Diagnosis of Hydrocephalus and its Associated Embryological Anomalies on Prenatal Ultrasound

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DEDICATION

I dedicate this thesis to my Almighty Allah, my beloved parents, my loving husband and my darling daughter who helped and supported me at every stage.

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LIST OF ABBREVIATIONS

S no.	ABBREVIATION	FULL FORM
1	CNS	Central Nervous System
2	CSF	Cerebrospinal Fluid
3	CH	Congenital Hydrocephalus
4	NPH	Normal Pressure Hydrocephalus
5	CHD	Congenital Heart Disease
6	NT	Nuchal Translucency
7	HC	Head Circumference
8	BPD	Biparietal Diameter
9	FL	Femur Length
10	HC/AC	Head to Abdominal Circumference Ratio
11	LV:HR	Lateral Ventricle to Hemisphere Ratio
12	ALV	Atrium of Lateral Ventricle

s

ABSTRACT

Introduction: Hydrocephalus is the enlargement or dilatation of ventricular system due to an increase in cerebrospinal fluid (CSF) volume due to an obstruction which may also lead to an increase in CSF pressure. It has a prevalence rate of 4.65 per 10,000 and an incidence of 1 in 10,000 live births in Pakistan. It is found to be much more common in male fetuses as compared to female fetuses.

Etiology of hydrocephalus ranges from idiopathic to chromosomal abnormalities. Maternal hypertension, diabetes, congenital infections and drugs like antidepressants are some of the risk factors. Neural tube defects like spina bifida, meningomyelocele have been found to be commonly associated with hydrocephalus.

Therefore, hydrocephalus can be safely and cost-effectively diagnosed by prenatal ultrasound scans done in 1st and 2nd trimesters of pregnancy.

Objective: The objective of this study was to identify

1. Hydrocephalus by prenatal trans-abdominal ultrasound in women of ages between 21-30 years and 31-40 years

2. Incidence of different central nervous system and extra-cranial congenital abnormalities associated with hydrocephalus

Methods: This was a comparative cross-sectional study, done on 37 patients over a period of 8 months (December 2018 – July 2019) at private ultrasound clinic in Karachi. One participant was excluded from the study because of maternal diabetes mellitus. The study group was divided into 2 groups based on maternal ages (21-30 years and 31-40 years) and transabdominal ultrasound was done in pregnant Pakistani females

Results: The results of the study proved that fetal hydrocephalus was more commonly found in fetuses of mothers of younger age group (21-30 years) with a p-value of (≤ 0.01), with maximum cases being of severe type (63%). It most commonly affected the male gender. Fetal hydrocephalus was found to be more commonly associated with cranial anomalies like spina bifida, meningomyelocele, Dandy Walker syndrome and stenosis of cerebra aqueduct, however, 13 of the diagnosed cases were isolated. Normal volumes of amniotic fluid were found to be associated with fetal hydrocephalus (91.7%). 55.6% patients had a positive family history. p-value of ≤ 0.05 was observed between the measurements of atrium of lateral ventricle and ventricular:hemisphere ratio. Highly significant results (p-value ≤ 0.000) were observed when biparietal diameter (BPD) was compared with measurement of atrium of lateral ventricle.

No correlation was found between BPD and atrium of lateral ventricle measurements, negative correlation was found between head circumference and head: abdominal ratio with atrium of lateral ventricle measurements and a positive correlation was observed between measurements of atrium of lateral ventricle and ventricular: hemisphere ratio.

Conclusion: Transabdominal prenatal ultrasound can hence prove to be a valuable tool in diagnosis of fetal hydrocephalus especially if done in 1^{st} and 2^{nd} trimesters. Hydrocephalus has strong association with male gender, parity, family history and consanguinity. Fetal hydrocephalus is commonly found to be associated with multitude cranial and extracranial anomalies. Therefore, based on these observations and results it is recommended that all pregnant females should undergo transabdominal ultrasound scans as it is a safe, cheap, sensitive and specific tool to diagnose fetal anomalies.

Key words: Hydrocephalus, Ventriculomegaly, Prenatal Ultrasound, Embryological anomalies, Congenital anomalies, biparietal diameter, head circumference, amniotic fluid.

CHAPTER 1

INTRODUCTION

1.1.Morphology:

Brain is divided into forebrain/prosencephalon, midbrain/mesencephalon and hindbrain/ rhombencephalon (Standring, 2015). The prosencephalon consists of diencephalon (thalamus, hypothalamus, epithalamus and subthalamus) and telencephalon (cerebrum). Rhombencephalon is divided into myelencephalon or medulla oblongata and metencephalon (pons and cerebellum) (Patestas & Gartner, 2016). Lying within the brain are 4 fluid filled cavities that make up the ventricular system. These include, a pair of lateral ventricles, 3rd ventricle and 4th ventricle, which in turn communicates via the medial foramen of Magendie with cisterna magna and laterally with cerebellopontine angle via the lateral foramens' of Luschka (Standring, 2015). The lateral ventricles are connected via the *interventricular foramen of Monro* with the 3rd ventricle, while the 3rd ventricle is connected to the 4th ventricle via the *Aqueduct of Sylvius* (figure 1) (Snell, 2010).

1.1.1 Lateral Ventricles:

These are paired horse-shoe shaped structures located in the right and left cerebral hemisphere respectively and are connected to each other via the *septum pellucidum* (Patestas et al., 2016; Standring, 2015). This specific shape of lateral ventricles is due to the anterior and inferior movement of *temporal lobe* by the growing and expanding lobes of the *cerebral hemisphere* (Standring, 2015). As a result of this orientation, the tail of *caudate nucleus* winds around the thalamus in a c-shaped manner and the fornix extends to the interventricular foramen (Standring, 2015).

1.1.1 (A) Parts of lateral Ventricle and Relations:

These are divided into a body, an anterior horn, an inferior horn and a posterior horn (figure 2) (Standring, 2015).

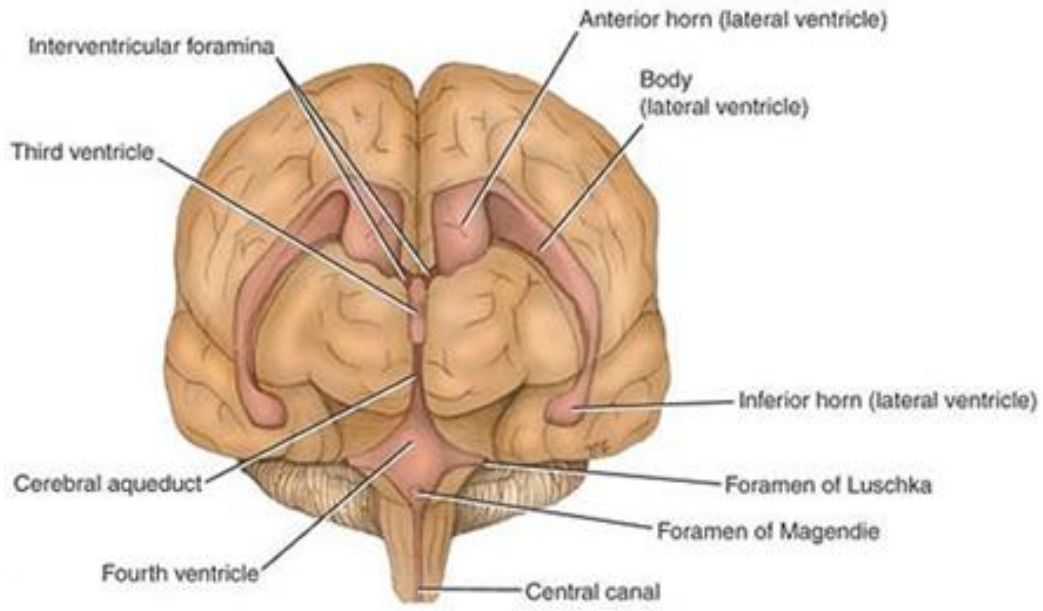


Figure 1: Ventricular System of Brain (*Clinical neuroanatomy, Snell 2010)*

1.1.1 (A i) Body:

Located in the parietal lobe, it extends from the interventricular Foramen of Monro up to the corpus callosum (Waxman, 2010). It is bounded laterally by the caudate nucleus and thalamus, superiorly by corpus callosum, medially by the septum pellucidum (Snell, 2010). Thalamostriate vein and stria terminalis occupy the slit between thalamus and caudate nucleus (Standring, 2015). The atrium or the trigone is the posterior part of the body that widens and becomes continuous with the inferior and posterior horn (Mortazavi, Adeeb, Griessenauer, Sheikh & Shahidi et al., 2014; Waxman, 2010). Its lateral boundary is formed by the decussating fibers of the corpus callosum called the tapetum (Stratchko, Filatova, Agarwal & Kanekar, 2016). The choroid plexus projects through the choroid fissure, a slit between fornix and thalamus (Shenoy & Lui, 2018).

1.1.1(A ii) Anterior horn:

Also known as the frontal horn, extends into the frontal lobe and at the interventricular foramen of Monro is continuous with the body. It is bounded by corpus callosum, caudate nucleus, septum pellucidum and anterior column of fornix which form its roof, floor and medial wall respectively (Snell, 2010).

1.1.1. (A iii) Inferior horn:

It is the largest part, curves around the pulvinar and ends at the uncus. The roof is bounded by tapetum of the corpus callosum, tail of caudate nucleus and stria terminalis (Snell, 2010). The floor is bounded by hippocampus (medially) and collateral eminence (laterally) (Standring, 2015). The choroid flexure lies between fimbria and stria terminalis in the roof of temporal horn (Standring, 2015; Waxman, 2010).

1.1.1. (A iv) Posterior Horn:

Also known as the occipital horn, is the most dependent portion. It is bounded superiorly by the corpus callosum whereas on the medial side is an elevation produced by the walls of the ventricle called the calcar avis and the collateral trigone forms its floor (Stratchko et al., 2016; Waxman, 2010).

1.1.2 Foramen of Monro:

The lateral ventricles are connected by paired, right and left interventricular foramina with the 3rd ventricle. Their shape is dependent on the size of the ventricle, they are small and crescent shaped when the ventricles are small, however, when the ventricles increase in size their shape changes to round. Medial posterior choroidal arteries, superior choroidal vein and septal veins pass through them (Shenoy et al., 2018; Stratchko et al., 2016; Waxman, 2010).

1.1.2 3rd ventricle:

The embryonic forebrain vesicle develops into a narrow slit-like, unilocular cavity, the third ventricle. Its lateral wall is formed by the thalamus, the hypothalamus and the subthalamus. (Corrales and Torrealba, 1976; Mortazavi et al., 2014; Shenoy et al., 2018; Standring, 2015). Hypothalamic sulcus separates the thalamus and hypothalamus (Standring, 2015; Waxman, 2010;). The anterior wall is formed by fornix, anterior commissure, lamina terminalis extending from the optic chiasm to the corpus callousm. The lamina terminalis roofs a small cavity, the cistern of lamina terminalis, which houses the anterior communicating artery, an aneurysm of which can be the cause of interventricular hemorrhage (Standring, 2015). The ventrally descending floor is formed by optic chiasma, tuber cinereum, infundibulum, mammillary body, posterior perforated substance and tegmentum of midbrain in sequence from above downwards (Shenoy et al., 2018). A triangular fold of pia mater, the tela choroidea, from which extends the choroid plexus hangs, form the roof of the 3rd ventricle (Shenoy et al., 2018; Waxman, 2010). 3rd ventricle forms 5 recesses, (Mortazavi et al., 2014; Shenoy et al., 2018; Waxman, 2010).

- Optic – between optic chiasm and lamina terminalis
- Infundibular – into the pituitary stalk
- Pineal – into the stalk of pineal body
- Suprapineal - also known as the pressure diverticulum of the 3rd ventricle, lies above the pineal recess, lined by ependyma and becomes dilated in hypertensive hydrocephalus
- Anterior – bounded by anterior commissure and fornix

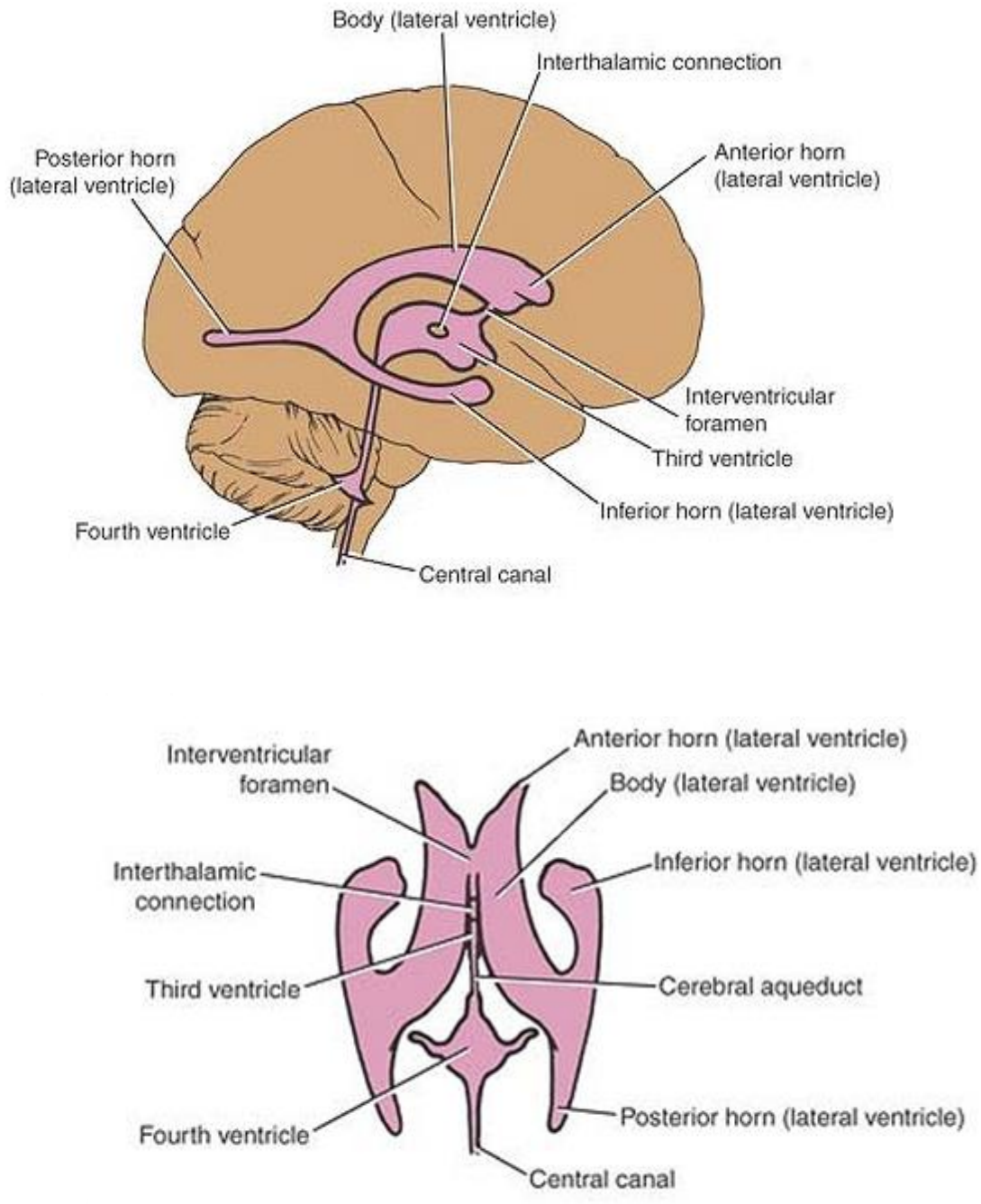


Figure 2: Parts of Lateral Ventricle and Interventricular Foramen of Monro (*Clinical neuroanatomy, Snell 2010)*

1.1.4 Cerebral Aqueduct of Sylvius:

As cited by Leite Dos Santos, it was first illustrated by Leonardo Da Vinci and described in 1521 by Berengarius Carpensis. It is named after a Dutch anatomist, François de le Böe (or Franciscus Sylvius in the Latinized form). The word Aqueduct is derived from a Latin word "aqueductus" in 1587 (Leite Dos Santos, Fratzoglou & Perneczky, 2004; Longatti, Fiorindi, Perin & Martinuzzi, 2007). It is a small, circular tube, 1-2 mm in diameter, allows the drainage of CSF from the 3rd to the 4th ventricle (Standring, 2015; Stratchko et al., 2016). It is divided into 3 parts by Woollam and Millen, pars anterior, ampulla and pars posterior (as cited in Mortazavi et al., 2014). It is 18 mm long and is the most common site of obstruction as it is the narrowest part of the ventricular system (Mortazavi et al., 2014; Snell, 2010).

1.1.5 4th ventricle:

Fourth ventricle is an irregular, tent/pyramid shaped cavity between the cerebellum and the brainstem. Lying in the posterior fossa, it is bordered by pons and medulla ventrally, laterally by the cerebellar peduncles and cerebellum dorsally and extends from the cerebral aqueduct to the obex (Mortazavi et al., 2014; Waxman, 2010). Laterally it is bounded by the superior cerebellar peduncles superiorly and caudally by the gracile and cuneate nuclei and the inferior cerebellar peduncles. The floor is divided into 3 triangles, upper, behind the pons; middle, formed by stria medullaris and lower, behind the medulla (Shenoy et al., 2018). Median sulcus divides the floor into two halves (Standring, 2015). Each half has sulcus limitans, medial to which is the medial eminence formed by the facial colliculus and lateral to it is the vestibular area containing the vestibular nuclei. The superior part of the sulcus is called superior fovea, superior to which is the bluish area called substantia ferruginea. Inferiorly is the inferior fovea, inferior to which is the sulcus limitans dividing the medial eminence into a hypoglossal and vagal triangle superiorly and inferiorly respectively Three triangles are present in the floor, hypoglossal, vagal and area postrema from medial to lateral (Matsushima, Rhoton & Lenkey, 1982; Snell, 2015). Roof is formed by superior cerebellar peduncles separated by superior medullary vellum. This superior medullary vellum is continuous with the white matter and is covered by superior vermis

(Standring, 2015). The inferior medullary vellum lacks neural tissue and is instead covered by ependyma and pia matter of the tela choroidea. A large opening, foramen of Magendie, is present in the roof which allows communication of 4th ventricle with the Cisterna Magna (Shenoy et al., 2018).

1.2 Embryology:

Numerous coordinated events lead to the development of central nervous system. Most of these processes occur prenatally while some continue in adulthood. It begins with the thickening of a fold of specialized ectoderm known as the neural tube at 3rd week of development and extends up to adolescence and involves gene expression and environmental factors (figure 3) (Lenroot & Giedd, 2006; Stiles & Jernigan, 2010).

Notochord induces the overlying ectodermal cells to thicken and form a plate of elongated thickened epithelial cells called neural plate. Being present dorsal to the notochord, it initially is of the same length as the notochord itself. (Moore, Persaud, & Torchia, 2011; Volpe, Inder, Darras, de Vries & du Plessis et al., 2017). However, later it grows and broadens to extend as far as the oropharyngeal membrane and ultimately extends beyond the notochord (Moore et al., 2011). By day 18 the neural tube starts to invaginate along its central axis to form a midline groove, the neural groove. This groove on either side has neural folds which are much more obvious on the cranial end (Sadler, 2011). These neural folds approach each other and begin to fuse, thereby converting the neural plate into neural tube which marks the primordium of central nervous system. Eventually this neural tube separates from the surface ectoderm by the 4th week of gestation (Schoenwolf, Bleyl, Brauer, & Francis-West, 2014). The neural tube up to the fourth somite, is wide and broad and gives rise to the brain, whereas the beyond the fourth somite it forms the spinal cord. The expanded cranial end forms the forebrain and this differentiation into fore, mid and hind brain is prominent in very early on (figures 3 and 4) (Moore et al., 2011; Sadler, 2011; Schoenwolf et al., 2014).The rostral neuropore closes by 25th day whereas the caudal neuropore closes 2 days later that is approximately at day 27 (Moore et al., 2011).

The neural crest cells which are present along the inner margin of neural plate begin to separate from the ectoderm. These cells assume a flattened irregular appearance and they later detach and divide into right and left halves which migrate dorsal to the neural tube.

Neural crest cells are the precursors of ganglia of cranial and spinal nerves (Moore et al., 2011; Schoenwolf et al., 2014).

1.2.1 Brain Vesicles and Flexures:

As the rostral neural pore closes, the neural tube develops 3 primary brain vesicles (figure 5) (i) The prosencephalon or forebrain (which at 5th week divides into telencephalon and diencephalon), (ii) mesencephalon (forms the mid brain) and (iii) rhombencephalon (which divides into metencephalon and myelencephalon). Eventually 5 brain vesicles form (figure 5). The midbrain flexure and the cervical flexure appear due to the rapid growth and ventral bending of the embryonic brain. Pontine flexure appears due to the unequal growth between the first two flexures. The appearance of pontine flexure results in the division of the rhombencephalon into metencephalon, which forms the pons and cerebellum and myelencephalon which develops into the medulla oblongata (Moore et al., 2011).

1.2.1.A Hindbrain:

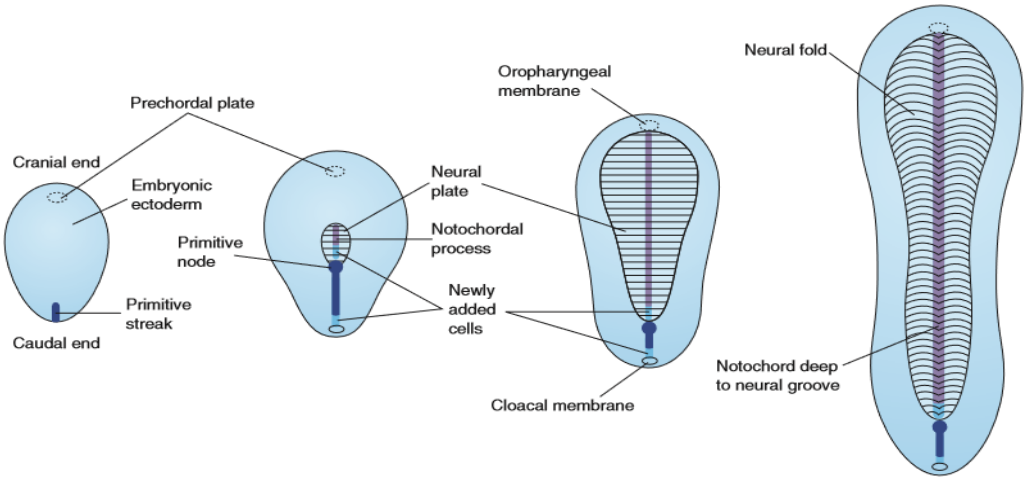
Cervical flexure separates the hindbrain from the spinal cord. The pontine flexure divides the hindbrain into myelencephalon and the metencephalon, which later develop to form the medulla oblongata and the pons and cerebellum respectively. Fourth ventricle and the central canal develop as the cavity of the hindbrain (Moore et al., 2011; Sadler, 2011).

1.2.1.B Midbrain:

This part undergoes the least changes during development. Neural canal in this region becomes narrow and forms the cerebral aqueduct (Sadler, 2011).

1.2.1.C Forebrain:

Optic vesicles appear as outpouchings on the lateral side after the closure of rostral neuropore. The telencephalic vesicles appear rostrally and dorsally. The cavities of the primordial cerebral hemispheres develop into lateral ventricle. The cavities of telencephalon and diencephalon (forming the rostral and the caudal parts of the cerebral hemispheres) form lateral and third ventricle respectively (Moore et al., 2011; Sadler, 2011).



Diagrammatic sketches of dorsal views of the embryonic disc showing how it lengthens and changes shape during the third week. The primitive streak lengthens by addition of cells at its caudal end, and the notochordal process lengthens by migration of cells from the primitive node. The notochordal process and adjacent mesoderm induce the overlying embryonic ectoderm to form the neural plate, the primordium of the CNS. Observe that as the notochordal process elongates, the primitive streak shortens. At the end of the third week, the notochordal process is transformed into the notochord.

Figure 3: Formation of notochord (*The Developing Human Moore et al., 2011)*

Scanning electron micrograph of a Macaque embryo comparable to a 20-day human embryo. The neural plate is clearly visible, and the expansions that will become the major subdivisions of the brain are apparent (arrows). Only a small region of the primitive streak remains. The primitive streak will disappear on day 25.

Figure 4: Development of Neural Plate (*Larsen's human embryology, Schoenwolf, 2014)*

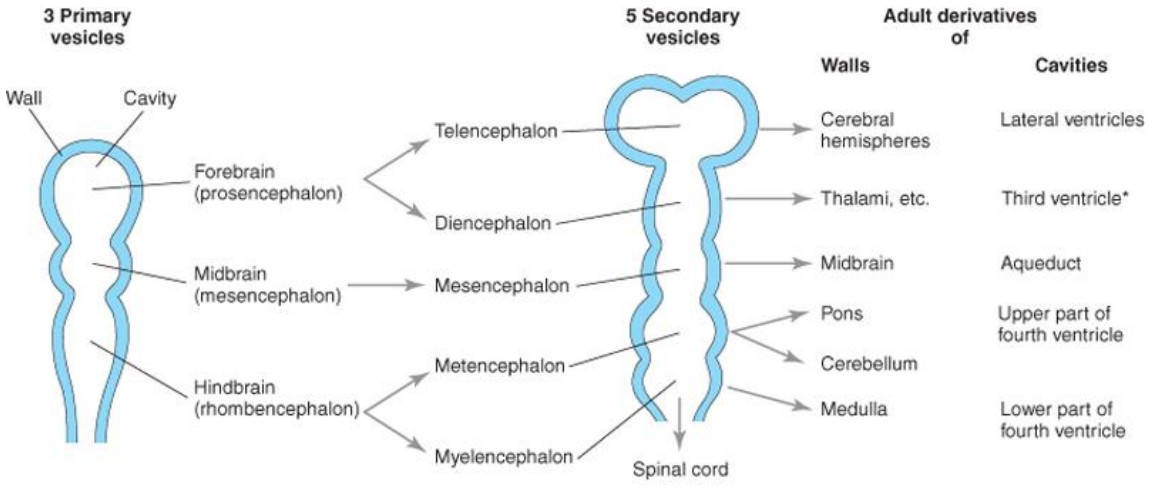


Figure 5: Formation of Primary and Secondary Brain Vesicles (*The Developing Human Moore et al., 2011)*

12.2 Development of spinal and cranial meninges

Primordial meninx is formed by the thickening of the mesenchyme surrounding the neural tube. The external layer of this later forms the dura mater. The internal layer, also known as the leptomeninges, consisting of pia and arachnoid mater, is derived from neural crest cells. Spaces which appear with in the leptomeninges merge to form the subarachnoid space (Moore et al., 2011).

1.3 **Histology**:

Choroid plexus present in the roof of ventricles is extremely vascular. It is highly folded and projects into the cavities of the ventricles (Junqueira, 2013). Each choroidal villus comprises of pia matter which is rich in capillaries and is covered by a layer of cuboidal cells forming the ependyma. The cells are connected via tight junctions on their lateral surface and have microvilli and cilia on the apical surface (figures 6 and 7) (Junqueira, 2013; Sakka, Coll & Chazal, 2011, Snell, 2010).

1.4. Cerebrospinal Fluid:

Cerebrospinal fluid (CSF) which is a clear, colorless fluid without any smell or odour surrounds the brain and spinal cord and has low concentrations of proteins and cells (Bim, Pinotti, Cmilo, Maset & Mansur et al., 2018; Sakka et al., 2011). The main purpose of this fluid is to protect the brain by acting as a mechanical shock absorber and to control, adjust and preserve the balance of ions. Besides these, it has major role in nutrient and protein distribution, eliminating metabolites and harmful substances and above all takes part in immune mechanism by distributing antibodies (Adam, Táaborsk, Sobek, Hildebrand & Kelbich et al., 2001; Bim et al., 2018).

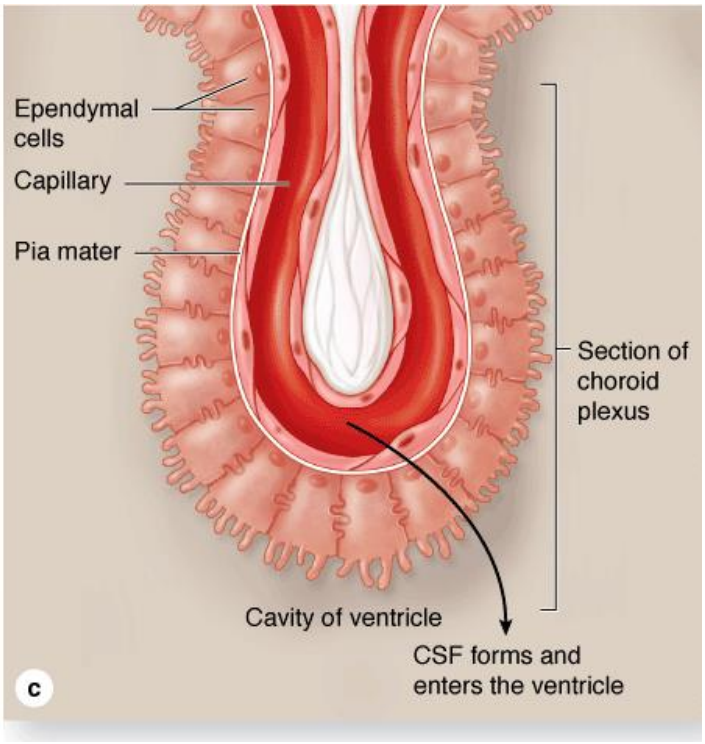


Figure 6: Choroid Plexus Consisting of Ependyma and Pia Matter (*Junqueira's Basic Histology, Junqueira, 2013*)

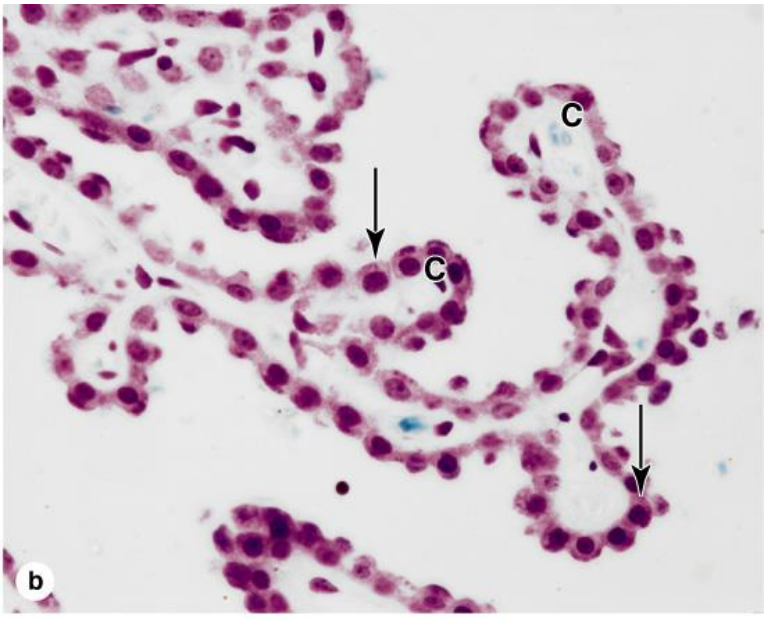


Figure 7: Vascularized Choroid Plexus with Capillaries and Cuboidal Epithelium (*Junqueira's Basic Histology, Junqueira, 2013*)

1.4.1. Composition:

Being odorless, it is also a hypooncotic and isosmotic fluid with a low concentration of Na^+, K^+ and Ca^+ and a higher concentration of Cl^- and Mg^+ than that of plasma (Adam et al., 2001). However, Sakka et al reported in their study a higher concentration of Na^+ which observes a *"chronobiological rhythm"* showing a peak in its values during the day i.e. 8 am to 6 pm (Harrington, Salomon, Pogoda, Oborina & Okey et al., 2010; Sakka et al., 2011). Glucose is >50% than that of serum (50–85 mg/100 ml) and protein is 15–45 mg/100 ml (Adam et al., 2001; Snell, 2010).

1.4.2 Pressure and Volume:

Pressure of CSF is 60–150 mm of water. Posture is the main factor that determines the normal intracranial pressure (Snell 2010). It varies between 5 mmHg and 15 mmHg when a person is lying in supine position and this range may vary from -5 to +5 mmHg when a person stands erect (Leinonen, Vanninen & Rauramaa 2018).

1.4.3. Secretion:

Eighty percent (100ml) of CSF volume being present outside the brain is extracerebral (subarachnoidal) and the remaining 20% (25ml) being present within the ventricles is intraventricular (Adam et al., 2001; Bim et al., 2018; Keep, Jones & Drewes, 2018; Leinonen et al., 2018; Sakka et al., 2011;). 80% of it is produced as an ultrafiltrate of blood by the choroid plexuses of ventricles but mostly by plexus present in the roof of lateral ventricle (Brinker, Stopa, Morrison, & Klinge, 2014; Patestas et al., 2016). The remaining 20% comes from the brain parenchyma and ependyma. It is produced at a rate of 20 ml/hr (0.35 – 0.40 ml/min) or 500 ml/day and the total volume being 150 ml with a unidirectional pulsatile flow in a rostrocaudal direction within the ventricles and a multidirectional flow in subarachnoid space (Brinker et al., 2014; Sakka et al., 2011; Standring, 2015; Yamada & Kelly, 2016). Its flow is regulated by pulse waves and varies with respiration (Sakka et al., 2011; Yamada et al., 2016; Yamada, Miyazaki, Yamashita, Ouyan & Yui, et al., 2013).

1.4.4 Flow:

After its production in the lateral ventricles CSF passes through the interventricular foramen of Monro to the 3rd ventricle (figure 8). Then via the cerebral aqueduct it enters the 4th ventricle and eventually enters the subarachnoid spaces via foramen of Magendie (median aperture) and foramen of Luschka (lateral apertures) (Hartman, 2008; Sakka et al., 2011; Snell, 2010). It then passes into cerebellomedullary (cisterna magna) and pontine cisterns via the tentorium cerebelli and finally it approaches the superior surface of cerebral cortex from where it is absorbed via the arachnoid granulations into the superior sagittal venous sinus (Snell, 2010). Some CSF also passes caudally to the spinal subarachnoid space and then to the cauda equina which is a dead end and here its absorption depends on the pulsations of vertebral and spinal arteries (Snell, 2010). Some of the CSF also drains via cribriform pate into the lymphatic channels within the walls of cerebral capillaries and into the lymphatic channels present in the dural venous sinuses (Leinone et al., 2018).

1.4.5. Absorption:

Absorption of CSF is via arachnoid villi (figure 9). These are endothelium lined finger like projections of the arachnoid matter which infiltrate the dura matter and project into the venous sinuses. (Junqueira, 2013; Pollay, 2010; Sakka et al., 2011;). To ensure appropriate drainage a pressure difference of 3 – 5 mmHg should be present between dural venous sinuses and subarachnoid space (Pollay, 2010). CSF has also been known to be absorbed into the lymphatic system, like the lymphatics of nasal system and then onto the cervical group of nodes via the cribriform plate and the lumbar nodes via the spinal nerve roots (Keep et al., 2018).

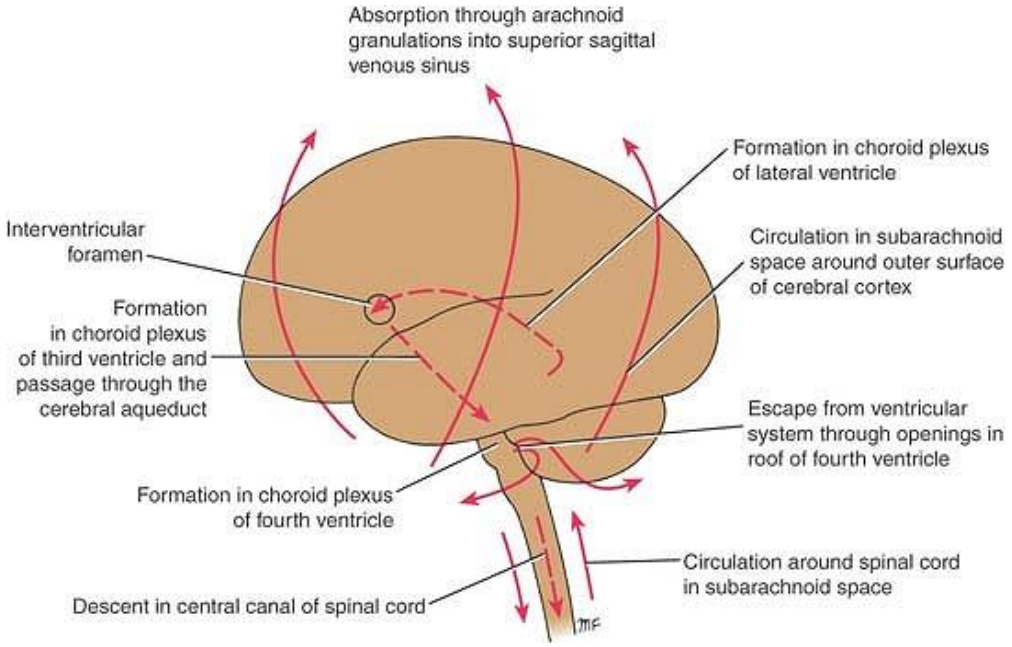


Figure 8: Flow of Cerebrospinal fluid (*Clinical neuroanatomy, Snell 2010)*

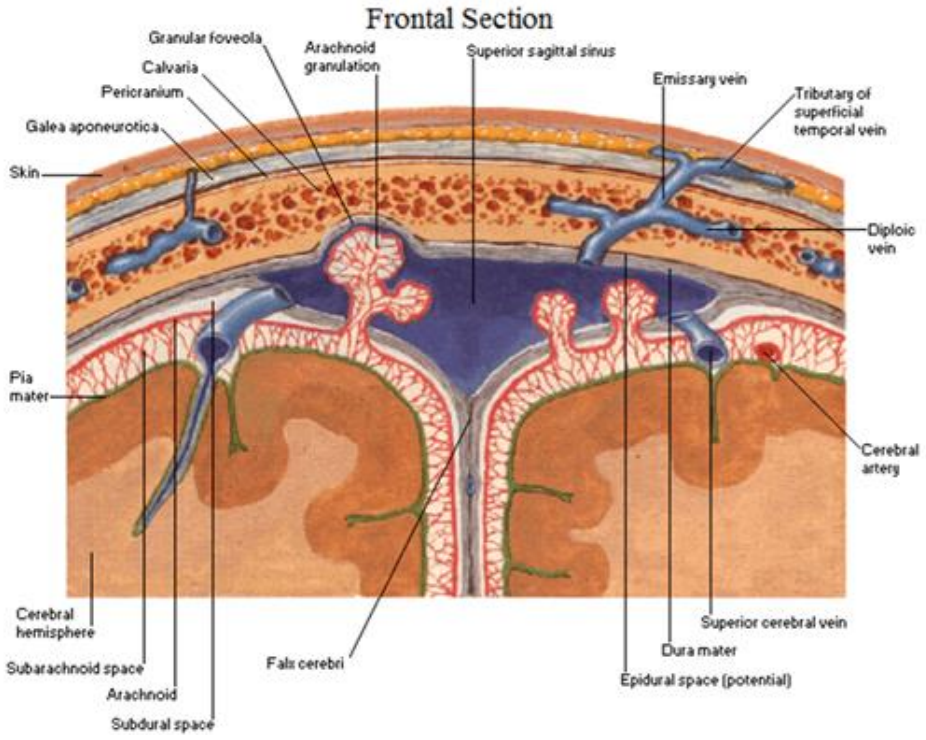


Figure 9: Arachnoid Granulations and Superior Sagittal Sinus *(Atlas of Human Anatomy, Netter Clinical neuroanatomy, Snell 2019)*

1.5. Epidemiology of Hydrocephalus:

Dewan et al., in their systematic review projected highest incidence of congenital hydrocephalus (CH) in Africa (145/ 100,000 births) and Latin America (316/100,000 live births) and lowest rates of 68/100,000 live births was noted in United States of America and Canada (Dewan, Rattani, Mekary, Glancz & Yunusa et al., 2018). Retrospective study conducted by Ekanem et al., in 2 provinces of Nigeria reported the prevalence 0.34/ 1000 births (Ekanem, Okon, Akpantah, Mesembe & Eluwa et al., 2008). Garne et al., reported a prevalence of 4.65/10,000 in four European regions and 8.1/10,000 live births was reported (Garne, Loane, Addor, Boyd & Barisic et al., 2005). An increase in total prevalence was noted because of increase in prenatal diagnosis which lead to termination of pregnancy because of this reason *live birth prevalence* of hydrocephalus has been reduced (Garne et al., 2005).

Munch et al., reported a prevalence of 1.1/1000 live births and 75% of these diagnosed cases have at least one other affected family member (Munch, Rostgaard, Rasmussen, Wohlfahrt & Juhler et al., 2012). Isaacs et al., in their metanalysis and systemic review observed a prevalence of 88/100,000 in children, 11/100,000 in adults and 175/100,000 in old age group (Isaacs, Riva-Cambrin, Yavin, Hockley & Pringsheim, 2018). A significantly higher prevalence was noted in countries with low income rates as compared to well-developed countries with a higher income rate (Hauerberg, Skibsted, Graem, & Maroun, 2012; Vogt, Blaas, Salvesen, & Eik-Nes, 2012).

Fernell et al., noted a prevalence of 13.69 per 1000 birth during the year 1991 – 1994 (Fernell, & Hagberg, 1998). Whereas Dai et al., report a prevalence of 7.03/10,000 live births (Dai, Zhou, Miao, Zhu & Wang et al., 2006) and a prevalence of 9.26/ 10,000 live births was observed by Huang et al., from 2006 to 2015 (Huang, Wu, Chen, Jiang & Gong et al., 2018). Salat et al., reported an incidence of 1 /1000 live births in Pakistan (Salat, Enam, Kazim, Godil & Enam et al., 2012).

1.5.1 Classification of Hydrocephalus:

In the year 1919, Dandy established models to explore and examine the pathophysiology of hydrocephalus. By these experimental models the author was also able to develop various therapeutic modalities for the treatment of hydrocephalus (Rekate, 2009). Based on these models the author was the first person who was able to establish and devise a simple model for the classification of hydrocephalus into communicating (without any obstruction in the flow of CSF) and non-communicating, where there is an obstruction in the flow of CSF (Rekate, 2011& Rekate, 2009).

Over the years numerous researchers have attempted to classify hydrocephalus. Raimondi called it as *"water head"* due to accumulation of CSF and therefore was able to incorporate all forms and states where with an increased amount of intracranial fluid under one umbrella, hydrocephalus, regardless of causes, risk factors, etiologies (Raimondi, 1994).

Mori et al., 1995, in their study conducted on 1450 Japanese cases of hydrocephalus, were able to categorize hydrocephalus by the impact of treatment modality (Mori, Shimada, Kurisaka, Sato & Watanabe, 1995).

In the context of obstruction in the flow of CSF Oi et al., 2006, classified it as (i) primary – due to obstruction at one specific point which may be due to a malformation like Arnold Chiarii malformation (ii) secondary – due to bleeding or hemorrhage with in the brain or due to any other cause like a tumor growth or mass (Oi & Di, 2006).

In another review article the author, Shakeri et al., categorized hydrocephalus on the basis of CSF pressure as (i) normal pressure, where in the pressure of CSF is within the normal range, (ii) high pressure where in the pressure of CSF is way higher than the normal range, and lastly as (iii) hydrocephalus due to stenosis of cerebral aqueduct of Sylvius. The author was also noted the frequencies as 47%, 27% and 15% respectively (Shakeri, Vahedi & Lotfinia, 2008).

Several other authors have classified hydrocephalus into (i) communicating hydrocephalus, due to inefficient absorption of CSF via the arachnoid granulations into the superior sagittal sinus (ii) non-communicating or obstructive due to any impedance in the flow (Liu et al., 2018; Shakeri et al., 2008). Non-communicating hydrocephalus has been further sub-

grouped into (i) acquired type of hydrocephalus and (ii) congenital type (Kalyvas, Kalamatianos, Pantazi, Lianos & Stranjalis et al., 2016).

Kalyvas et al has described CH as that which develops during infancy period, exhibits at birth and usually has no known causative factor associated with it (Kalyvas et al., 2016).

A very simple classification has been proposed by Tully et al., Hydrocephalus occurring at birth is congenital, one that is due any extrinsic cause like hemorrhage, infection or mass is acquired. Other types include obstructive due to any obstruction in the flow, communicating, syndromic which presents itself in relation to other conditions and non-syndromic where in the findings are restricted only to regions of central nervous system (Tully, Capote & Saltzman, 2015).

1.5.2 Risk factors of Hydrocephalus:

The etiology of CH is broad and extensive and ranges from unknown and idiopathic to defects in structure to chromosomal abnormalities (Kalyvas et al., 2016).

Mass or tumor growth, hemorrhage, infections like meningitis, cytomegalovirus, toxoplasmosis, prenatal intraventricular hemorrhage and drugs like misoprostol, metronidazole, antidepressants are some of the known causes of acquired hydrocephalus.

Stenosis of aqueduct most likely due to hemorrhage and obstructive cysts are some of the causes of non-communicating hydrocephalus (Tully, Ishak, Rue, Dempsey & Browd et al., 2016).

Communicating hydrocephalus has been found to be due to hemorrhage which can affect both production of CSF by the choroid plexus as well as its reabsorption via the arachnoid granulations (Govaert, Oostra, Matthys, Vanhaesebrouck & Leroy, 1991).

Syndromic form of hydrocephalus is due to L1CAM associated mutation, Fried syndrome, Walker-Warburg/Muscle -Eye-Brain disease (Tully & Dobyns, 2014).

Lesions of the brain like holoprosencephaly, agenesis of corpus callosum, lissencephaly are also some of the other causes of hydrocephalus as identified in literature by several authors (Paul, Brown, Adolphs, Tyszka & Richards, et al., 2007; Plawner, Delgado, Miller,

Levey, & Kinsman et al., 2002; Sheen, Basel-Vanagaite, Goodman, Scheffer & Bodell et al., 2004).

Maternal hypertension, diabetes, drugs like antidepressants, alcohol and illicit drug abuse and congenital infections are some more risk factors identified in literature and known to cause fetal hydrocephalus (Morisaki, Togoobaatar, Vogel, Souza, & Rowland et al., 2014; Tully, Capote, & Saltzman, 2015).

1.5.3 Associations of Hydrocephalus:

Several cranial and extra cranial congenital abnormalities have been citied in literature which are known to be associated with hydrocephalus. Some of these can be very easily identified on ultrasound scan done prenatally. A Sudanese study conducted by Mahmoud et al., (2014), observed cerebral aqueductal stenosis to be most commonly and repeatedly occurring anomaly with hydrocephalus (Mahmoud, Dinar, Abdulla, Babikir & Sulieman 2014).

Spina bifida is found to be associated in 30% cases, Arnold Chiari malformation is found in 20% cases, and Dandy Walker malformation in 5 % cases (Mahmoud et al., 2014; Tully et al., 2014). Gastroschisis, diaphragmatic hernia, ventricular septal defect, tetralogy of Fallot and several urinary system abnormalities have also been known to be associated with CH (Hauerberg, Skibsted, Graem, & Maroun, 2012; Vogt et al., 2012).

15.4 Diagnosis of Hydrocephalus:

With advent of new era, advancement and upgradation of the technology used for ultrasound and with the development and enhancement of expertise of sonologists the diagnosis of congenital abnormalities and malformations during prenatal scans has become an easy task (Hauerberg et al., 2012; Vogt et al., 2012). Decades of work and researches prove that ultrasound scans done prenatally is not only one of the safest, useful, most sensitive tests but also one of the cheapest and most easily accessible even in developing countries (Ortega, Muñoz, Luza, Guerra & Guerra et al., 2016). Sensitivity of ultrasound scan was noted to be 93.5% by Addario et al., (2012), especially if it is performed in the early weeks of gestation (24 weeks). However, the author also observed a decline in its

sensitivity during later weeks of gestation, most likely due to the progressive course of disease itself (D'addario, & Rossi, 2012).

The meeting point of the occipital horn, temporal horn and body of the lateral ventricle is called the atrium. Scans done in axial planes allow maximum visualization of the frontal horns and the atria of the lateral ventricles, thereby stressing the importance of early diagnosis of hydrocephalus (D'addario et al., 2012). Atrial width remains stable between 15 – 40 weeks at <10mm, however, any increase in this measurement falls into the category of hydrocephalus (D'Antonio & Zafeiriou, 2018; Emery, Hogge & Hill, 2015).

1.5.5 Impact of Hydrocephalus:

The severity and gravity with which hydrocephalus presents itself determines its clinical consequence and future implications on the patient (Munch et al., 2012). Due to raised CSF pressure the affected are at risk of developing impaired cognitive function, memory problems, impediment in planning and organizing, visual field defect and cerebral palsy (Dreha-Kulaczewski, Joseph, Merboldt, Ludwig & Gärtner et al., 2017; Fernell & Hagberg, 1998; Lindquist, Persson, Fernell & Uvebrant, 2011). Infantile hydrocephalus: declining prevalence in preterm infants. *Acta Paediatrica*, 87(4), 392-396). About 8% fetuses with mild-moderate and 58% with severe hydrocephalus endure atypical neurodevelopment (D'Antonio et al., 2018).

Munch et al observed a recurrence risk of 56% in twins having the same gender, 7% recurrence risk was observed in 1st degree relatives and 2 % in 2nd degree (Munch et al., 2012).

1.5.6 Management of Hydrocephalus:

The management starts with observations and placement of the affected in neonatal intensive care unit where they can be observed closely (Pisapia, Sinha, Zarnow, Johnson & Heuer, 2017). However, with obvious and massive ventricular dilation and CSF pressure and volume abnormalities, options of ventricular shunt, endoscopic 3rd ventriculostomy or options of draining the fluid externally are available (Pisapia et al., 2017; Venkataramana, 2011; Wang, Lee, Kim, Phi & Cho, 2011).

1.6 Hypothesis

- Incidence of hydrocephalus is more common in women of 31-40 years
- Incidence of congenital hydrocephalus occurs commonly with other central nervous system and extra-cranial congenital abnormalities

1.6.1. Null Hypothesis

- Incidence of hydrocephalus is not common in women of ages 31-40 years on pre-natal transabdominal ultrasound
- Hydrocephalus is not associated with different central nervous system and extra-cranial congenital abnormalities

1.6.2 Alternate Hypothesis

- Incidence of hydrocephalus is common in women of ages 31-40 years on prenatal transabdominal ultrasound.
- Hydrocephalus is associated with different central nervous system and extra-cranial congenital abnormalities

1.7 Objectives of the Study

The objective of this study was to identify:

1. Hydrocephalus by prenatal trans-abdominal ultrasound in women of ages between 21-30 years and 31-40 years

2. Incidence of different central nervous system and extra-cranial congenital abnormalities associated with hydrocephalus

1.8 Statement of Problem:

The enlargement of the ventricles of the brain is mostly due to an overproduction of CSF by the choroid plexus of ventricles or it's under absorption via the arachnoid villi into the superior sagittal sinus, this condition is commonly known as hydrocephalus. This excess in the volume of cerebrospinal fluid (CSF) in turn can lead to a raised intracranial pressure.

The ventricular system being related to several important structures like basal nuclei, thalamus, corpus callosum, optic chiasm, pituitary stalk and various other anatomically and functionally important areas, can be a major cause of various debilitating and serious complications in children.

Literature on the other hand also has proven congenital hydrocephalus to be a very common occurring condition causing cognitive impairment, defects in vision, cerebral palsy etc. It can be fatal to the children on one hand while it can cause severe maternal bleeding and maternal death on the other. Keeping these serious complications in view, both maternal and fetal, early in-utero identification of hydrocephalus and its associated congenital anomalies is critical so as to provide the parents with a choice of opting for termination of pregnancy or to rehabilitate the affected child after birth or opt for surgical options like in-utero ventriculo-peritoneal shunt surgeries. These options would not only reduce the disease burden and improve the quality of life but also reduce fetal and maternal mortality rate.

1.9 Significance of Study

Prenatal anomaly scan is a routinely done scan in each pregnancy. This study will help bring forth the early diagnosis of congenital hydrocephalus by a safer, cheaper and non-invasive technique which will help reduce the burden of the disease as it can lead to mental retardation and multiple other debilitating conditions which can increase the disease burden and severely affect the state of living of the affected person.

The diagnostic parameters described and used in this study can be used in future to diagnose hydrocephalus prenatally. This study will enable the parents and the clinician to decide the best method to deal with such cases. The clinicians will be able to council the parents about rehabilitation, termination of pregnancy and treatment modalities like ventriculoperitoneal shunting which can be done both prenatally and postnatally. Hence, early diagnosis enables quicker decisions as termination of pregnancy even on medical grounds not just bears a higher risk factor to the health of the mother as pregnancy progresses but also has religious factors and concerns attached to it.

1.10 Operational definitions

1.10.1 Atrium of lateral ventricle

Is defined as

- The point of union of body, posterior horn and temporal horn of lateral ventricles is termed as the atrium
- *mild: 10-12mm*
- *moderate: 12.1-14.9 mm*
- *severe: greater than or equal to15 mm*

  (Mari, G., Norton, M. E., Stone, J., Berghella, V., Sciscione, A., Tate, D., & Schenone, M. (2018). Seven recommendations for mild fetal ventriculomegaly. Contemporary OB/GYN, 63(8), 9-32).

1.10.2 Hydrocephalus:

is defined as

- A mean increase in head circumference greater than 2 standard deviation of the mean
- Increased cerebral fluid volume as detected by ultrasound, showing ventricular dilatation by showing an abnormal ventricular:hemisphere ratio (from falx cerebri – lateral ventricle)
  (Benacerraf, B. R. (1988). Fetal hydrocephalus: diagnosis and significance. Radiology, 169(3), 858-859).

1.10.3. Congenital Anomaly/ malformation:

- Any structural or anatomical defect, including malformation, deformation, disruption or dysplasia, that is present at birth and which can be detected on transabdominal prenatal ultrasound

(Levi, S., Hyjazi, Y., Schaapst, J. P., Defoort, P., Coulon, R., & Buekens, P. (1991). Sensitivity and specificity of routine antenatal screening for congenital anomalies by ultrasound: the Belgian Multicentric Study. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology, 1(2), 102-110).

1.10.4 Polyhydramnios:

- A condition in which amniotic fluid volume is greater than normal for that gestational age

- Amniotic Fluid index greater than or equal to 24

  (Alavi, A., Mosallanezhad, N., Hamadiyan, H., Oskooe, S., Amin, M., & Dolati, K. (2016). Cutoff point amniotic fluid index and pregnancy prognosis in the third trimester of pregnancy in Shariati Hospital of Bandar Abbas in 2013-14. IJMRHS, 5(12), 212-216).

CHAPTER 2

Literature Review

Hydrocephalus was first identified in the year 460 BC by Hippocrates. The author identified the symptoms of headache, vomiting and visual disturbance to liquefaction of brain (Aschoff, Kremer, Hashemi & Kunze, 1999). This discovery was later endorsed in the year 130 AD by Galen and several Arabian physicians added to the finding of enlarged brain (Venkataramana, 2011). Aschoff et al., (1999) suggested that hydrocephalus developed due to '*extracerebral collection of water'*. The basic understanding of the ventricles of the brain and the flow of cerebrospinal fluid within them was provided by Thomas Willis in the 17th century. In the late 17th and 18th century scientists, Francis Sylvius, Alexander Monroe and Francois Magendie were able to make significant discoveries about Aqueduct of Sylvius, foramen of Monro and foramen of Magendie (Venkataramana, 2011). However, Key and Retzeus in the year 1886 were able to decipher the current perceptions and concepts of the flow of CSF (Venkataramana, 2011).

Dilatation of the brain ventricular system is due to any discrepancy between production and absorption of CSF and results in the accumulation of fluid in the ventricular system of the brain. This condition has been labeled in literature as hydrocephalus (Jouibari, Baradaran, Amiri, Nejat & El Khashab, 2010; Walsh, Donnan, Morrissey, Sikora & Bowen et al., 2017). Literature also classifies it as ventricular dilatation which may or may not occur with CSF obstruction (Kashyap, Pradhan, Singh, & Yadav, 2015; Pretorius, Davis, Manco-Johnson, Manchester & Meier et al., 1985; Smith, 2007; Volpe, 2008).

CSF, which is an ultrafiltrate of blood, is produced by choroid plexuses of the lateral, 3rd and 4th ventricles, it then flows through-out the ventricular system and eventually leaves the system, passes into the subarachnoid space and at last is resorbed via the arachnoid granulations into the systemic circulation via the dural venous sinuses (Pretorius et al., 1985).

An incidence of 0.2 – 2 /1000 live births was observed in a study conducted in Pakistan (Rehman, Bukhari & Abid, 2015). Murshid et al., observed a prevalence of 1.6/ 1000 live births in a study conducted in Madina Munawarah, Saudia Arabia (Murshid, Jarallah & Dad, 2000). A very high prevalence of 4-12/10000live births was found in Chinese population and 0.4/10000 live births in Sudanese population (Mahmud et al., 2014; Yi, Wan, Deng, Li & Deng et al., 2017). Huang et al., (2018) observed in their study a very high prevalence of 13.73/10,000 in Chaoyang city of China. Previous literature has shown a decline in the development of congenital hydrocephalus in Asian population but Yi et al., (2017) in their comparative study proved contradictory results and observed a higher incidence in Asian race in comparison to European and those of US descent (Yi et al., 2017). Another important point highlighted in the study was the fact, that the widespread use of folic acid during gestation showed a decline in the incidence of congenital hydrocephalus (Yi et al., 2017). Literature also labeled the legal termination of pregnancy on medical grounds as another important factor contributing to the decline in the number of cases of hydrocephalus (Huang et al., 2018; Jeng, Gupta, Wrensch, Zhao & Wu, 2011; Kashyap, 2015; Mahmoud et al., 2014). The recurrence risk was noted to be 1.4 – 4 % in siblings (Mahmoud et al., 2014) and 28.6 in monozygotic twins (Munch, Rasmussen, Wohlfahrt, Juhler & Melbye, 2014).

Fifty percent of all hydrocephalus is of congenital type and its etiology is variable (Verhagen, Schrander-Stumpel, Krapels, Die-Smulders & Van Lint et al., 2011). Literature has revealed a multitude of causes and risk factors for hydrocephalus and based on the causal factors hydrocephalus is classified as congenital, which occurs without any known cause and acquired which occurs during postnatal time duration and is due to multiple causative agents (Kalyvas et al., 2016). These causative factors include infections like toxoplasmosis, cytomegalovirus, mass, tumors, hemorrhage, traumatic brain injury, teratogens etc (Van Landingham, Nguyen, Roberts, Parent & Zhang, 2009; Verhagen, 2011). Van Landingham et al., (2009) in their study found maternal diabetes as a major risk factor to be associated with congenital anomalies especially neural tube defects and defects of cardiovascular system. Maternal hypertension and obesity were also identified as risk factors (Stothard, Tennant, Bell & Rankin, 2009; Van Landingham et al., 2009). Use of vaginal metronidazole, selective serotonin reuptake inhibitors by the mother during

2nd and 3rd trimester showed a high relative risk of congenital hydrocephalus in fetus (Munch et al., 2014). Liu et al., (2018) identified vitamin deficiencies like B12, folate, vitamin A and zinc as some of the other causes of hydrocephalus (Liu, Jin, Li, Zhang & Zhang et al., 2018).

Genetic factors, especially X-linked was identified as another very important cause according to literature (Mahmoud et al., 2014; Yi et al., 2017). A case report published by Metwalley et al., (2009) showed an Egyptian male child with trisomy 18 associated with congenital hydrocephalus. All signs of Edward's syndrome like high arched palate, depressed nasal bridge, rocker bottom feet, ventricular septal defect and hydrocephalus were strongly evident (Metwalley, Farghalley & Abd-Elsayed, 2009). Several maternal and genetic factors causing a high recurrence risk in following pregnancies (1.4%) have been identified by literature. These studies have observed an increased risk ratio in twins of same genders, as well as 1st and 2nd degree relatives (Mahmoud et al., 2014; Munch et al., 2012 & 2014). L1CAM genes have been strongly linked to congenital hydrocephalus and has been seen to exhibit mutations in 7% cases (Finckh, Schröder, Ressler, Veske & Gal, 2000; Weller & Gärtner, 2001). Adle-Biassette et al., (2013), observed, as reported by Kahle et al., (2016) that most commonly occurring inherited form of hydrocephalus is X-linked and constitutes at least 10% of cases in boys. Two additional gene mutations, MPDZI encoding MUPP-1 which is a protein for tight junctions and CCDC88C encoding DAPLE a protein involved in cell migration, have been found to be one the causes of congenital hydrocephalus (Kahle et al., 2016) Strong correlations have been observed between low socioeconomic status and hydrocephalus (Jeng et al., 2011; Mahmud et al., 2014).

Experimental brain models were developed by Walter Dandy to investigate the pathophysiology behind hydrocephalus and to develop treatment methods for this condition in 1919. Based on these models he was able to observe the obstruction of *Aqueduct of Sylvius* and hence classify hydrocephalus into communicating and non-communicating types (Rekate, 2009 & 2011). Over the years, based on these model researchers have developed models where arterial systolic pressure entering the brain was found to have temporal relationship with the flow of CSF (Wagshul, Eide & Madsen, 2011). These models helped identify the pathophysiology of CSF and hence enabled the

authors to identify the causes of conditions like idiopathic hydrocephalus in infants, idiopathic hypertension in adults and normal pressure hydrocephalus in elderly (Bateman, Smith & Siddique, 2007).

Due to the accumulation of CSF because of increased volumes Raimondi et al., (1994) called it *"water head"* and included factors and other causative elements responsible for vascular edema and hence accumulation of CSF in brain ventricles.

In a study conducted in Japan, Mori et al.,1995, classified hydrocephalus based on treatment. Based on the flow of CSF and its obstruction, Oi et al., 2006, categorized hydrocephalus into (i) primary - when the flow faces an obstruction at a single point and (ii) secondary - due to tumor or growth of any other mass lesion or bleeding within the brain. Arnold Chiari malformation is also included under the heading of primary hydrocephalus (Oui et al., 2006).

Based on the pressure of cerebrospinal fluid, hydrocephalus has been classified as normal pressure hydrocephalus (NPH) with a frequency of 47% and develops in elderly and exhibits a triad of loss control over urination, disturbance in gait and loss of memory (Corns and Martin, 2012; Shakeri, Vahedi & Lotfinia, 2008).). High-pressure hydrocephalus presents with a frequency of 47% (Shakeri et al., 2008). Hydrocephalus occurring due to stenosis of Aqueduct of Sylvius displays a frequency of 15% (Shakeri et al., 2008). Middle aged adults develop *"transient hydrocephalus"* due to subarachnoid hemorrhage (Corns et al., 2012).

Presently it is classified as communicating/ non-obstructive and non-communicating/ obstructive hydrocephalus (Liu et al., 2018; Rekate, 2011). In non-communicating type, the communication between the ventricle is blocked and the flow of CSF through the ventricular system is obstructed. The most common site of blockade is aqueduct of Sylvius (Rizvi & Anjum, 2005). Communicating hydrocephalus in which there is no obstruction, but ventricular dilatation is either due to over production or inadequate reabsorption of CSF (Rizvi et al., 2005). The most common cause identified in literature is infection or hemorrhage (Rizvi et al., 2005). Congenial and acquired are sub-categories of noncommunicating hydrocephalus (Rizvi et al., 2005; Tully et al., 2014). CH is present at birth and is usually due to an intrinsic reason (Kalyvas et al., 2016; Tully et al., 2014).

Acquired hydrocephalus is due to causes like tumor mass, bleeding within the brain or some infection (Tully et al., 2014).

It has also been classified as syndromic i.e. which presents itself in association with a specific syndrome and exhibits additional physical features of that syndrome, example, hydrocephalus which occurs with Fried syndrome or Walker Warburg disease (Tully et al., 2014). Non-syndromic hydrocephalus on the other hand demonstrates abnormalities present within the brain only (Tully et al., 2014). Verhagen et al., (2011) defines it as *"congenital hydrocephalus without major congenital anomalies and with a maximum of two minor anomalies".* Whereas syndromic is defined as *"hydrocephalus accompanied by atleast one major congenital abnormality or three minor congenital anomalies"* (Verhagen et al., 2011).

Multiple congenital abnormalities, intracranial as well as extracranial, are known to be associated with hydrocephalus. Neural tube defects for instance are found to be most commonly associated with it (D'addario & Rossi 2012; Mahmud et al., 2014). Spina bifida is found in 30% cases, 20 % showed association with Arnold Chiari malformation, 5 % with Dandy Walker and 5% with aqueductal stenosis (Mahmud et al., 2014). Jeng et al., (2011) noted that spina bifida was found in 27% of cases of hydrocephalus. A decrease in the incidence of neural tube defects was observed most likely due to widespread use of folic acid and other significant multivitamins during pregnancy (Jeng et al., 2011; Mahmud et al., 2014). Congenital heart diseases (CHD) like arterial hypertension, infarction, was found in 12 % cases (Eide & Pripp, 2016; Jeng et al., 2011).

It was observed that the risk for association of chromosomal abnormalities was highest with severe forms of hydrocephalus. In their case report, Metwalley et al., (2009), reported an unusual association of Edward's syndrome with hydrocephalus (Metwalley et al., 2009; D'addario et al., 2012).

Mahmoud et al., (2014), observed 0.4% cases of the CH to be associated with stenosis of aqueduct, neural tube defects like spina bifida, Arnold Chiari malformation and Dandy Walker syndrome.

Hydrocephalus has been found to be commonly associated with meningomyelocele. The reason for this is loss of CSF into the sac covering the meningomyelocele as a result a pressure is created within the brain which results in the herniations of the hindbrain and eventually hydrocephalus (Rehman et al., 2015).

It is known to be associated with several other anomalies like cleft lip, cleft palate, abnormalities related to the face, renal system abnormalities, anomalies of the musculoskeletal system and abnormalities involving the vertebral column, anorectal region, cardiovascular system, tracheoesophageal fistula, atresia of the esophagus, kidney (renal) or radial and limb defects , also known as VACTERL (Schrander-Stumpel & Fryns, 1998).

Several complications of hydrocephalus like variable degree of cognitive impairment, cerebral palsy and visual defects have been cited in literature (Mahmoud et al., 2014).

Ortega et al. (2016) observed a case of hydrocephalus in a female patient diagnosed prenatally by ultrasound scan at 28 weeks of gestation, it was progressive form of hydrocephalus confirmed on postnatal MRIs. The motor development of the affected child like sitting, speech and walking at 7, 8 and 17 months all were normal. However, her coordination was lower than normal (Ortega et al., 2016). A decline was observed in global cognitive functions. Her hand-eye coordination was poor along with poor working and short-term memory and she exhibited decrease in the level of maturity (Ortega et al., 2016).

Premature birth, still birth and neonatal morality rates particularly in low birth weight infants occurs as a major consequence of congenital hydrocephalus (Jeng et al., 2011; Salat et al., 2012; Yi et al., 2017). Mortality rate ranging between 1.6 % - 21.7% was noted by Salat et al., (2012). A higher risk of mortality was observed in very low birth weight and low birth weight infants born with hydrocephalus as compared to those born with normal weight (Jeng et al., 2011). Pretorius et al., (1985) identified cause of death as infections, decompression at delivery and respiratory system failure.

The pharmacological management ranges from the use of antibiotics, anticonvulsants mannitol and steroids (Salat et al., 2012). Diuretic have been used to reduce the amount of CSF and intraventricular fibrinolytic treatment has been used in case of post-hemorrhagic hydrocephalus (Chumas, Tyagi & Livingston, 2001). Surgical management can include excision or cauterization of choroid plexus, decompression of ventricles by ventricular punctures, and shunts. Wernicke developed the first method of drainage of CSF by puncture, this effort was followed later by ventriculo-subarachnoid-subgaleal shunt which was created in 1893 by Mikulicz. Over the decades and centuries all these methods were refined till the development of present-day shunts (Venkataramana, 2011). Ventriculoperitoneal shunt being the most commonly used procedure, ventriculoarterial shunt and third ventriculostomy is another option practiced and suggested in literature (Rizvi et al., 2005).

According to Metwalley et al., (2009) ultrasound is one of the cheapest, most convenient, easily accessible, safest and above all most sensitive test which can easily diagnose congenital anomalies with minimal possible exposure and risk (Metwalley et al., 2009). The lateral ventricle measurements are therefore advocated and implemented a part of routine screening for congenital anomalies (D'addario et al., 2012). Scans done in axial plane allow clear visualization and hence measurement of lateral ventricles. Atrium of the lateral ventricles is therefore the recommended site for measurement (D'addario et al., 2012).

The 1st and 2nd trimesters of pregnancy encompasses the first 14 weeks from last periodic cycle and from 15-28 weeks respectively (Rayburn, Jolley & Simpson, 2015). However, clinically gestational age is used to identify the number of weeks and days. Period of pregnancy extending between fertilization of the germ cells till the implantation of the zygote is termed pre-implantation period, from 4th to 10th week is embryonic and includes the period of organogenesis (Rayburn et al., 2015). This being the duration of maximum significance and being most crucial period of development of the fetus on one hand, is also the most vulnerable as major organs like brain, heart and gonads begin to develop. Therefore, any harmful insult during this period can influence the growth and maturity of the fetus significantly (Rayburn et al., 2015). Since its advent in the year 1960, the

methodology and technique of fetal imaging using ultrasound has developed and evolved over time and therefore in the present day it helps detect normal and developmental defects, both structural and chromosomal with 44% accuracy before 24 weeks of gestation (Canty, Leopold & Wolf 1981; Oztekin et al., 2009; Rayburn et al., 2015).

First trimmest screening requires the maternal urinary bladder to be full in order to identify landmarks like gestational/yolk sac, heartbeat of the fetus and the crown rump length measurement at 5, 6 and 7 weeks respectively via transabdominal scans (Canty et al., 1981; Oztekin et al., 2009).

Central nervous system (CNS) of the fetus begins to develop in the 4th week of development, therefore, anomalies of CNS like acrania anencephaly and hydrocephaly etc. are the first ones to be detected on first trimester ultrasound scans (Oztekin et al., 2009; Pilu & Hobbins, 2002).

Measurements of nuchal translucency (NT) recorded during 11-14 weeks of gestation implies the risk of developing structural abnormalities in the developing fetus. It has been labelled by literature as the perfect and ideal instrument to detect chromosomal abnormalities especially when maternal age is taken into consideration (Oztekin et al., 2009; Rayburn et al., 2015). Being the basic and fundamental modality for screening of fetal abnormalities, values of NT > 3mm is considered abnormal and is a sure sign of developing fetal anomaly (Oztekin et al., 2009; Rayburn et al., 2015). Oztekin et al., (2009) quoted dr. Langdon Down as *"skin of the individuals was too large for their bodies".* Based on these observations done 100 years ago, evolved the foundations of screening done in first trimester by Pandey in 1995 (Oztekin et al., 2009; Rayburn et al., 2015). NT therefore aids in detecting various fetal anomalies like cardiac, skeletal, chromosomal like Down's syndrome, Edward's syndrome and Turner syndrome (Oztekin et al., 2009).

However, to assess a normal or an abnormally developed fetus with utmost accuracy and minimal false positive results requires the precise and correct use of ultrasound machine, the transducer and above all it banks not just on the skill and talent of the sonologist but also on his thorough anatomical knowledge of the developing fetus because as the

hindbrain develops it presents a large cavity in 7-9 weeks of gestation which can easily be misinterpreted as an abnormality of the fetal brain by a novice (Oztekin et al., 2009; Rayburn et al., 2015).

First trimester screening being the first screening test, a complete survey of the fetal anatomy done at 18-22 weeks remains the main method for uncovering fetal anomalies as certain countries allow legal termination of pregnancy on medical grounds (Canty et al., 1981; Oztekin et al., 2009; Rayburn et al., 2015). Second trimester scans allow reassessment and confirmation the gestational age of the fetus, presence of aneuploidy and number of fetuses by measuring head, neck, face, heart, abdomen, spine, genital regions and skeleton (Rayburn et al., 2015). They have the tendency to diagnose the presence of fetal anomalies at a rate 16-44% which can hike up if the anomaly is a life threatening one (Rayburn et al., 2015). Boundaries of fetal lateral ventricles of the brain can be easily seen at 9 weeks, 3rd and 4th ventricles can be observed at 10 weeks, cerebellum and thalamus can be seen at 12 weeks (Souka, Snijders, Novakov, Soares & Nicolaides, 1998).

The breadth of atrium of the lateral ventricle, meeting point of body, posterior and inferior horns, is taken to be constant at less than 10 mm between 1-40 weeks of gestation. Any variation in its width leads to the diagnosis of ventriculomegaly and hydrocephalus (D'addario et al., 2012). Several authors are in agreement at these classification on ventriculomegaly on the basis of width of that atrium as mild (10-12 mm), moderate (12.1-14.9 mm) and severe (≥ 15 mm) (D'addario et al., 2012; D'Antonio & Zafeiriou 2018; Emery, Hogge, & Hill, 2015).

The diameter of choroid plexus increases from 2mm to 5 mm from 10 week of gestation to 13 weeks and the ventricle to hemisphere ratio of lateral ventricle also exhibits a decline from 72% to 67% in weeks 12 and 13 respectively. Cerebellar diameters, however, increase from 6 mm in week 12 to 12 mm in week 14 (Souka et al., 1998).

At 18-20 weeks of gestation hydrocephalus can easily be diagnosed on transabdominal scans. Ortega et al., 2016, in their study were able to detect hydrocephalus and dilated ventricles at 28 weeks of gestation using ultrasound scans. These findings were later

corroborated and confirmed by postnatal Magnetic Resonance Imaging. Thereby further confirming the sensitivity and specificity of prenatal ultrasound scans (Metwalley et al., 2009; Ortega et al., 2016). Measurements of 3rd ventricle are considered normal if it is 1 mm between 12-28 weeks (Emery et al., 2015).

Several authors have attempted to compare ultrasound findings with other modalities thereby validating its sensitivity and specificity. Hauerberg et al., (2012) compared prenatal ultrasound diagnosis with autopsy and found concordance in 46% fetuses. Ninety percent of the main findings noted on ultrasound were endorsed by autopsy (Hauerberg, Skibsted, Graem & Maroun, 2012). The most detected anomalies on ultrasound and confirmed by autopsy were those of central nervous system like hydrocephalus/ Dandy-Walker and spina bifida (Hauerberg et al., 2012).

In another study 84% of the ultrasound findings corroborated with that of autopsy exhibiting statistically significant p values for 98% of cases. Thirty eight percent cases identified and confirmed were those of central nervous system followed by congenital heart defects (33%) and urinary system abnormalities in 245 cases (Vogt, Blaas, Salvesen & Eik-Nes, 2012).

In a retrospective study by Rodriguez et al., (2014) 91.3% CNS anomalies consisting of anencephaly, hydrocephaly, Dandy Walker malformation, corpus callosum agenesis, neural tube defects etc. were confirmed by postmortem examination. This study also corroborated the prenatal diagnosis of cardiovascular and renal system anomalies in 91.5 and 90.2% cases (Rodriguez, Prats, Rodríguez, Cusí & Comas, 2014).

Researchers have also compared successfully the ultrasound findings with both prenatal and postnatal CT scans and MRIs. Perlman et al., (2014), observed ƙ score of 0.94 and 0.84 for narrow and wide ventricle after establishing a cut off value of 10 mm for ventriculomegaly. By this comparative study it was established that normal ventricle measurements in fetus remains constant throughout and that the future prognosis rests heavily on the presence or absence of cranial or extracranial anomalies (Perlman, Shashar, Hoffmann, Yosef & Achiron et al., 2014). However, in case of maternal obesity

MRI has proven to be the modality with much more accuracy and precision (Perlman et al., 2014).

Emery et al., 2014, confirmed the presence of aqueductal stenosis diagnosed by prenatal ultrasound with that of postnatal MRI and CT scans. In a sample of 62 fetuses bilateral mid ventriculomegaly was observed in 58% cases. This observation was seen to exhibit a stable dilatation in 45% cases, progressed in 13% and a regression of ventriculomegaly was observed in 4.5% cases. All these findings were in coherence with MRI findings in 85% cases (Tonni, Vito, Palmisano, de Paula Martins & Júnior, 2016).

As seen in literature infants born with major brain lesions are at a high risk of developing multitude of neurodevelopmental deficits ranging from nystagmus, visual impairments, neuromotor delay to cognitive impairment, cerebral palsy to epilepsy, therefore early detection enables the physicians to counsel the parents appropriately who in turn can make timely decisions (Liu et al., 2018; Mahmoud et al., 2014; Munch et al., 2012).

CHAPTER 3

Methodology

3.1. Research Design:

This comparative cross-sectional study was done in pregnant women of age groups 21– 30 years and 31– 40 years. The study was conducted during a period of 8 months and the two age groups were compared. Correlation of other embryological anomalies with hydrocephalus was also seen.

3.2. Ethical approval:

Prior to obtaining ethical review committee approval the synopsis was first accepted by the research review committee (RRC). The study was conducted after obtaining ethical approval by the ethical review committee (ERC) of Bahria University Medical and Dental College, Karachi. The ERC reference number for this study is ERC 47/ 2018.

3.3. Setting

Study was conducted at a private ultrasound clinic, Institute of Ultrasound Imaging/Musarrat Ultrasound, Karachi. The clinic which comprised of latest ultrasound machineries and skilled personals offers free (gratis) ultrasound facilities to patients. The study included all pregnant females between age groups 21-30 years and 31-40 years.

3.4. Inclusion criteria

- Maternal age – 21-30 years and 31- 40 years
- Parity – uniparous and multiparous

3.5. Exclusion criteria

- Essential hypertension:
  Patients with essential hypertension were excluded as it was identified in literature as a major risk factor for development of periventricular hemorrhage in fetus which can lead to the development of fetal hydrocephalus.

- Diabetes Mellitus:
  Diabetes mellitus though is a causative factor of hydrocephalus has been excluded from this study because large head circumference can be a confounder in head circumference measurements.

- Chromosomal abnormalities:
  Can be easily excluded on pre-natal ultrasound by the presence of increased nuchal thickness measured during 11-14 gestational week and later by the presence of dysmorphic facial and other gross features on complete anomaly scan at 18-21 weeks. These findings may later be confirmed by amniocentesis.

3.6. Duration of study

Individual Study Period:

The duration of individual study period was 4 months. During this time the synopsis of the research topic was suggested and finalized. It was then submitted to the chairperson and head of postgraduate committee. After the presentation of the research proposal, approval was first obtained from the RRC and ERC of Bahria University Medical and Dental College

Total Study Period:

The collection of data comprising of 8 months started in December 2018 and continued till July 2019 at Institute of Ultrasound Imaging/Musarrat Ultrasound, Karachi. The data

was then entered in Statistical package for Social Sciences (SPSS) version 23. During this time a review article was also written which is currently under publication.

3.7 Sample size estimation

Sample size was estimated using the method of comparing proportions by using OpenEpi Version 3, open source calculator SS proper. The sample size was based on population prevalence and was calculated using www.openepi.com. The prevalence of population was 50%. The sample was calculated with a 5% margin of error and 95% confidence interval. We calculated the minimum sample size of N= 33. However, this study included 37 patients and 1 patient fulfilling the exclusion criteria was excluded from the study, so n=36.

3.8 Sampling technique

Non-probability purposive sampling technique was used.

All pregnant women who came for prenatal ultrasound scans during the 21-39 weeks of gestation were included in the study and all those who fulfilled the exclusion criteria were excluded from the study. The fetuses were examined by ultrasound, ventricles were seen in coronal plane and fetuses with dilated ventricles, > 10mm, were diagnosed as hydrocephalus.

3.9 Human Subjects & Consent

Pakistani pregnant female patients falling into the age groups of 21-30 years and 31-40 years, with a gestational age of 21-39 weeks and with no known history of diabetes mellitus and essential hypertension were included in the study.

A written, understood and informed consent was signed by the patients in both English and Urdu language after explaining all the study parameters and the rationale of the study by the principal investigator. The study participants were free to leave the study at any point or they had the option of not participating in the study at all.

3.10 Materials

All scans were done using Toshiba APLIO 300 machine and 2.5-3.5 MHz Standard convex transducer was used (figure 10).

Figure 10: Toshiba Aplio 300 Ultrasound Machine (Courtesy: Institute of Ultrasound Imaging/Musarrat Ultrasound)

3.11 Lab. Parameters:

Following parameters were included in the study

3.11.1 Head Circumference (HC):

It was noted as an ellipse around the skull bones on the calvarium as measured by trackball method on ultrasonic equipment. Measurement of +2 standard deviation from mean was taken as macrocephaly (figure 11).

3.11.2 Biparietal Diameter (BPD):

It was visualized and measured in transaxial plane of fetal head where thalami could be seen with falx equidistant from temporoparietal bones and where cavum septum pellucidum (CSP) was visualized. It was measured from outer skull bone to inner skull bone (one leading edge to the other leading edge). This measurement was used to assess and confirm gestational age of fetus (figure 12).

3.11.3 Femur length (FL):

Femur being the largest and least movable bone is the easiest to visualize and can be measured from 14 weeks of gestation till delivery. It was measured along its long axis horizontally from one osseous portion at one end to the other (curvature was ignored). Femoral neck and proximal and distal epiphyses being cartilaginous were excluded from measurements (figure 13).

3.11.4 Head to Abdominal Circumference Ratio (HC/AC):

Abdominal circumference (AC) was measured in trans-axial plane of fetal abdomen and was measured at the level of fetal liver and stomach (slightly caudad to fetal heart and cephalad to fetal kidneys) and umbilical and left portal veins were visualized as a fetal landmark. Measurements were taken from outer most aspects of fetal soft tissue by trackballing of ultrasonic equipment.

This measurement allows accuracy in assessing the growth of fetus and weight of the baby.

However, in case of any asymmetry between the growth of the head and abdomen a ratio between the HC and AC (HC/AC ratio) is used.

3.11.5 Lateral Ventricular: hemisphere ratio (LV:H):

Images were obtained in axial plane. The lateral wall of frontal horn was visualized. Lateral ventricle was measured from the lateral wall till the midline echogenic mass. The hemispheric width was measured from the central echogenic mass to the inner edge of the parietal bone (figure 14). A ratio of these measurements was then obtained. Measurements of 0.61- 0.29 from 14^{th} - 29^{th} week of gestation were considered within normal range. These values remain static till birth.

3.11.6 Atrium of lateral ventricle measurements (atrium of LV):

Image was taken in coronal plane at the level of atrium of lateral ventricle with visualization of choroid plexus. It was measured, from inner wall of ventricle to the inner wall of choroid plexus (figure 15). Values of <10 mm were considered normal.

3.11.7 Amniotic Fluid Index (AFI):

It was measured by dividing the uterus into 4 quadrants by 2 imaginary lines, first passing through the linea nigra and dividing it into right and left halves and the second passing through the umbilicus and dividing into upper and lower halves. The transducer was kept parallel to the patient's longitudinal axis and perpendicular to the floor. The deepest, most clearly visualized pocket was measured in each quadrant. Measurements of all 4 quadrants was then added to calculate AFI.

3.11.8 Gender:

Male genitalia were assessed by taking two images. First a mid-sagittal image of lower abdomen was taken below the cord where penis and scrotum were visualized. This was further confirmed by a transverse image at the level of the urinary bladder where penis and scrotum were visualized between the parted thighs.

Female gender was assessed by taking a mid-sagittal view of the lower abdomen first where flat mons pubis was seen. The second confirmatory image was taken in transverse section at the level of the bladder where no penis was visualized between the parted thighs.

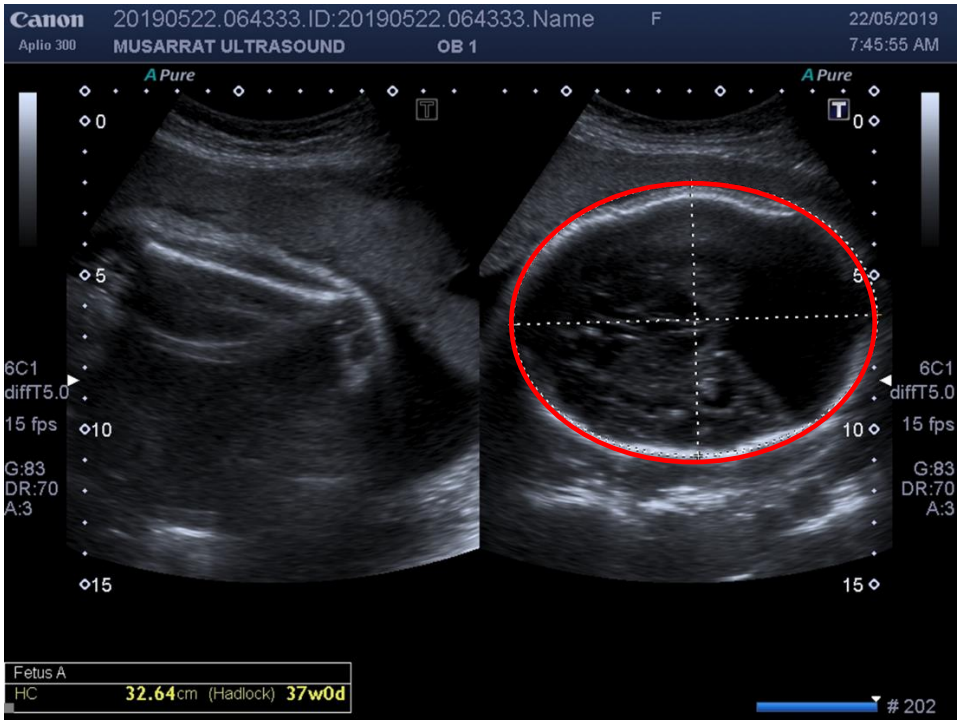


Figure 11: Fetal Head circumference *(image taken at Musarrat Ultrasound)*

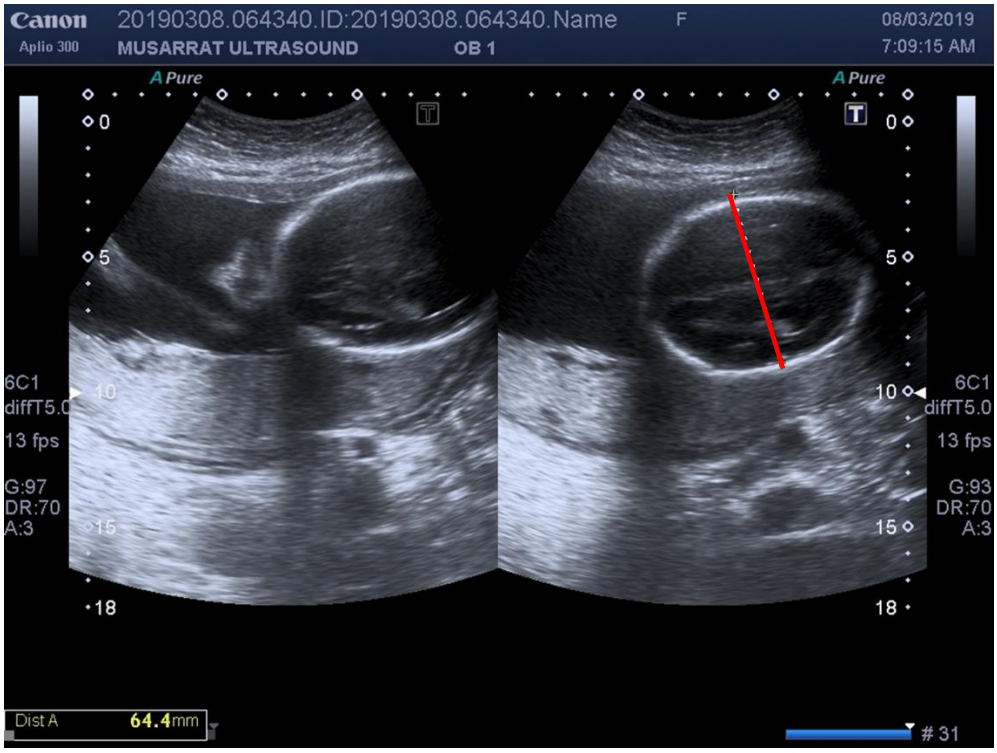


Figure: 12 Biparietal diameter *(image taken at Musarrat Ultrasound)*

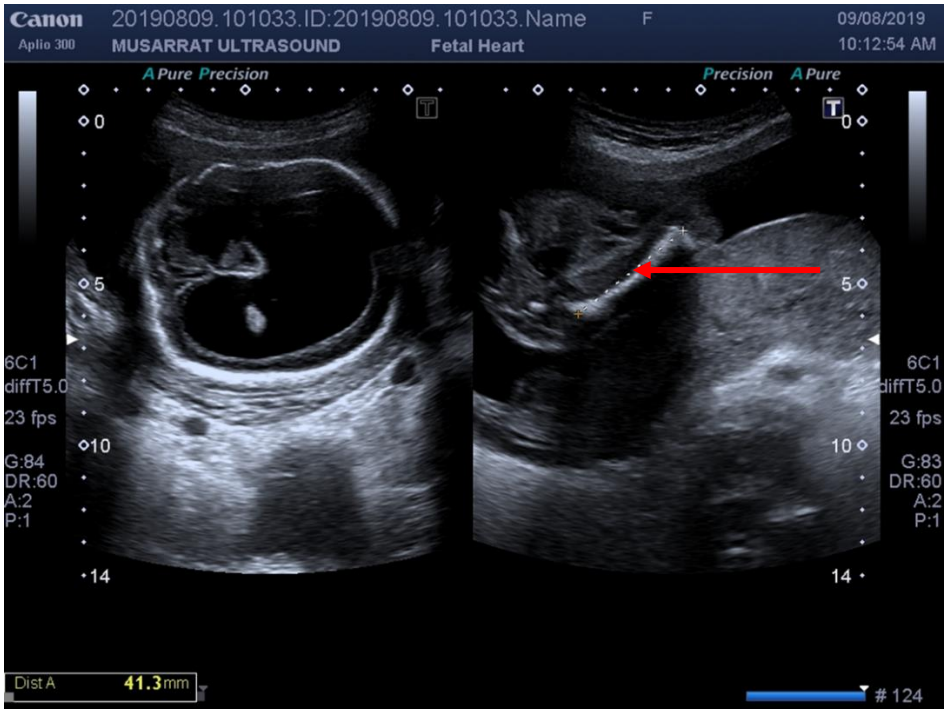


Figure: 13 Femur length ***(image taken at Musarrat Ultrasund)***

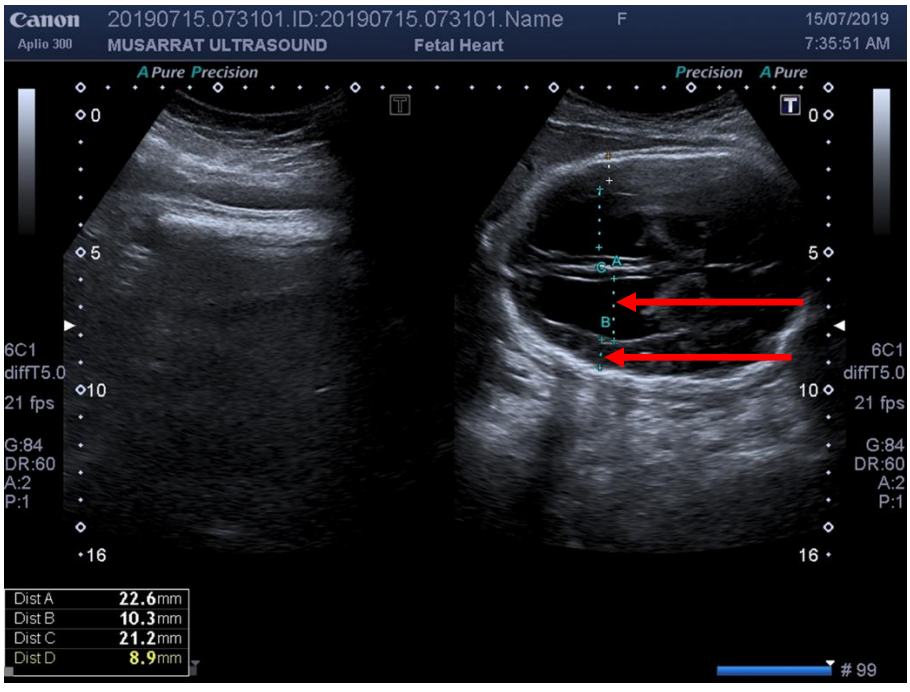


Figure 14: Ventricular: hemisphere ratio ***(image taken at Musrrat Ultrasound)***

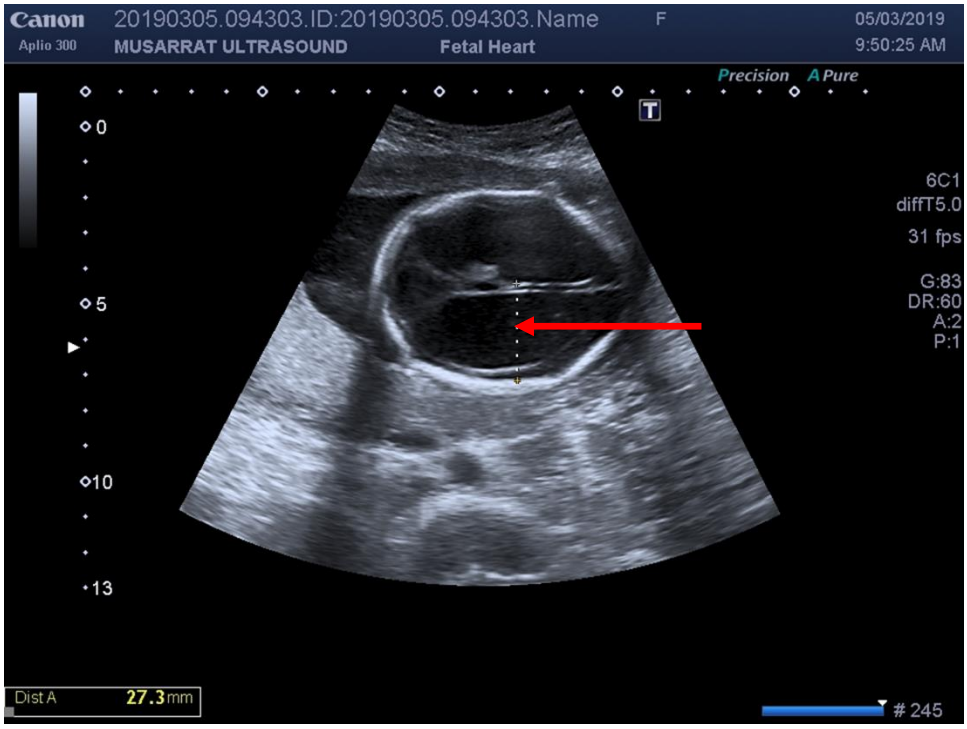


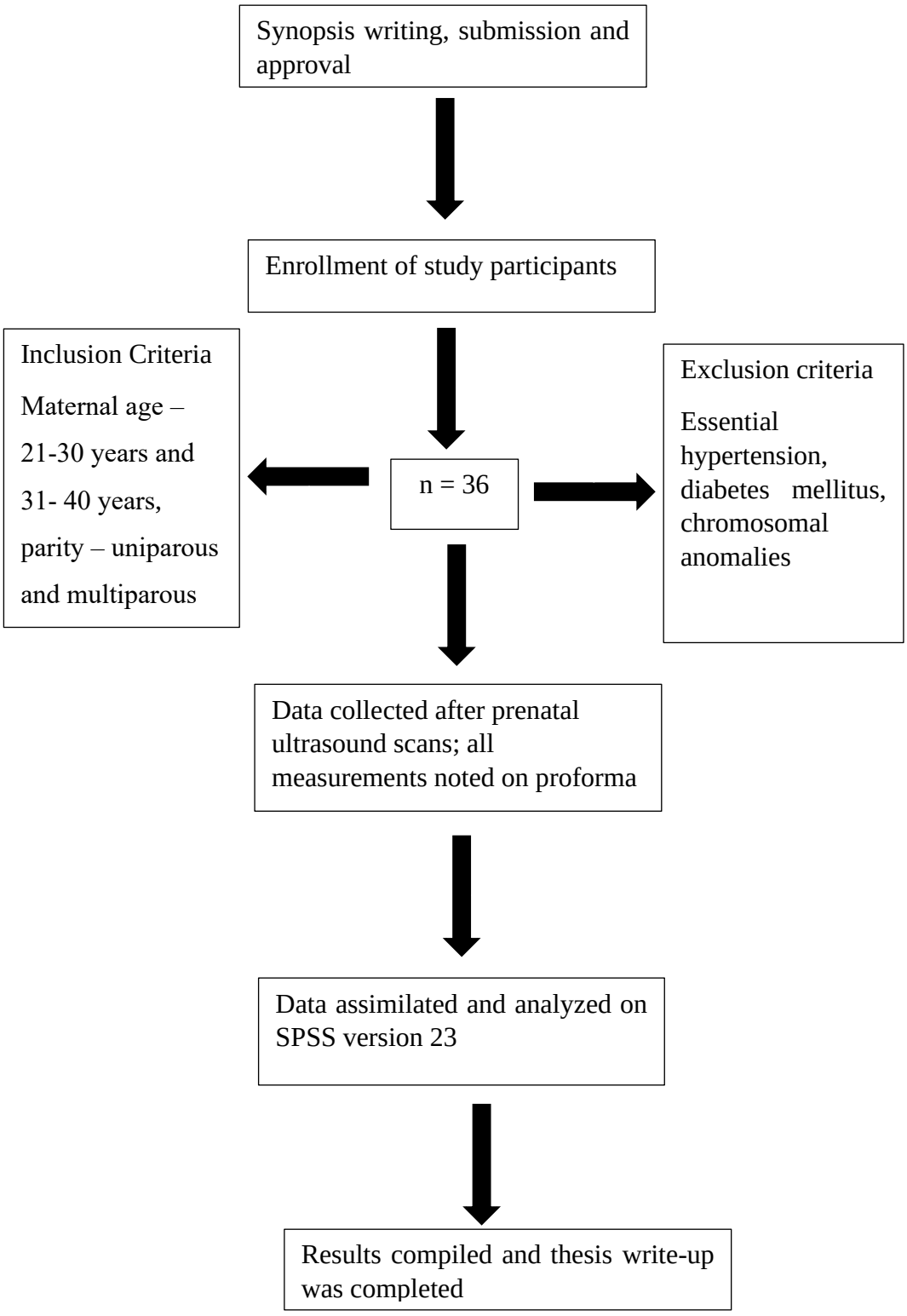
Figure 15: Atrium of lateral ventricle *(image taken at Musarrat Ultrasound)*

3.12 Protocol of the Study:

After taking informed and understood consent from the participants of the study, the proforma (attached in the annexure 7.2- E) was filled in by the principal investigator. Detailed sonographic evaluation comprising of all the above parameters was conducted. All measurements were noted in cm and then converted to mm.

Data collection was completed in 8 months (December 2018 – July 2019) followed by analysis and thesis compilation.

3.13Algorithm of the Study:



3.14 Statistical Analysis:

All the collected data was entered in excel spreadsheet. Data was then incorporated and analyzed using SPSS version 23 for windows. The analyzed results were provided as mean and standard deviation of quantitative variables like BPD, femur length, head to abdominal circumference ratio, lateral ventricular system measurements, ventricular: hemisphere ratio, atrium of lateral ventricle measurements, amniotic fluid index. All categorical data was expressed as frequency and percentage.

T-test was used where 2 groups were compared and p- value of ≤ 0.05 was taken as significant and values of ≤ 0.01 as highly significant. ANOVA was used when comparison was done between 3 groups (for e.g. hydrocephalus with congenital anomalies)

Pearson's correlation was used between continuous data.

CHAPTER 4

Results

4.1. Presentation of fetal hydrocephalus in maternal age groups:

The current study involved 36 pregnant females divided into two age groups of, 21-30 years and 31-40 years. Females of different parity and different weeks of gestation were included. One patient with a history of diabetes mellitus was excluded from the study. Fetal hydrocephalus was diagnosed by measuring the atrium of lateral ventricles, meeting point of body, posterior and inferior horns.

The study included 22 patients with a mean of 15.83 ± 3.62, of age group 21-30 years and 14 patients of age group 31- 40 years, with a mean of and 19.18 ± 3.61 (figure 16 and table 1). When the two maternal age groups were compared for the presence of hydrocephalus, the study revealed that fetuses of mothers between age group of 21-30 years had a higher tendency to be affected by hydrocephalus as compared to the fetuses of mothers of older age group and therefore, statistically significant results (p-value ≤0.011) with a confidence interval of 95% were observed (table 1).

4.2 Frequency of hydrocephalus based on severity and its association with maternal age:

In table 2 A, hydrocephalus was classified based on the measurements of atrium of lateral ventricle. Measurement of 10-12 mm were considered mild form whereas measurements of 12.1-14.9 mm and ≥15 mm were considered moderate and severe forms respectively. Out of the 36 patients included in the study 63.9% of the cases were of severe type with measurement values of ≥15 mm. Twenty five percent cases were of moderate type and remaining 11.1% exhibited milder forms of hydrocephalus (table 2A). Thus, we conclude that severe forms of hydrocephalus, 11 and 12 cases respectively, were observed in both 21 -30 years and 31- 40 years of maternal age (figure 17).

Table 2 B compares severity of fetal hydrocephalus among maternal age groups of 21-30 years and 31-40 years and showed that 85.7% cases of severe forms of hydrocephalus were present in mothers of age group 31-40 years, whereas 14.3% cases were of moderate type and no cases of mild forms were observed in the same age group. However, in mothers of younger age group (21-30 years), 50% cases were of severe variety followed by moderate and mild, 31.8% and 18.2% respectively.

4.3 Correlation of fetal hydrocephalus with cranial and extracranial embryological anomalies:

Thirteen cases of fetal hydrocephalus with a mean measurement of atrium of lateral ventricle of 18.48 ±4.72 were isolated and were not associated with any form of other congenital anomaly (figure 18). Only 3 cases with a mean measurement of 21.77±3.87 of atrium of lateral ventricle was found to be associated with extracranial embryological anomalies. However, our study exhibited statistically significant results (p-value of 0.033 with 95% confidence interval) and found fetal hydrocephalus to be strongly associated with various types of cranial embryological anomalies (20 cases) with mean of 16.07 and standard deviation of 3.01 (table 3A). Figure 18 depicts the mean and standard deviation of the measurements of atrium of lateral ventricle measured in millimeters.

Table 3B shows that 30.8 % of moderate forms of hydrocephalus and 69.2% of severe forms were of isolated type that is, without any associated anomaly. However, cranial anomalies (like spina bifida, meningomyelocele and Dandy Walker Syndrome) were maximum in severe type of dilatation (11 cases) followed by moderate (5cases) and mild types (4 cases), 55%, 25% and 20% respectively. Only 3 cases of extracranial anomalies (like fetal ascities, urinary tract malformations, pleura effusion and dilated bowels0 were found to be associated with severe type of dilatation.

4.4 Association of fetal hydrocephalus with fetal gender:

Table 4 depicts the presence of 30 cases of fetal hydrocephalus in male fetuses with a mean of 17.22 ±4.19 of the measurements of atrium of lateral ventricle used to diagnose hydrocephalus (as shown in the bar chart, figure 19). Only 6 cases of female fetuses were observed with hydrocephalus with a mean of 16.71 and standard deviation of 2.53 (bar chart, figure 19). However, no statistically significant results were observed (p-value 0.780) because of very little difference between the mean values of the measurements of atrium of lateral ventricle measurements (table 4).

4.5 Association of hydrocephalus with amniotic fluid volume:

As shown in table 5 A, the study observed that 33 out of 36 cases (91.7%) of fetal hydrocephalus were associated with normal volumes of amniotic fluid (10 -19) whereas only 2 cases were found to be associated with polyhydramnios (volume 20-25) and only 1 case was observed with oligohydramnios (≤ 9) (table 5 A and figure 20) and highly significant correlation (p-value $\leq$ 0.000) with 95% confidence interval was observed in our study between amniotic fluid volume and measurements of the atrium of lateral ventricles thereby strengthening the fact that fetal hydrocephalus is more commonly associated with normal volumes of amniotic fluid (table 5 B). However, no correlation was found between the two variables (scatter plot, figure 21).

4.6 Correlation between ventricular:hemisphere ratio and lateral ventricular measurement:

Mean values of 17.13± 3.93 and 2.90 with standard deviation of 1.90 were observed in measurements of atrium of lateral ventricle and ventricular:hemisphere ratio respectively, in this study (table 6 A, figure 23). A highly significant relationship (p-value ≤0.000) was observed between the two variables indicating a strong association and a positive correlation (r= 0.542) between the two variables (table 6 B & figure 22).

4.7 Correlation between lateral ventricular measurements and BPD:

This study observed that BPD increased with increase in the measurements of atrium of lateral ventricle. Both, BPD and atrium of lateral ventricle, exhibited mean and standard deviation of 7.35 and 1.16 (for BPD) and 17.41 and 4.06 (for atrium of lateral ventricle) respectively with highly significant (p-value ≤ 0.000) showing association between the two variables with 95% confidence interval (table 7 and figure 24). However, no correlation was observed between the two variables (scatter plot, figure 25).

4.8 Association of hydrocephalus with family history and consanguinity:

A strong association was observed between family history and fetal hydrocephalus. 55.6% (20 cases) patients diagnosed with fetal hydrocephalus had a positive family history as compared to 44.4% (16 cases) (table 8A and figure 26). Tale 8 B shows that 45% patients with positive family history had consanguineous marriage while 55% with positive family history did not have consanguineous marriage.

Table 8C shows a highly significant result (p-value ≤ 0.014) between hydrocephalus and consanguinity.

4.9 Correlation between head circumference and measurements of atrium of lateral ventricle:

As seen in the scatter plot (figure 27) and table 9, negative correlation (r = - 0.014) was observed between measurements of atrium of lateral ventricle and head circumference however a good association was seen between the two variables in our study.

4.10 Correlation between measurements of atrium of lateral ventricle and head:abdominal circumference ratio:

Our study conducted on 36 patients showed negative correlation (r = - 0.416) between measurements of atrium of lateral ventricle and head:abdominal circumference ratio (table 10 and figure 28).

4.11 Association of hydrocephalus with maternal parity:

Our study was able to diagnose more cases of congenital hydrocephalus in fetuses born to mothers with lower parity (figure 29). Ten cases were observed in mothers with parity of 3, followed by 8 and 6 cases in mothers with parity of 1 and 2 respectively.

4.12 Frequency of hydrocephalus in single and twin pregnancy:

As shown in table 11, single fetus was observed in 35 cases, with a mean of measurement of atrium of lateral ventricle 17.19 ±4.06, whereas only 1 case of twin pregnancy was diagnosed.

Table 1

Association of fetal hydrocephalus with maternal age groups

(n=36)

Maternal Age	n	Atrium of Lateral Ventricle (mm)		
		Mean	Standard deviation	p- value
21-30 years	22	15.83	3.62	0.011*
31- 40 years	14	19.18	3.61	

p-value ≤ 0.05 is significant and shown with asterisk *

T-test used: Independent t -test

mm: millimeter

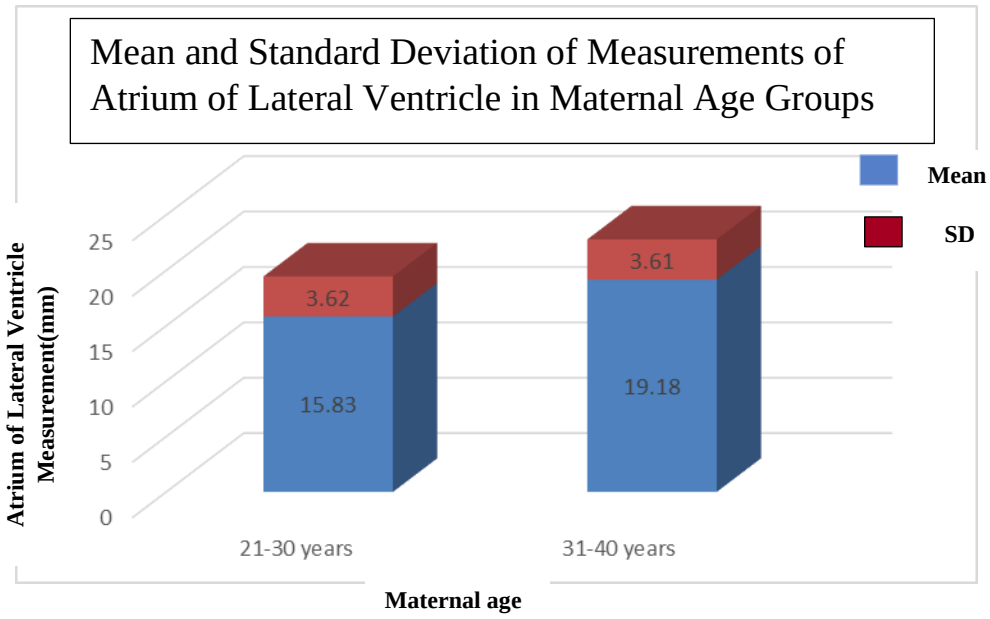


Figure 16: Bar chart showing comparison of mean and standard deviation of atrium of lateral ventricle measurements between maternal age groups

Table 2 A

Frequency of fetal hydrocephalus based on severity

(n=36)

Severity of hydrocephalus	n	Percentage
10-12 mm (mild)	4	11.1%
12.1- 14.9 mm (moderate)	9	25%
≥15mm (severe)	23	63.9%

mm: millimeter

Table 2B

Association of fetal hydrocephalus based on severity with maternal age

(n=36)

		Hydrocephalus (mm)			
		10-12 (mild)	12.1-14.9 (moderate)	≥ 15 (severe)	Total
Maternal age	21-30 years	4	7	11	22
		18.2%	31.8%	50%	
	31-40 years	0	2	12	14
		0%	14.3%	85.7%	
Total		4	9	23	36

mm: millimeters

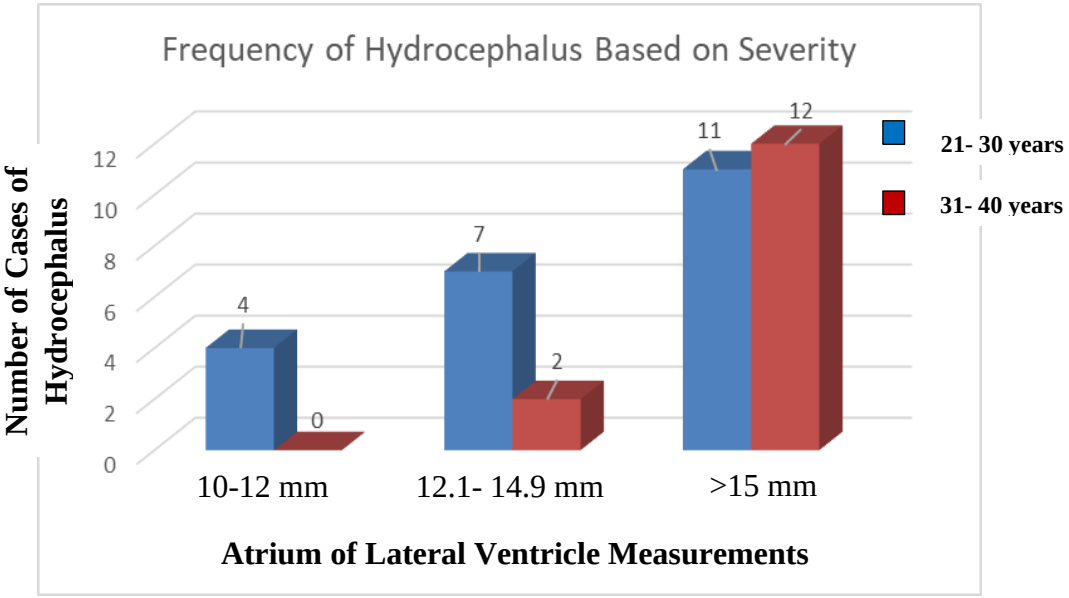


Figure 17: Bar chart showing comparison of frequency of hydrocephalus based on severity

Table 3 A

Association of fetal hydrocephalus with the cranial and extracranial embryological anomalies

(n=36)

	n	Measurements of atrium of lateral ventricle (mm)		p-value
		Mean	SD	
Isolated hydrocephalus	13	18.48	4.72	0.033*
Cranial anomalies	20	16.07	3.01	
Extracranial anomalies	3	21.77	3.87	

p-value ≤ 0.05 is significant and shown with asterisk *

Test used: Independent t-test

mm: millimeter

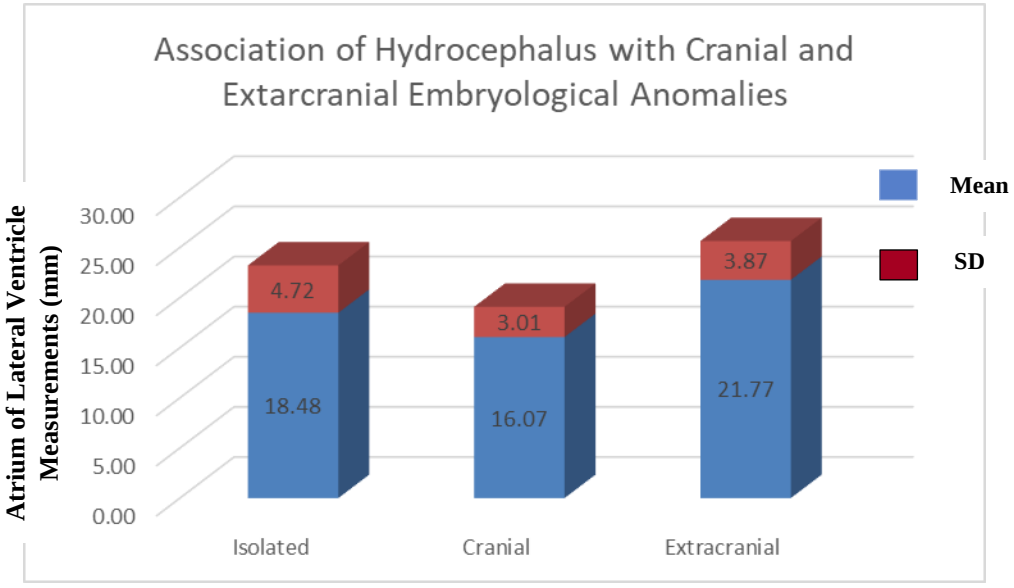


Figure 18: Bar chart showing mean and standard deviation of fetal hydrocephalus with cranial and extracranial embryological anomalies

Table 3 B

Frequency of distribution of congenital anomalies based on severity

(n=36)

Hydrocephalus	Congenital anomalies		
	Isolated	Cranial anomalies	Extracranial anomalies
10-12mm	0	4	0
	0.0%	20.0%	0.0%
12-14.9mm	4	5	0
	30.8%	25.0%	0.0%
≥15mm	9	11	3
	69.2%	55.0%	100%
Total	13	20	3
	100.0%	100.0%	100.0%

mm:millimeters

Table 4

Association of fetal hydrocephalus with gender

(n=36)

Fetal Gender	n	Measurements of Atrium of Lateral Ventricle (mm)		
		Mean	SD	p-value
Male	30	17.22	4.19	0.780
Female	6	16.71	2.53	

p-value ≤ 0.05 is significant

Test used: Independent t-test

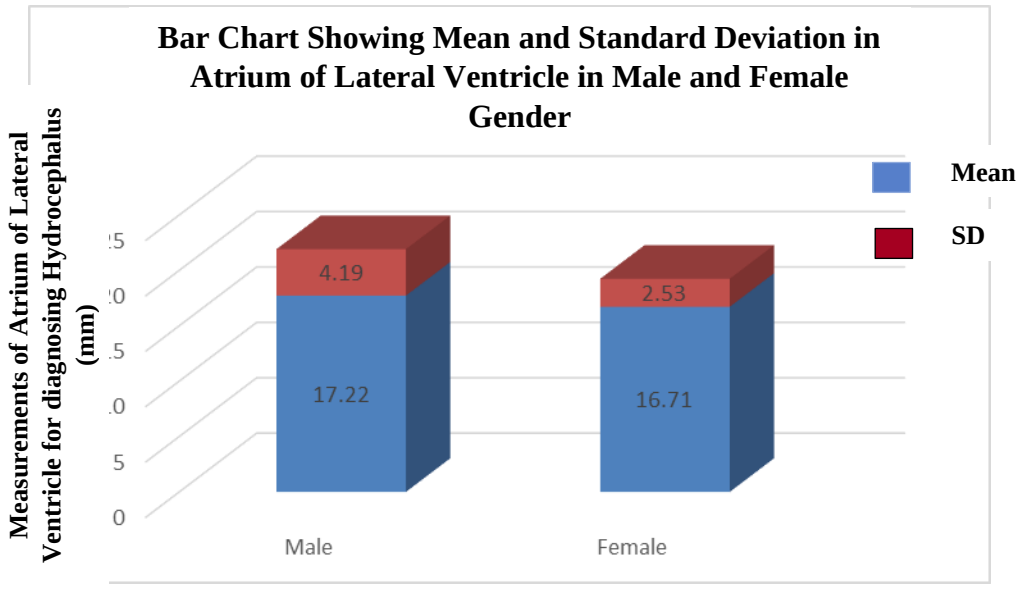


Figure 19: Bar chart showing mean and standard deviation of measurements of hydrocephalus with fetal gender

Table 5A

Frequency of fetal hydrocephalus in different volume of amniotic fluid

(n=36)

	Amniotic fluid volume (cm)			
Hydrocephalus		≤ 9	10 -19 (normal)	20-25
	Frequency	1	33	2
	Percentage	2.8%	91.7%	5.6%

cm: centimeter

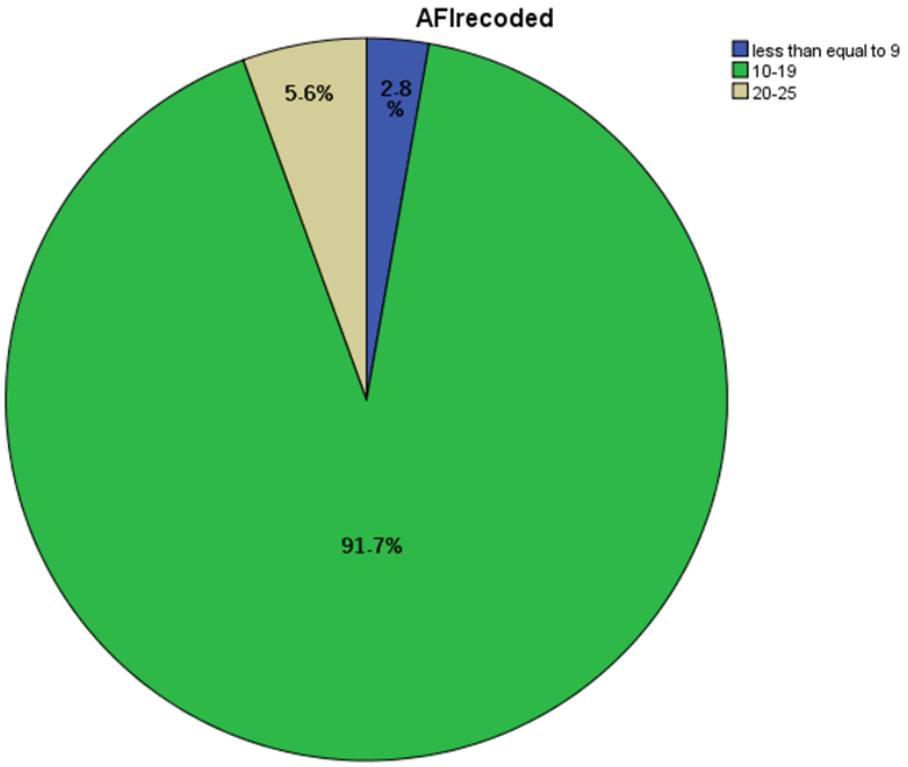


Figure 20: Pie chart showing frequency of distribution of fetal hydrocephalus in different volumes of amniotic fluid

Table 5 B

Association of fetal hydrocephalus with amniotic fluid volume

(n=36)

	Mean	Standard deviation	p-value
Atrium of lateral ventricle (mm)	17.13	3.93	0.000*
Amniotic fluid index	13.97	2.71	

p-value ≤ 0.05 is significant and is shown with asterisk *

Test used: Independent t- test

mm: millimeters

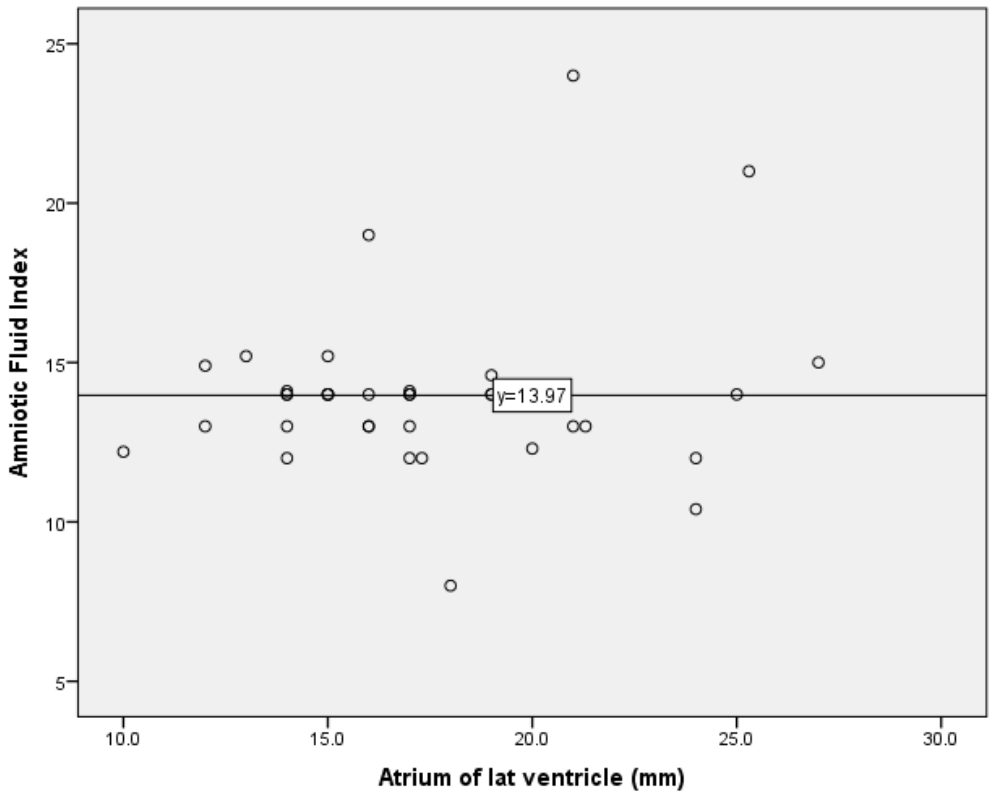


Figure 21: Scatterplot showing correlation between atrium of lateral ventricle measurements and amniotic fluid volume

Table 6 A

Association between atrium of lateral ventricle measurements and ventricle:hemisphere ratio

(n=36)

	Mean	SD	p-value
Atrium of lateral ventricle (mm)	17.13	3.93	0.000*
Ventricle: hemisphere ratio	2.90	1.90	

p-value ≤ 0.05 is significant and is shown with asterisk *

Test used: independent t-test

mm: millimeters

Table 6 B

Correlation between atrium of lateral ventricle and

lateral ventricle:hemisphere ratio

(n= 36)

	Lateral ventricle: hemisphere ratio and atrium of lateral ventricle
Pearson's correlation	0.542
p-value	0.001

Test used: Pearson's correlation

Significant +1 to -1

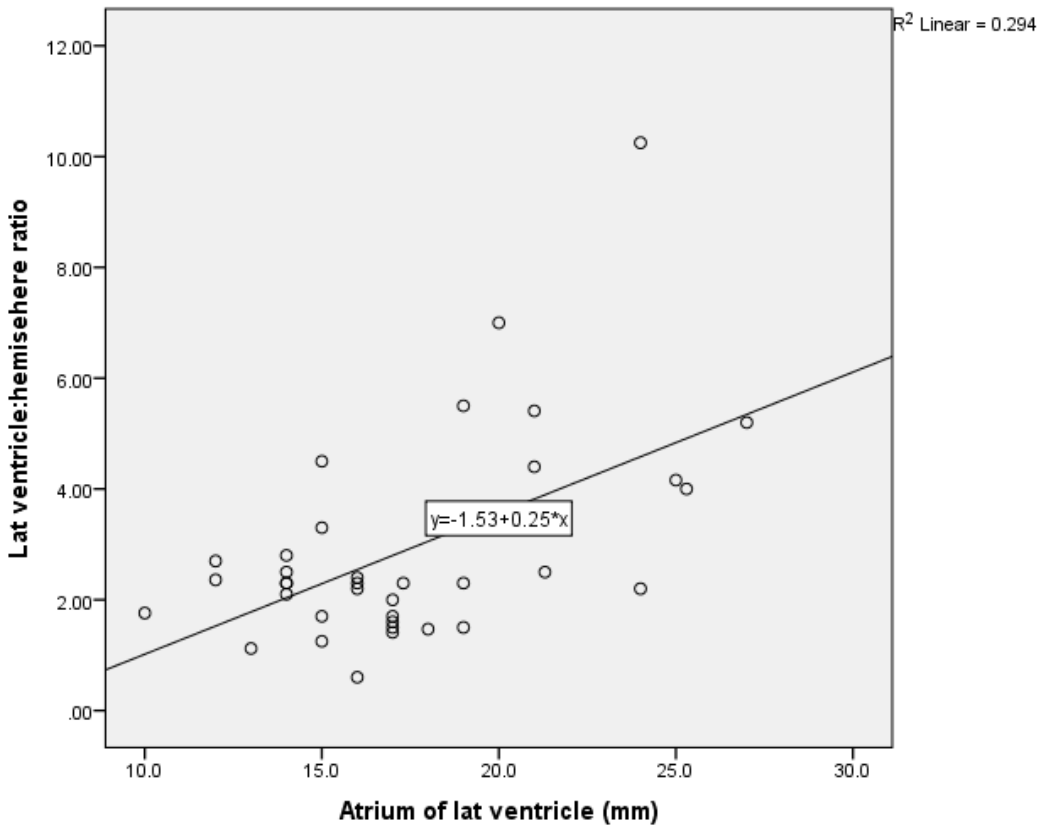


Figure 22: Scatter plot showing positive correlation between lateral ventricle to hemisphere ratio and atrium of lateral ventricle measurements

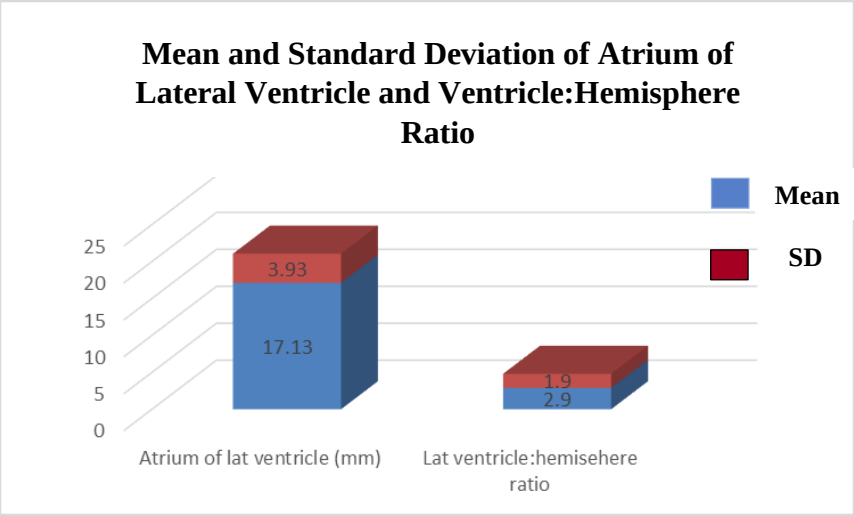


Figure 23: Bar chart showing mean and standard deviation of atrium of lateral ventricle measurements and ventricular:hemisphere ratio

Table 7

Association between atrium of lateral ventricle measurement

and biparietal diameter

(n=36)

	Mean	SD	p-value
Atrium of lateral ventricle (mm)	17.41	4.06	0.000*
Biparietal diameter (mm)	7.35	1.16	

p-value ≤ 0.05 is significant and is shown with asterisk *

Test used: Independent t--test

mm: millimeters

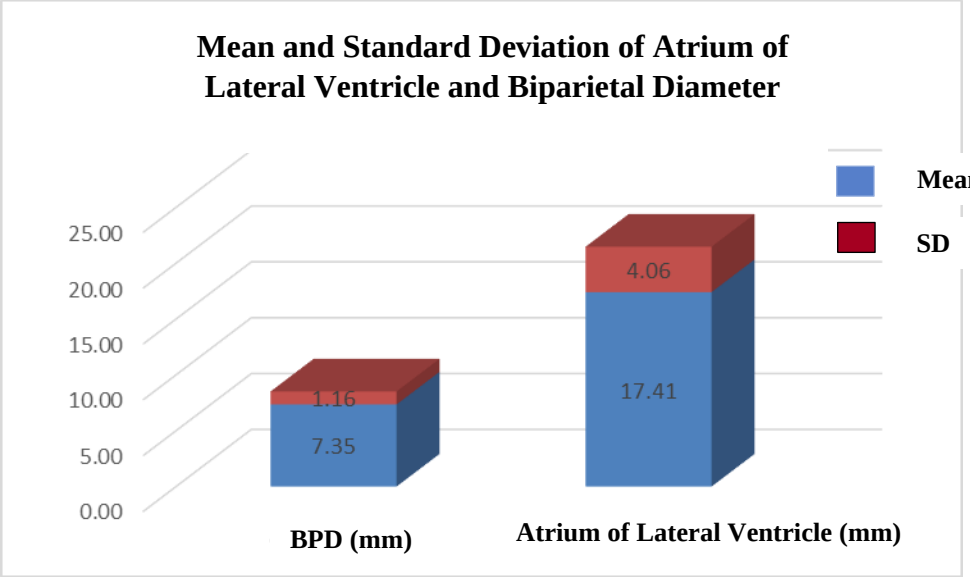


Figure 24: Bar chart showing mean and standard deviation of BPD and atrium of lateral ventricle

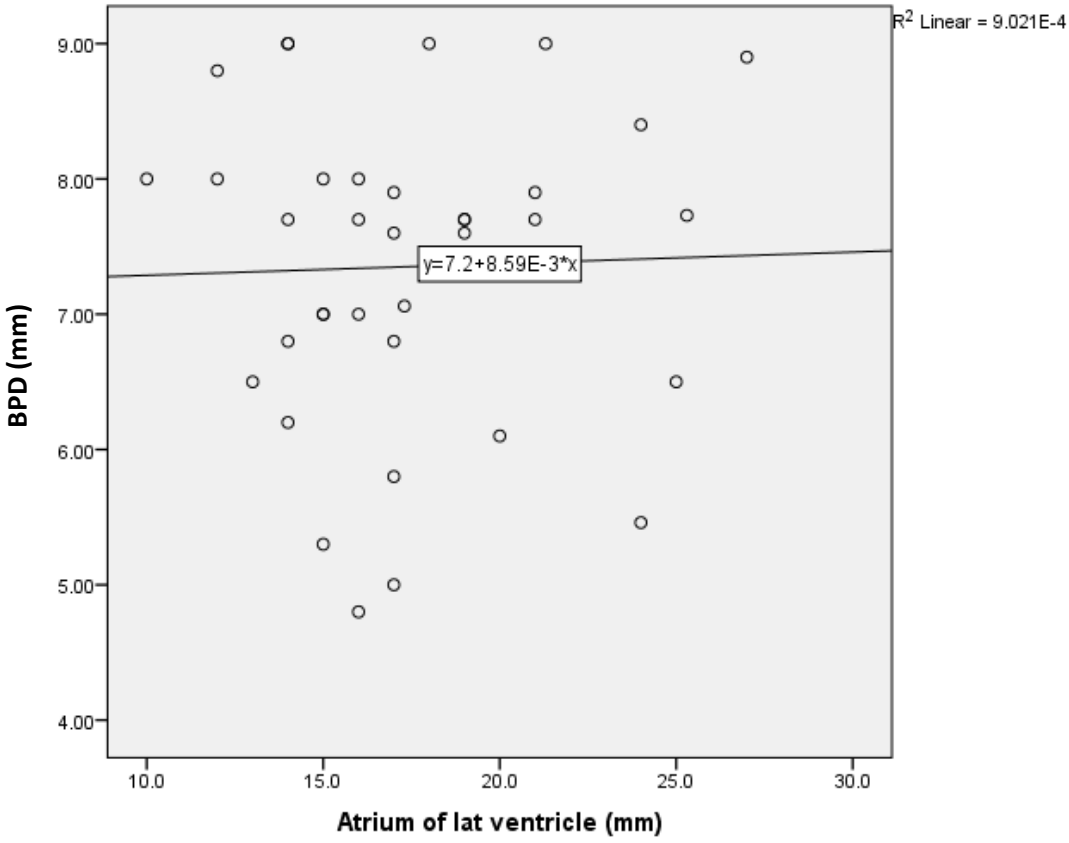


Figure 25: Scatter plot showing correlation between atrium of lateral ventricle measurements and BPD

Table 8 A

Association of fetal hydrocephalus with family history

(n=36)

	Hydrocephalus		
		n	Percentage
Family History	Yes	20	55.6%
	No	16	44.4%

Table 8 B

Cross tabulation between family history of patients with hydrocephalus and consanguinity

(n=36)

		Family History		
		Yes n (%)	No n (%)	Total n (%)
Consanguinity	Yes n (%)	9 (45%)	8 (50%)	17 (47.2%)
	No n (%)	11 (55%)	8 (50%)	19 (52.8%)

Table 8 C

Association of hydrocephalus with consanguinity

(n=36)

	n	Mean of Atrium of Lateral Ventricle (mm)	p-value
Yes	17	19.13	0.014*
No	19	15.87	

p-value ≤ 0.05 is significant and is shown with asterisk *

Test used: Independent t–test

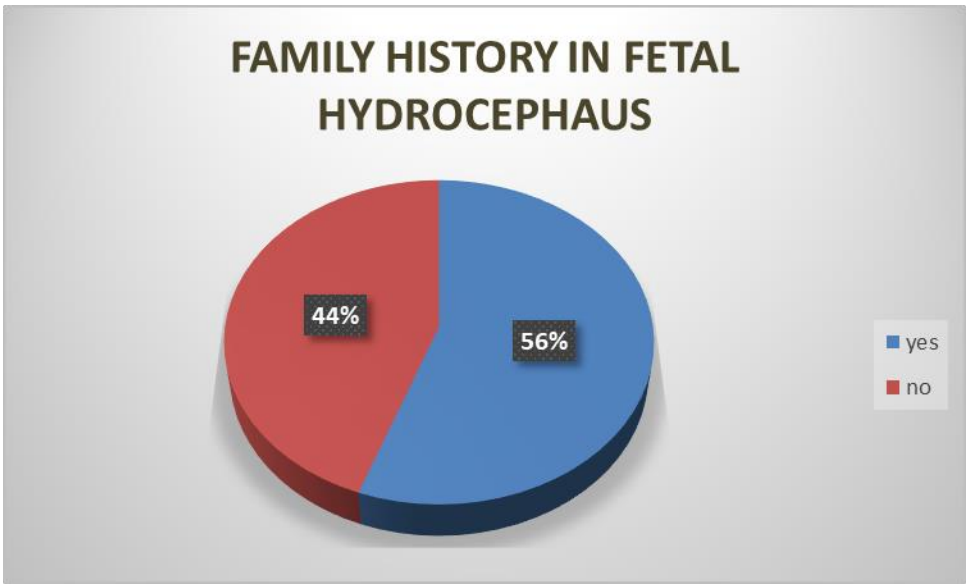


Figure 26: Pie chart showing family history in cases of fetal hydrocephalus

Table 9

Correlation between head circumference and atrium of lateral ventricle

(n=36)

	Head circumference and atrium of lateral ventricle
Pearson Correlation	-0.014
p-value	0.936

Test used: Pearson's correlation

Significant +1 to -1

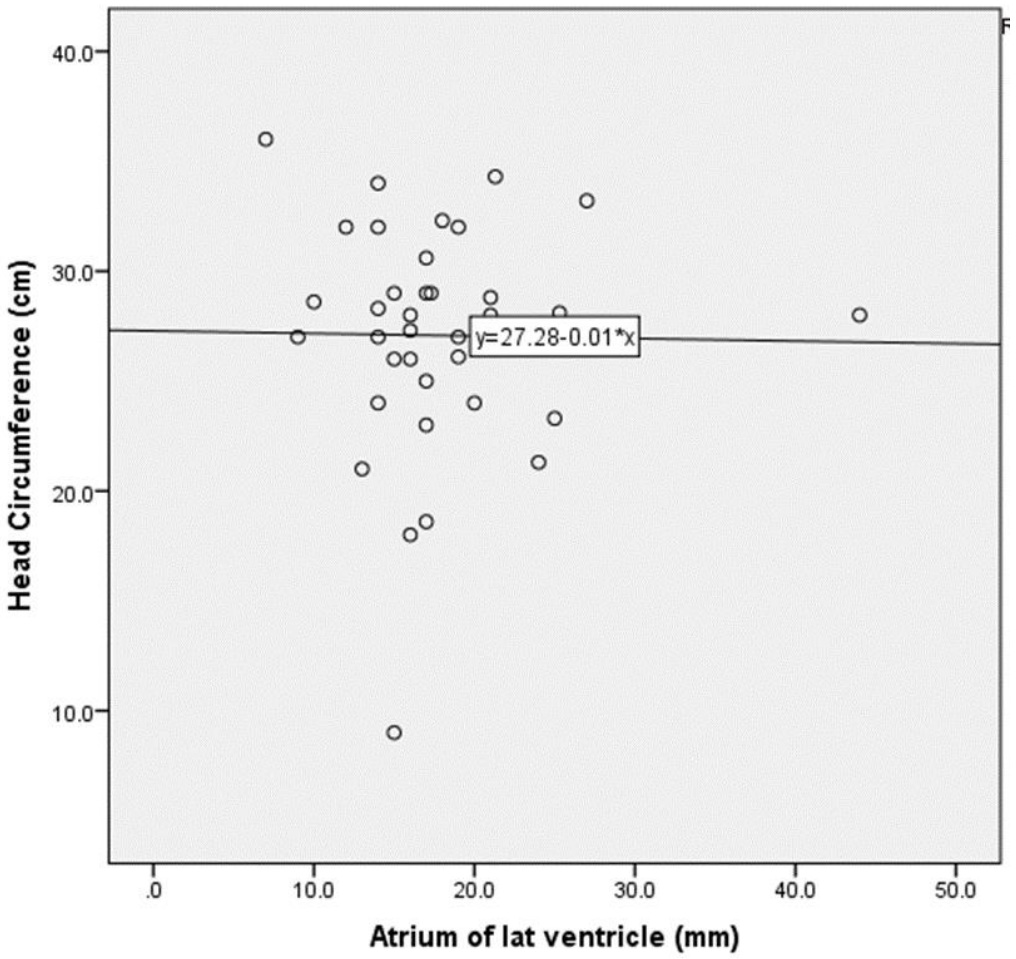


Figure 27: Scatter plot showing correlation between measurements of atrium of lateral ventricle and head circumference

Table 10

Correlation between atrium of lateral ventricle and

head:abdominal circumference ratio

(n=36)

	Head:abdominal circumference ratio vs atrium of lateral ventricle
Pearson's correlation	-0.416
p-value	0.012

Test used: Pearson's correlation

Significant +1 to -1

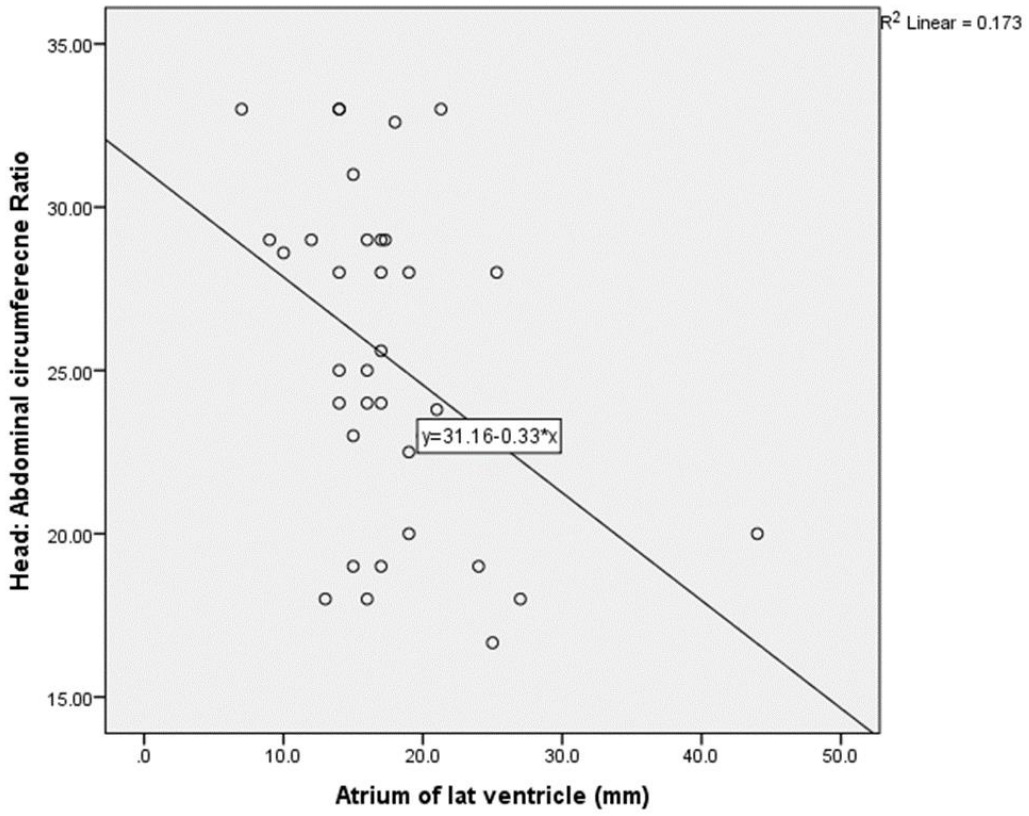


Figure 28: Scatter plot showing correlation between atrium of lateral ventricle and head to abdominal circumference ratio

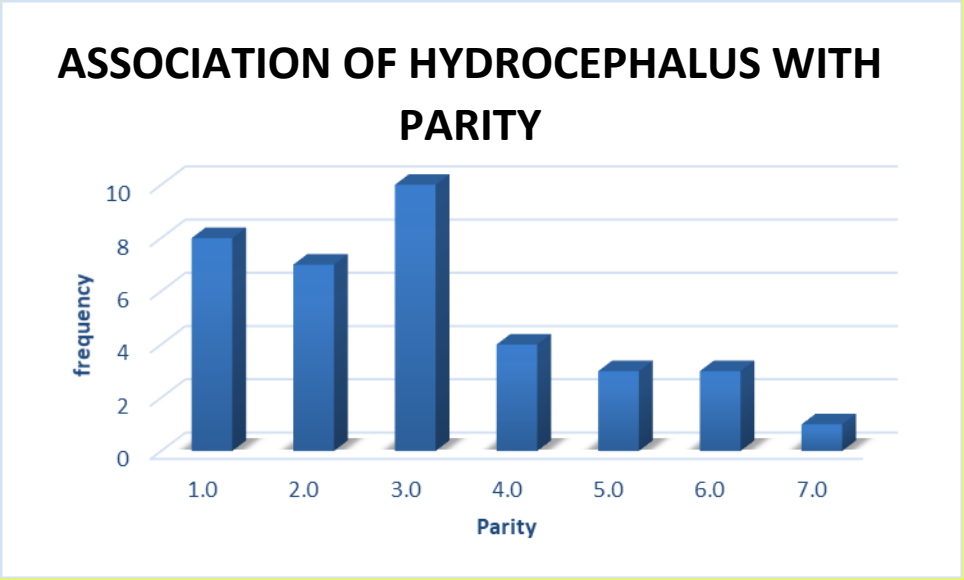


Figure 29: Bar chart showing association between frequency of distribution of hydrocephalus with maternal parity

Table 11

Frequency of hydrocephalus in single and twin pregnancy

(n=36)

	Atrium of Lateral Ventricle Measurement of atrium of lateral ventricle for diagnosing Hydrocephalus (mm)		
	n	Mean	SD
Single fetus	35	17.41	4.06
Twins	1		

mm: millimeters

CHAPTER 5

Discussion

This pioneer study is one of its kind as it compares various parameters used to diagnose congenital hydrocephalus by a simple, cost effective yet a very sensitive modality, that is ultrasound, in pregnant females.

Our study concluded that hydrocephalus was more prevalent in mothers of 21-30 years (22 patients) with p- value of ≤0.011. This being a new finding in our set up where literature shows higher maternal age group related to multitude of congenital anomalies (Tonni et al., 2016; Tully et al., 2015). In another prospective cross-sectional study conducted by Ishola, Asaleye, Ayoola, Loto, & Idowu, (2016), on 400 patients the authors found 222 patients of maternal age ranging between 30-35 years and above which is contradictory to our results. However, a retrospective study conducted by Nomura, Barini, De Andrade, Milanez & Simoni et al., (2010), on 287 patients, found the mean maternal age to be 25 years which is in concordance to our study results.

In a prospective study conducted in Tripoli on 74 patients, it was observed that 43% patients in the age group of 20-30 years gave birth to fetuses with hydrocephalus whereas 62% belonged to age group 30 years or more (Taleb, Ajaj, Abudia & Albakoush, 2018).

Another study conducted by Joó, Tóth, Beke, Papp & Csaba, et al., (2008), found the median maternal age to be 25 ± 4.2 years. In another study teenaged mothers (14-19) were found to be at higher risk for giving birth to fetuses with anencephaly and hydrocephalus with neural tube defects as compared to mothers of older age groups (Reefhuis et al., 2004).

A study conducted by Yi et al., (2017) showed that congenital hydrocephalus was more prevalent in fetuses of mothers < 20 years and in >35 years.

Another study supporting our result was conducted by Kadian, Verma, Kajal, & Duhan, (2017), on a sample of 83422 patient, found 18 cases (14.6%) in age group of < 20, 72 cases (58.53%) in maternal age group of 21-25 years. 27 cases (71.95%) in age group of 26-30 years and only 4 (3.2%) and 2 cases (1.62%) belonged to age groups 31-35 years and > 35 years respectively.

Sunitha, Prasoona, Kumari, Srinadh & Deepika et al., (2017), identified 37 out of 3301 cases of hydrocephalus in women of age group < 25 years (p-value ≤ 0.002).

Our study proved fetal hydrocephalus to be associated with multiple congenital/embryological anomalies. Most prevalent (20 out of 36 patients, p-value of 0.033) of these were cranial anomalies of which neural tube defects like spina bifida and meningomyelocele were most commonly associated. Dandy walker syndrome, dangling choroid, dilated 3rd and 4th ventricles and cerebral aqueduct dilatation were also identified. Isolated cases, without any other congenital anomaly, were 13 followed by 3 cases of extracranial anomalies comprising of fetal ascites, fetal pleural effusion and anomalies of fetal kidneys.

Our results are in concordance with the finding from other studies (Joó et al., 2008) where spina bifida was found to be associated most commonly with hydrocephalus with a prevalence of sacral spine involvement. A prospective study conducted on 267 patients, 172 patients were diagnosed with spina bifida, 58 case were isolated and 37 had multiple other malformations (Nicolaides, Berry, Snijders, Thorpe-Beeston & Gosden, 1990). Another prospective study where 21 patients were followed postnatally for neurodevelopment outcome showed 3 cases to be isolated and 6 were associated with stenosis of aqueduct of Sylvius (Letouzey, Chadie, Brasseur-Daudruy, Proust & Verspyck et al., 2017). Madazli, Şal, Erenel, Gezer & Ocak, (2011) in their prospective study on 102 cases spanning over a period of 8 years were able to deduce that 79 of these cases of hydrocephalus were associated with various congenital malformations. Of these spina bifida was found in 52 cases, followed by Dandy walker syndrome in 7 cases. These results are in coherence with our study.

In another retrospective study on 86 patients, 40 cases of hydrocephalus were found to be associated with cranial anomalies, most common of which spina bifida and meningomyelocele (13 patients) and 3 cases were associated with extracranial anomalies like urinary tract, hydrops fetalis and ventricular septal defect (Gómez-Arriaga, Herraiz, Puente, Zamora-Crespo & Núñez-Enamorado et al., 2012). Similarly, another study which is in concordance with our study exhibited 3rd and 4th ventricular dilatation is associated

with hydrocephalus (Tonni et al., 2016). Coherent with our study results 40 patients with hydrocephalus were found to have meningomyelocele (Rehman et al., 2015). In a study conducted on Sudanese children, congenital hydrocephalus was found to be associated with stenosis of Aqueduct of Sylvius (30%) (Mahmoud et al., 2014). In a retrospective study conducted in eastern province of Saudi Arabia, 75% patients were found to have the central nervous system anomalies (meningomyelocele, Dandy Walker & encephalocele) in conjunction with hydrocephalus (Al Anazi & Nasser, 2003).

Forty-three cases of hydrocephalus were found to be associated with stenosis of aqueduct of Sylvius and demonstrated enlargement of 3rd ventricle and abnormalities of corpus callosum (Heaphy-Henault, Guimaraes, Mehollin-Ray, Cassady & Zhang et al., 2018) hence further strengthening the results of our study. The results of our study and that of others prove that hydrocephalus is found to be most commonly associated with neural tube defects like spina bifida and meningomyelocele.

Based on the results of our study we were able to categorize hydrocephalus into mild (10 – 12 mm), moderate (12.1 -14.9 mm) and severe (≥15 mm) categories based on the measurements of atrium of lateral ventricle. Our study found maximum number (63.9%) of cases in severe category where atrium of lateral ventricle measure more than 15 mm in several cases. Followed by moderate (25%) and mild dilatation (11.1%). 85% of the severe cases were found in fetuses where maternal age was between 31-40 years. Maximum number of cases were of severe variety in both age groups, however maximum number of moderate forms were present in maternal age group of 21-30 years. Hence, we were able to deduce that in our population hydrocephalus presents with severe form irrespective of maternal age. These findings are contrary to a prospective study in 278 patients conducted by Barzilay, Bar-Yosef, Dorembus, Achiron & Katorza, 2017, where 73% cases were of mild type, 22.7% of moderate and 12% of severe on magnetic resonance imaging (MRI). Contrary to our study results, Behrendt, Zaretsky, West, Galan & Crombleholme, et al., (2017) diagnosed 54 cases of mild dilatation of left lateral ventricle and 52 cases of mild dilatation of right lateral ventricle and only 4 and 3 cases of severe dilation of lateral ventricle on left and right sides respectively. In another prospective study conducted on

304 patients 62.2% cases were of mild type, 23.2% of moderate and only 14.4% cases of severe type were diagnosed on parental ultrasound scans. (Chu, Zhang, Yan, Ren & Wang et al., 2016).

Our study was able to deduce that 55% cranial anomalies were associated with severe type of ventricular dilatation whereas 25% and 20% with moderate and mild type respectively and all cases of extracranial congenital anomalies were found to be associated with severe type of dilatation. Barzilay et al., (2017) found congenital anomalies to be associated with moderate type of ventricular dilatation. Behrendt et al., (2017) on the other hand identified > 60% risk of developing congenital anomalies in severe type of ventricular dilatation. Lam & Kumar, (2014) identified maximum number of cranial anomalies to be associated with severe type of ventricular dilatation.

An Indian prospective study comprising of 102,216 research participants identified 85.9% cases of severe hydrocephalus as compared to 14.1% cases of mild form. It also enunciated the fact that 36.9 % of these severe cases were associated with spina bifida (Kumar, Garg, Hasija, Pritam & Shukla et al., 2018). These results strongly support and strengthen our s nsstudy results.

Based on the results of our study we were able to conclude that hydrocephalus has a male predilection (30/36 cases). These results are consistent with a retrospective analysis done in 44 patients which identified 26/44 as males (Dall'Asta, van Oostrum, Basheer, Paramasiva & Ghi et al., 2018). Contrary to our results, another prospective study conducted on 685 patients by Udoh, Ugwu, Ali, Chiegwu, & Eze et al., (2019) identified a female prediliction (374) for hydrocephalus as compared to males (311). However, Taleb et al., (2018), in their study conducted on 74 patients, found 34 (45%) male fetuses and 40 (54%) females

Udoh, Sylvanus, Uduak, & Ulu, (2019), identified equal distribution of hydrocephalus in both male and female fetuses.

Kumar et al., (2018), in their prospective study also identified equal distribution between genders. A case study reporting a case of bilateral ventriculomegaly associated with VACTERL identified the affected fetus as 46XY on cordocentesis (Sivanathan & Omar, 2018). Perlman et al., (2014) identified 57.89% male fetuses affected by hydrocephalus as compared to 42.11% females. Baffero, Crovetto, Fabietti, Boito, & Fogliani et al., (2015) in their 135 patient study identified 8 cases of male and 55 cases of female fetuses born with hydrocephalus. Kadian et al., (2017) also observed a male preponderance (64 cases, 52.03%) in their sample of 83422 congenital anomalies of 123 cases were of congenital hydrocephalus. Thus, based on our result and results of other researchers present in literature we can conclude that hydrocephalus has prominent male preponderance.

An increased amniotic fluid volume has been known in literature to be associated with congenital anomalies in fetuses. However, in our study we observed a normal volume of amniotic fluid (10-19) in 33 out of 36 cases (91.7%) and only 2 cases (5.6%) had polyhydramnios and 1 case was identified with a volume of < 9 and categorized as oligohydramnios.

Our results were analogous with a study conducted over a period of 10 years by Ali & Abdelaal, (2015) in Egypt on a sample size of 240 patients, they identified 205 patients with normal volumes of amniotic fluid in fetuses with congenital hydrocephalus (p-value ≤ 0.05) and 18 and 17 patients were diagnosed with polyhydramnios and oligohydramnios respectively.

Qadir & Amir, (2017) in their cross-sectional design on 201 patients found various degrees of polyhydramnios to be associated with congenital anomalies, 58% of mild polyhydramnios, 33% cases of moderate polyhydramnios, and only 9% cases of severe polyhydramnios were diagnosed.

A case report on a 33-year-old female published by (Kline-Fath, Merrow, Calvo-Garcia, Nagaraj & Saal, 2018) observed severe ventriculomegaly (20 mm dilatation) with polyhydramnios.

In another study conducted by Lalchan, Sharma & Gurung, (2018) on 39 pregnant females observed mild polyhydramnios (AFI 25.1 -30) in 27 (71.1%) to be associated with various types of congenital anomalies in fetuses.

The results of one of the seminal studies conducted by Pretorius et al., 1985 conducted on 38 patients, hydrocephalus was observed in 16 fetuses with normal volumes of amniotic fluid while 31.5% (12 cases) were diagnosed with polyhydramnios.

Results of our study revealed a positive family history in 20 cases (55.6%) out of these 9 had consanguineous marriage and showed a p-value of 0.014. These results are like the findings of Tully, Laquerriere, Doherty & Dobyns, (2018) where they identified association of L1CAM gene mutation in fetuses with congenital hydrocephalus. In fetal autopsy they identified 90% of these cases had aqueduct stenosis. L1CAM association was also observed in x-linked hydrocephalus (Adle-Biassette, Saugier-Veber, Fallet-Bianco, Delezoide & Razavi et al., 2013). Similar findings were identified by Duan, Wang, Zhu & Li, (2018) where they identified positive family history in 1 out 13 fetuses with congenital hydrocephalus due to mutation in L1CAM gene.

Shaheen, Sebai, Patel, Ewida & Kurdi et al., (2017) in their study on 27 families with congenital hydrocephalus found mutation in MPDZ gene but no positive family history was identified in 57% of them. Their study also observed that 6 of these families had male gender association (Shaheen et al., 2017).

Furey, Choi, Jin, Zeng & Timberlake et al., (2018) were able to identify 4 new genes, TRIM 1, SMARCC 1, PTCH and SHH, involved with congenital hydrocephalus.

Ameen, Alalaf & Shabila, (2018), in their study on congenital malformations identified 37.7% cases of central nervous system anomalies out of which majority (12.3%) were diagnosed as congenital hydrocephalus. Out of their total study population it was identified that 149 affected were male, 10.8% of their cases had a history of congenital anomalies in previous pregnancies and 129 cases (49.6%) had consanguineous marriage.

These results are in coherence with our study findings. Kline-Fath et al., (2018) in their case study identified fetal hydrocephalus repeatedly in subsequent pregnancy of a 33-year-old lady and identified the recurrence risk of 25% in every pregnancy.

Khan, Zuhaid, Fayaz, Ali & Khan et al., (2015) in their study conducted in Peshawar observed 31 newborns with hydrocephalus and 6.77% of these were a result of consanguineous marriage.

Yi et al., (2017) observed a higher prevalence rate (4.8) with increasing parity. Similar results were observed in our study where 10 cases of hydrocephalus were observed in women with parity of 3 followed by 8 cases with parity of 1 and 1 case of twin pregnancy was identified.

Okmen, Köroğlu, Turkgeldi, Cetin & Aslan, (2017) in their study on 10,138 patients observed that major congenital anomalies had a higher risk of developing in fetuses of women with increased parity and gravidity. Their study showed 19% cases of hydrocephalus is women $\leq$ 34 years and 32% in women > 34 years. Tully et al., (2015) observed 43.9%, 29.2% and 26.9% in women with parity of 0, 2^{+} and 1.

Kumar et al., (2018) observed similar results of 47%, 34.6%, 13.7% and 4.6% in women with parity of 0, 1, 2, $\geq$ 3. They also identified 9 cases of twin pregnancies out of 236 However, Kaidan et al., (2017) observed highest frequency of 56.9% in para 1 followed by 37% in para 0.

Ali et al., (2015) observed 53.3% cases in uniparous women (p value <0.0001) and 2.94% twin pregnancies. Joó et al., (2008) also identified 4.34% (10/230cases) of multiple pregnancies in their study. These results are in accordance with our study findings.

When we correlated the measurements of atrium of lateral ventricle with ventricular: hemisphere ratio, we observed a positive correlation between the two variables (r = 0.542). Hence, we can say both the variables can be used for the diagnosis of hydrocephalus. Ishola et al., (2016) observed a decline in the measurement with a mean of 61.20% and 42.84%

at 14 and 40 weeks respectively. However, no data correlating the two variables was available in literature.

Our study showed no correlation between atrium of lateral ventricle measurements and BPD with a r = 0.032. Thereby concluding that BPD does not increase with the increase in the measurements of atrium of lateral ventricles. However, limited to no data was found correlating the two parameters. Results of another study showed strong correlation with a r = 0.80 (Taketani, Yamada, Uwabe, Okada & Togashi et al., 2015).

Similar results were observed by Gollop & Eigier, (1987) in their case report where normal values of BPD for the gestational age were correlated unlike our study results. Pretorius et al., (1985) found BPD to be abnormal in only 28/40 cases (37%) and therefore concluded that BPD is not a reliable indicator for diagnosing hydrocephalus. However, Joó et al., (2008) noted BPD measurements in percentiles and observed 50% of their patients to be in 75^{th} percentile. Therefore, based on our results and compared to other studies, we can conclude that BPD has no correlation with width of the atrium of lateral ventricle.

Our study showed negative correlation of head circumference with atrium of lateral ventricle (r = - 0.14). Joó et al., (2008) interpreted values of head circumference in percentiles and observed 45% patients in 75^{th} percentile or higher. Udoh et al., (2019) observed in their study that though head circumference does increase with gestational age, but it has no correlation with the increase in width of atrium of lateral ventricle. These results are therefore like our study.

Our study observed a negative correlation of head: abdominal circumference ratio with the measurements of atrium of lateral ventricle (r = - 0.416). However, due to limited availability of data correlating the two variables no similar contradictory studies were found.

CHAPTER 6

Conclusion

Hydrocephalus which is present in the community can easily be diagnosed by transabdominal prenatal ultrasound scans done during 18-42 weeks of gestation. The study concluded that most of the diagnosed cases were mostly found in fetuses of women aged 21-30 years with maximum cases being of severe type of dilatation in both maternal age groups. However, moderate dilatation was found only in fetuses of maternal age group of 21-30 years.

Hydrocephalus showed a positive correlation with various cranial anomalies like spina bifida, meningomyelocele, 3rd ventricular dilatation, Dandy Walker Syndrome, fetal pleural effusion and fetal edema while some of the cases were isolated cases of hydrocephalus. It was found more commonly in male fetuses and showed a positive significant correlation with family history, consanguinity and maternal parity.

It was found to be associated with normal volumes of amniotic fluid. A positive correlation was observed between measurements of atrium of lateral ventricle and ventricle:hemisphere ratio. However, a negative correlation was found between atrium of lateral ventricle measurements and that of head circumference and head:abdominal circumference ratios.

Transabdominal prenatal ultrasound scans can safely and effectively be used for early detection of hydrocephalus thereby also reducing the disease burden in the society and decreasing the maternal and fetal mortality rates.

It can thus help provide the affected families the time required to make appropriate decision regarding rehabilitation, counselling or termination of pregnancy.

6.1. Recommendations:

This study warrants,

1. Other prospective studies with larger sample size over a longer period to be able to generalize the results in Pakistani population.
2. Other follow up studies should be conducted to see the postnatal outcomes and prognosis of patients diagnosed with different severities of hydrocephalus.
3. Interventional studies can be conducted by identifying risk factors and providing appropriate antenatal care in pre-disposed families.
4. Studies can be conducted on different treatment modalities and the impact of these postnatally
5. Research should be conducted to assess the recurrence rates of hydrocephalus among siblings especially those with a family history based on genetic make-up.
6. Gene level studies should be carried out to assess the gene involved in fetal hydrocephalus in families with positive histories.

6.2. Strengths of the Study

1. This being a basic, yet pioneer study which has compared most of the parameters comprehensively

2. First of its kind in Pakistan to identify the association of fetal hydrocephalus with cranial and extracranial anomalies

6.3. Limitations of the Study

To the best of our knowledge this is an original work done with utmost dedication and sincerity. However, the limitations of the study are

1. Sample size is small therefore results cannot be generalized

2. This is a single center study

3. Time duration was limited

CHAPTER 7

7.1 References

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7.2 Appendices:

7.2. (A) FRC Approval Letter

Ref no: FRC/BUMDC/Ana/002 MS-11

Approval of Research Proposal

Mr/Miss/Ms/Mrs/ **Dr. Ambreen Surti**

Registration No. **06-113172-001**

Dear MS/MPhil Student,

I am pleased to inform you that your research proposal on **"Diagnosis of hydrocephalus and its associated embryological anomalies on prenatal ultrasound"** has been approved. You may, therefore, continue you research on this theme and produce a quality thesis, as per the HEC requirements.

I take this opportunity to remind you that you must complete your thesis, and defend it successfully, by **SPRING 2020**; this is the date which marks the end of the Extended Duration of your programme. However, to remain eligible for honours and awards, you must complete the thesis, and successfully defend it, by the end of 10 week into the next semester after the final semester.

I wish you every success.

Dated: 24/09/18

(CHAIRPERSON FRC)

Distribution:

- DG
- Principal
- Student's File (with the HOD/PGP Coordinator)
- Student

7.2. (B) ERC Approval Letter:

BAHRIA UNIVERSITY MEDICAL AND DENTAL COLLEGE

Defence phase II, Sailor Street, adjacent to PNS Shifa, Karachi. Tel: 021-35319491-9

ETHICAL REVIEW COMMITTEE

LETTER OF APPROVAL

Date: 01.10.18

PATRON
Prof. Asad Ullah Khan
Principal & Dean
Health Sciences(BU)

CHAIRPERSON
Prof. Ambreen Usmani

SECRETARY
Prof Reza H Syed

MEMBERS
Prof M Alamgir
Prof Anis Jafarey
Ms Nighat Huda
Surg Cdre Amir Ejaz
Ms Shabina Arif
Mr M Amir Sultan
Surg Lt Cdr Farah
Surg Lt Cdr Sadia

Dr. Ambreen Surti
Senior Lecturer
Department of Anatomy
BUMDC-Karachi

Subject: Institutional Approval of research study

Title of Study: Diagnosis of Hydrocephalus and its Associated Embryological Anomalies on Prenatal Ultrasound

Principal Investigator: Dr. Ambreen Surti , Senior Lecturer Department of Anatomy, Bahria University Medical and Dental College.

Reference No: ERC 47/2018

Dear Dr. Ambreen Surti

Thank you for submitting the above mentioned study proposal. ERC Bahria University has reviewed this project in the meeting held on 24th-Sep-2018 and gives approval. Kindly notify us when the research is complete.

Regards,

PROF DR AMBREEN USMANI
Chairperson
BUMDC

Cc:
DG-BUMDC
Principal BUMDC
Chairperson ERC

7.2 (C) Consent Form (Urdu):

مریض کے لیے رضامندی فارم

میں رضا کارانہ طور پر اپنی مرضی سے اس ریسرچ Diagnosis of Hydrocephalus and its Associated Embryological Anomalies میں شمولیت پر رضامند ہوں جس کا مقصد hydrocephalus کی موجودگی کی تشخیص اور prenatal, transabdominal ultrasound. میں associated embryological anomalies دیکھنا ہے۔

مجھے اس ریسرچ پروجیکٹ میں شمولیت کی نوعیت اور اہمیت تفصیل سے بتادی گئی ہے اور میں نے فراہم کردہ وضاحت کو سمجھ لیا ہے۔

مجھے بتادیا گیا ہے کہ میری بیماری کے متعلق معلومات اور اعدادوشمار مکمل طور پر خفیہ رکھے جائیں گے اور انہیں صرف عوامی مفاد نیز مقالات کی تیاری اور پیشکش کے لیے استعمال کیا جائے گا۔

میں تحقیق کنندہ کو متعلقہ معلومات جو ضروری ہوں، مکمل اور اپنے علم کے مطابق دینے پر بھی رضامند ہوں۔ تحقیق کنندہ نے مجھ پر واضح کردیا ہے کہ اس اسٹڈی میں شامل ہونے کا کوئی معاوضہ نہیں ملے گا ماسوائے لیبارٹری تحقیق کے اخراجات جو تحقیق کنندہ برداشت کرے گا۔ جبکہ مجھے یہ حق حاصل ہے کہ کسی بھی وقت اس اسٹڈی سے علیحدگی اختیار کرلوں۔

مجھے یہ مشورہ دیا گیا ہے کہ میری بیماری سے متعلق کسی بھی سوال / ہنگامی صورت میں ڈاکٹر امبرین سورتی سے موبائل 0321-8218372 پر رابطہ کروں یا بحریہ یونیورسٹی میڈیکل اینڈ ڈینٹل کالج کا وزٹ کروں۔

مریض کا نام---

شوہر کا نام---

مریض کے لیے مقرر کردہ علاج--

مریض کے دستخط یا انگوٹھے کا نشان--

تحقیق کنندہ کا نام---

تحقیق کنندہ کے دستخط--

تاریخ--------------------------------

7.2 (D) Consent Form (English):

INFORMED CONSENT FORM FOR PATIENT

You are giving your consent to participate voluntarily and at your own will in this research "Diagnosis of Hydrocephalus and its Associated Embryological Anomalies" that aims to diagnose the presence of hydrocephalus and its associated embryological anomalies on prenatal, transabdominal ultrasound.

You have been explained in detail the nature and significance of participating in the project and you understand the provided explanation.

You have been told that findings of your disease and your data will be kept strictly confidential and will be used only for the benefit of the community, publications and paper presentations.

You also agree to give all relevant information needed, in full and to the best of your knowledge to the researcher. It is clarified to you by the researcher that no incentive will be provided to you for participating in the study except for the cost of lab investigations that will be borne by the researcher whereas you do have the right to withdraw from the study at any time.

You are advised to contact Dr. Ambreen Surti on mobile number 0321-8218372 or visit Bahria University Medical and Dental College in case of any query/ emergency related to your disease

Name of Patient: _____

W/o: _____

Signature/ Thumb Impression of Patient: _____

Name of Researcher: _____

Signature of Researcher: _____

Date: _____

7.2 (E) Subject Evaluation Proforma:

SUBJECT EVALUATION FORM

BAHRIA UNIVERSITY MEDICAL AND DENTAL COLLEGE

PROFORMA: 1

Case #: _____ Date : _____

Name: _____ Age:_____

W/O: _____

Address: _____

Contact #:_____

Personal history:

LMP: _____ Parity: _____

History of vaginal Bleeding: _____

History of diabetes mellitus *: _____

History of essential hypertension*: _____

Other syndromic conditions*: _____

Family History: _____

Consanguinity: _____

FIELDS MARKED WITH * ARE TO BE EXCLUDED

PROFORMA: 2

ULTRASOUND FINDINGS

Case # : _____ Date:_____

Name:_____ Age:_____

W/O:_____ Contact #:_____

Address:_____ Gestational Age:_____

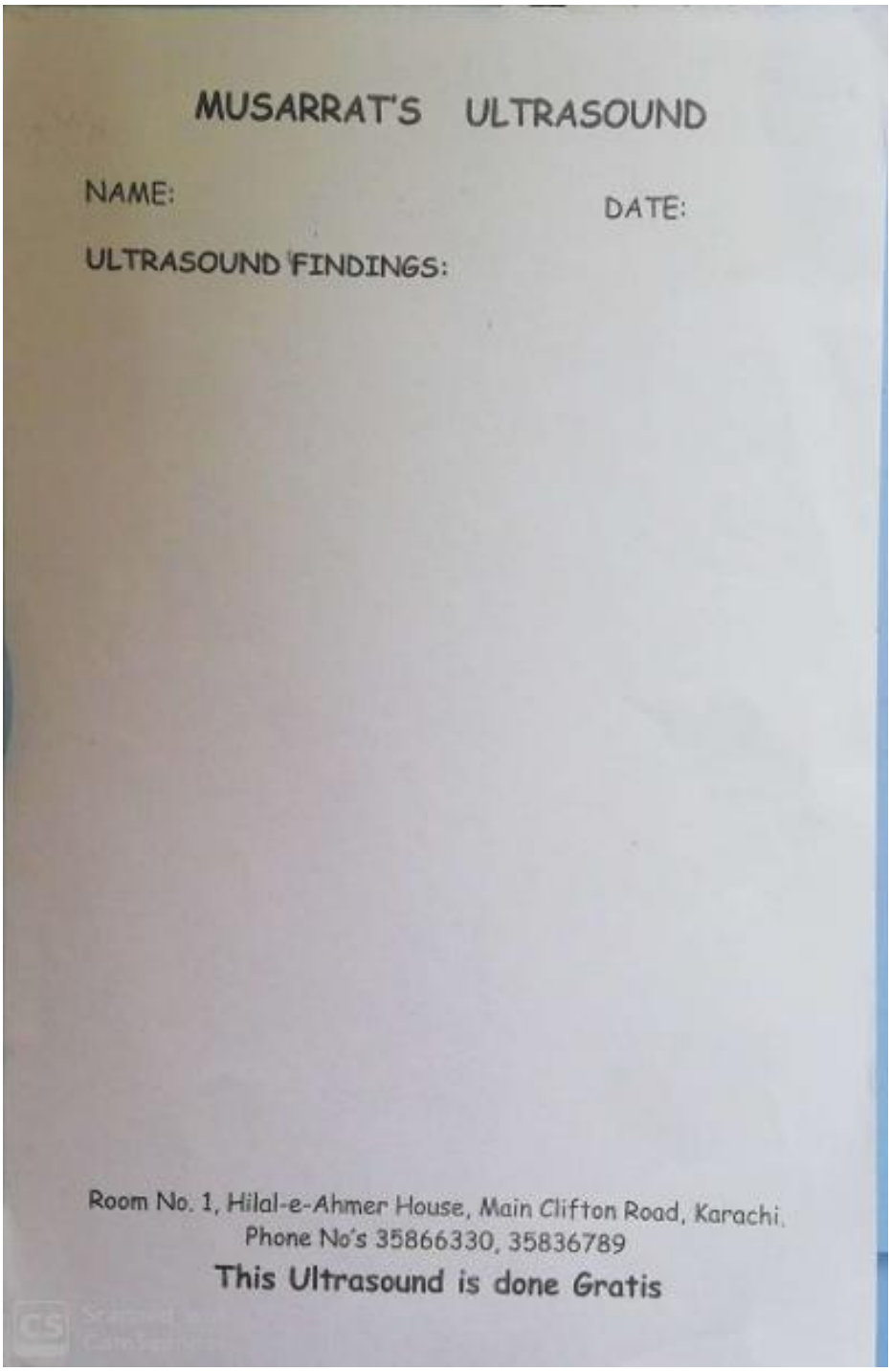
Transabdominal Scan

PARAMETERS	READING 1	READING 2	READING 3	MEAN
Head circumference				
BPD				
Femur length				
Head: abdominal circumference ratio				
Ventricular: hemisphere ratio				
Atrium of lateral ventricles measurements				
Amniotic fluid index				

Other embryological anomaly/ies

_____

7.2 (F) Hospital Card:



MUSARRAT'S ULTRASOUND

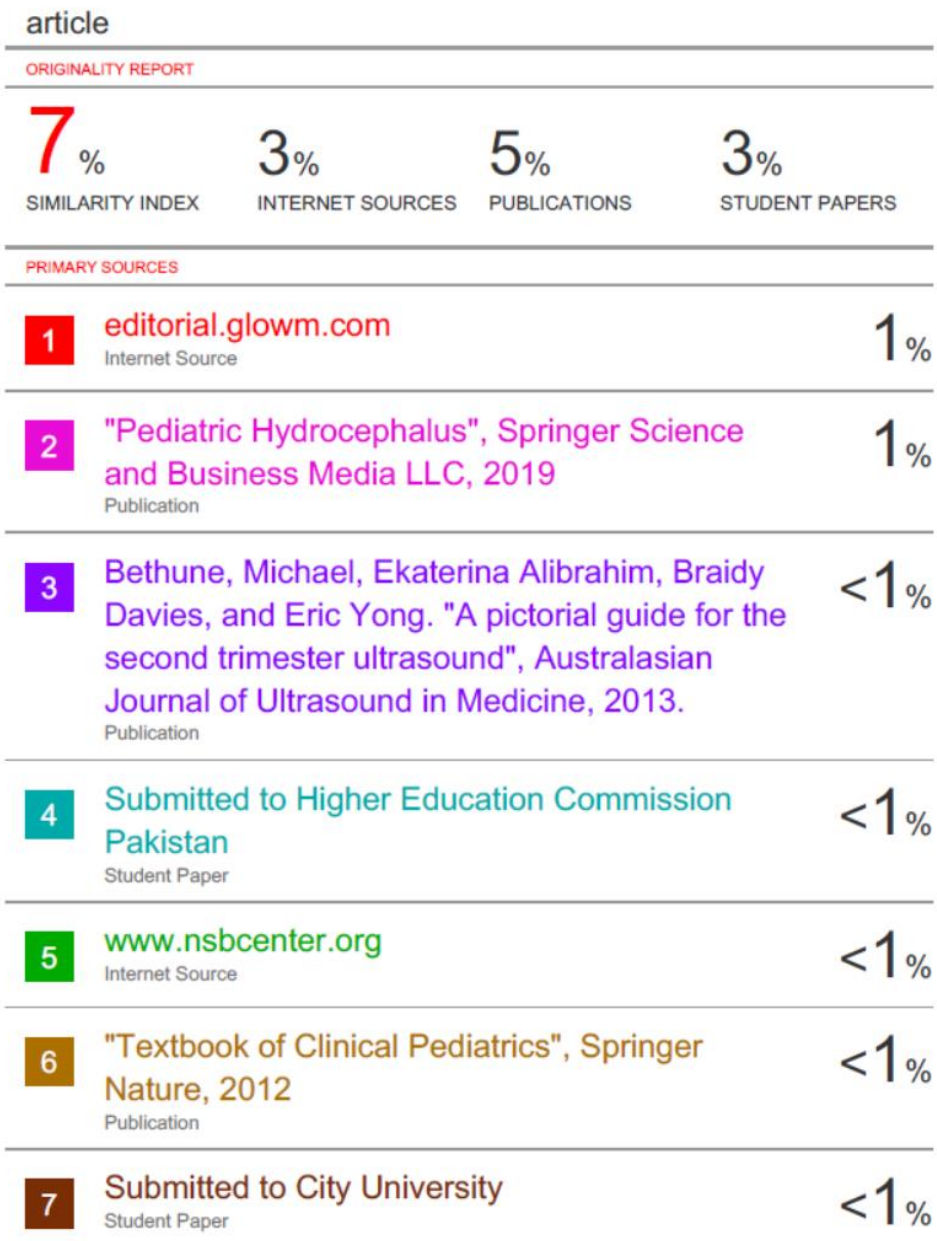
NAME: DATE:

ULTRASOUND FINDINGS:

Room No. 1, Hilal-e-Ahmer House, Main Clifton Road, Karachi.
Phone No's 35866330, 35836789

This Ultrasound is done Gratis

7.2 (G) Turnitin Plagiarism Report:



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