plays a very important role in imaging various adrenal lesions and plays a complimentary role to functional and hormonal evaluation. It can also reduce the amount of invasive sampling done in patients for diagnosis of various adrenal lesions. The importance of imaging in adrenal gland lesions is for differentiating benign from malignant lesions, metastatic and non- metastatic lesion and for providing a definitive diagnosis.

1. **Ultrasonography:**

   Ultrasound is a widely available modality for diagnosis of variety of abdominal pathologies and is usually the first line imaging modality. Adrenal glands can be very accurately imaged in infants and neonates using ultrasonography. However, in adults the adrenal glands may be obscured due to obesity or bowel gas. Although imaging of adrenals is not easy using ultrasound, it has a very important role in incidentally detecting adrenal masses, monitoring changes in an already

diagnosed adrenal lesion while the patient is on treatment for the same or for imaging other abdominal structures within the same setting while at the same time being cost effective and causing nil to minimal radiation exposure to the patients.[28,29]

High frequency transducer probes are used for imaging of adrenal glands in neonates because the size of the adrenal gland is large relative to the body of the neonate.[30]

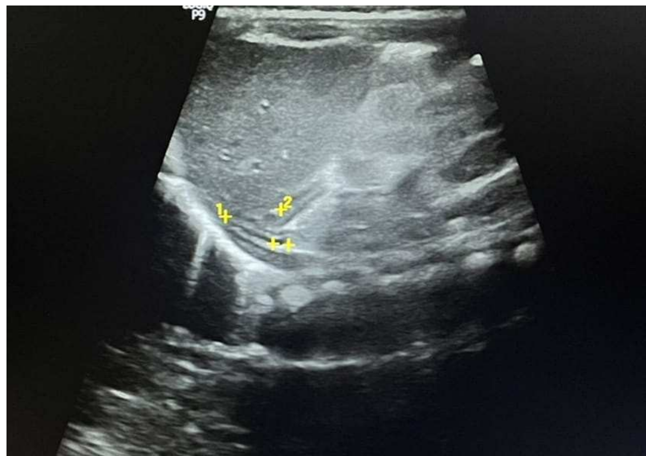


Figure 8: Ultrasonography of adrenal gland

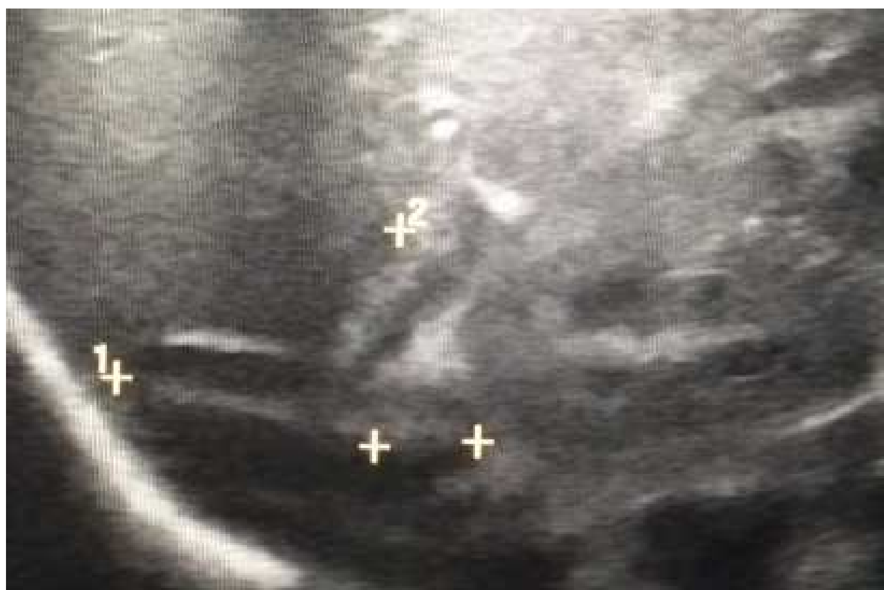


Figure 9: Zoomed image of ultrasound of adrenal gland

2. **Contrast enhanced ultrasound:**

Contrast enhanced ultrasonographic evaluation is particularly useful for the diagnosis of various adrenal masses. The sensitivity and specificity for diagnosing adrenal malignancies using contrast enhanced ultrasound is almost comparable to that of multiphase CT scan. CEUS should be advocated as the primary imaging modality for suspected adrenal lesions as it reduces the radiation exposure to the patient while at the same time reduces the cost and time required to perform an MRI examination.

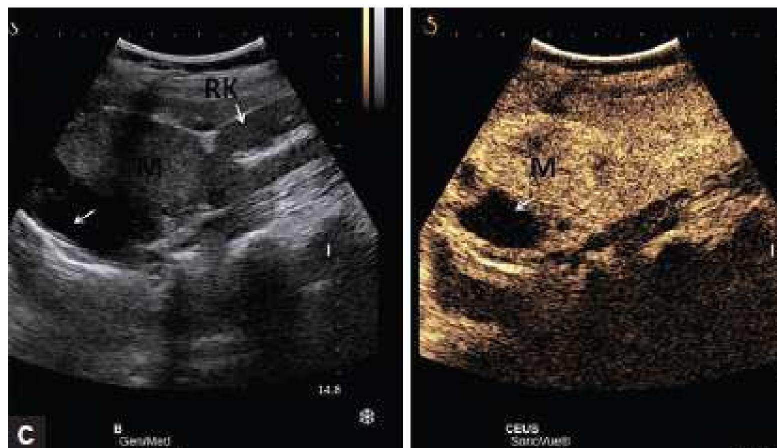


Figure 10: CEUS of adrenal gland showing a mass

3. **Computed tomography:**

Computed tomography (CT) is the mainstay for imaging adrenal glands. Normally, adrenals are viewed as inverted V or Y shaped structures situated antero-superiorly to bilateral kidneys. They can be easily identified due to large amount of retroperitoneal fat surrounding the glands.

The CT protocol used for adrenal imaging consists of a baseline unenhanced scan followed by a post-contrast scan in the porto-venous phase (60-70 seconds) and then a delayed scan at 15 minutes.[31] This imaging protocol is based on the fact that both adrenal adenomas and adrenal malignancies show rapid uptake of

contrast, however malignant lesions show slower washout as compared to adenomas.

Using these scans, Absolute percentage washout (APW) (Attenuation in delayed scan/ Attenuated in unenhanced scan X 100) and Relative percentage washout (RPW) (Attenuation in delayed scan/ Attenuation in enhanced scan X 100) can be calculated for characterization of adrenal lesions.

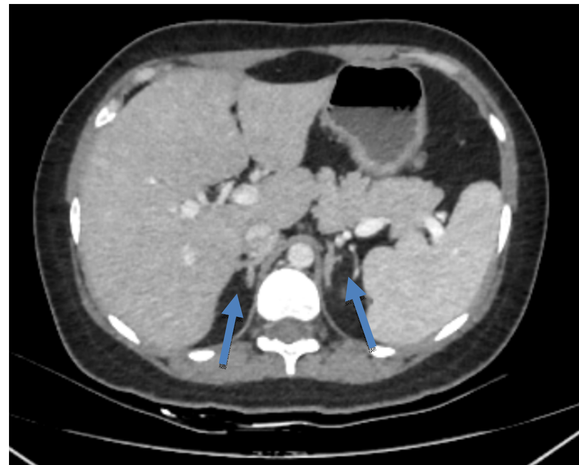


Figure 11: CT of adrenal gland

4. **Magnetic Resonance Imaging (MRI):**

   MRI is used for very specific indications in cases of adrenal imaging. It is used only when contrast enhanced CT scan is contraindicated as it does not provide a significant difference in spatial resolution as compared to CT scan. Adrenal glands show low to intermediate signal intensity on both T1 and T2 weighted images.

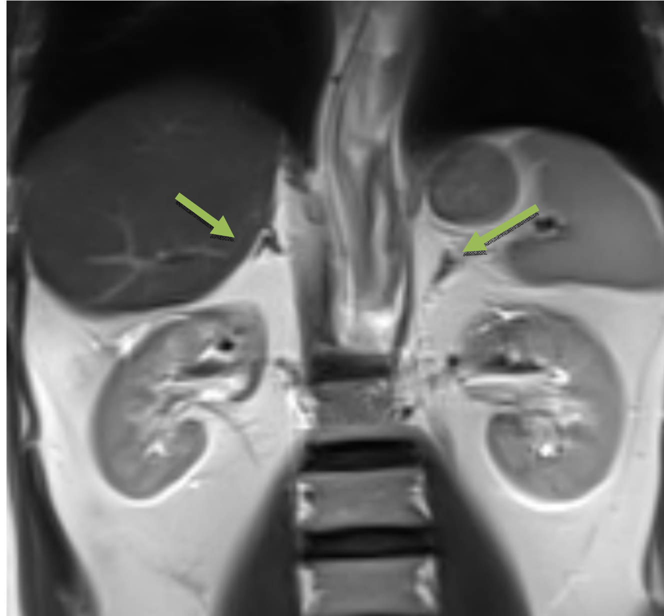


Figure 12: MRI of adrenal gland

5. **Positron Emission Tomography (PET):**

   PET-CT, with the combined advantages of PET as well as CT helps in assessing the functional nature of the adrenal lesion while at the same time measuring the Hounsefield unit (HU) values of the lesion using unenhanced CT scans. By assessing a lesion both qualitatively and quantitatively, benign and malignant lesions can be differentiated with high sensitivity (98-100%) and specificity (93-98%).[32,33]

DEVELOPMENTAL ABNORMALITIES OF THE ADRENAL GLAND

Accessory or ectopic adrenal tissue and adrenal heterotopia are the two common abnormalities of development of adrenal gland.

Accessory adrenal gland tissue, also known as adrenal rest tissue happens when a portion of the tissue breaks off during the process of adrenal gland development. These ectopic tissues may contain only the adrenal cortex or both adrenal cortex and

medulla depending on the stage of development when the tissue separated from the adrenal gland. Such tissues are seen in nearly 50 % of neonates, however majority of them regress and persist only in 1% of the adult population.[34,35,36] The accessory adrenal glands usually have no significance but they become important if they undergo malignant transformation.[37,38,39]

Adrenal heterotopia is a rare developmental disorder and occurs when an accessory tissue of adrenal gland gets incorporated into adjacent organs like the liver or kidney as a result of incomplete separation of cells of primitive adrenal cortex from the coelomic mesothelium. [40,41,42,43] Rarely death may occur as a result of excision of the heterotopic adrenal tissue due to adrenal insufficiency.

IMPORTANCE OF ADRENAL GLAND SIZE EVALUATION IN FETUS AND NEW BORNS

The adrenal gland maturation has been closely linked to the use of steroids during the antenatal period, parturition as well as the levels of oxygen after birth.[44]

In a study conducted by Arkadiusz Krzyzanowski et al in 2014, it was found that fetal adrenal gland size and onset of preterm labour had a direct relationship.[45] During a normal pregnancy the relationship between the fetal adrenal zone and the whole gland remains constant throughout the pregnancy, however any disruption in the same is an indicator of preterm labour.

Normal parturition is initiated by the activation of fetal HPA (Hypothalamic-pituitary-adrenal axis) and a cross talk between the endocrine signaling pathways of the placenta and the fetal adrenal gland. This results in an increased production of dehydroepiandrosterone-sulfate by the fetal zone of the adrenal gland. As a result,

there is an increase in the size of the fetal adrenal gland, predominantly due to an increase in the size of the fetal zone of the adrenal gland. Thus measurement of adrenal gland size can be an important predictor of preterm birth.[46]

Use of steroids in the antenatal period can cause variations in the steroid profile which might affect the outcome of a neonate in the postnatal period.[47]

However, it has been observed that administration of steroids like betamethasone to preterm neonates, although causes a reduction in the production of endogeneous 17 hydroxyprogesterone and cortisol, but the size of adrenal gland remains unaffected.[48]

Few of the very low birth weight infants show episodes of hypotension in the immediate post natal period which do not show any response to vasopressors and volume expanders, however show immediate response to corticosteroids. This is termed as glucocorticoid-responsive circulatory collapse which can be associated with adrenal insufficiency. [49,50] Very premature infants fail to produce adequate quantities of cortisol. The fetal zone of the adrenal gland cannot produce cortisol. It is responsible for the production of majority of adrenal androgens. Therefore, such babies show an increase in the size of the adrenal gland with a significantly enlarged fetal zone.

Ultrasound evaluation of adrenal gland size in neonates can serve as an adjunct to various laboratory parameters like serum cortisol or low dose serum ACTH levels.[51]

In babies with Trisomy 18, the length of the adrenal gland is significantly lower than those with normal healthy neonates consistent with hypoplasia of adrenal gland.[52]

The volume of adrenal gland in fetuses during a normal gestation correlates well with the gestational age as well as the estimated fetal weight of the fetus. Thus normal growth of the fetus can be assessed by measuring the size of the adrenal glands.[53]

REVIEW OF STUDIES

The study conducted by Oppenheimer et al in 1983 found the adrenals to be located in the suprarenal position having a 'V' or 'Y' shaped configuration in the sagittal and coronal projection.[54]

Elaine Scott et al, in their study conducted in 1990 found that in adrenal glands the central hyper echogenic area surrounded by a hypo echogenic zone becomes difficult to distinguish with age as the gland becomes smaller and differences in echogenicity become less marked.[55]

In a study conducted by V Klingmuller et al, ultrasound was performed on 205 healthy new borns with the aim of determining the adrenal gland volume. The study revealed that the adrenal gland undergoes an involution of 67% by the end of first week of life.[56]

Tijen Karsli et al, in their study in 2017 studied 80 appropriate for gestational age infants and calculated the adrenal volume. They found it to be related to gestational age, pre eclampsia and intraventricular hemorrhage.[4]

Shigeo Iijima in 2018 studied 350 neonates within the first 3 hours of life and found the adrenal gland area to be correlating with gestational age.[49,50]

M Bronshtein conducted a study in which pregnant females between 12 to 17 weeks of gestation underwent transvaginal sonography and the length of adrenal gland of the fetus and the ratio between the length of adrenal and kidney were determined. The study showed that there was a linear increase in the length of the adrenal gland and a decrease in the adrenal to renal ratio in healthy fetuses during these gestational periods. Also, mothers who had history of being treated for congenital adrenal hyperplasia had fetuses with a smaller sized adrenal gland.[57]

METHODOLOGY

7.1 Source of data:

A one year Hospital based comparative study will be conducted in the department of Radio-diagnosis, on the neonates who meet the inclusion criteria, from January 2021 to December 2021 at KLE's Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

7.2 Method of collection of data:

(a) Study design: Hospital based comparative study

(b) Sample size:

The minimum sample size was calculated using the following formula:-

$$N = \left[\frac{Z\alpha + Z\beta}{c}\right]^2 + 3$$

Given r = 0.35[2]

$$c = 0.5 \times \ln\left[\frac{(1+r)}{(1-r)}\right]$$

c= 0.365

For α= 10%, $Z\alpha$ = 1.68

β = 20%, $Z\beta$ = 0.84

N= 51

51 babies with comorbidities and 51 normal healthy neonates will be examined for this study.

(c) All babies will be evaluated clinically and then undergo an ultrasonography of the abdomen to look for adrenal gland size using MINDRAY M7 Premium machine The adrenal gland size will then be correlated with the various clinical data obtained.

(d) **Sampling method**: Universal sampling

(e) DURATION: One year – between January 2021 to December 2021

(f) Inclusion criteria:

Neonates admitted to the NICU immediately after birth or neonates coming to the department of radio diagnosis between the age group of day 1 to day 4.

(g) Exclusion criteria:

1. Major congenital anomalies
2. Parental refusal of participation

(h) Proposed method of Statistical data analysis:

For the continuous quantitative variables mean and standard deviation will be calculated. For the purpose of comparison if the data is divided into two groups with respect to certain qualitative characteristic, the continuous variables will be compared using suitable tools of statistics like unpaired student's t test.

Discrete variables will be represented by median. Suitable graphs will be used to depict the comparison.

The categorical data will be expressed in terms of rates, ratios and percentages. The association between the outcome, clinical and demographic characteristics will be tested using Chi-square test, test of proportion or Fisher’s exact test.

When we compare two independent groups having quantitative values, generally student's unpaired t test is applied. For discrete variables nonparametric tests will be used.

Apart from the above suitable tools like ANOVA, correlation, regression etc., will be used according to the need.

For all the tests the value of p less than 5% (0.05) will be considered significant.

(I) METHODOLOGY: A written informed consent will be obtained from all the parents of the subjects. The above mentioned study population who meet the inclusion criteria will be subjected to ultrasonography of abdomen to look for adrenal gland on MINDRAY M7 Premium machine equipped with a 7.5–12 MHz high frequency linear array transducer. The neonates will be examined on real-time two-dimensional grey-scale and the images will be stored securely on a portable drive. Clinical details of the mother and their neonates will be obtained. The adrenal gland size measured by ultrasound will then be compared with the clinical details to look for correlation. Amongst stressed neonates (neonates with fetal or materal comorbidities) correlation between adrenal gland size and the number of stressors will be established.

Follow up: No

EQUIPMENT: MINDRAY M7 Premium machine

RESULTS

Table 1: Age wise distribution of cases

AGE	NO. OF CASES	PERCENTAGE
DAY 1	11	10.80%
DAY 2	16	15.70%
DAY 3	16	15.70%
DAY 4	59	57.80%
TOTAL	102	100%

In this study, a total of 102 neonates between days 1 to 4 were studied. Out of these neonates 11 (10.8%) were day 1 old neonates, 16 (15.7%) were days 2 and 3 old and 59 neonates (57.8%) were 4 day old.

Table 2: Sex wise distribution of cases

SEX	NO. OF CASES	PERCENTAGE
FEMALE	50	49%
MALE	52	51%
TOTAL	102	100%

Out of the 102 cases studied, 50 were females (49%) and 52 were males (51 %).

Graph1: Pie chart showing sex wise distribution of cases

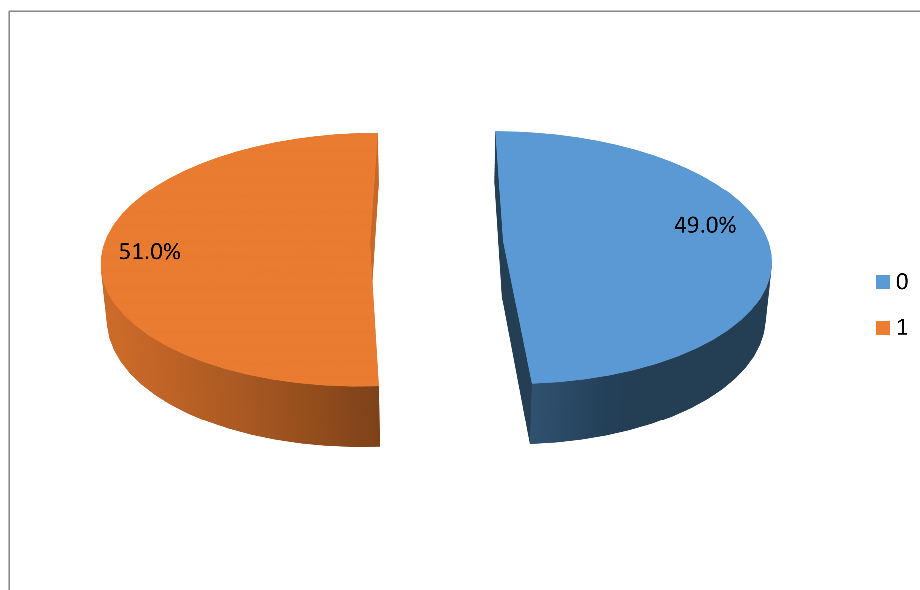


Table 3: Visibility of left adrenal gland on sonography

VISIBILITY OF LEFT ADRENAL GLAND	NO OF CASES	PERCENTAGE
YES	24	23.5%
NO	78	76.5%
TOTAL	102	100%

All neonates who fulfilled the inclusion criteria of the study underwent ultrasonographic examination of the abdomen to look for the adrenal gland size. Out of 102 neonates, the left adrenal gland was visualized only in 24 cases (23.5 %) while the right adrenal gland was visualized in all the cases that were examined.

Graph 2: Pie chart showing visualization of left adrenal gland on sonography

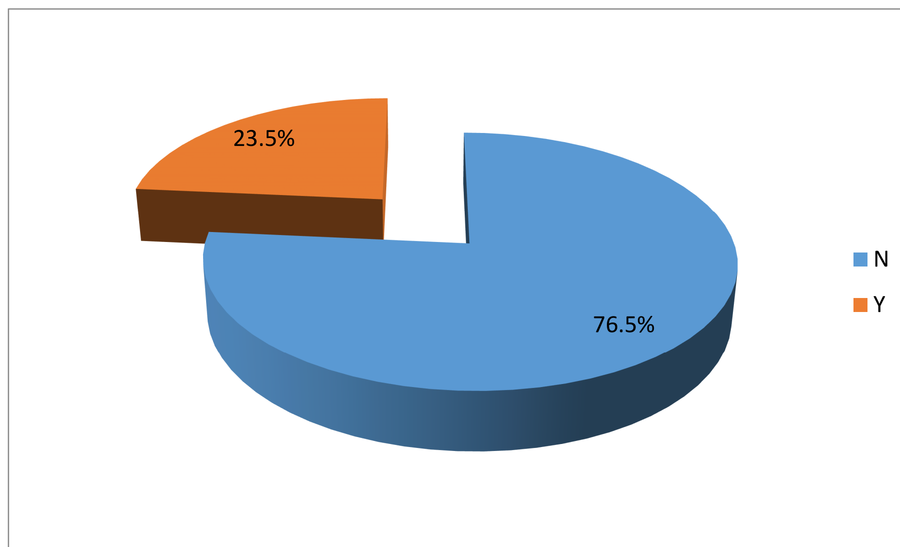


Table 4: Comparison of volumes of right and left adrenal gland

ADRENAL GLAND	NO OF CASES	MEAN VOLUME	STD DEVIATION
RIGHT	102	1269.27	530.97
LEFT	24	800.71	176.17

In the present study, out of 102 neonates who were studied, the right adrenal gland could be visualized in all 102 cases while the left adrenal gland could be visualized in only 24 cases.

The mean right adrenal gland volume was found to be 1269.27 +/- 530.97 mm^3 while the mean left adrenal gland volume was found to be 800.71 +/- 176.17 mm^3.

Table 5: Comparison of adrenal gland volume in male and female neonates

SEX	NO OF CASES	MEAN VOLUME	STD DEVIATION
MALE	52	1284.27	520.48
FEMALE	50	1253.68	546.52

In the present study, out of a total 102 neonates studied, 52 were males and 50 were females. The mean adrenal gland volume in male neonates was found to be 1284.27 +/- 520.48 mm^3 while mean adrenal gland volume in females was found to be 1253.68 +/- 546.52 mm^3.

Graph 3: Bar graph comparing adrenal gland volume in males and females

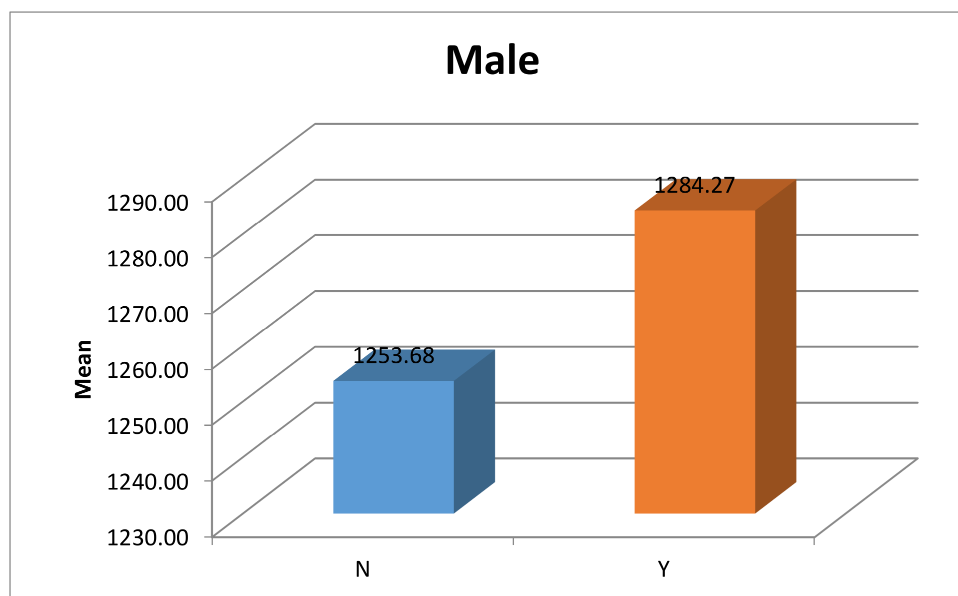


Table 6: Various comorbidities observed in stressed neonates in the study

COMORBIDITY	NO OF CASES	PERCENTAGE
PRETERM	32	31.4%
LOW BIRTH WEIGHT	11	10.8%
HYPOCALCEMIA	2	2.0%
SEPSIS	2	2.0%
SGA	2	2.0%
PRE ECLAMPSIA	9	8.8%
MECONIUM STAINED LIQUOR	8	7.8%
FGR	2	2.0%
PERINATAL ASPHYXIA	1	1.0%
HYPOXIC ISCHEMIC ENCEPHALOPATHY	3	2.9%
RESPIRATRORY DISTRESS	4	3.9%
CONGENITAL INFECTIONS	2	2.0%
PROM	4	3.9%
MATERNAL HYPOTHYROIDISM	2	2.0%
OLIGOHYDRAMNIOS	1	1.0%

The present study consisted of a total of 102 neonates out of which 51 were normal neonates while the remaining 51 were neonates with any fetal or maternal, peripartum or postpartum complications. Amongst the stressed neonates, 32 babies were preterm babies (31.4 %) while 11 (10.8 %) were low birthweight. 8 neonates (7.8 %) had meconium stained liquor, 1 (1.0%) had perinatal asphyxia, 3 neonates (2.9%) had hypoxic ischemic encephalopathy and 4 (3.9%) had congenital infections. 2.0% of the babies had hypocalcemia, sepsis, were small for gestational age or had fetal growth restriction. Mothers of 9 neonates (8.8%) had pre eclampsia, 4 (3.9%) had premature rupture of membranes, 2 (2.0%) had maternal hypothyroidism while 1 (1.0%) had oligohydramnios.

Graph 4: Bar graph depicting various comorbidities amongst stressed neonates

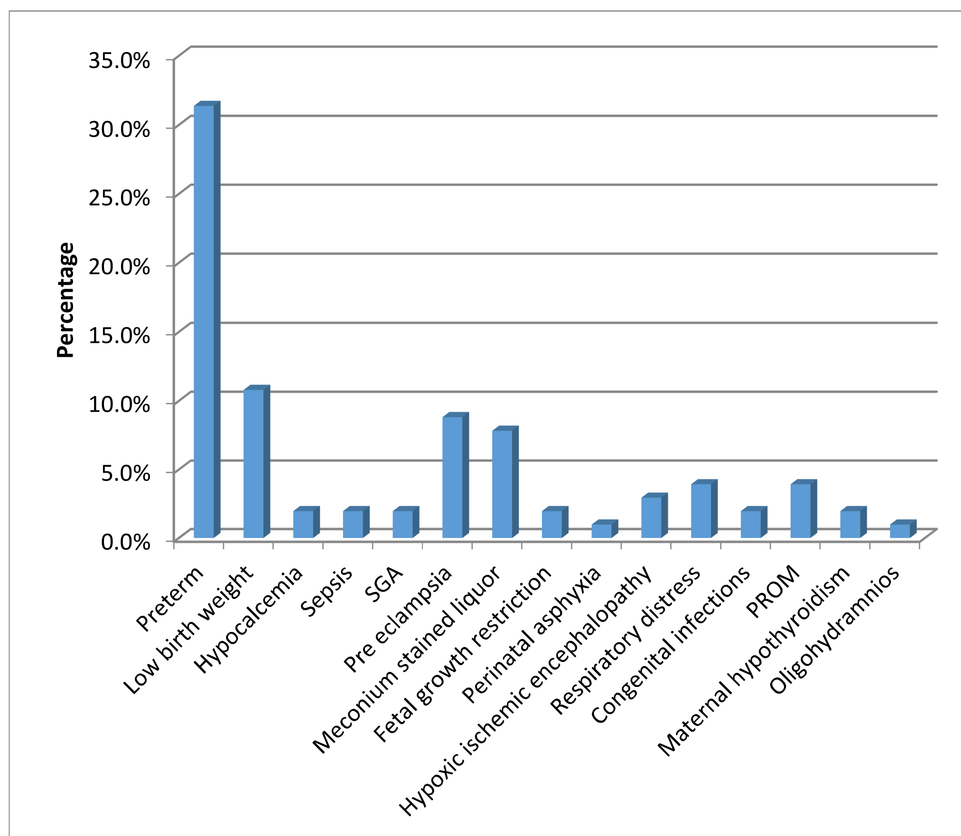


Table 7 : Comparison of adrenal gland volume in stressed and non-stressed neonates

STRESSORS	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	51	1034.67	324.98	0.00
YES	51	1503.88	592.96	

In the present study, out of a total of 102 neonates studied, 51 neonates had no stressors while 51 neonates had 1 or more stressors. The mean adrenal gland volume in non-stressed neonates was found to be 1034.67 +/- 324.98 mm^3 and the mean adrenal gland volume in stressed neonates was found to be 1503.88 +/- 592.96 mm^3.

Graph 5: Bar graph comparing adrenal gland volume in stressed and non-stressed neonates

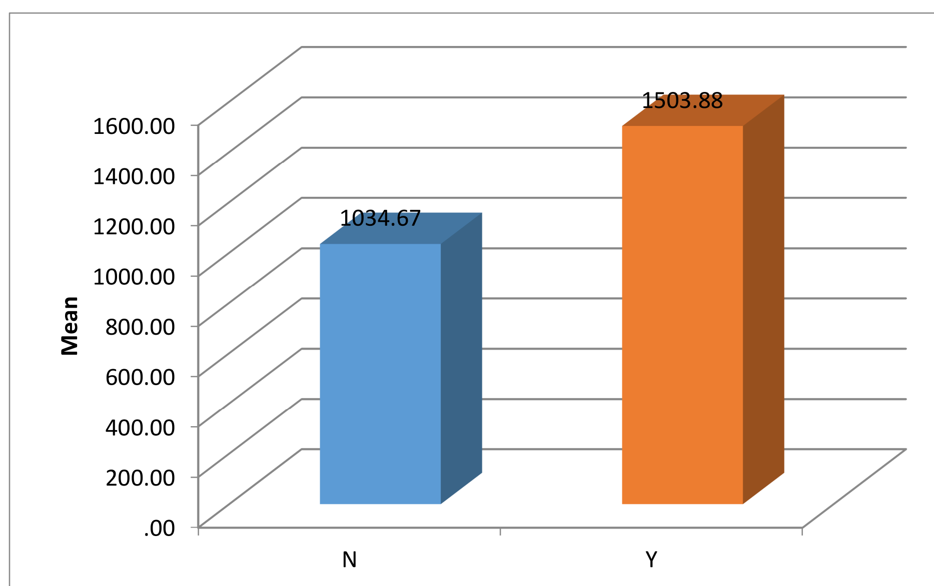


Table 8: Table depicting total number of comorbidities in neonates

NO. OF COMORBIDITIES	NO. OF CASES	PERCENTAGE
0	51	50.0%
1	28	27.5%
2	13	12.7%
3	9	8.8%
4	1	1.0%
TOTAL	102	100.0%

Amongst the 51 neonates with comorbidities, 28 neonates (27.5%) had only 1 stressor, 13 of them (12.7%) had two different comorbidities, 9 (8.8%) had three different comorbidities while 1 baby (1.0%) had four different comorbidities.

Graph 6: Pie chart depicting the number of stressors in the neonates

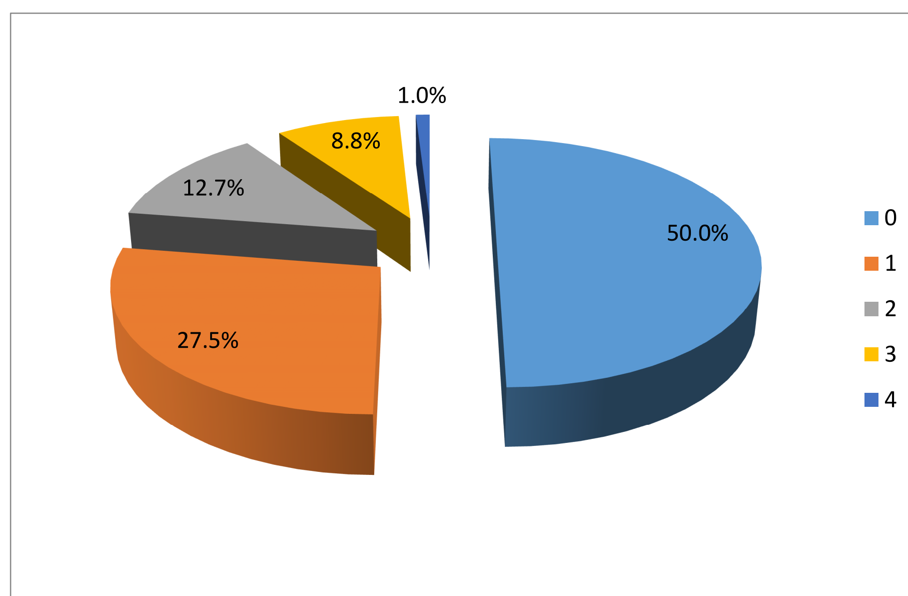


Table 9: Comparison of adrenal gland volume between normal neonates and preterm neonates

PRETERM	NO. OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	70	1129.84	469.73	0.001
YES	32	1180.53	529.88	

Amongst the 102 neonates observed in the present study, 32 were preterm neonates. The mean volume of the adrenal gland in preterm neonates was found to be 1180.53 +/- 529.88 mm^3. On comparing this volume with the volume of normal healthy neonates, the adrenal gland volume in preterm babies was found to be higher than normal babies with a p value of 0.001 indicating that the data was statistically significant.

Graph 7: Bar graph depicting adrenal gland volume in preterm babies as compared to normal babies

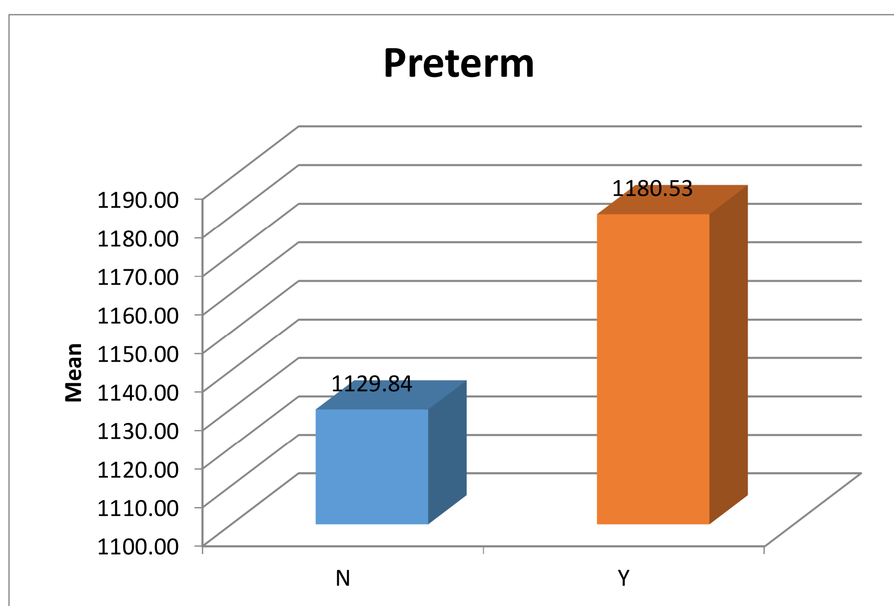


Table 10: Comparison of adrenal gland volume between normal neonates and neonates with low birth weight

LOW BIRTH WEIGHT	NO. OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	91	1228.7	536.67	0.026
YES	11	1604.91	341.31	

In the present study, a total of 11 low birth weight babies were studied. The mean adrenal gland volume in the low birth weight group was 1604.91 +/- 341.31 mm^3. On comparing this volume with the adrenal gland volume of normal healthy neonates, the volume of the adrenal gland in low birth weight babies was found to be higher in the babies with low birth weight with the p value of 0.026 making this data statistically significant.

Graph 8: Bar graph comparing adrenal gland volume between low birth weight babies and normal healthy neonates

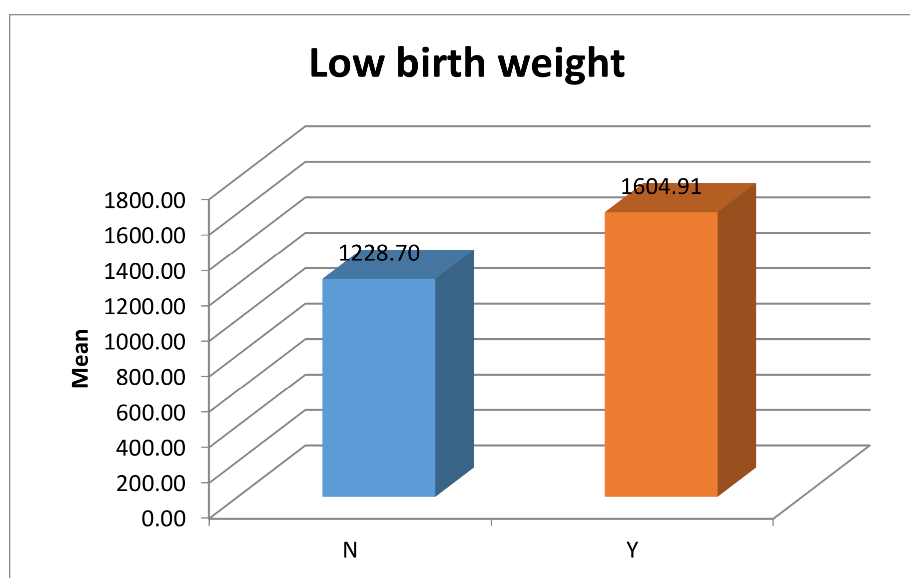


Table 11: Comparison of adrenal gland size among normal healthy neonates and neonates with hypocalcemia

HYPOCALCEMIA	NO. OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	100	1262.26	533.94	0.348
YES	2	1620.0	0.00	

In the present study, 2 neonates with hypoglycemia were studied. The mean adrenal gland volume in these neonates was found to be 1620.0 +/- 0.00 mm^3. On comparing the volume of adrenal gland in neonates with hypocalcemia with normal healthy neonates, the volume in babies with hypocalcemia was found to be higher as compared to the normal neonates with a p value of 0.348. This data was not found to be statistically significant likely due to the less number of cases included in the present study, which serves as a limitation of the study.

Graph 9: Bar graph comparing the adrenal gland size in neonates with hypocalcemia and normal healthy neonates

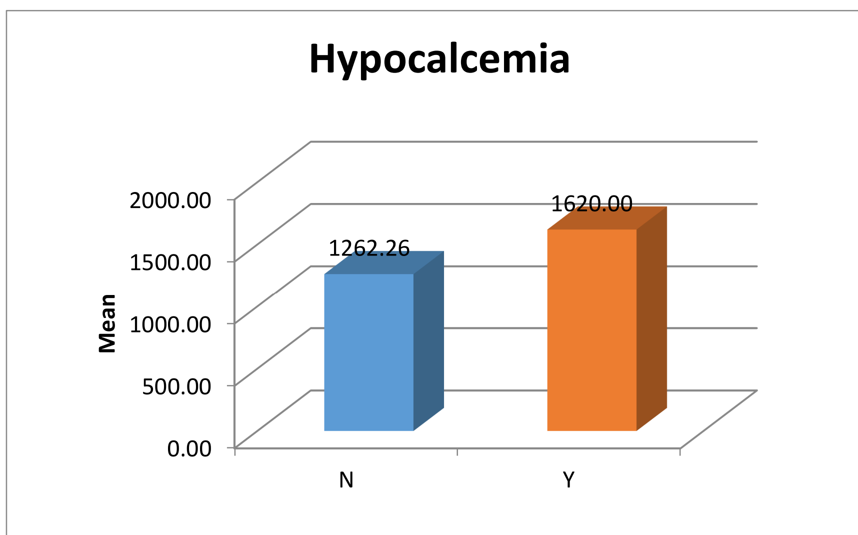


Table 12: Comparison of adrenal gland volume in neonates with sepsis and normal healthy neonates

SEPSIS	NO. OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	100	1262.26	533.94	0.348
YES	2	1620.0	0.00	

In the present study, 2 neonates with sepsis were studied. The mean adrenal gland volume in these neonates was found to be 1620.0 +/- 0.00 mm^3. On comparing the volume of adrenal gland in neonates with sepsis with normal healthy neonates, the volume in babies with sepsis was found to be higher as compared to the normal neonates with a p value of 0.348. This data was not found to be statistically significant likely due to the less number of cases included in the present study, which serves as a limitation of the study.

Graph 10: Bar graph comparing the adrenal gland volume in neonates with sepsis and normal healthy neonates

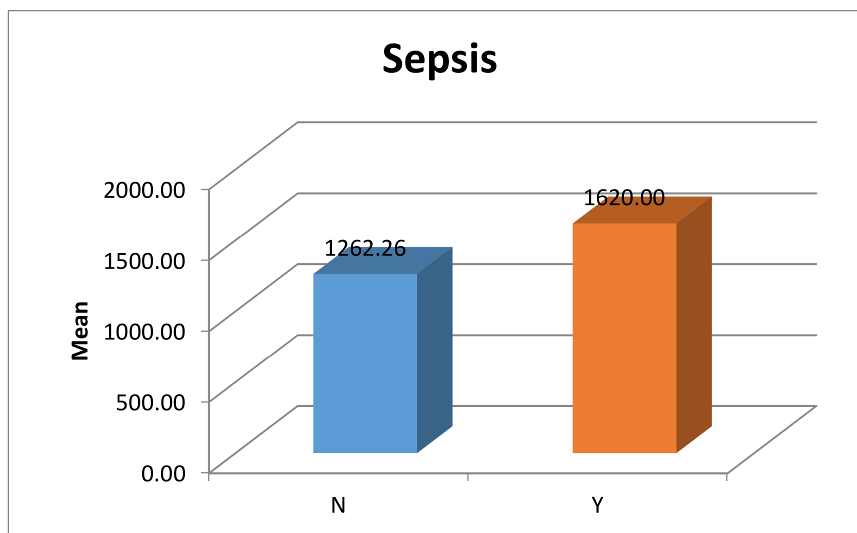


Table 13: Comparison of adrenal gland volume in small for gestation age neonates and normal healthy neonates

SGA	NO. OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	100	1254.02	520.18	0.04
YES	2	2032.00	707.11	

In this study, 2 neonates who were small for gestational age were studied. The mean adrenal gland volume in these neonates was found to be 2032.00 +/- 707.11 mm^3. The adrenal gland volume in small for gestational age neonates was found to be higher than normal healthy neonates with a p value of 0.04 making this data statistically significant.

Graph 11: Bar graph comparing the adrenal gland volume in small for gestational age neonates and normal healthy neonates

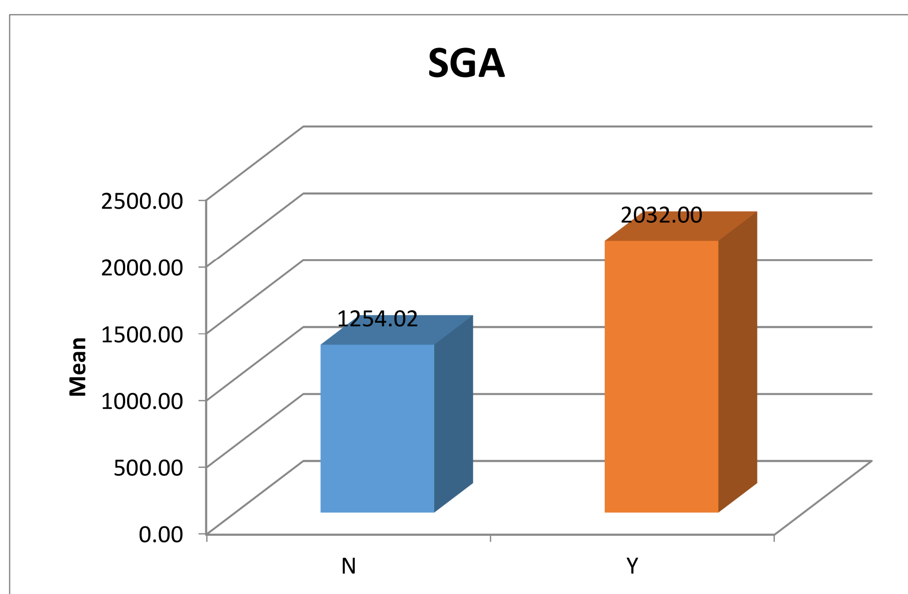


Table 14: Comparison of adrenal gland volume in neonates whose mothers had pre eclampsia with normal healthy neonates

PRE ECLAMPSIA	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	93	1199.42	493.87	0.001
YES	9	1991.11	333.98	

9 neonates whose mother had pre eclampsia were included in the present study. The mean adrenal gland volume in these neonates was found to be 1991.11 +/- 333.98 mm^3, which was higher when compared to normal healthy neonates with a p value of 0.001 indicating that this study was statistically significant.

Graph 12: Bar graph comparing the adrenal gland volume in normal healthy neonates and neonates whose mother had pre eclampsia

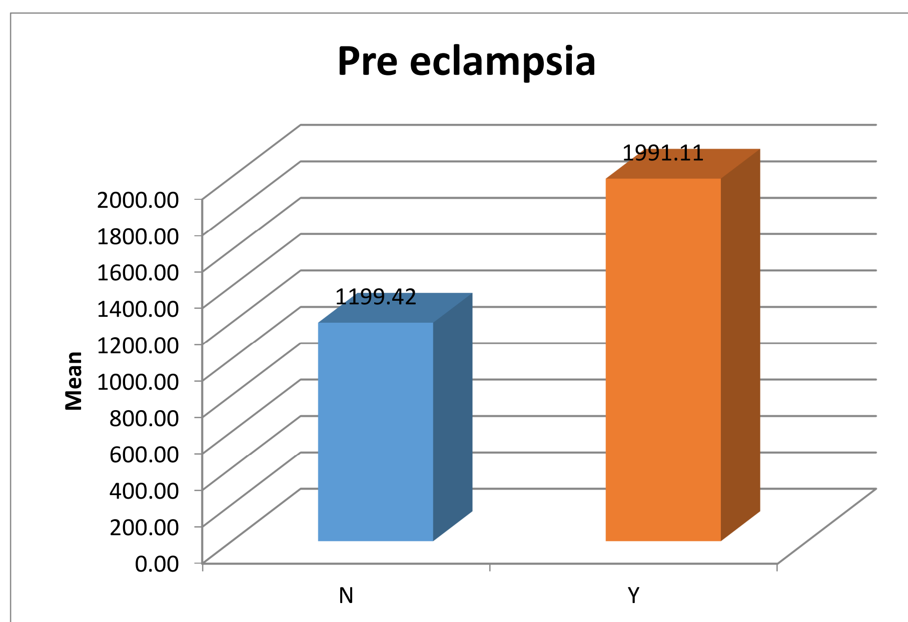


Table 15: Comparison of adrenal gland volume in neonates with meconium stained liquor and normal healthy neonates

MECONIUM STAINED LIQUOR	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	94	1215.17	486.97	0.001
YES	8	1905.00	645.04	

In the present study, 8 neonates with meconium stained liquor were evaluated for adrenal gland size. The mean volume of adrenal gland in these neonates was found to be 1905.00 +/- 645.04 mm^3, which was found to be higher when compared to normal healthy neonates with a p value of 0.001 making this study statistically significant.

Graph 13: Bar graph comparing the adrenal gland volume in neonates with meconium stained liquor and normal healthy neonates

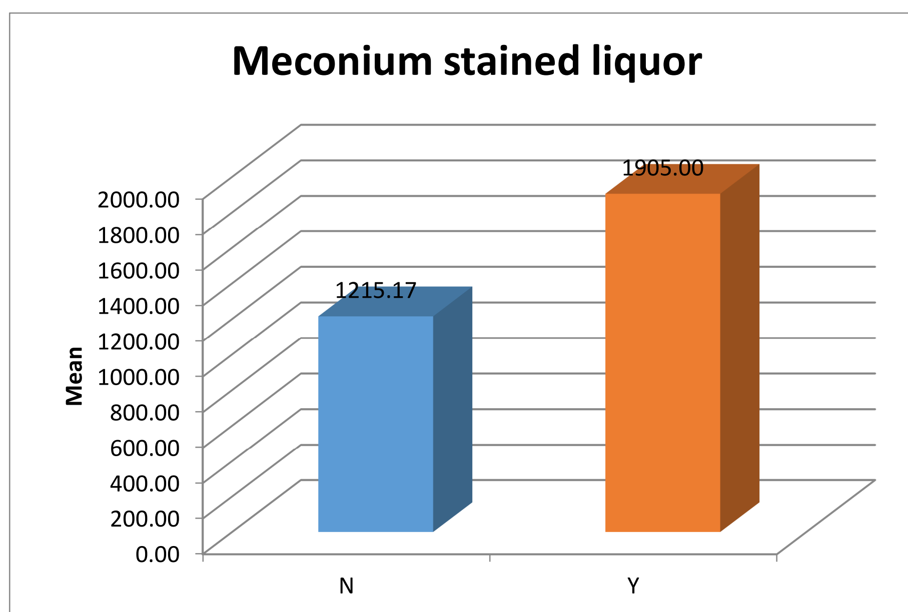


Table 16: Comparison of adrenal gland volume in neonates with fetal growth restriction and normal healthy neonates

FGR	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	100	1279.62	531.14	0.165
YES	2	752.00	0.00	

A total of 2 neonates with fetal growth restriction were included in the present study. The mean adrenal gland volume in these neonates was found to be 752.00 +/- 0.00 mm^3, which was found to be less than that of normal healthy neonates with a p value of 0.165. This data was not found to be statistically significant, likely due to the less number of babies with fetal growth restriction included in the present study serving as a limitation to this study.

Graph 14: Bar graph comparing volume of adrenal gland in neonates with fetal growth restriction and normal healthy neonates

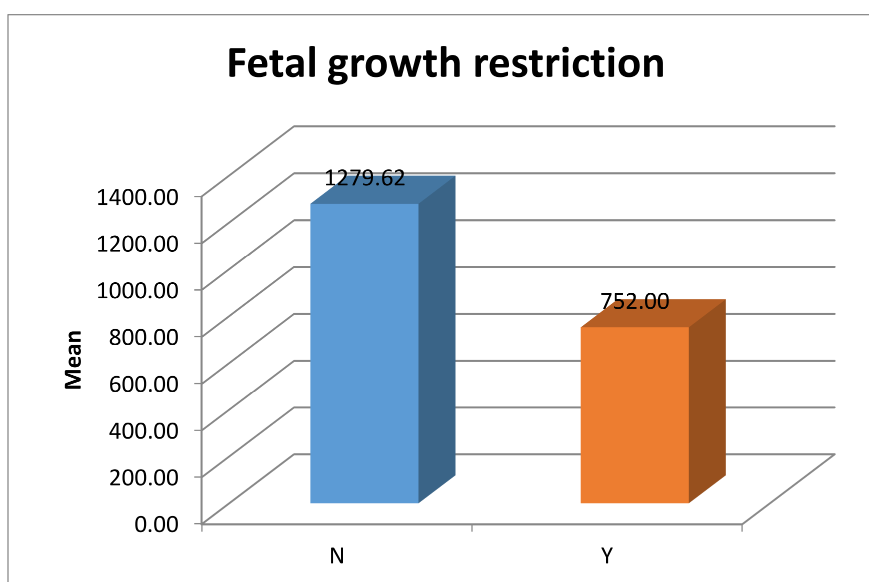


Table 17: Comparison of adrenal gland volume in neonates with perinatal asphyxia and normal healthy neonates

PERINATAL ASPHYXIA	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	101	1256.63	517.97	0.015
YES	1	2546.0		

In the present study, 1 neonate with perinatal asphyxia was included and the adrenal gland volume was calculated. The volume of adrenal gland in this baby was found to be 2546.0 mm^3. This volume was found to be higher when compared to normal healthy neonates with a p value of 0.015 making it statistically significant. However, due to the lack of cases in the present study, another study with more neonates with perinatal asphyxia need to be studied.

Graph 15: Bar graph comparing the adrenal gland volume in neonates with perinatal asphyxia and normal healthy neonates

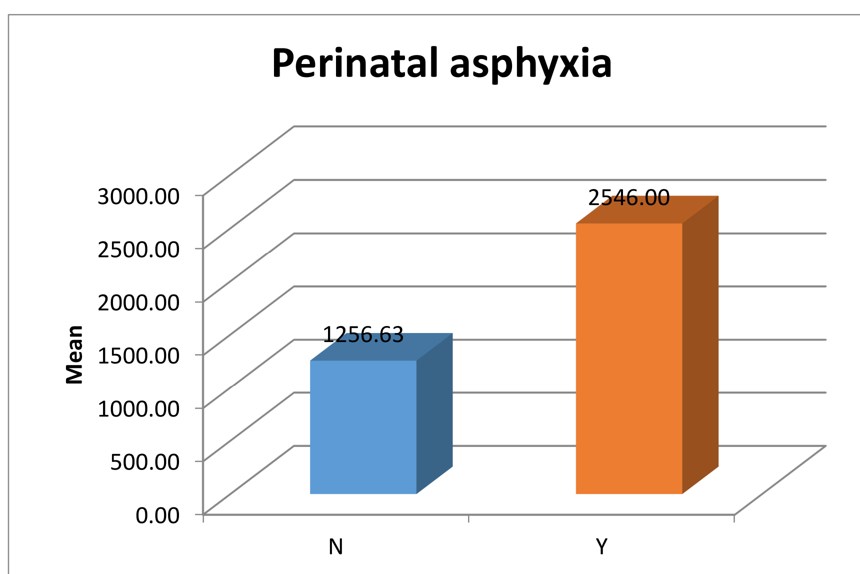


Table 18: Comparison of adrenal gland volume in neonates with hypoxic ischemic encephalopathy with normal healthy neonates

HIE	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	99	1261.66	521.99	0.408
YES	3	1520.67	887.96	

In the present study, 3 neonates with hypoxic ischemic encephalopathy were included and their adrenal gland volume was calculated. The mean volume in these neonates was found to be 1520.67 +/- 887.96 mm^3. This volume was found to be higher than the volume of normal healthy neonates, however the p value for this data set was found to be 0.408 making it statistically insignificant.

Graph 16: Bar graph comparing adrenal gland volume in neonates with hypoxic ischemic encephalopathy and normal healthy neonates

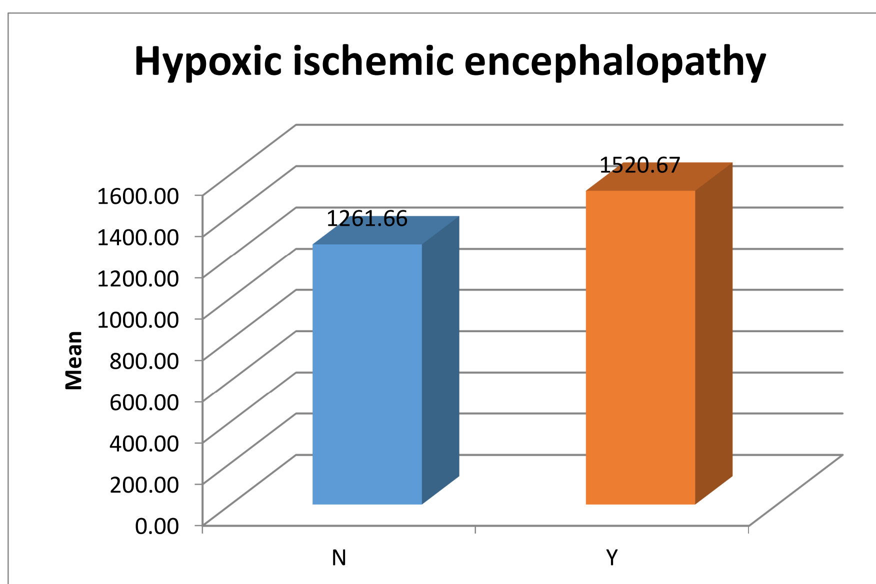


Table 19: Comparison of adrenal gland volume in neonates with respiratory distress with normal healthy neonates

RDS	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	98	1253.08	534.58	0.128
YES	4	1666.0	182.44	

In the present study, adrenal gland volume of 4 neonates with respiratory distress syndrome was calculated and the mean volume was found to be 1666.0 +/- 182.44 mm^3, which was higher than the adrenal gland volume of normal healthy neonates. However, the p value for this data set was found to be 0.128 making it statistically insignificant, likely due to less number of cases studied.

Graph 17: Bar graph comparing the mean adrenal gland volume in neonates with respiratory distress syndrome and normal healthy neonates

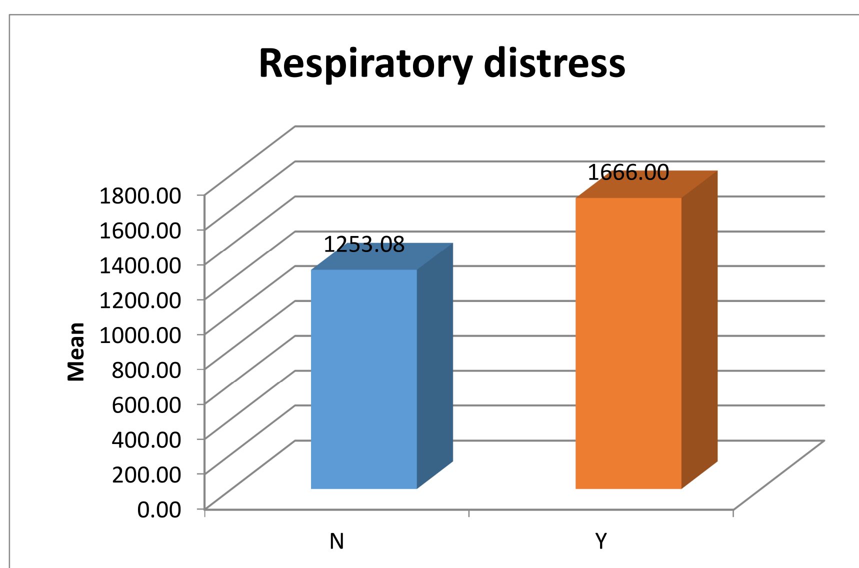


Table 20: Comparison of adrenal gland volume in neonates with congenital infections and normal healthy neonates

CONGENITAL INFECTION	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	100	1275.42	534.49	0.411
YES	2	962.00	0.00	

In the present study, 2 neonates with congenital infections were included and the adrenal gland volume was calculated. The mean volume in this group of neonates was found to be 962.00 +/- 0.00 mm^3, which was lower than the volume of normal healthy neonates. However the p value in this study group was found to be 0.411, making it statistically insignificant likely due to less number of neonates studied.

Graph 18: Bar graph comparing the adrenal gland volume in neonates with congenital infections and normal healthy neonates

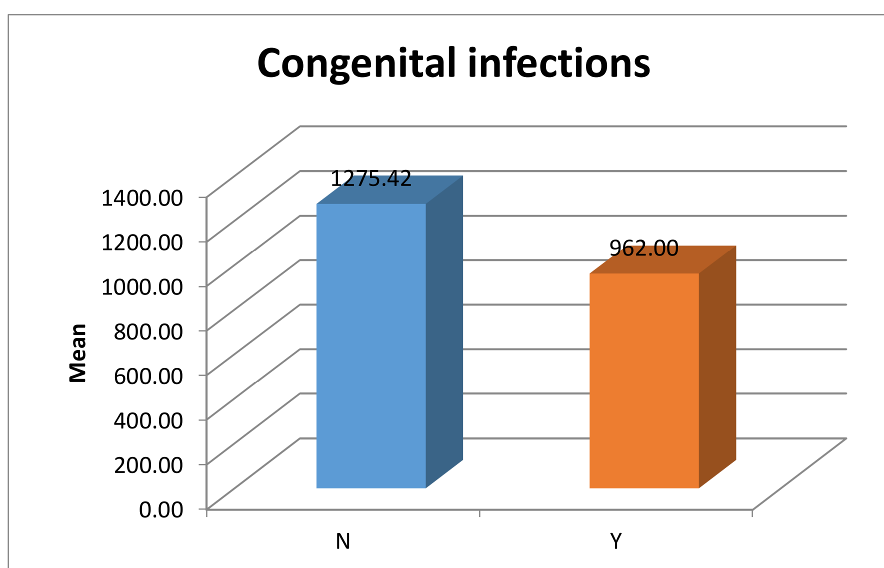


Table 21: Comparison of adrenal gland volume in neonates whose mother had premature rupture of membranes and normal healthy neonates

PROM	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	98	1281.16	536.98	0.265
YES	4	978.00	225.17	

In the present study, 4 neonates whose mother had premature rupture of membranes were studied. The mean adrenal gland volume in these neonates was found to be 978.00 +/- 225.17 mm^3, which was found to be lower than that of normal healthy neonates. However, the p value for this data set was found to be 0.265 making this data statistically insignificant.

Graph 19: Bar graph comparing the adrenal gland volume in neonates whose mother had premature rupture of membranes with normal healthy neonates

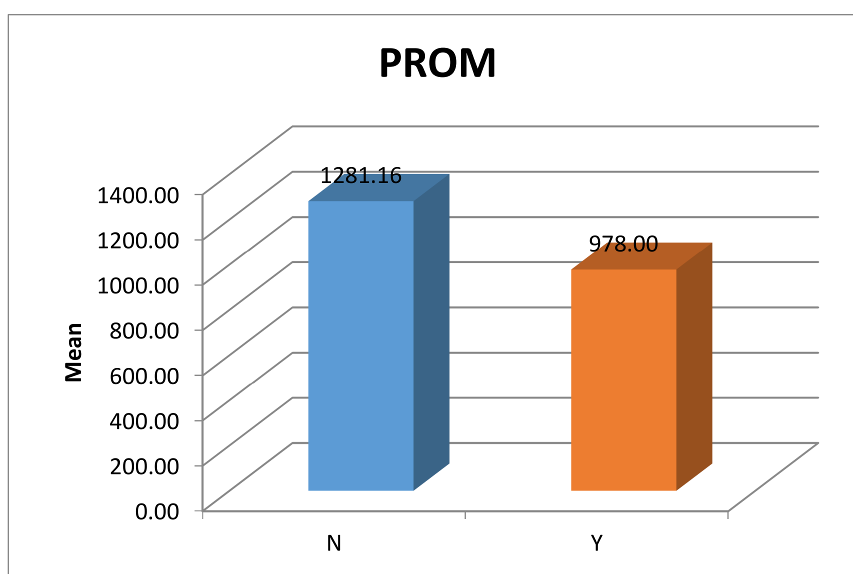


Table 22: Comparison of adrenal gland volume in neonates with hypothyroid mothers and normal healthy neonates

MATERNAL HYPOTHYROIDISM	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	100	1280.74	529.96	0.124
YES	2	696.00	0.00	

In the present study, 2 neonates whose mothers had hypothyroidism were included and their adrenal gland volume was calculated. The mean adrenal gland volume was found to be 696.00 +/- 0.00 mm^3 which was lower as compared to normal healthy neonates. However, the p value for this set of data was 0.124 making it statistically insignificant.

Graph 20: Bar graph comparing adrenal gland volume in neonates with hypothyroid mothers and normal healthy neonates

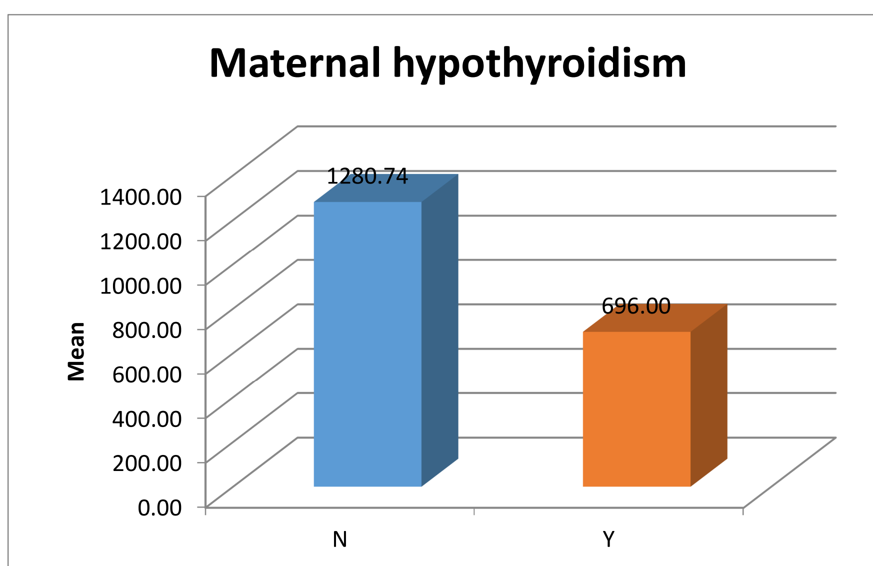


Table 23: Comparison of adrenal gland volume in neonates whose mothers had oligohydramnios and normal healthy neonates

OLIGOHYDRAMNIOS	NO OF CASES	MEAN VOLUME	STD DEVIATION	P VALUE
NO	101	1256.77	518.31	0.016
YES	1	2532.0		

In the present study, 1 neonate whose mother had oligohydramnios was included and the adrenal gland volume was calculated. The adrenal gland volume in this neonate was found to be 2532.0 mm^3. The volume of adrenal gland in this neonate was found to be higher than normal healthy neonates with a p value of 0.016 making the data statistically significant. However, further study with more number of neonates with mothers having oligohydramnios need to be done for better analysis of this parameter.

Graph 21: Bar graph comparing adrenal gland volume in neonates whose mothers had oligohydramnios and normal healthy neonates

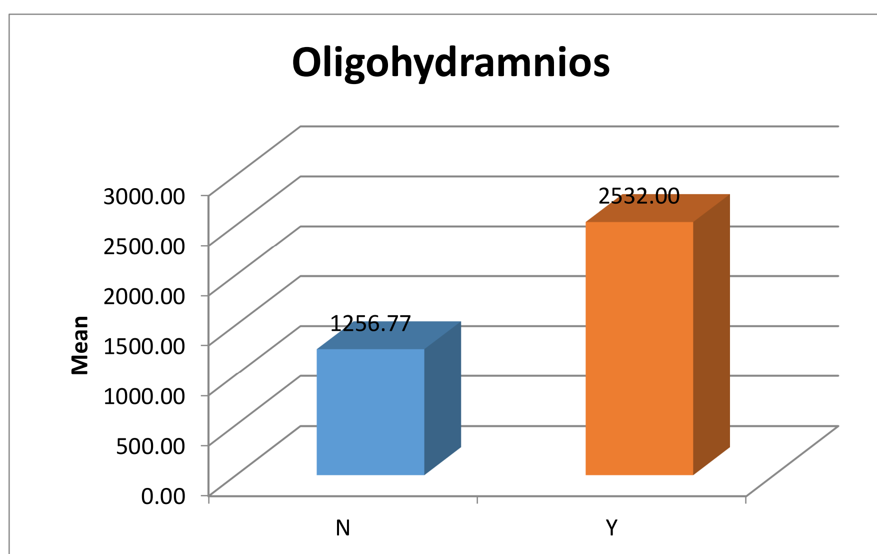


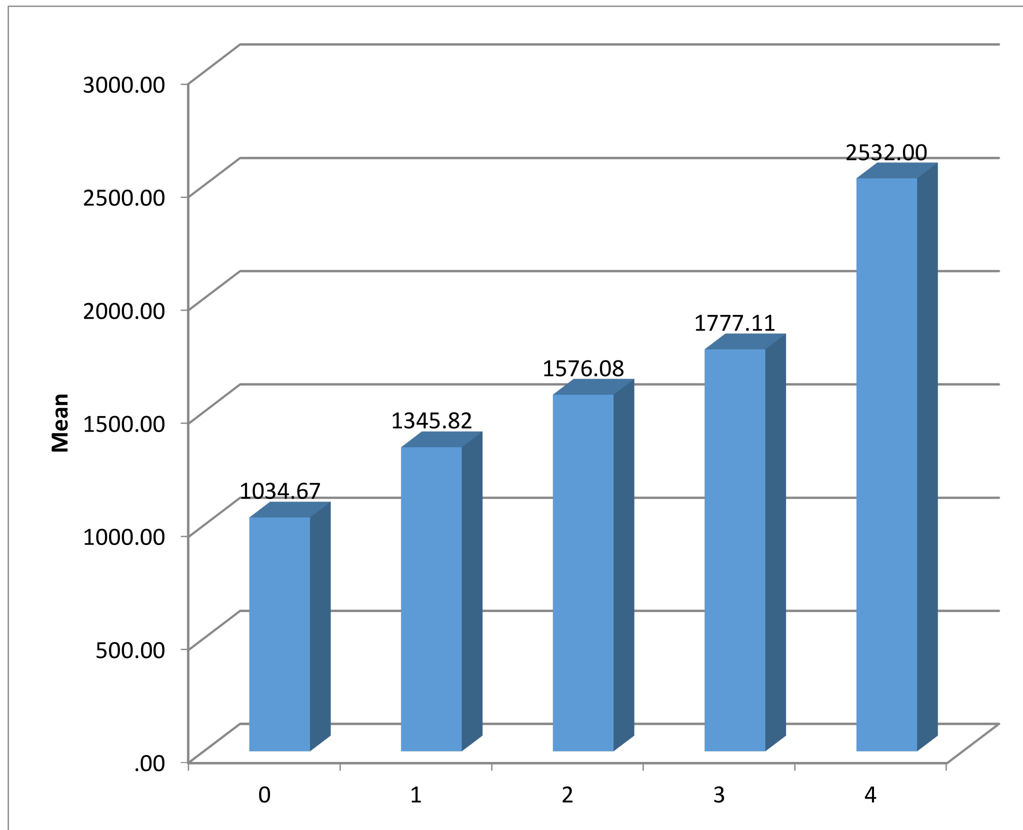
Table 24: Comparison of adrenal gland volume in neonates and number of stressors

NO OF STRESSORS	NO CASES	MEAN VOLUME	STD DEVIATION	P VALUE
0	51	1034.67	324.982	0.001
1	28	1345.82	624.287	
2	13	1576.08	604.814	
3	9	1777.11	146.523	
4	1	2532.00	-	

In the present study, a total of 102 neonates were studied. 51 neonates had no maternal or fetal stressors and their mean adrenal gland volume was found to be 1034.67 +/- 324.982 mm^3.

51 stressed neonates were included in this study, out of which 28 neonates had only 1 stressor and had a mean adrenal gland volume of 1345.82 +/- 624.287 mm^3, 13 neonates had 2 stressors with a mean volume of 1576.08 +/- 604.814 mm^3, 9 neonates had 3 stressors with a mean adrenal gland volume of 1777.11 +/- 146.523 mm^3 and 1 neonate had 4 stressors with an adrenal gland volume of 2532.00 mm^3.

Graph 22: Bar graph comparing number of stressors and adrenal gland volume in neonates



DISCUSSION

The present study was conducted with the aim of evaluating adrenal gland size in neonates (healthy and stressed) using transabdominal sonography and try to establish the mean adrenal gland volume in normal healthy neonates and comparing that volume with various clinical parameters, which might act as stressors and determine the relationship between the adrenal gland size and the stressors. It was also aimed to determine which parameter most significantly affects the adrenal gland volume in neonates.

Babies within the age range of Day 1 to Day 4 of life without any known congenital anomalies were included in the study.

After taking informed consent from the parents, transabdomal sonography was performed on these neonates and adrenal gland volume was determined. This volume was then compared to various clinical parameters (maternal and fetal) and looked for any correlation.

102 neonates were evaluated in the present study with 51 being normal healthy neonates and the other 51, stressed neonates. There was a near equal distribution of male and female neonates in the present study. Most of these neonates were evaluated on day 4 of life.

Out of the 102 neonates included in the present study, the right adrenal gland was visualized in all the neonates while the left adrenal gland could be visualized in only 23.5 % neonates. This can be due to difficulty in visualization of the left adrenal gland due to its anatomical location with the air in the stomach and bowel loops

masking its appearance. The mean volume of right adrenal gland (1269.27 +/ - 530.97 mm^3) was found to be higher than that of the left adrenal gland (800.71 +/- 176.17 mm^3).

This was similar to a study conducted by Elaine M Scott in 1990 , in which they could not demonstrate the left adrenal gland in 14 % cases. The size of left adrenal gland was also found to be smaller than that of the right adrenal gland.[55]

The study did not show any significant difference between the adrenal gland size in males and females with the mean adrenal gland volume in males being 1284.27 +/- 520.84 mm^3 and the mean adrenal gland volume in females being 1253.68 +/- 546.52 $mm^{3.}$

A study conducted by Tijen Karsli in 2017 depicted that the adrenal gland size was smaller in females as compared to males. This was in contradiction to the results of the present study where no significant difference between the two was found.[4]

The mean adrenal gland volume in stressed neonates (1503.88 +/- 592.96 mm^3) was found to be significantly higher than normal healthy neonates (1034.67 +/- 324.98 mm^3). Study conducted by Shigeo Iijema yielded a similar result.[49,50]

However, a study conducted by David Oppenheimer in 1983 did not find any significant difference between the size of adrenal glands in stressed and non stressed neonates.[54]

In the present study, it was found that as compared to normal healthy neonates, the volume of adrenal gland in preterm neonates (1180.53 +/- 529.88 mm^3), low birth weight neonates (1604.91 +/- 341.31 mm^3), small for gestational age neonates (2032.00 +/- 707.11 mm^3), neonates whose mothers had pre eclampsia

(1991.11 +/- 333.98 mm^3), neonates with meconium stained liquor (1905.00 +/- 645.04 mm^3), neonates with perinatal asphyxia (2546.0 mm^3) and neonates whose mothers had oligohydramnios (2532.0 mm^3) was significantly higher.

Similar findings were observed in the study conducted by Shigeo Iijema in 2018 who showed a positive correlation between adrenal gland size and small for gestational age neonates while a negative correlation was found between adrenal gland size and gestational age.[49,50]

This study also showed that the adrenal gland volume in neonates with perinatal asphyxia was higher when compared to normal healthy neonates. These changes might occur because in response to the stressfull stimuli of perinatal asphyxia, there is redistribution of blood to important organs like adrenal glands resulting in their vascular congestion, and in turn enlargement in the size.

Study conducted by Tijen Karsli in 2017, showed that presence of pre eclampsia in the mother correlated positively with the adrenal gland size in neonates.[4]

This study also showed that such neonates with perinatal stressors and increased adrenal gland size are more prone to develop intraventricular hemorrhage.

The present study also establishes a relationship between the number of stressors and the adrenal gland volume. It was found that the volume of adrenal gland significantly increases with the number of stressors. The mean adrenal gland volume in a neonate with 1 stressor was found to be 1345.82 +/- 624.287 mm^3 while the mean adrenal gland volume in a neonate with 2 or more stressors was found to be1696.3 +/- 500.291 mm^3. This type of comparison has not been established in any previous studies.

CONCLUSION

- Adrenal gland size can be easily evaluated using transabdominal sonography owing to the reduced amount of abdominal fat in neonates and the reduced depth of the adrenal gland from the surface
- Right adrenal gland can be more readily evaluated as compared to the left adrenal gland owing to obliteration due to gas present in the stomach and bowel loops.
- On comparing the adrenal gland size among stressed and non stressed neonates, the following observations were made:
    - ❖ The size of adrenal gland does not vary significantly between male and female neonates
    - ❖ The volume of the right adrenal gland was found to be higher than the volume of left adrenal gland
    - ❖ The adrenal gland volume in stressed neonates was found to be higher than the volume in non stressed neonates
    - ❖ Amongst stressed neonates, babies with low birth weight, preterm neonates, small for gestational neonates had a higher adrenal gland volume
    - ❖ On comparing maternal complicating factors, mothers with pre eclampsia and premature rupture of membranes had babies with a higher adrenal gland volume
    - ❖ The volume of adrenal glands increases significantly depending on the number of stressors that the baby was exposed to
    - Scope for future studies:

- Another study with a higher number of babies who are small for gestational age, have sepsis, hypoxic ischemic encephalopathy, respiratory distress syndrome, fetal growth retardation, hypocalcemia, neonates with hypothyroid mothers and mothers with oligohydramnios should be conducted to obtain a statistically significant result
- Long term follow up should be conducted to monitor babies with a higher adrenal gland volume to look for any long term complications
- Studies should be conducted to obtain a nomogram for adrenal gland volume in fetal life and assessed for any changes in adrenal gland volume in stressed fetuses so that further complications in the neonatal life can be avoided

SUMMARY

- The study conducted was a comparative study
- 102 neonates were studied after observing the various inclusion and exclusion criterias
- Out of the 102 neonates, 51 were normal healthy neonates and 51 were stressed neonates
- After taking written informed consent from the parents, the neonates underwent transabdominal sonography for the assessment of adrenal gland size and the volume of the adrenal gland was compared between normal and stressed neonates
- Right adrenal gland was more readily imaged by ultrasonography as compared to left adrenal gland
- The volume of adrenal gland in stressed neonates was found to be higher than the volume of non stressed neonates
- The adrenal gland volume increases significantly compared to the number of stressors the neonate has been exposed to
- The results obtained during this study correlated well with studies conducted by other authors previously

LIMITATIONS

- The study had limited number of babies who were small for gestational age, had sepsis, hypoxic ischemic encephalopathy, respiratory distress syndrome, fetal growth retardation, hypocalcemia, neonates with hypothyroid mothers and mothers with oligohydramnios, therefore a statistically significant result could not be established.
- This study did not focus on following up these neonates for various long term complications
- This study did not compare adrenal gland size in fetal life to correlate with any stressors that the fetus might have

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ANNEXURE I

INFORMED CONSENT

TITLE OF THE STUDY: Role of Transabdominal Ultrasonography In The Evaluation Of Adrenal Gland Size In Neonates- A One Year Hospital Based Comparative Study

PRINCIPAL INVESTIGATOR: ____________________

INTRODUCTION AND PURPOSE:

Adrenal gland is a very vital organ in the human body and the hormones produced by it play a significant role in the growth and development of a fetus and survival in a neonate in the post natal period. There is a lack of data regarding the change of adrenal gland size during gestation and with response to various in- utero conditions. The purpose of the study is to find a correlation between adrenal gland size with various demographic and clinical parameters and find out if adrenal gland size at birth can help predict adverse neonatal outcomes.

PROCEDURE:

I request you to kindly allow the participation of your baby in the study titled study "Role Of Transabdominal Ultrasonography In The Evaluation Of Adrenal Gland Size In Neonates- A One Year Hospital Based Comparative Study" is being conducted by

__________________, post graduate in Radio diagnosis at J. N. Medical College Belgaum, Karnataka, under the guidance of _______________, Professor and Head, Dept. of Radio diagnosis, J. N. Medical College, Belgaum and ____________, Principal, J.N. Medical College, Belgaum, Sr. Consultant Paediatrics , KLES Dr. Prabhakar Kore Hospital, Belgaum.

We request you to allow the participation of your baby in this study as he/she is eligible to be included. During the study you will be asked questions regarding your present and past medical and obstetric history and your baby's medical history and you will be required to answer to the best of your knowledge. Your baby will also have to undergo an ultrasound of the abdomen.

If you agree for the participation of your baby in the study, please furnish the details pertaining to the study.

BENEFITS:

- Noninvasive modality

COMPLICATIONS:

- No risk to the patient has been documented from ultrasound imaging of the abdomen earlier.

ALTERNATIVES:

If the parents are not willing for their baby to take part in the study, the child's treatment or any other further investigations that he/she wants to undergo, in future, in KLE will not be affected by their decision.

VOLUNTARY PARTICIPATION/WITHDRAWAL:

Taking part in this study is voluntary. I may choose for my child not to take part in this study, or if I decide for him/her to take part I can later change my mind and withdraw my child from the study. My decision will not change the present or future health care or other services that my child receives. The study doctor or the sponsor may stop my child's participation in this study. I will tell of any important new findings that may change my willingness to continue to take part. If I choose for my child to not to take part in the study I will receive the standard treatment for patients with my child's condition.

COSTS:

NIL

Payment for Participation: No incentive will be paid to you for allowing your child to participate in this study.

COMPENSATION:

In the event that my child becomes injured as a result of taking part in this study, treatment whatever available at KLE charitable hospital, Belagavi, will be offered to him/her. No reimbursement, compensation or free medical care is given.

CONFIDENTIALITY:

All information collected about my child during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify him/her in this research record. Information from this study may be published but his/her identity will be confidential in any publication.

QUESTION:

If any enquiries in the future or in case of research related injury/ illness, you may contact following person.

- **Dr. Aakanksha Nayyar** Post-Graduate, Department of Radio-Diagnosis. J.N.Medical College, Belgaum Ph.0831-2473777, Ext. 1163 Mob-09743520983
- **DR ASHWIN S. PATIL** Guide Professor& Head, Department of Radio-Diagnosis, J.N. Medical College, Belagavi. Ph. No. 0831-2473777, Ext. 1163
- **DR HARSHA HEGDE** Chairperson, JNMC, IEC& Scientist D, ICMR, National Institute of Traditional Medicine, Belagavi Ph. No: 0831-2473777, Ext. 1529 Mob No: 9480422500

CONSENT TO PARTICIPATE IN RESEARCH STUDY:

1. I understand that my child will be participating in the study, which includes ultrasound of the abdomen.
2. I confirm that I have read and understood the information in the patient information sheet. Procedure is explained to me in detail along with information about the advantages and disadvantages of my child taking part in the study. I have been given the opportunity to discuss all aspects of the trial, to ask questions and hereby consent my child to participate in the trial outlined above.
3. I understand that the decision to take part in this study is completely voluntary and I am aware that I can choose to withdraw my child from the study at any point of time.
4. I consent to the photographing or recording of the procedure to be performed including appropriate portions of my child's body, for medical, scientific or educational purposes provided his/her identity is not revealed in the pictures or by the descriptive texts accompanying them.
5. I understand that there is no significant risk involved in the test that would be done in this study.
6. No guarantee or assurance has given by anyone as to the results that may be obtained.
7. My signature on this form signifies that I have willingly decided for my child's participation after understanding the above information.

Participant's Name/ legally authorized ______________________

Representative Signature ______________________

Name and signature of witness ______________________

Name and signature of interviewer ______________________

Date:

Place:

ANNEXURE II

KAHER

J.N. MEDICAL COLLEGE, BELAGAVI

DEPARTMENT OF RADIODIAGNOSIS

TITLE: ‘’ ROLE OF TRANSABDOMINAL ULTRASONOGRAPHY IN THE EVALUATION OF ADRENAL GLAND SIZE IN NEONATES- A ONE YEAR HOSPITAL BASED COMPARATIVE STUDY ’’

PROFORMA FOR DATA COLLECTION

NAME________________________________

AGE___________

SEX: **OP/IP NO ___________**

PARENTS’S MOBILE_______________

ADDRESS ____

____

USG NUMBER: ____________

CHIEF COMPLAINTS:

HISTORY OF PRESENTING ILLNESS

OBSTETRIC HISTORY

BIRTH HISTORY

USG FINDINGS:-

a) Adrenal length-

b) Adrenal width

c) Adrenal depth

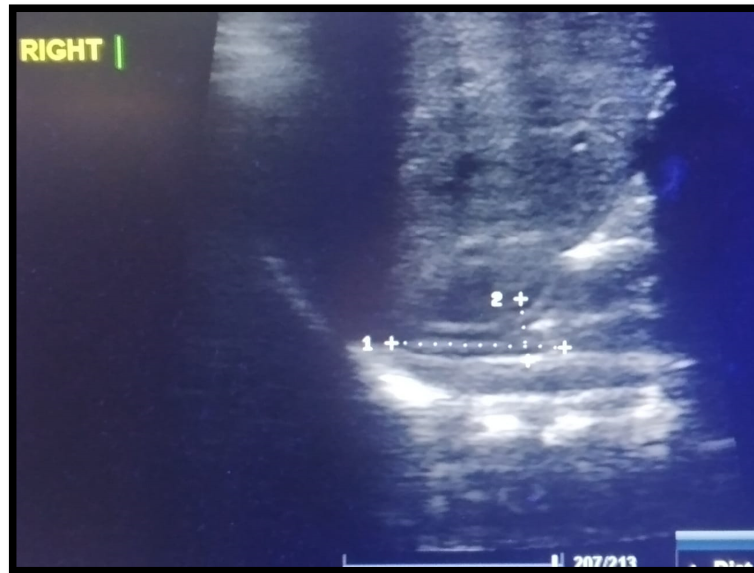
ANNEXURE III

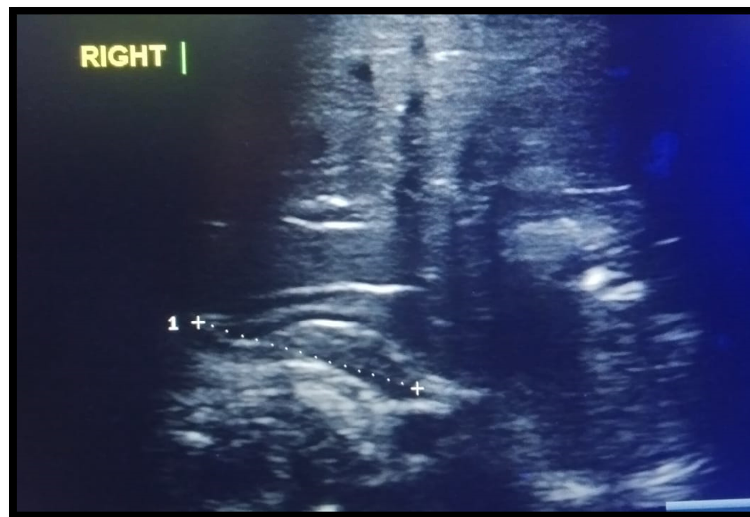
PHOTOGRAPH OF MINDRAY M7 PREMIUM MACHINE AT KLES DR. PRABHAKAR KORE HOSPITAL, BELAGAVI

PHOTOGRAPH OF CASES

CASE 1: 3 day old female term baby born via normal vaginal delivery who cried immediately after birth with no fetal or maternal comorbidities

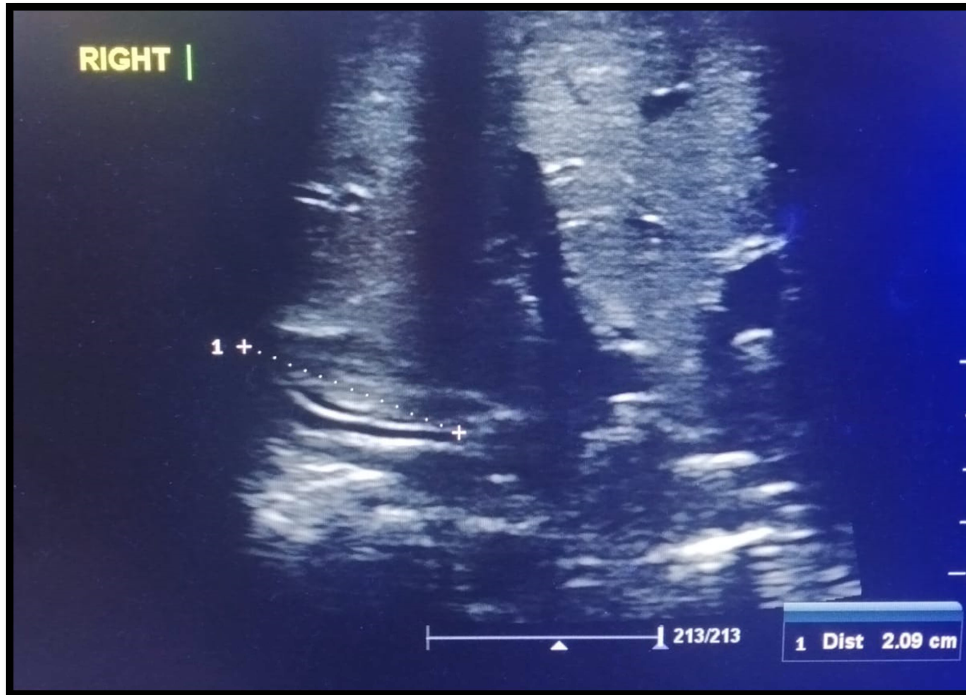
Right adrenal gland volume measures 1176.0 mm^3 while the left adrenal gland could not be visualized.

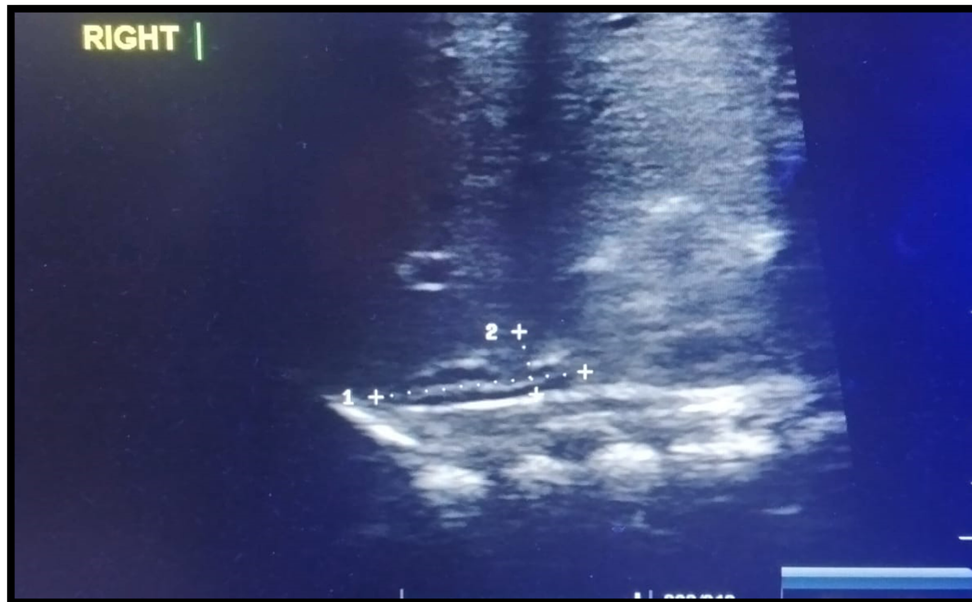




CASE 2: 4 day old term male baby with history of meconium stained liquor at birth

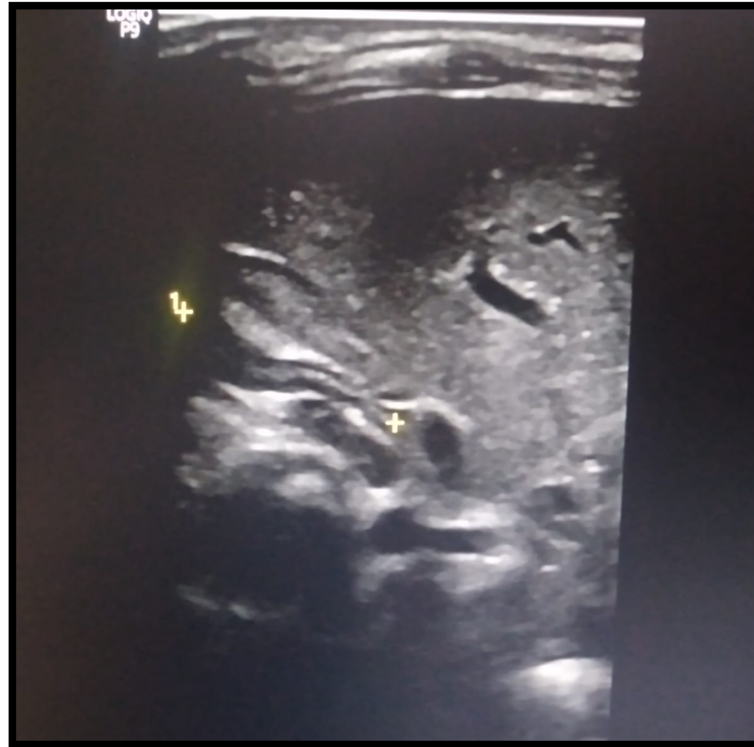
Right adrenal gland volume measures 1078.0 mm^3

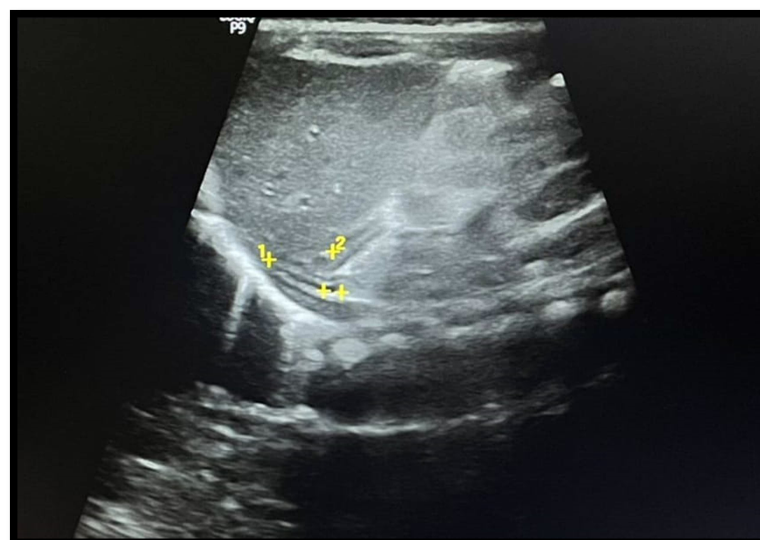




CASE 3: 4 day old term female baby born via normal vaginal delivery who cried immediately after birth with no fetal or maternal comorbidities

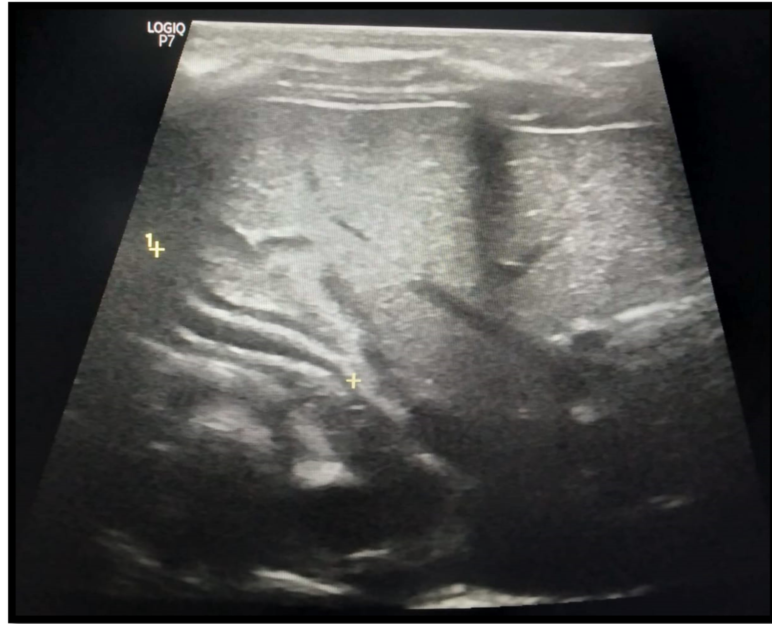
Right adrenal gland volume measures 1001.0 mm^3

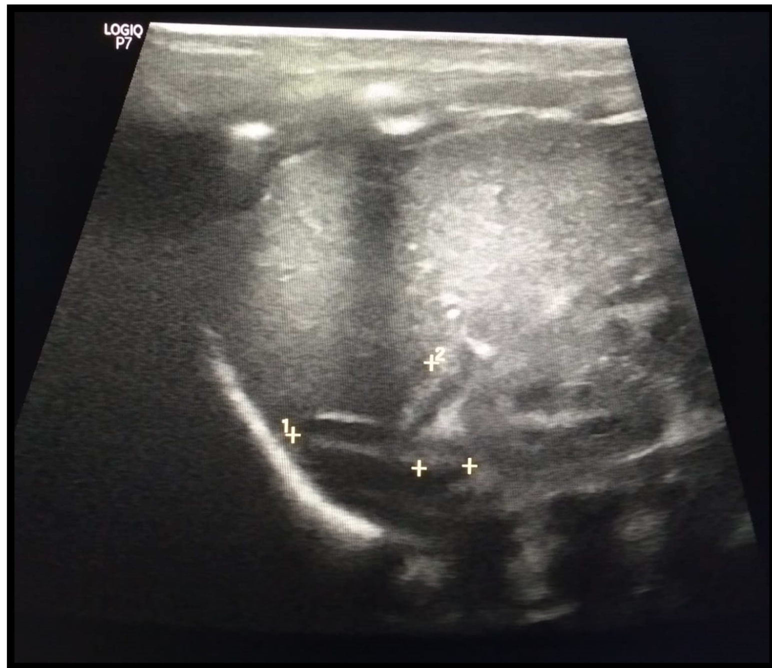




CASE 4: 4 day old preterm male baby born via caesarean section who cried immediately after birth

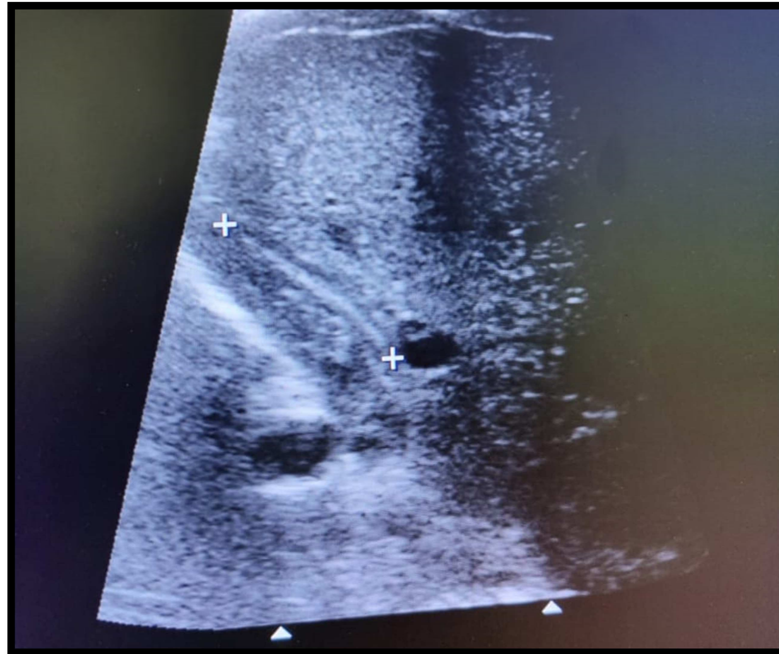
Right adrenal gland volume measures 1320.0 mm^3

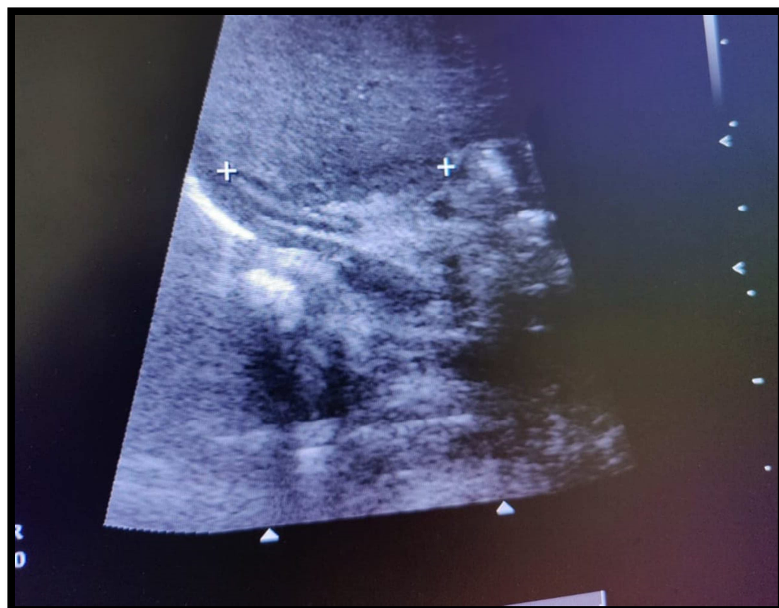




CASE 5: 4 day old term male baby born via normal vaginal delivery who cried immediately after birth with no maternal or fetal comorbidities

Right adrenal gland volume measures 1067.0 mm^3





ANNEXURE IV

KEY TO MASTER CHART

1	PRESENT
0	ABSENT
RT	RIGHT
LT	LEFT

ANNEXURE V

MASTER CHART

S. No	Name	Age	Rt Volum	Lt Volume	Male	Female	Preterm	Low birth weight	Hypocalcemia	Sepsis	SGA	Pre eclampsia	Meconium stained liquor	Fetal growth restriction	Perinatal asphyxia	Hypoxic ischemic encephalopathy	Respiratory distress	Congenital infections	PROM	Maternal hypothyroidism	Oligohydramnios
1	B/o Deepali	Day 4	1620	920	1	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0
2	B/o Gouravva twin 2	Day 4	1047		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
3	B/o Gouravva twin 1	Day 4	924		0	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
4	B/o Ashwini	Day 3	1837		0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
5	B/o Rajeshwari	Day 4	2781		1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
6	B/o Alfiya	Day 3	752		1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
7	B/o Sonal	Day 1	1235	854	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	B/o Sunita	Day 2	1800		1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	B/o Shashi	Day 1	2340		0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	B/o Umashree	Day 4	863		0	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0
11	B/o Vidya	Day 1	1532	1049	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0
12	B/o Sarojini	Day 4	1151	770	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
13	B/o Aisha Mulla	Day 4	2546		0	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0
14	B/o Preeti	Day 4	1008	840	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
15	B/o Anupama	Day1	1508		1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
16	B/o Anita	Day 4	1078		1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
17	B/o Mashida	Day 4	841		0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
18	B/o Priyanka	Day 4	962		1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
19	B/o Tejaswi Narayan	Day 4	783		0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
20	B/o Babita	Day 4	690		0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	B/o Anuja	Day 4	696		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
22	B/o Priya Patil	Day 4	1173		0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
23	B/o Arati Sagar	Day 2	889		0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	B/o Sumaya	Day 4	521		1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
25	B/o Laxmi	Day 2	824		1	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0
26	B/o Bhakti	Day 4	1296		1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
27	B/o Sairabanu	Day 4	1001		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	B/o Savita	Day 3	1102		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	B/o Smitha	Day 4	1320		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	B/o Radhika	Day 4	1064	467	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	B/o Megha	Day 4	1274	658	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	B/o Mohini	Day 3	935	599	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	B/o Swati	Day 4	502		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
34	B/o Kiran	Day 2	527		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	B/o Divya	Day 2	883		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	B/o Rashmi	Day 4	916		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	B/o Ashwini	Day 4	1067		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	B/o Kalavati	Day 3	1536	944	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
39	B/o Sonali	Day 1	1691	1014	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	B/o Pooja	Day 2	984		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
41	B/o Anjali	Day 2	998		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42	B/o Amruta Patil	Day 3	984		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
43	B/o Shruti	Day 4	363	561	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	B/o Aishwarya	Day 4	1128		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	B/o Jayashree	Day 3	1176		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
46	B/o Mandira	Day 4	669		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	B/o Laxmi Mugukar	Day 3	1312		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48	B/o Vidyashri	Day 4	862		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	B/o Bhagyashree	Day 2	705		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	B/o Shashikala	Day 4	668	794	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
51	B/o Shrutika	Day 4	815		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
52	B/o Malashri	Day 4	1670		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
53	B/o Madhushri	Day 4	1025	907	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	B/o Shantamma	Day 3	1696		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
55	B/o Shashikala	Day 2	1438		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
56	B/o Madhuri	Day 3	1305		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
57	B/o Anamika	Day 4	1139		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
58	B/o Pranali	Day 1	1169		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

59	B/o Deepashree	Day 4	791	725	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
60	B/o Pratyusha	Day 4	779		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
61	B/o Ashwini	Day 3	984		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
62	B/o Shaurya	Day 4	634		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
63	B/o Zeenat	Day 2	854		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
64	B/o Asha	Day 4	1001		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
65	B/o Tanvi	Day 3	1102		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
66	B/o Poornima	Day 4	1320		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
67	B/o Shobha	Day 4	1064	467	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
68	B/o Sheetal	Day 4	1274	658	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
69	B/o Meghana	Day 3	935	599	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
70	B/o Amrita	Day 4	502		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
71	B/o Roopa	Day 2	527		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
72	B/o Deepashri	Day 2	883		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
73	B/o Anamika	Day 4	916		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
74	B/o Roopashri	Day 4	1067		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
75	B/o Fatima	Day 3	1536	944	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
76	B/o Samanvita	Day 1	1691	1014	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
77	B/o Tanvita	Day 2	984		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
78	B/o Rupali	Day 4	1620	920	1	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0
79	B/o Avnika	Day 4	1047		0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
80	B/o Sapna	Day 4	924		0	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
81	B/o Divya	Day 3	1837		0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
82	B/o Farzana	Day 4	2781		1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
83	B/o Pratyushi	Day 3	752		1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
84	B/o Gayatri	Day 1	1235	854	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
85	B/o Ratnamma	Day 2	1800		1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
86	B/o Shivani	Day 1	2340		0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
87	B/o Tasneem	Day 4	863		0	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0
88	B/o Suman	Day 1	1532	1049	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	1
89	B/o Jyoti twin 1	Day 4	1151	770	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
90	B/o Jyoti twin 2	Day 4	2546		1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
91	B/o Sanvi	Day 4	1008	840	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
92	B/o Demamma	Day 1	1508		1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
93	B/o Aruna	Day 4	1078		1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
94	B/o Sonakshi	Day 4	841		0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
95	B/o Rashmi	Day 4	962		1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
96	B/o Bhagyashri	Day 4	783		0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
97	B/o Rohini	Day 4	690		0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
98	B/o Sonali	Day 4	696		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
99	B/o Versha	Day 4	1173		0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
100	B/o Priya	Day 2	889		0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
101	B/o Gangamma	Day 4	521		1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
102	B/o Vanashri	Day 2	824		1	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0