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ORIGINAL ARTICLE

A study relating fetal hydrocephalus with family history and consanguinity in Pakistani population.

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ABSTRACT... Objective: To correlate the amniotic fluid index (AFI) measurements of biparietal diameter (BPD) and head circumference (HC) with atrium of lateral ventricle measurements (ALV) and relate the association of fetal hydrocephalus with family history and consanguinity. **Study Design:** Cross-sectional study. **Setting:** Private Ultrasound Clinic, Karachi. **Period:** December 2018 – July 2019. **Material & Methods:** Thirty six patients were inducted in the study. Female patients of age range of 18-41 years with gestational age of 21-39 weeks were inducted into the study after informed consent. Toshiba Aplio 300 ultrasound machine was used to measure, atrium of lateral ventricle, biparietal diameter, fetal length, head circumference and amniotic fluid index. Association between ALV and BPD, family history and consanguinity was seen by applying independent t-test while Pearson's correlation was used to correlate the measurements of ALV and head circumference. **Results:** Atrium of lateral ventricle measurements >10mm were diagnosed as hydrocephalus. It was observed that hydrocephalus was associated with normal volumes of amniotic fluid with highly significant results (<0.000). Furthermore, the study also reported a strong association of family history and consanguineous marriages with hydrocephalus. A negative correlation was however observed between measurements of atrium of lateral ventricle and head circumference. **Conclusion:** Hydrocephalus was found to be associated with normal volumes of amniotic flid and had a strong association with family history and consanguinity.

Key words: Atrium of Lateral Ventricle, Biparietal Diameter, Family History, Hydrocephalus, Ventriculomegaly.

INTRODUCTION

Cerebral anomalies constitute 9% of all congenital anomalies which can cost-effectively be diagnosed by prenatal transabdominal ultrasound. Fetal ventriculomegaly, spina bifida, corpus callosum agenesis, anencephaly, Dandy Walker syndrome and microcephaly are some of the most encountered anomalies.[1] Fetal hydrocephalus is characterized by the dilatation of the ventricular system of the brain either due to obstruction in the flow of cerebrospinal fluid or due to it's over production. This anomaly is an intracranial finding that can be easily detected on transabdominal prenatal ultrasound.[2,3] Being prevalent in low to middle socioeconomic classes, its prevalence is noted to be 2.5:1 in Pakistan.[4] Ventriculomegaly is classified in literature based on the measurements of atrium of lateral ventricle as mild (10 -12mm), moderate (13 -15mm) and severe (>15mm).[2] Literature reports various causes of fetal hydrocephalus ranging from acquired to genetic causes involving gene mutation of L1CAM gene causing X-linked hydrocephalus thereby signifying the fact of familial association.[1] Hydrocephalus has been reported by authors to have an impact on brain development, thereby impairing its functioning.[1]

Ultrasound being routinely used in clinics is the most effective way to measure fetal biometric parameters along with detecting the congenital anomalies like hydrocephalus in fetuses. These parameters which are recommended by International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) include crown rump length (CRL), biparietal diameter (BPD), head

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circumference (HC), femur length (FL) and abdominal circumference (AC). These parameters help not just in assessing the gestational age of the fetus but are also helpful in monitoring fetal growth at various weeks of gestation.[5,6] Measurement of these significant parameters requires a clear image with accurate placement of the caliper. BPD and HC can be measured from 14 weeks onwards and these values are later reported by means of reference charts.[5] Rafeeq et al, in their study on fetal parameters reported, larger BPD and HC for male fetuses as compared to female.[6] Similarly, amniotic fluid index (AFI) is the standard way to monitor the adequacy of liquor at the time of survey of the fetus.[7] It is measured by dividing the uterus into 4 quadrants, the transducer is then placed perpendicular and the deepest pocket in each quadrant is measured and the four measurements are eventually summed up for final value of AFI.[7] Values less than 5 cm is labelled as oligohydroamnios while values greater than 25 cm is called polyhydramnios. [(7)] Polyhydramnios and oligohydramnios have been cited in literature to be associated with various congenital anomalies.[7] Hydrocephalus is known to have a familial transmission. Gene studies have proved various mutations in different sites. Thereby indicating a familial, especially X-link transmission which is enhanced by cousin marriages.[8]

To the best of our knowledge this study, for the first time in the current set up, aims to correlate the AFI, measurements of BPD and HC with atrium of lateral ventricle measurements and also relates the association of fetal hydrocephalus with family history and consanguinity.

MATERIAL & METHODS

This cross-sectional study was conducted on 36 patients, using OpenEpi Version 3, open source calculator SS proper based on population prevalence (www.openepi.com). The prevalence of population was 50%. The sample was calculated with a 5% margin of error and 95% confidence interval. This study was conducted from December 2018 – July 2019, at a private ultrasound clinic in Karachi, Pakistan.

Pregnant females patients within the age bracket of 18- 40 years and at a gestational age of 21 – 39 weeks, using non-probability purposive sampling technique, were included in the study after taking the ethical approval from ERC of Bahria University Medical and Dental College (ERC letter number: ERC 47/ 2018). Pregnant females with history of diabetes, hypertension and fetuses with chromosomal anomalies were excluded from the study.

Transabdominal ultrasound scans were performed using 2.5 -3.5 MHz standard convex probe on Toshiba APLIO 300 machine to note measurement of atrium of lateral ventricle (ALV) to diagnose fetal hydrocephalus, biparietal diameter (BPD), femur length, head circumference (HC) and amniotic fluid index (AFI). Biparietal diameter and femur length were assessed to identify the fetal age.

Measurements of atrium of lateral ventricle > 10 mm done in coronal plane after visualization of choroid plexus was used to diagnose fetal hydrocephalus. Amniotic fluid index was calculated by dividing the abdomen into 4 quadrants by 2 imaginary lines. Deepest and most clearly visualized pocket was measured by keeping the transducer parallel to the patient's longitudinal axis. All 4 measurements were added to analyse the AFI.

Results were analyzed by using Statistical Package for Social Science version 23. All results were presented as mean and standard deviation for quantitative. Independent t-test was applied to see the association between atrium of lateral ventricle measurements and amniotic fluid volume, BPD and consanguinity. Pearson's correlation was applied to see the correlation in between atrium of lateral ventricle and BPD and head circumference.

RESULTS

Our study observed normal volumes of amniotic fluid (10 -19) in 33 cases (Figure-1) with a highly significant association between the two variables (p-value $\leq$ 0.000) with 95% confidence interval. However, the study showed no correlation between

atrium of lateral ventricular measurements and amniotic fluid volumes.

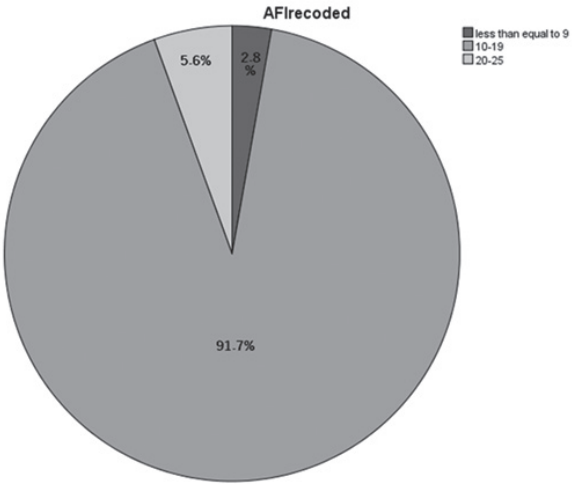

Figure-1. Pie chart showing frequency of distribution of fetal hydrocephalus in different volumes of amniotic fluid

A highly significant association was observed, between BPD and ALV measurements (Table-I). It was observed that as the measurements of ALV increased, BPD increased simultaneously with a mean and standard deviation of 17.41 and 4.06 for ALV and 7.35 and 1.16 for BPD. Unfortunately, no correlation was observed between the two variables.

	Mean±SD	P-Value
Atrium of lateral ventricle	17.41±4.06	0.000*
Biparietal diameter	7.35±1.16	

Table-I. Association between atrium of lateral ventricle measurement and biparietal diameter

A strong association was seen between measurements of ALV, used for diagnosing fetal hydrocephalus and family history. Twenty patients who were (55.56%) diagnosed with fetal hydrocephalus, also exhibited a positive family history in siblings or close first degree relatives. Out of these 45% had consanguineous marriage while the others only demonstrated a positive history of family members with fetal hydrocephalus as shown in the cross tabulation in Table-II. A very strong association and highly significant results with a p-value of ≤ 0.014 was seen between fetal hydrocephalus and consanguinity.

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

Table-II. Cross tabulation between family history of patients with hydrocephalus and consanguinity

While observing the association between ALV and head circumference an insignificant result (p-value of 0.936) was observed thereby showing no association between the two variables. A weak negative correlation where r = 0.014 was found between the two variables. This correlation was found to be insignificant.

DISCUSSION

The growth and proper development of the fetus is dependent on amniotic fluid. It acts as a protective agent against infections on one hand and on the other provides a cushioning effect to the fetus.[9] However, an increased amniotic fluid volume has been known in literature to be associated with congenital anomalies in fetuses.[10,11] Our study however, observed that 91.7% cases had normal volumes of amniotic fluid while, only 2.8% cases of oligohydramnios and 5.6% of polyhydramnios were observed. Lalchand et al in their study observed only 3 cases of fetal hydrocephalus associated with amniotic fluid index greater >25.[9] In another case-report published in 2018, the authors observed an association of polyhydramnios with severe fetal ventriculomegaly in successive pregnancies. Another cross-sectional study on 201 patients noted the association of various congenital anomalies to be associated with mild, moderate and severe types of polyhdramnios.[12] The reason for difference in our results could be small sample size along with the scans done during 18 -39 weeks, a wide maternal age group and above all this study had excluded diabetic and hypertensive patients, both of which have been named in literature as one of the maternal causes of polyhydramnios.[13]

Literature has cited a male predilection of

hydrocephalus and hints towards the association of dilation of fetal ventricular system with family history due to genetic mutations and X-linked transmissions. Cases of consecutive abortions and miscarriages have been reported in in case-studies.[14,15] Likewise this study was also able to observe a significant association (p-value 0.014) of family history in 55.6% (20 cases). Out of these 9 cases exhibited fetal hydrocephalus due to consanguinity. Mutations of L1CAM gene in fetuses with congenital hydrocephalus have been cited in literature. In a fetal autopsy study, it was observed that 90% cases of aqueductal stenosis had L1CAM gene mutation thereby indicating a familial transmission.[16] Non-sense, missense and frameshift mutations have been observed in association with fetal X-linked hydrocephalus in male fetuses.[14,17] Authors have identified MPDZ mutation, TRIM 1, SMARCC 1, PTCH, SHH and POMT2 in association with congenital hydrocephalus in male fetuses with or without any positive family history.[18,19]

In a case-control study in Ethiopia, only 2 cases of enlarged fetal ventricular system were reported to be associated with consanguinity.[20] Cousin marriages or consanguinity is a common phenomenon in developing nations like Pakistan as compared to the developed Western world. Our study observed that 45% cases of hydrocephalus were associated with consanguinity while 50% exhibited consanguineous marriages but without any family history of hydrocephalus. Similar to our study results, a study in Peshawar on 200 patients reported that 68% of congenital malformations were associated with consanguineous marriages with 55% of them being congenital hydrocephalus.[21] Another study reported 25% cases of hydrocephalus due to first degree marriages.[22] Similar results were reported by another study where congenital hydrocephalus was observed in 38% consanguineous marriages.[23] Atrial diameter >10mm is labeled as ventriculomegaly whereas biparietal diameter is used to assess gestational age. Studies have been conducted to measure and correlate the atrial width measurements with fetal biometric parameters but, to the best of our knowledge, this study is the first of its kind in this set up to see an association between these two fetal measurements. A highly significant association (p-value <0.000) was observed in our study between ALV and BPD. Similar results were noted in Iran in a case-control study on 258 pregnancies.

The authors of the current observed a significant association with a p-value of <0.001, between atrium of lateral ventricle measurements and BPD. Similar results were reported by Fishel-Bartal et al in their study. Their study conducted on 101 patients in Israel, reported that fetuses with mild ventriculomegaly with atrial measurements of 10.5mm, had larger head circumference and biparietal diameter with p-values of 0.009 and 0.001 respectively as compared to fetuses with no ventriculomegaly.[9] In our study, we were able to observe a negative correlation of measurements of atrium of lateral ventricle and head circumference. Similar results were observed by Udoh et al., where they reported that as the gestational age of the fetus increased the head circumference also increased however it had no correlation with the increase in measurement of atrial width.[24]

Another retrospective study observed that mild form of fetal ventriculomegaly showed a correlation with BPD and head circumference. They reposted in one case the BPD in 99th percentile and head circumference in 98th percentile in 38 weeks of gestation with mild atrial dilatation of 11 mm, while the same study in another case observed both fetal biometric measurements to be in 99th percentile at 38 weeks with mild ventriculomegaly (10.5 mm).[11] A retrospective study done on 2500 fetuses in New Delhi, India, reported a positive correction between measurements of BPD and head circumference with lateral ventricle width.[25] The difference of our study results could be because of 2 reasons; a small sample size and the cases identified in our study were of severe ventricular dilatation while the correlation between fetal biometric parameters and ventricular measurements in literature is mild types of fetal hydrocephalus.

Limitations of the current research are that's its size of the sample was small and involvement of a single center. However, this study can be

used to base future prospective studies on larger cohorts especially in Pakistan as there is a dearth of literature in this field and very limited to no data is available which compares these parameters. Furthermore, this study adds to the fact that ultrasound, which is a routine screening modality used everywhere in Pakistan, can easily and cost-effectively be used to diagnose and screen out fetuses with hydrocephalus. Contributing to early diagnosis and treatment and thereby, reducing the disease burden of the society.

CONCLUSION

Hydrocephalus as diagnosed by measurement of ALV exhibited strong association with normal volumes of amniotic fluid and BPD. Family history especially consanguineous marriages have been observed to have a strong association with fetal hydrocephalus thereby indicating towards gene mutations and familial transmission.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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1	Ambreen Surti	Conceived, designed, data collection, literature search and writing of the manuscript.	
2	Ambreen Usmani	Review, Proof reading, Editing and final approval of manuscript.	
3	Quratulain Javaid	Literature search, Manuscript writing and editing.	