ASSOCIATION OF CONGENITAL MALFORMATIONS WITH MATERNAL RISK FACTORS

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ASSOCIATION OF CONGENITAL MALFORMATIONS WITH MATERNAL RISK FACTORS

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(06-113212-002)

A thesis submitted in fulfillment of the
requirements for the award of the degree of
Master of Philosophy (Anatomy)

DEPARTMENT OF ANATOMY

BAHRIA UNIVERSITY HEALTH SCIENCES
CAMPUS KARACHI

OCTOBER 2023

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I would like to dedicate this thesis to my beloved parents
(Late Cdr Muhammad Aslam Awan TI(M) (Retd)) and (Razia Aslam Awan) as a token of my deepest appreciation and as a testament to the profound impact they have had on my life.

ACKNOWLEDGEMENTS

First and foremost, I thank Allah (SWT) for all his blessings, for instilling in the strength and perseverance to complete my thesis on time. I am profoundly grateful to my supervisor, Prof. Dr. Aisha Qamar Senior Professor, Department of Anatomy, Bahria University Health Sciences Campus, Karachi, for her guidance, expertise, and patience. Her invaluable advice and feedback have been instrumental in shaping my research and strengthening my thesis. I would also like to acknowledge her tireless support and belief in my abilities. I am extremely honored to have had the opportunity to work with such an exceptional supervisor. In addition to my supervisor, I would like to thank my Co-Supervisor Prof. Dr. Tariq Mahmood, Head of Department of Radiology & Cyberknife Robotic Radiosurgery, JPMC for his assistance from the start of the thesis until its completion. I would like to extend my heartfelt thanks to Dr. Tanveer Zubairi for her invaluable contribution to my research by providing me access to the necessary resources and facilities at her esteemed facility. I am indebted to the staff and faculty of Jinnah Postgraduate Medical Centre and Tanveer Ultrasound Clinic for providing me with a conducive research environment and access to resources. Their support and encouragement have been crucial in the successful completion of my thesis. I am most thankful to the participants of my study for their willingness to contribute their time and knowledge. Without their cooperation, this research would not have been possible. My most profound thanks to the senior faculty members and colleagues of BUDC, Prof. Dr. Wahab Kadri, Prof Dr. Kulsoom Rizvi, Prof. Dr. Daud Mirza, Dr Afsheen Maqsood, Dr Madiha Anwar and Dr Samra Faheem for their constant support and guidance. Their contributions have been invaluable and I am truly grateful to have such a supportive network of people in my academic journey. My deepest appreciation to my classmates especially Dr. Rubab, Dr. Ejaz, Dr. Sitwat and Dr. Sana for being a part of my journey. I will always treasure the memories we have made together as we go on our own paths, and I look forward to seeing all the wonderful achievements that each of us will make in the future. I would also like to express my gratitude to my family for their encouragement and understanding especially my mother who has been my biggest cheerleader. Their

unconditional love and belief in me have been a continual source of inspiration. Last but not least, I am extremely grateful to my husband, who has been a constant source of motivation and my rock throughout this journey. His unwavering support both, emotionally and practically, has allowed me to focus on my research and pursue my academic goals. To my beloved children Haniyyah and Ayaan for their patience, understanding and flexibility during this time. Your love, hugs and words of encouragement have brightened even the toughest days. I am extremely appreciative for the sacrifices each of you has made to support me in pursuing my education. In conclusion I am thankful to everyone who has played a part in the completion of my thesis, your support, guidance, and encouragement have been invaluable.

Dr. Jawaria Aslam Awan

ABSTRACT

Congenital malformations (CMF) are structural or functional defects of the human body that arise during development. These malformations can be detected during antenatal examination, at birth or at times can also be discovered in early childhood. The occurrence of congenital malformations in developing countries is close to that seen in developed countries, however, it has a severe impact in middle and low income countries. Every year, around three million children under the age of five die as a result of birth abnormalities worldwide, around 3.2 million live-born infants are physically or intellectually challenged for life, and approximately 270,000 newborns die during the first twenty-eight days of life due to congenital abnormalities. The objectives of this research were to determine the association of congenital malformations with maternal risk factors in different ethnicities and to determine the association of craniofacial congenital malformations with anomalies of other systems. At the Jinnah Postgraduate Medical Centre (JPMC) and Tanveer Ultrasound Clinic in Karachi, this observational, case-control research was carried out. A total of one hundred and twenty pregnant women between the age of 18 - 45 years were included in the study, of them, 60 (the case group) had fetuses with structural abnormalities and 60 (the control group) had fetuses with normal structural development. The Participants were categorised into five groups based on their ethnicity (Balochi, Pashtun, Punjabi, Sindhi and Urdu speaking). An informed and understood consent was obtained and a detailed history followed by a thorough obstetric ultrasound was performed by a consultant radiologist to evaluate the type of congenital malformations. All the findings were noted in the subject evaluation form. Age of the mother, level of education, social status, body mass index, systolic and diastolic blood pressure, parity, multiple pregnancies, consanguinity, diabetes mellitus, hypertension, thyroid diseases, cardiac diseases, epilepsy, asthma, psychiatric diseases, kidney diseases, family and past history of congenital anomaly, exposure to rubella, maternal use of folic acid supplement/antenatal supplements and use of medicine (other than antenatal supplements) considered as risk factors were evaluated. Anomalies of the central nervous system (CNS) were most often identified. 26.7% (32), followed by

genitourinary anomalies 17.5 % (21) miscellaneous anomalies 9.2% (11), craniofacial anomalies 6.7% (8), musculoskeletal anomalies 5% (6), anomalies of GIT 2.5% (3), anomalies of abdominal wall 1.7% (2) and, finally, cardiovascular defects 0.8% (1). Maternal age (25 – 29 years) (OR = 3.043, 95% CI = 1.010 – 9.163), education (secondary level) (OR = 11.500, 95% CI = 2.345 – 56.393), family income (OR = 3.348, 95% CI = 1.122 – 9.994), use of medications (other than antenatal supplements) (2^{nd} trimester) (OR= 6.696, 95% CI = 2.069 – 21.671), history of consanguinity (OR = 3.429, 95% CI =1.582 – 7.433) and family history of birth defects (OR = 5.535, 95% CI = 1.736 – 17.646) were significantly associated with an increased risk of congenital malformations. Our study further showed a significant association between congenital malformations of central nervous system and Urdu speaking mothers (p = 0.016) compared to Balochi, Pashtun, Punjabi, and Sindhi, however the results cannot be generalized to the population as a whole due to the small sample size and time constraints. There was also a significant association between craniofacial congenital anomalies and the central nervous system (p = 0.000), the musculoskeletal system (p = 0.004), and miscellaneous congenital abnormalities (p = 0.030).

Key words: Congenital, Malformations, Antenatal, Mentally or Physically challenged

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AC	-	Abdominal circumference
AFP	-	Alpha-fetoprotein
ANC	-	Antenatal care
ASD	-	Atrial septal defect
AVSD	-	Atrioventricular septal defect
BDs	-	Birth defects
BMI	-	Body mass index
BOH	-	Bad obstetric history
BPD	-	Biparietal diameter
CAKUT	-	Kidney and urinary tract anomalies
CAs	-	Congenital abnormalities
CHD	-	Congenital heart defects
CL/P	-	Cleft lip and/or palate
CLP	-	Cleft lip and palate
CM	-	Consanguineous marriage
CMF	-	Congenital malformations
CM-I	-	Chiari I malformation.
CM-II	-	Chiari II malformation
CMV	-	Cytomegalovirus
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
CTD	-	Conotruncal defects
CV	-	Cardiovascular
CVS	-	Chorionic villus sampling
DM	-	Diabetes mellitus
FA	-	Folic acid
FDIU	-	Fetal deaths in utero

FGFR2	-	Fibroblast growth factor receptor 2
FL	-	Femur length
GDM	-	Gestational diabetes mellitus
GERD	-	Gastroesophageal reflux disorder
GI	-	Gastrointestinal
HbA1c	-	Glycated haemoglobin
HC	-	Head circumference
HRP	-	High risk pregnancy
HTN	-	Maternal hypertension
IUFD	-	Intrauterine fetal death
LA	-	Left atrium
LMIC	-	Low and middle-income country
LV	-	Lateral ventricles LV
MMC	-	Meningomyelocele
MRI	-	Magnetic resonance imaging
MS-AFP	-	Maternal Serum Alpha fetoprotein
NTDs	-	Neural Tube Defects
OFC	-	Orofacial clefts
PPIs	-	Proton pump inhibitors
RV	-	Right ventricle
S	-	Spine
SCM	-	Split cord malformation
SSRIs	-	Selective serotonin reuptake inhibitors
T2D	-	Type 2 diabetes
TOP	-	Pregnancy termination
ToPFA	-	Termination of Pregnancy for Fetal Anomaly
TORCH	-	Toxoplasmosis, rubella cytomegalovirus, herpes simplex & HIV
VSD	-	Ventricular septal defect
WHO	-	World Health Organization

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CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Malformations, whether discovered at birth or afterward, are frequently referred to as congenital abnormalities. Therefore, it is important to distinguish between actual flaws, also known as "primary defects," and distortions and disruptions, often known as "secondary defects," which are caused by external factors. This difference is crucial for creating genetic counseling it enables risk assessment for the development or recurrence of malformations and prevention recommendations. Structural faults that manifest during the embryonic or fetal development phase is known as congenital malformations *(*CMF*)*. According to their shapes, locations, and sizes, malformations, which afflict an estimated 6% of newborns globally, may cause functional, psychological, or aesthetic problems. 20% of stillbirths and 3% of live births are caused by congenital abnormalities. They are a common contributor to illness, disability, and newborn death in industrialized nations. The 'WHO' (World Health Organization) estimates that there is no explanation for about 50% of congenital abnormalities. There are three etiological groups, each with its own set of risk factors:
Multifactorial causes (20 -25%); Extrinsic environmental causes (10–15%): infectious agents, mechanical, medicinal, metabolic physical, toxic, and Genetic intrinsic causes (10 -15%):chromosomal & genetic (Forci et al., 2020).

All emerging nations, especially Morocco, rank congenital abnormalities among the top sources of disease and mortality. According to the most current "National Survey of Population and Family Health" (ENPSF) 2017-2018 statistics, "Morocco" has infant death rates of "13.56 / 1000" live births and neonatal mortality rates (less than 1 year) of "18%." As there isn't a national system for monitoring congenital malformations,

regrettably, the prevalence of congenital abnormalities and their etiology is not yet understood on a nationwide level (National Population and Family Health Survey (ENPSF -2018) | UNICEF, n.d.).

Congenital abnormalities are classified into two categories: single-system malformations and multiple-system malformations... One organ system or part of the body is affected by the first type, while multiple organ systems or parts of the body are affected by the second. Significant congenital malformations are those that, if unchecked, can impair a person's capacity to perform regular body functions or even decrease their life expectancy (Ameen Alalaf, & Shahbila, 2018).

Majority of the congenital defects are caused by major structural malformations, which result in fatalities, illness, and disability (Table 1.1). Contrarily, mild congenital defects are structural modifications that, despite being more common in the population, have little to no social or aesthetic impact and pose a minimal health danger to newborns. Examples include clinodactyly and single palmar crease (Table 1.2) (1.4 Congenital Anomalies - Definitions | CDC, n.d.).

Congenital abnormalities occur more frequently and in different types depending on the country and region. This depends on how they were defined, how they were discovered, how long the population was observed, and the ethnic and socioeconomic makeup of the community under investigation. Major and small congenital defects necessitate surgical treatment or even have the potential to harm the newborn. Mild congenital defects have a negative impact on a newborn's health and quality of life. 6% to 9% of perinatal fatalities are caused by congenital disorders in Pakistan. 40% to 60% of these cases have undetermined causes, 20% are the result of several circumstances, 7.5% are caused by a single gene abnormality, 6% are caused by congenital anomalies, and 5% are the result of maternal conditions. 495,000 people die each year as a result of congenital abnormalities. They are often regarded as the major cause of prenatal mortality, sickness, and disability in children worldwide. In 60% of cases, these can be avoided, although epidemiological data is required. Congenital anomalies are linked to undesirable pregnancy outcomes, such as ‘perinatal mortality’, ‘neonatal mortality’ and ‘morbidity’, ‘intrauterine growth restriction’, ‘premature births’, ‘breech presentation’,

‘preeclampsia’, and ‘placental abruption’, and are undoubtedly stressful for the expectant mother if found antenatally. The issue of congenital malformations has existed for generations and is widely acknowledged. The significant occurrence and potentially disastrous effects they can have on the newborn and the family make it a topic for research (Qadir , Amir, & Bano, 2017).

Congenital abnormalities are one of the most common causes of mortality in children under the age of five. 270,000 infants per year pass away during their first 28 days of life, and it is believed that 3 to 7% of children worldwide are born with birth abnormalities. CA mortality is still not acknowledged as a public health concern in underdeveloped countries, despite the fact that it is the leading cause of mortality among children in developed countries. Congenital abnormalities have become significant contributors to perinatal death in nations like Brazil because of the management of infections and disorders caused by nutritional deficiencies, which tend to lower newborn mortality for these reasons. 60% of the causes of congenital anomalies in people are still unknown at this time. Nonetheless, the aetiology of around 25% of congenital malformations appears to be complicated, indicating a complex interaction of both known and undiscovered genes and environmental variables, such as social, cultural, racial, and ethnic features (De Moraes, Melo, & Do Amaral, 2020).

Table 1.1 Major Congenital Defects	
EXTERNAL	**INTERNAL**
'Club foot' 'Exomphalos' (Omphalocele) 'Gastroschisis' 'Hypospadias' 'Microcephaly' 'Microtia/Anotia 'Neural tube defects' - *"Anencephaly"* - *"Craniorachischisis"* - *"Encephalocele"* - *"Iniencephaly"* - *"Spina bifida"* 'Orofacial clefts - *"Cleft lip" only* - *"Cleft palate" only* - *"Cleft lip and palate"* 'Reduction defects of upper & lower limbs	'Anorectal atresia/stenosis 'Congenital heart defects - *"Common truncus"* - *"Hypoplastic left heart syndrome"* - *"Interrupted aortic arch"* - *"Pulmonary valve atresia"* - *"Tetralogy of Fallot"* - *"Transposition of great arteries"* - *"Tricuspid valve atresia"* 'Esophageal atresia' 'Large Intestinal atresia' 'Renal agenesis'
'Chromosomal'	
'Trisomy 21'	

Table 1.2 External Minor Congenital Defects	
'Absent nails'	*'Lop ear'*
'Accessory tragus'	*'Micrognathia'*
'Anterior anus'	*'Natal teeth'*
'Auricular tag'	*'Overlapping digits'*
'Bifid uvula'	*'Plagiocephaly'*
'Brachial tag/pit'	*'Polydactyly type B tag', involves hand & foot*
'Camptodactyly'	*'Preauricular appendage, tag or lobule'*
'Cup ear'	*'Redundant neck folds'*
'Cutis aplasia'	*'Rocker-bottom feet'*
'Ear lobe crease'	*'Single crease, 5th finger'*
'Ear lobe notch'	*'Single transverse palmar crease'*
'Ear pit'	*'Single umbilical artery'*
'Facial asymmetry'	*'Small penis'*
'Hydrocele'	*'Syndactyly'*
'Hypoplastic fingernails'	*'Tongue-tie'*
'Hypoplastic toenails'	*'Umbilical hernia'*
'Iris coloboma'	*'Undescended testicle'*
'Supernumerary nipples'	*'Webbed neck'*

The most prevalent and important congenital anomaly among infants is ‘congenital heart abnormalities’. One percent of live births and ten percent of stillbirths are affected by them. The causes of these disorders are unclear, however, both environmental and genetic factors have been found to play a role. One-fifth of all cardiac abnormalities are ‘conotruncal defects (CTD),’ one of the most prevalent types of congenital heart disease. ‘Trisomy 21,’ ‘22q11.2’ deletions, as well as other genetic disorders were found in around 25% of patients having ‘CTD’ abnormalities, although the cause of the majority of these instances is unclear. Many unexplained ‘CTDs’ are still believed to have a genetic cause because of the high chance of repetition and hereditary in families. ‘Type 2 diabetes’ (T2D), ‘Maternal hypertension’ (HTN), and ‘Obesity’ are significant factors that are commonly connected to congenital cardiac abnormalities. Even after adjusting for medication use, it has been discovered that women with hypertension (HTN) before conception have a higher probability of giving birth to a child with a CTD. These issues are more frequent in children of diabetes or obese mothers. Given the magnitude of the relationships between these maternal illnesses and the risks of CTDs, as well as the comparatively high incidence of these conditions among females of reproductive age in the population as a whole, it is likely that these maternal abnormalities are to blame for a sizable portion of the risk of CTDs in newborns. While the precise processes behind the relationship between these frequent chronic maternal diseases and fetal cardiac abnormalities are unknown, they may be linked to irregular placental blood flow (as in HTN), abnormal glucose metabolism (as in T2D, obesity), or even other pathways. Even in the lack of an overt maternal phenotype, a hereditary tendency to develop one of these illnesses in the mother may nevertheless increase the risk of CTD in her children due to a gradual but persistent alteration of the embryonic environment, (Kaplinski et al., 2019).

Congenital conditions that are most often present are “congenital heart defects” (CHD) (Figure 1.1), which also account for a considerable portion of neonatal mortality. The ‘EUROCAT (European Registration of Congenital Anomalies and Twins) registry suggests that when underlying genetic anomalies are taken into consideration, CHD occurs in 0.61% of all newborns and 0.76% of surviving births. However, a small number of studies estimate an incidence of up to 1.5% when they consider all cases of intrauterine

fetal death (IUFD), pregnancy termination (TOP), and stillbirth. Early spontaneous miscarriages should be taken into account when determining the occurrence of CHD because they are extremely challenging to document. Less than 15% of CHD are caused by chromosomal defects (especially Down, Edwards, Patau, Turner, and Di George syndromes) and inherited disorders and in the majority of instances, the cause of CHD is still unclear. To increase the probability of identification and perhaps the result in afflicted cases, it is crucial to investigate possible new risks for CHD (Giorgione et al., 2018).

As one of the most prevalent birth disorders, congenital heart defects (CHDs) impact 6-12 out of every 1000 live births. CHDs are also responsible for the majority of neonatal mortality caused by birth defects. Many of those who are impacted and survive will have lifetime morbidities and/or need extensive medical care. The majority of those who experience CHDs have no recognized cause, even though they are relatively common and highly important. Numerous maternal traits and illnesses, including maternal weight gain and diabetes, are thought to be CHD potential causes. 'Maternal hypertension' is one of the medical diseases during gestation which has been determined to be a possible risk factor for CHDs because of the possibility of changes in uterine blood flow during gestation. 'Pregestational' as well as 'gestational (beginning during pregnancy) hypertension' affects about 2–10% of pregnant women. Antihypertensive drug-treated and untreated hypertensive women have been linked to an increased risk of CHDs in their kids in numerous reports; however, not all of the findings from prior studies have been consistent, and these findings have not been examined as a whole (Ramakrishnan et al., 2015).

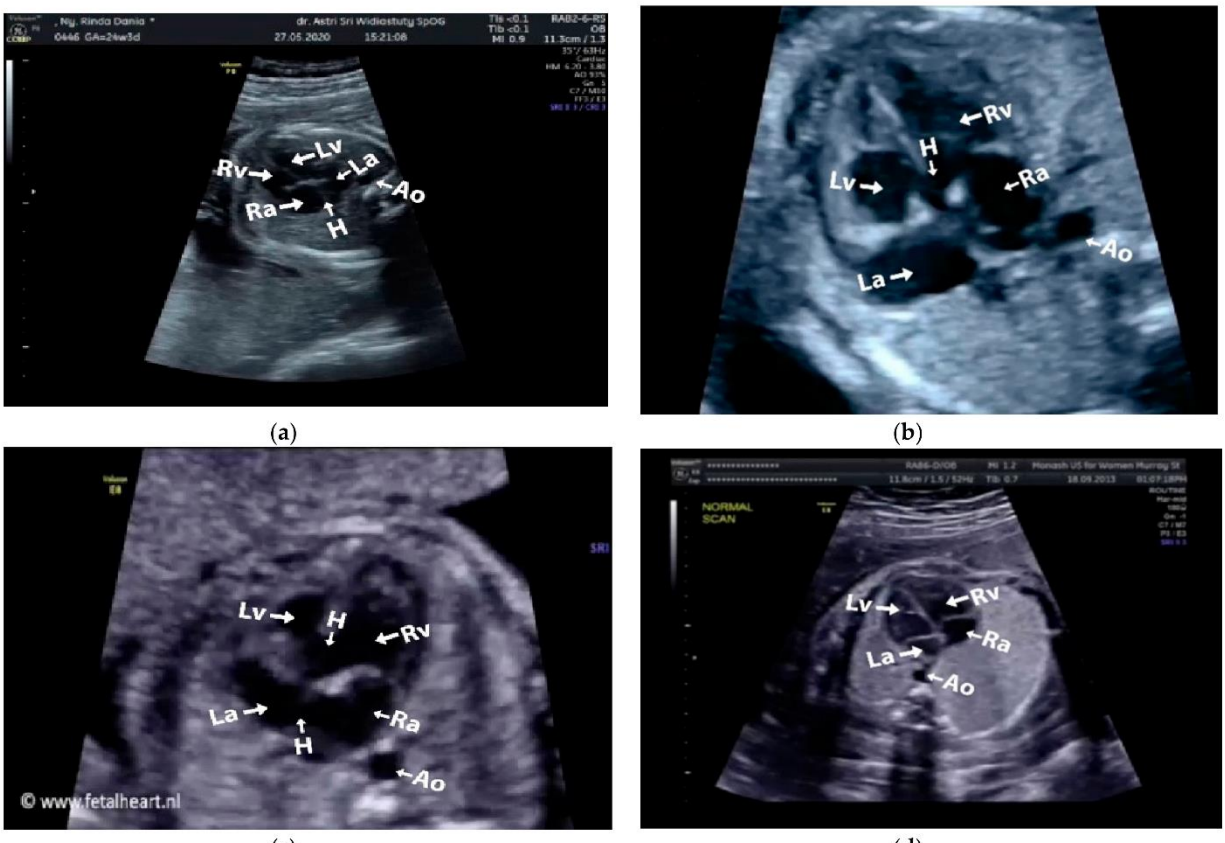

Figure 1.1: A 2 – D ultrasonography of the fetal heart in 4 chamber view for congenital heart defects detection at 18weeks of gestation: (a) ASD, (b) VSD, (c) AVSD, and (d) Normal Left ventricle (LV), left atrium (LA), right ventricle (RV), right atrium (RA), aorta descendens (AO), hole (H) (Nurmaini et al., 2021)

Neural tube defects are congenital malformations brought on by persistent neural tube non-closure or reopening after closure (Table 1.3). The edges of the neural plate known as the neural folds., merge at roughly 25 and 27 days of intrauterine (IU) life, respectively, for the cranial/upper and caudal/lower ends.

In general, open defects are characterized as the protrusion or exposure of brain tissue from the outside. The neural tissue is completely or partially covered by an epithelial covering (either full or fractional skin thickness). The elevated levels of acetylcholinesterase and fetoprotein in amniotic fluid make it possible to diagnose open malformations biochemically. Closed malformations, on the other hand, do not have this metabolic anomaly. Clinically, children with closed anomalies do better neurologically than those with open lesions (Ravi et al., 2021).

According to estimates from the World Health Organisation (WHO), 400 000 to 270,000 newborns worldwide die each year as a result of neural tube defects (NTDs), which account for more than 10% of all infant mortality. NTDs are a problem in both industrialized and underdeveloped nations. In countries where folic acid supplementation is not available, the incidence ranges between 0.5 and 2 per 1000 births. Even though its occurrence varies greatly depending on location and socioeconomic status, neural tube defects, which accounts for 29% of all newborn fatalities, is the main contributor to the death of newborns in nations with low or middle incomes. (Berhane & Belachew, 2022).

Table 1.3 Neural Tube Defects

CRANIOSPINAL	CRANIAL	SPINAL
Craniorachischisis (Figure 1.2)	Anencephaly (Figure 1.3)	Spina bifida (Figure 1.5) Spina bifida cystica Spina bifida occulta
	Encephalocele	Meningocele
	Iniencephaly	Myelomeningocele (Figure 1.4)

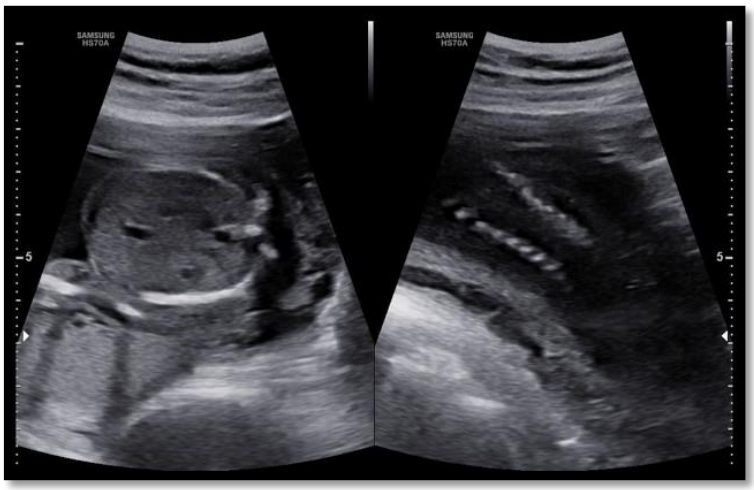

Figure 1.2: A 2 – D ultrasonography of the fetal spine showing rachischischis totalis (Rachischisis | Radiology Case | Radiopaedia.Org, n.d.)

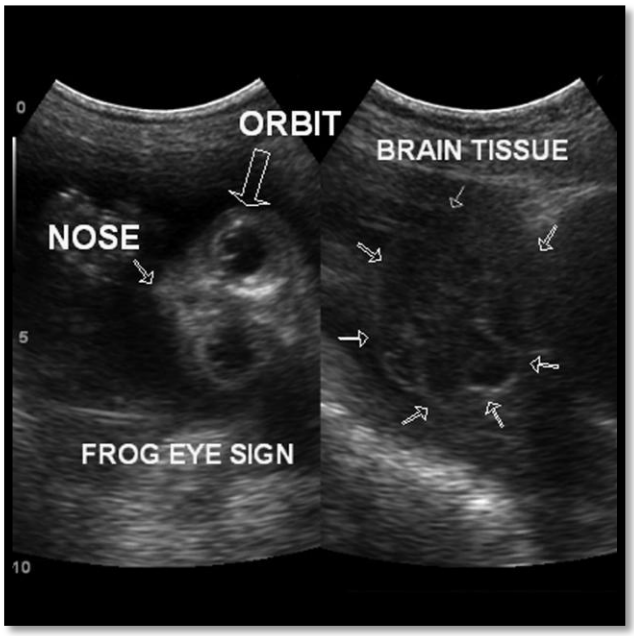

Figure 1.3: A brain structure without a cranial vault that is unevenly delineated and freely extends into the amniotic fluid..(*Acrania-Exencephaly Sequence | Radiology Case | Radiopaedia.Org*, n.d.)

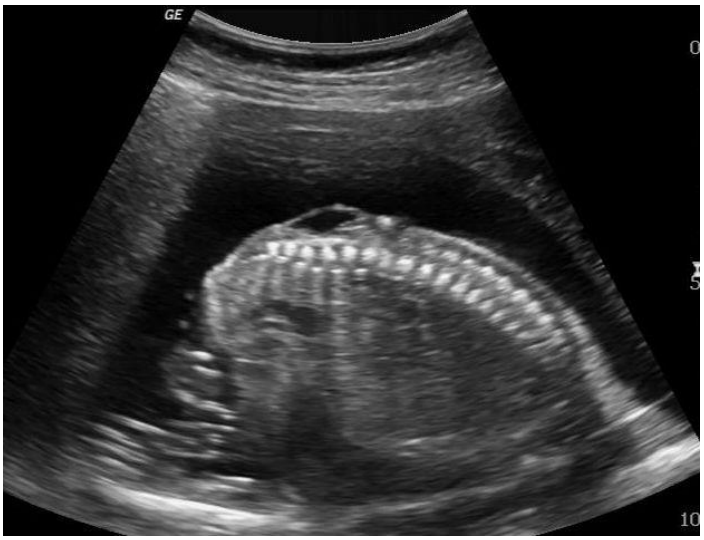

Figure 1.4: A 2 – D ultrasonography of the fetal spine at 19 weeks of gestation showing myelomeningocele (Hapugoda & Patel, 2013)

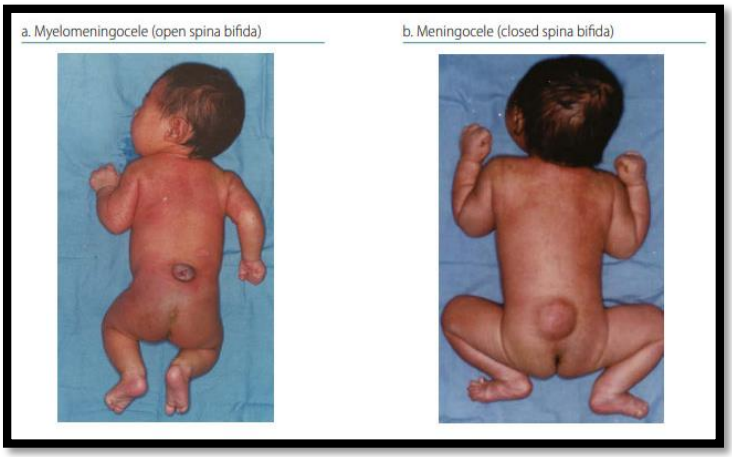

Figure 1.5: A photograph of the newborn showing (a) myelomeningocele and (b) meningocele (Spina Bifida _ NCBDDD _ CDC, n.d.)

In nations with low resources, where prevention interventions and long-sustained care for neural tube defects survivors are scarce, the effects of neural tube defects are particularly obvious. The most usual neural tube defects is ‘spinal bifida’(Figure 1.5 & 1.6), and patients with this condition frequently have ‘neurologic disorders’ (Lo, Polsek & Sidhu, 2014).

Numerous genetic and environmental factors have been associated to neural tube abnormalities; nevertheless, the most prevalent preventable cause of neural tube abnormalities is a deficiency of folic acid. Although it is expected that supplements containing folic acid would be widely used, "folate non-responsive" neural tube defects will exist, continue to be reported worldwide The magnitude of the problem is rather significant in Ethiopia, where one in three women suffer from folic acid deficiency and low folic acid coverage among women of reproductive age. Additionally, ‘dietary deficiencies’, ‘overweight’, ‘diabetes’, ‘poverty’, ‘misuse of alcohol’, ‘elevated core temperature’ before conception, and ‘prescription medications’ have all been linked to the development of neural tube defects. Neural tube defects prevalence has been dangerously rising in Ethiopia in recent times. According to a recent Tigray region research, the neural tube defects incidence was at 13/1000 live births, with the Southern Zone of Tigray having the highest prevalence at 30/1000 live births. With an occurrence of 4 per 1000 births, research done in two locations (Addis Abeba and the Amhara region) revealed the lowest prevalence. Other primary surveys conducted in Ethiopia also report a significant percentage of pregnancies linked to neural tube defects (Bitew et al., 2020)

The "mildest variety of spina bifida," Spina bifida occulta, is distinguished by a dermal sinus, a little dimple, and a tuft of hair in the lumbosacral region. It affects about 10% of the population in the L5 or S1 vertebrae. Another birthmark or a dermal sinus may be present, in addition to an overlaying lipoma. It usually indicates the presence of an underlying problem Spina bifida cystica is an anomaly that develops when the meningeal sac that resembles a cyst or the spinal cord protrudes through a vertebral arch defect. Spina bifida has a severe type in which the neural tissue deforms when exposed to amniotic fluid (Ravi et al 2021).

When a defect in the vertebral column causes the cyst to contain meninges and cerebrospinal fluid (CSF), this condition is known as spina bifida with meningocele. The roots and spinal cord continue to operate normally. This sac is largely made up of CSF. Meningomyelocele (MMC) is caused by cysts containing the spinal cord that extends above the vertebral arch defect. In comparison to meningocele, meningomyelocele is a more frequently occurring and dangerous abnormality. Because neural tissue is directly exposed to amniotic fluid, it displays varying degrees of neurological loss depending on the site and extent of the abnormality. Myelomeningocele is also related with anomalies in cerebral ventricle in >90% of cases, syringomyelia in 88% of cases, brainstem malformations in 75% of cases, cerebral heterotopias in 40% of cases, polymicrogyria in 15–30% of cases, Chiari malformations in 80–9% of cases, and corpus callosum agenesis in 12% of cases. (Salih, Murshid, & Seidahmed, 2014).

Lumbosacral meningomyelocele, which can also cause saddle anesthesia, is known for causing bladder or anal sphincter paralysis. The abnormality causes urinary and fecal incontinence, limb paralysis, skin anaesthesia, and hip, knee, and foot abnormalities. Because of the presence of an Arnold Chiari malformation (Figure 1.7), more than 90% of patients had concomitant hydrocephalus. Meningomyelocele has been linked to split cord malformation (SCM). Similar to pure SCM, the prognosis is likewise worse. Magnetic resonance imaging (MRI) screening of the spine and skull is indicated for both SCM and hydrocephalus detection in these individuals. When MMC and cord tethering are both present at more than two locations, the name "Spina Bifida Multiplex" has been coined. Spina bifida aperta is the most prevalent kind in humans, affecting 1.8 out of every 10,000 live births in the United States, according to the CDC. The Arnold-Chiari type II malformation, which is linked with the majority of afflicted people, is a deformation near the base of the brain. This defect is most likely the source of the well-documented hydrocephalus, which affects around 80% of people at birth. Rachischism is the most severe variety of spinal bifida, marked by an open neural tube lesion in the back. It occurs when the posterior neuropore of the neural tube fails to close during the fourth week of development, most often in the lumbosacral area. In most cases, this syndrome causes lifelong lower limb weakness or paralysis. The spinal cord in the affected region is open due to the non-fusion of the neural folds, which has led to a mass of nerve tissue

at the defect level. The lower limbs are typically permanently paralyzed or weakened as a result of myeloschisis (Ravi et al., 2021).

The cerebellar vermis, tonsils, and spinal myelomeningocele are all displaced downward, and the midbrain is beaked in the Chiari II malformation (CM-II). It's common to think that this abnormality is a more severe variety of the Chiari I malformation. (CM-I). However, while having similar imaging results, these two illnesses are different. Surprisingly, the majority of myelomeningocele patients also have CM-II and are frequently linked with hydrocephalus. Cerebellar dysplasia, lower pons and medulla extension, and 4^{th} ventricle displacement into the cervical canal are only a few of the numerous malformations associated with CM-II. The neuroanatomy of the patient's MRI is the most important aspect in the diagnosis. Typically, surgical procedures are the focus of the treatment. The severity of the abnormalities and the patient's symptoms will determine the prognosis (Kuhn & Emmady, 2022).

Food fortification programmes have been adopted in a number of countries as it has been demonstrated by different clinical research that peri-conceptional folic acid aid use in primary prevention. Ultrasound prenatal diagnosis allows for pregnancy termination. Among the associated issues that are surgically treated in those who make it to delivery are the hydrocephalus, Chiari II malformation, and urological and orthopaedic consequences (Copp et al., 2015).

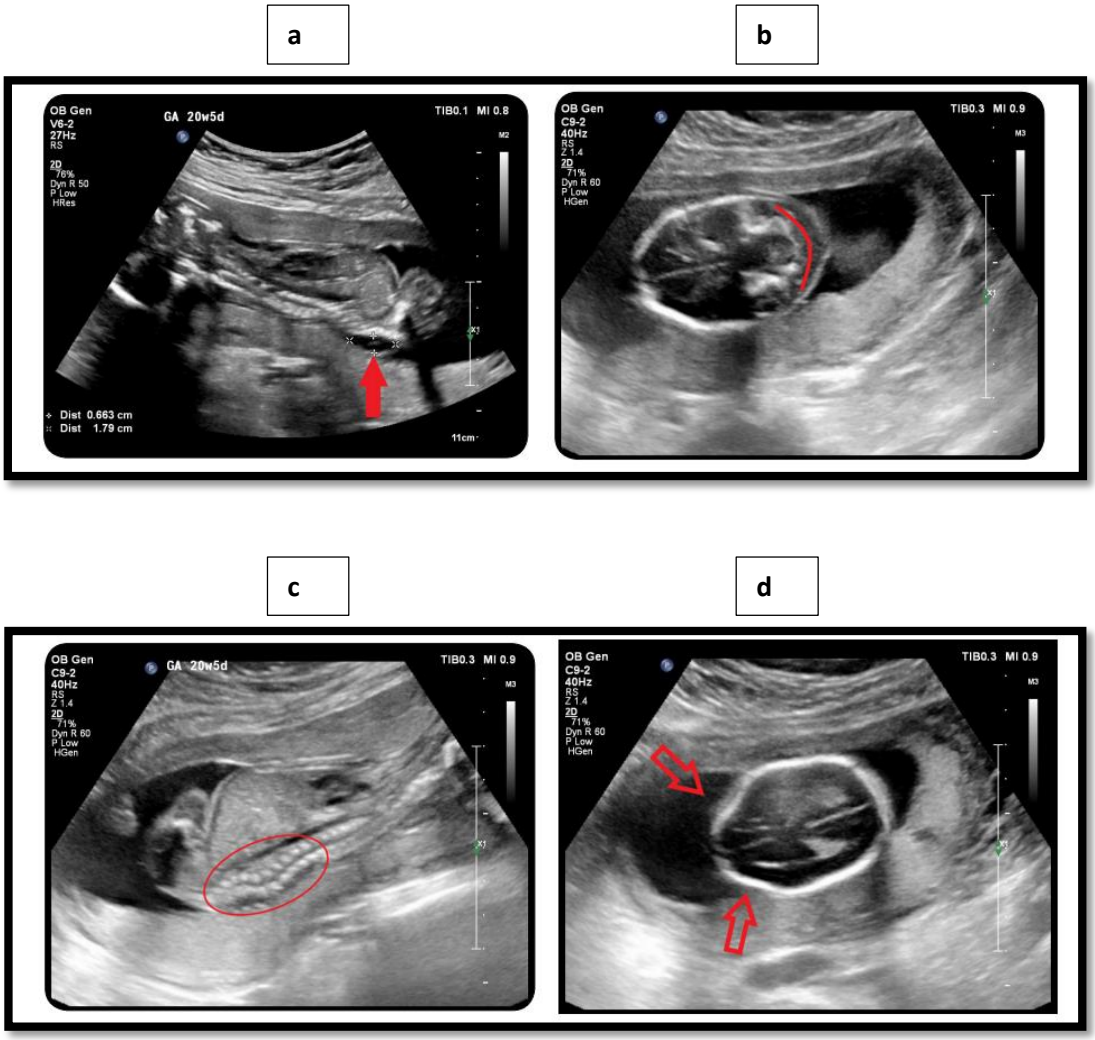

Figure 1.6: A 2 – D ultrasonography of the fetus at 20 weeks and 5 days of gestation showing (a) meningomyelocele in the lumbosacral region (b) posterior cranial fossa defect – "Banana sign" (c) kyphoscoliosisin lumbosacral region of spine (d) concavity of the frontal bones "lemon sign" (Simona et al.2021)

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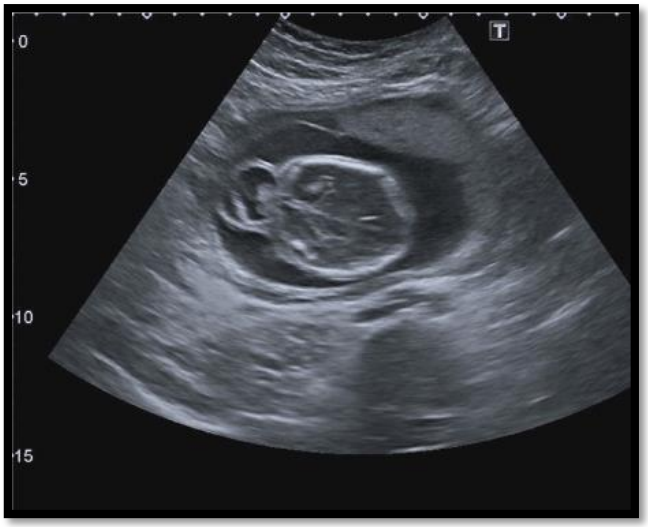

Figure 1.7: A 2 – D ultrasonography of the fetal brain at 18 weeks of gestation showing encephalocele (Altunkeser & Kara, 2018)

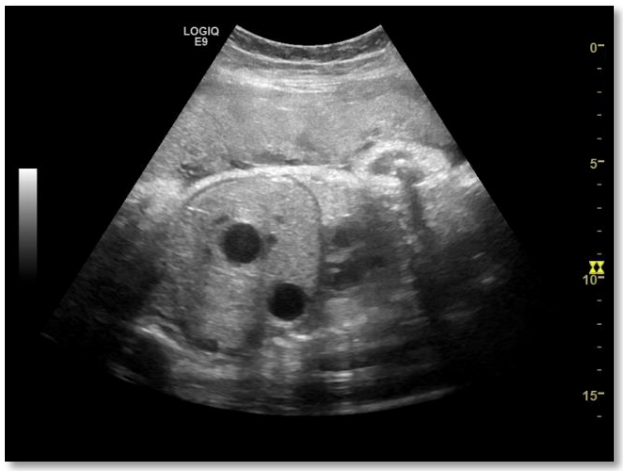

Figure 1.8: A 2 – D ultrasonography of the fetal abdomen at 31 weeks of gestation showing dilated stomach and the 1st part of the duodenum (duodenal atresia) (El-Feky, 2022)

The majority of congenital gastrointestinal (GI) defects cause some sort of intestinal blockage, which commonly presents as emesis, distention, and difficulty eating at birth or within a day or two. Congenital diaphragmatic hernia, for example, has a bad prognosis (mortality rate of 10 to 30%), in contrast to other GI anomalies, such as malrotation, which have a relatively favourable prognosis. Atresia is a frequent form of abnormality in which a portion of the gastrointestinal system either does not form or develop normally, or it develops only to be destroyed by an intrauterine occurrence (vascular disruption). The most prevalent kind is esophageal atresia, which is followed by jejunoileal atresia and duodenal atresia (Figure 1.8). Bowel decompression and transfer to a newborn surgical facility are among the immediate therapy options. Continuous nasogastric suction is used to prevent emesis, which can cause aspiration pneumonia or additional abdominal distention with respiratory compromise. Maintaining the baby's body temperature, preventing hypoglycemia with IV 10% dextrose and electrolytes, treating or preventing acidosis, and treating infections are all essential for getting the baby to the best possible state for surgery. Because up to 70% of infants with omphalocele and up to 50% of those with congenital diaphragmatic hernia have additional congenital anomalies, Infants with GI defects should be examined for defects in other organ systems, including the heart, kidneys, and central nervous system. (Cochran, 2022)

Mortality rates are higher in nations with low to middle incomes (LMIC). Gastroschisis (Figure. 1.9 & 1.10) and omphalocele (Figure.1.11), significant congenital abnormalities of the abdominal wall, contributed for approximately 21% of emergency neonatal procedures in the LMIC. However, it is unclear what causes these anomalies or what variables contribute to their formation. Small diameter 4 cm, lack of sac, and presence of just the small intestine, rarely with the gonad or stomach, are characteristics of the birth condition known as gastroschisis, in which an infant's internal organs protrude from the body via a defect. It is almost often found on the right side, close to the umbilical cord. Contrary to those who have omphalocele, patients with gastroschisis are more susceptible to have intestinal anomalies including atresia but rarely have related birth defect. During the sixth and eleventh weeks of development, an omphalocele may form, when the physiologic herniation via the umbilical cord occurs, the intestinal loops fails to

return into the abdomen A variety of factors have been connected to the pathogenesis of gastroschisis.

One explanation claims that because the umbilical coelom was unable to form, the elongating bowel ruptured out of the body wall to the right of the umbilicus, causing the abnormality. It's also possible that the embryonic parts don't entirely fuse with the umbilical cord. A number of environmental factors as well as socioeconomic risk factors are also thought to contribute to its formation, according to experts. The most common fetal anterior abdominal wall anomalies are gastroschisis and omphalocele. Fetal imaging is typically used to diagnose both prenatally, and those who are impacted are handled at a facility that offers high-risk obstetric treatments, neonatology, and paediatric surgery (Tiruneh et al., 2022).

Figure 1.9: A photograph of a male neonate showing stomach, loops of small and large intestines protruding from the abdominal wall (Gledina & Singh, 2022)

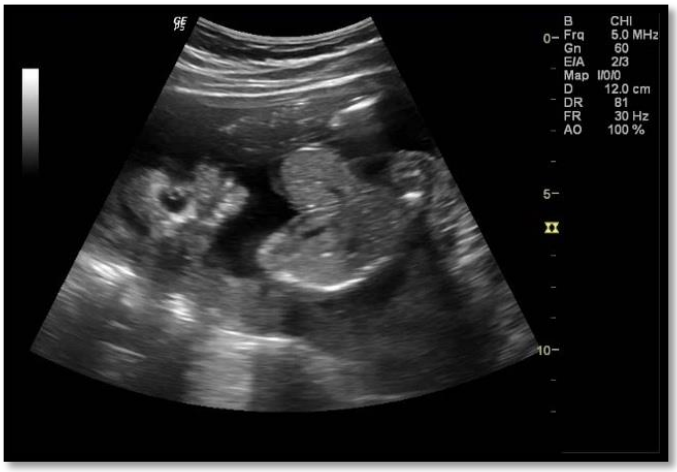

Figure 1.10: A 2 – D ultrasonography of the fetal abdomen at 17 weeks of gestation showing abnormal herniation of bowel loops outside the abdominal cavity (Hacking & Saied, 2015)

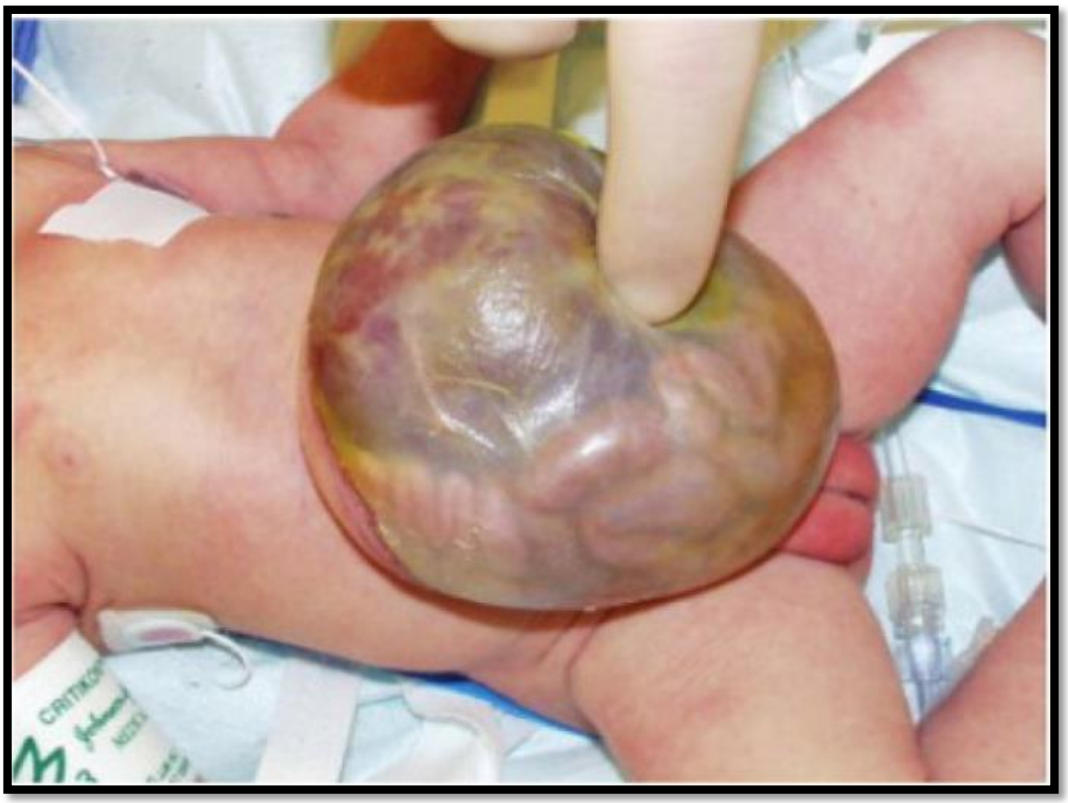

Figure 1.11: A photograph of a male neonate showing massive omphalocele including bowel and a part of the liver (Bence & Wagner, 2021)

Craniofacial and musculoskeletal anomalies are frequent in children. They may just affect one particular area (cleft lip (CL), cleft palate (CP), or clubfoot) (Figure: 1.12 & 1.13) or they may be a combination of several congenital defects (Treacher Collins syndrome or the velocardiofacial syndrome). The improper growth and/or development of the head and face soft-tissue structures and/or bones results in congenital craniofacial deformities. CL and CP are the two most typical facial deformities. Cranium bifidum or other associated ossification anomalies, macrocephaly, microcephaly, and craniosynostosis are a few of the craniofacial disorders that can damage the skull. There are several congenital limb abnormalities. A limb may be absent or partial at times. A foot or hand may be absent in whole or in part. The child may have polydactyly or syndactyly, for example. Clubfoot is a condition in which the ankle and foot become twisted out of form or position. The knees appear to be bent outward in genu varum (bowlegs). Knees appear to be bent inward in genu valgum (knock-knees). Other leg problems include femoral and tibial torsion. Congenital craniofacial and musculoskeletal defects should be investigated in patients, and chromosomal microarray, specific gene testing, or larger gene panel tests should be considered (Boyd, 2022)

1 in 500 live babies result in congenital anomalies, 20% of which are "*kidney*" and "*urinary tract*" anomalies (CAKUT). CAKUT causes juvenile end-stage renal disease. (40% - 50%) and adult end-stage renal disease (7%) globally. Monogenic conditions including polycystic kidney disease and ciliopathies are caused by pathogenic variations in the genes that cause CAKUT, as well as syndromes that combine isolated kidney disease with other abnormalities. Ultrasonography is the prenatal diagnosis method of choice; however, a number of testing techniques may be used to make a more thorough genetic diagnosis. The ability to make a prenatal diagnosis of CAKUT can also be aided by information from a pathologic examination and family history (Talati, Webster & Vora, 2019).

On prenatal ultrasonography, fetal hydronephrosis (dilatation of the renal pelvis with or without renal calyces' dilation) (Figure 1.14) is a frequent observation. Although renal pelvic dilatation is most of the time a transient physiological state, fetal hydronephrosis can arise in congenital abnormalities of the kidney and urinary tract

(CAKUT) due to urinary tract obstruction and vesicoureteral reflux (VUR). These diseases may result in renal damage or be linked to altered renal development. However, the majority of fetal hydronephrosis cases are not clinically important, and consequently, undue worry may result in unnecessary testing of newborn babies and stress for parents and healthcare professionals (Baskin, 2018).

Up to 80% of pregnant women experience gastroesophageal reflux disorder (GERD), making it a frequent occurrence during pregnancy. A significant number of patients frequently need to take acid-suppressive drugs to manage their poorly controlled symptoms, even though moderate symptoms can often be reduced by lifestyle changes. Proton pump inhibitors (PPIs) in particular have become more popular all around the world during pregnancy, possibly as a result of their ability to reduce stomach acid. PPIs are widely used, however the existing research on their safety during pregnancy is still contradictory. PPI use has been linked to an increased incidence of congenital heart problems, cleft palate, hydrocephalus, and hypospadias, contrary to prior research that identified no links between PPI use and serious congenital deformities. Accordingly, the most recent meta-analysis, which took into account the earlier research, found a 28% rise in the incidence of total abnormalities when PPI usage was present during pregnancy (Choi et al., 2023).

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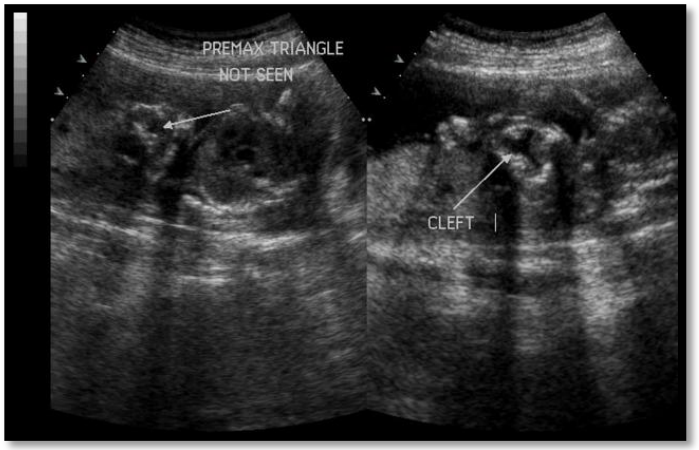


Figure 1.12: A 2 – D ultrasonography of the fetal face showing cleft lip. (Ansari, 2011)

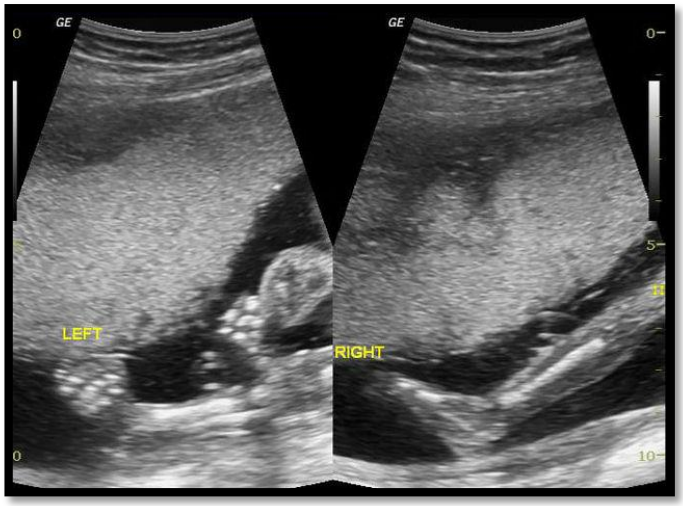


Figure 1.13: A 2 – D ultrasonography of the fetal lower limb showing clubfoot in the left foot and normal right foot (Patel, 2014)

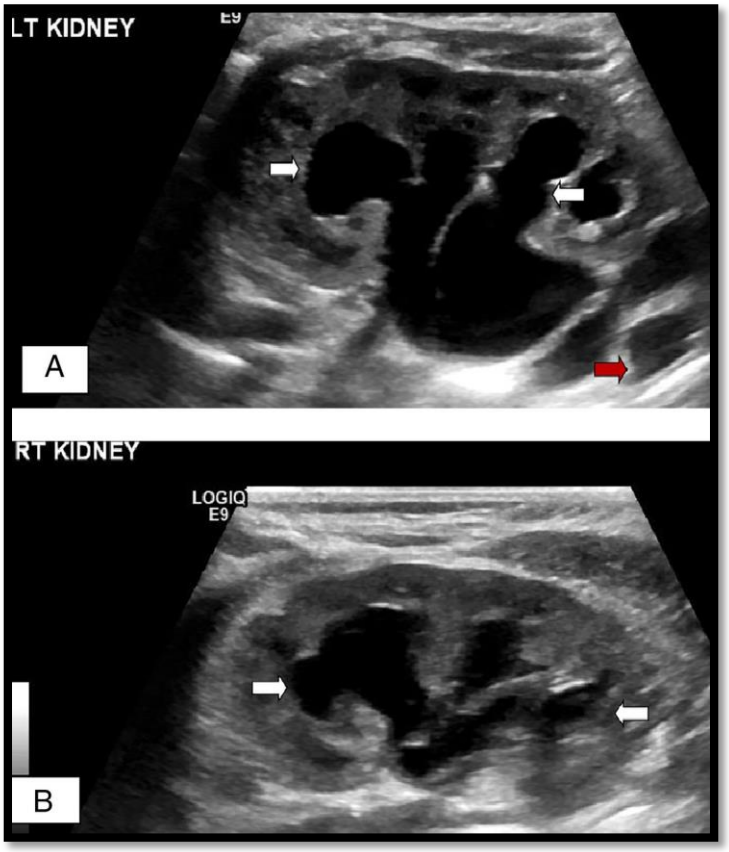


Figure 1.14: A 2 – D ultrasonography of the fetal left and right kidney (a & b) showing bilateral hydronephrosis (white arrows) and hydroureters (red arrows) (Rabah & Al-Nabhani, 2018)

There are several risk factors connected to the development of birth defects (BDs) in offspring. Age-related maternal and paternal factors have been the subjects of the greatest investigation. The yearly proportion of live births to women aged 35 and up is progressively increasing as more women postpone having children. The probability of numerical chromosomal problems in kids is correlated with older mother age, with trisomy 21 being the most common (Down syndrome). At birth, this condition affects newborns whose mothers are between the ages of 25 and 30 by roughly one in 1000, 1 in 385 by the age of 35, and 1 in 25 by the age of 45. The general public has a notion that these mothers' new born only have a chance of having Down syndrome; no consideration is given to further aneuploidies or birth abnormalities. Miller et al. (2011) discovered a substantial connection between cardiac abnormalities and other BDs and maternal age of 35 years or older. Though numerous biological causes of ageing and BD susceptibility have been theorised, they have not yet been fully explained.

The likelihood of spontaneous congenital problems and frequent complicated diseases (including several malignancies, schizophrenia, and autism) has been linked to advanced paternal age, but the processes behind these alterations are poorly understood. "Apert syndrome", "fibroblast growth factor receptor 2" (FGFR2 mutations), "Achondroplasia", "Thanatophoric dysplasia", "Fibroblast growth factor receptor 3 (FGFR3 mutations)", and "Costello syndrome" Harvey rat sarcoma viral oncogene homolog (HRAS), are a tiny fraction of other illnesses that serves as a helpful model for study into the biology and molecular basis of this occurrence (Goriely & Wilkie, 2012).

Parental consanguinity is another risk factor for BDs. Since ancient times, it has been understood that paternal consanguinity had an impact on BDs. The frequency of consanguineous marriages varies by nation and depends on a number of variables, including ethnicity, population type, region, culture, religion, etc. Countries where consanguineous marriages are widespread are now home to around 1.1 billion people, making it difficult for some groups to accept the uncommon consanguineous marriages that are common in modern nations. BDs appear to arise in offspring of consanguineous marriages due to both parents' homozygozity of harmful recessive genes (Oliveira & Fett-Conte, 2013)

Some environmental hazardous agents (physical, chemical, and biological) can raise the risk of birth defects in the fetus if they are exposed during pregnancy. By interfering with the initially normal development of the embryo or fetus, these disruptive teratogenic chemicals can cause subsequent abnormalities that do not alter the genotype. Ionizing radiation, alcohol, specific pharmaceuticals like anticonvulsants, anticoagulants, and chemotherapeutics, viruses like rubella, and maternal illnesses like diabetes are some of these agents (Oliveira & Fett-Conte, 2013).

Teratology is the study of congenital anomalies, their causes, and therapeutic possibilities. Anomalies are often caused by infections, physical agents, metabolic disorders, or chemicals, and can result in mortality as well as physical, behavioral, and cognitive deficiencies. The term toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV (TORCH) infections refers to the most commonly recognized infectious teratogens. These infections are known to cause congenital birth abnormalities if a woman is infected during pregnancy, perinatal, postpartum period, or even after delivery. TORCH infections can spread vertically in addition to horizontally (from one person to another), (from mother to infant). The fetus of a pregnant mother who contracts an infection may also get the illness. In general, the consequences of teratogens are worse the sooner they are exposed. Congenital abnormalities in the developing embryo are likely to become more severe if an infection occurs during the first trimester. When an infection arises later in pregnancy, the fetus is more likely to suffer a neonatal infection rather than congenital defects (Belanger & Lui, 2022).One in 300 women of childbearing age suffer from epilepsy, which is also regarded as a maternal condition that can impede the development of an otherwise healthy neonate; the anticonvulsant drugs have a known teratogenic effect too. Additionally, it has been suggested that a poor diet during pregnancy and a lack of nutrients may raise the incidence of BDs. For instance, a diet low in folate raises the incidence of neural tube closure problems in fetuses who are genetically predisposed to them with a lower risk of heart and extremities problems, 400 mcg of folic acid daily for at least one month before conception and throughout the first trimester of pregnancy may prevent 50 to 70% of neural tube defects. Given that infant mortality is strongly related to factors like maternal health, the standard of living in a

community or country, is one of the most crucial situations to take into account when considering congenital defects (Oliveira & Fett-Conte, 2013).

At both the global and national levels, public health programs have acknowledged that one of the most crucial objectives is to enhance the health of mothers and infants. The public health system is tasked with gathering information that can be used to track birth abnormalities, conduct genetic and epidemiological research, and create and assess prevention initiatives. As a result, networks of registries for the monitoring of birth abnormalities have been set up throughout the world. Congenital anomaly prevention and medical treatment planning are made possible through registries, which are often the only informational source available. 2-3% of infants in Europe are born with at least one serious congenital abnormality, according to statistics. Congenital defects contribute significantly to prenatal and neonatal mortality and morbidity, accounting for 25–30% of infant fatalities in Latvia. Congenital malformations in Europe are monitored through a network called the European Surveillance of Congenital Anomalies (EUROCAT), which provides standardized epidemiological data. The member registries of EUROCAT gather information on all significant structural and hereditary defects from a variety of sources. It should be noted, nevertheless, that the EUROCAT total incidence rates of congenital malformations include instances of live births, stillbirths, and pregnancy terminations for fetal abnormalities. Epidemiology research on congenital malformations are scarce since they call for the examination of sizable populations, reliable data, and consistent diagnosis. Each country has different standards for registration completeness and coding validity, which may also change over time. In Europe and other nations, there are observed regional and socioeconomic variations in the occurrence of congenital abnormalities. Variations in the rates of prenatal discovery and termination of pregnancy also affect the prevalence and contribute to the observed differences, as do variations in the distributions of risk and protective factors that affect overall prevalence (Zile & Villeruša, 2013).

Type 1 or type 2 maternal diabetes that existed prior to conception raises the likelihood of congenital abnormalities, a diabetic consequence known as "diabetic embryopathy." Congenital abnormalities have grown in diabetes pregnancies by up to 5

times even in past few years. Just about any organ system can be impacted by malformations that happen during the first 10 weeks of pregnancy during initial organ development, although NTDs, such as “anencephaly” and “spina bifida”, and CHDs have become increasingly common. The same birth abnormalities that arise in diabetic pregnancies are also more common in obese mothers, which may be caused by undetected type 2 diabetes or decreased glucose tolerance. As of right now, the only methods to lower the risk of diabetic embryopathy are pre-pregnancy counselling to implement strict glucose control before conception and folic acid supplementation as recommended for all women of reproductive age. Tight glycemic control is risky, even in planned, well-managed pregnancies for diabetic women since the likelihood of severe hypoglycemia increases throughout the 1st trimester. Therefore, it is essential to comprehend how maternal diabetes contributes to congenital abnormalities in order to develop preventative measures (Loeken, 2020).

Hyperglycemia is a symptom of diabetes mellitus (DM), a metabolic condition brought on by either low insulin levels or insulin resistance. The metabolic syndrome is defined by WHO as having strong correlations with age, physical activity, dyslipidemia, hypertension, use of oral anti hyperglycemic drugs, and glycated haemoglobin HbA1c levels >7%. A glucose intolerance that is first identified during pregnancy is known as gestational diabetes mellitus (GDM). Pregnant women who were obese and who had diabetes had children who were three times more likely to be born with a craniofacial anomalies (CFA) than those whose mothers were neither obese nor diabetic, suggesting that obesity and diabetes mellitus may be factors in the etiology of congenital deformities. The detrimental effect of hyperglycemia during the early months of pregnancy may be responsible for the hypothesis that GMD is linked to an increased incidence of syndromes and abnormalities. Inadequate glucose control during pregnancy consequently increases the likelihood of congenital defects. However, it is still debatable whether extremely high levels of hyperglycemia are linked to an increased risk of unfavorable pregnancy outcomes. One of the world's greatest socioeconomic issues, along with diabetes, is the use of drugs during pregnancy since it increases the likelihood of developing a number of congenital abnormalities, such as orofacial clefts. Orofacial clefts (OFC) are morphological and functional anomalies that occur from aberrant maxillary complex

development during embryogenesis. They are distinguished by the partial or total absence of continuity in the upper lips, upper alveolar ridge, and palate (Trindade-Suedam et al., 2016)

According to an estimate, 8–11% of women in high-income nations have antenatal depression, and over the past 20 years, more pregnant women have been taking antidepressants than ever before. The prenatal depression must be managed since untreated cases might have negative implications. Considering the dangers of congenital anomalies in particular, there is mixed information about the safety of antidepressant usage during early pregnancy. There have been more research examining the possible teratogenicity of antidepressants, with practically all of them concentrating on selective serotonin reuptake inhibitors (SSRIs), since drug companies issued warnings in 2005 concerning paroxetine-associated heart abnormalities, based on extremely scanty data (Ban et al., 2014).

In 3% - 5% of cases, pregnancies are impacted by birth defects or hereditary illnesses. Approximately 1 in 150 live births are affected by genetic abnormalities, and congenital anomalies remain the leading cause of newborn and child mortality. These chromosomal abnormalities include translocation, duplication, and deletion, as well as aneuploidy, which is characterized by having one or more excess or missing chromosomes. At a frequency of 1 per 800 live births, the most common chromosomal disorder is trisomy 21 (Down syndrome). However far less frequently, trisomies 13 and 18 can also cause live births. Autosomal aneuploidies are more frequent than sex chromosome aneuploidies (“Practice Bulletin No. 163: Screening for Fetal Aneuploidy,” 2016).

Monosomy X is the only known viable monosomy (Turner syndrome). Age of the mother increases the risk of aneuploidy. Patients' risk in any specific pregnancy is influenced by the presence of birth abnormalities, soft ultrasonography signs, past obstetric history, especially if it is noteworthy for a previous pregnancy that was impacted by aneuploidy or the other genetic illness. Whereas most cases are rare and due to chromosomal nondisjunction, a historical family history of aneuploidy raises the

likelihood of aneuploidy in the present pregnancy, particularly if one of the parents carries a balanced “Robertsonian translocation gene”. All patients who are interested in screening or testing should speak with their doctor or a genetic counsellor. It is important to keep in mind that choices for aneuploidy screening and testing are heavily impacted by value (Carlson & Vora, 2017).

A patient's probability of having a fetus with a genetic abnormality can be easily evaluated through prenatal testing for genetic defects. There are several different prenatal screening and diagnostic procedures available; each one has relative benefits and limits and gives differing amounts of information and performance. When it comes to screening test characteristics, no one test is superior than another in every circumstance, demanding thoughtful, patient-centered counsel from the obstetric care provider and challenging decisions from the patient. Every pregnant woman should seek information about the various fetal chromosomal abnormalities testing options. Obstetric care providers should be prepared to discuss the benefits and limitations of different screening and diagnostic methods, as well as the risk of fetal genetic diseases. A patient's decision to undergo chromosomal abnormality testing should be based on the availability of appropriate and reliable information, the patient's clinical setting, readily available resources for medical care, and the patient's views, preferences, and objectives. All patients should be offered the option and the right to undertake diagnostic testing and screening after obtaining counselling (Rose et al., 2020).

Organogenesis in fetuses can be particularly harmed by some infectious agents. As the gestational infection with the strongest teratogenic effect, rubella is mentioned. Development of the fetus or embryo is virtually always affected and it can cause heart problems, deafness, blindness, and lesions of the CNS. Toxoplasma gondii, Treponema pallidum, Cytomegalovirus, and Herpes Simplex are also known to be dangerous. (Oliveira & Fett-Conte, 2013)

Ultrasound is the primary diagnostic technique for fetal congenital abnormalities. It enables investigation of the fetus's external and internal anatomy and aids in the diagnosis of chromosomal and genetic diseases that manifest as a variety of deformities

in addition to serious congenital defects. The anomaly scan, a type of ultrasound taken between 18 and 23 weeks of gestation, is crucial in this regard. Neural tube defects are frequent anomalies. Anencephaly and spina bifida are more prevalent among them. Hydrops fetalis, skeletal dysplasias, and renal abnormalities are additional congenital conditions that are frequently found on ultrasonography (Rehan, 2019).

Ultrasound in medicine was first used in a number of settings across the world during and soon after World War II. The oldest piece of literature on medical ultrasonography was published in 1942, in a paper by Dr Karl Theodore Dussik on transmission ultrasound investigation of the brain in Austria. Although other workers in the USA, Japan, and Europe have also been recognised as pioneers, Professor Ian Donald and his Glasgow colleagues' work throughout the middle of the 1950s significantly contributed to the advancement of useable technology and applications. Ultrasonography became widely used in medical practises as a result in the decades that followed. (Donald et al., 1958).

The detection and management of medical conditions are aided by ultrasonic imaging, also known as sonography, a noninvasive, painless, and secure process. Images of the inside of the body are produced using sound vibrations. A woman's uterus, ovaries, and an embryo or fetus inside the womb can all be seen on an obstetric ultrasound image. The console of an ultrasound machine (Figure 1.15) includes a computer, a visual monitor, and a transducer that is attached to it. A small, moving object that resembles a microphone is the transducer. Infrared, inaudible sound pulses are transmitted into the body via the transducer, and the device then listens for any echoes that emerge. Following the application of a small quantity of gel, the transducer is positioned on the area being inspected. The transducer and the region being studied can exchange sound waves with the help of the gel. On a video display, the ultrasound picture is instantly apparent. The image is created by the computer using the amplitude (loudness), frequency (pitch), and length of the ultrasonic signal's return to the receiver. The type of tissue or body structure through which the sound is travelling is also taken into consideration A specialized ultrasound technique called Doppler ultrasonography monitors and evaluates the pace and direction of blood cells flowing through arteries. Blood cell movement causes frequency

changes in sound waves that are returned. (called the Doppler effect). Computer software collects and analyses the sounds to produce graphs or visually appealing pictures that depict the blood moving through the arteries.

BENEFITS OF ULTRASOUND:

• Ultrasonography exams are noninvasive.
• The use of ultrasounds may be uncomfortable at times, but it should not harm.
• Ultrasound is easily available, less expensive and easy to use than the bulk of other imaging methods.
• Ultrasonic scanning is extremely secure and radiation-free, and it offers a clear view of delicate organs that are challenging to see on X-ray images.

• Ultrasonography is the ideal imaging modality for pregnant women and their unborn infants for diagnosis and monitoring.

• Pregnancy ultrasounds have been used for over 40 years, and there has never been any proof that the patient, the embryo, or the fetus were harmed.

A lot of information regarding the pregnancy may be learned by ultrasound, which lets the doctor view within the uterus (Obstetric Ultrasound, n.d.).

RISKS OF ULTRASOUND:

Routine diagnostic ultrasonography does not appear to harm anyone (Obstetric Ultrasound, n.d.)

LIMITATIONS OF OBSTETRICAL ULTRASOUND IMAGING:

All fetal abnormalities cannot be detected by obstetric ultrasonography. So, a pregnant woman may need to undergo non-radiologic tests to assess the health of the fetus, such as a blood test, amniocentesis, or chorionic villus sample, or she may be sent to a perinatologist by her primary care physician (Obstetric Ultrasound, n.d.).

Figure 1.15 A photograph showing Sonoscape S22 ultrasound machine used for fetal wellbeing in the current study

Congenital abnormalities can cause long-term disability, which can have a substantial effect on people, families, healthcare systems, and nations. Infections, environmental conditions, and genetic factors are only a few of the risk factors linked to congenital malformations. In other instances, the etiology is complex or there is no known cause.

Alpha-fetoprotein (AFP) is a plasma protein produced by the fetal umbilical vesicle. Maternal serum and amniotic fluid AFP are used for the purpose of screening defects of birth and genetic disorders. Increased levels of AFP have been seen in babies with NTDs such as “spina bifida” and “anencephaly”, however, reduced AFP levels have a close association with genetic conditions such as trisomy 21 (Adigun, Yarrarapu, & Khetarpal, 2023).

In the 1950s, the first method for prenatal chromosomal diagnostic testing, amniocentesis was originally revealed. Amniocentesis offers a variety of applications and has become safer, including checking for infectious diseases and doing genetic analyses. Another diagnostic procedure is chorionic villus sampling (CVS), which can be done early in the gestational period (Carlson.& Vora, 2017). Amniocentesis, an invasive procedure involves the removal of small amount of amniotic fluid for testing. It is mainly used for diagnosing antenatal abnormalities of the chromosomes, infections of fetus and determination of gender (Jindal, Sharma, & Chaudhary, 2022).

Using chorionic villus sampling, placental tissue is sampled between 10 and 13 weeks of gestation for prenatal genetic testing. The fundamental advantage of chorionic villus collection is that genetic data is available earlier in the pregnancy. With this knowledge, patients can seek obstetric therapy and suggestions, immediate referral to paediatric subspecialists, or earlier and safer options of terminating a pregnancy if the results are abnormal. American College of Obstetrics and Gynecology recommends that women of all ages have prenatal testing for aneuploidy by screening or diagnostic procedures. Because prenatal genetic testing cannot detect every anomaly, it should concentrate on the patient's risk, goals for reproduction, and preferences. The first obstetric appointment is the ideal time to bring up genetic testing (Jones TM, n.d.).

Advanced paternal age has been linked to an increase in aneuploidy in sex chromosomes and autosomes. Due to the substantial influence of maternal age and the frequent similarity of partner ages, it is challenging to research the autosomal trisomies with regard to paternal age. With the exception of sex chromosome aneuploidy, which has an equal paternal and maternal frequency of origin, maternal origin of the aneuploidy predominates in majority of trisomies. In fact, fathers over 50 have a 160% higher chance of having sperm that is XY- bearing than fathers under 30 (Conti & Eisenberg, 2016).

The health and wellbeing of women before, during, and after pregnancy depend on their dietary supplementation and ability to gain weight. Pregnancy problems are believed to be less common in women who gain weight normally during their pregnancy.

Contrarily, unfavorable pregnancy outcomes include spontaneous miscarriage, hypertension issues, fetal development restriction, and preterm delivery have been linked to low birthweight and malnutrition in pregnant women (Triunfo & Lanzon, 2015).

Overweight mothers may experience issues during and after pregnancy and may be an obstetric risk factor, with consequences for both the mother and the fetus. Pregnancy-related risks include preeclampsia and gestational diabetes mellitus (DM), whereas fetal risks include congenital abnormalities (CAs), macrosomia, stillbirth, neonatal mortality, and preterm. (Ebrahimi-Mamaghani et al., 2015).

Around 276,000 babies die each year due to congenital abnormalities globally. However, a number of causative factors, including viral, genetic, dietary and/or environmental ones, have also been found. Among them nutritional condition of the mother is particularly important. Currently, the cause of 50% of CAs is unclear (Sitkin & Farmer, 2016). Despite this, there aren't many studies on the occurrence of CAs and the relationship involving pregnant women's "body mass index" (BMI) and the development of CAs in the field of epidemiology. These studies are only open to overweight or obese child bearing women. The prevalence of CAs in pregnant women with different food patterns is therefore unclear (Macumber, Schwartz & Leca, 2017).To help healthcare systems develop CA preventive strategies, it is important to do research on the connection between maternal BMI and the risk of CAs (Moraes et.al., 2019).

There are no known negative health effects from folate consumption below the 1000_g/day upper intake level (UL) for the general population. The safety of increased folic acid consumption has been called into question in light of public health efforts to decrease the frequency of folic acid-responsive neural tube defects by increasing consumption of folic acid at levels lower than the UL. Despite substantial proof to the contrary regarding its beneficial benefits on lowering the development of neural tube defects and possibly other congenital deformities, several nations do not require that the food supply be enriched with folic acid for neural tube defects prevention. Nevertheless, supplementing with folic acid is advised for everyone, focusing on women of childbearing age, at dietary levels of at least 400 µg/day and up to 5 mg/day. When the neural folds do not merge during embryogenesis, neural tube defects, which cause persistent, debilitating medical diseases are created. Randomized controlled trials and other research conducted in the 1980s and 1990s demonstrated that providing folic acid-containing multivitamins to pregnant women prevents the formation or recurrence of neural tube defects. Fortification is the most effective way to increase folic acid consumption and prevent neural tube defects because up to 50% of pregnancies in the United States are unplanned and only a small portion of pregnant women abide by public health recommendations to take folic acid supplements (Field & Stover, 2018).

1.2 RESEARCH GAP

In Pakistan there is a lack of data on the incidence of congenital anomalies and the associated maternal risk factors across various ethnic groups. A case-control study that attempts to describe the incidence of structural congenital abnormalities and identify any relevant maternal risk factors connected to them is therefore justified given the paucity of comprehensive studies on congenital malformations. This study aims to determine the association of congenital malformations with maternal risk factors in different ethnicities living in the city of Karachi and also to furnish latest data for health care facilities in order to take effective preventive measures as well as raise awareness.

1.2.1 Theoretical Gap

There is a gap in the existing theoretical understanding of how these factors may interact and contribute to the occurrence of congenital malformations in various ethnic groups in Karachi because there are no theoretical frameworks or models that specifically address the relationship between maternal risk factors and congenital malformations in various ethnic groups. To address this theoretical gap, theoretical frameworks that may guide the inquiry and provide a deeper understanding of the underlying mechanisms and processes involved in this relationship would need to be developed or adjusted.

1.2.2 Contextual Gap:

The larger socioeconomic, cultural, and environmental elements that can affect the prevalence of congenital abnormalities in various ethnic groups in Karachi are not well understood or taken into account. This may involve elements including socioeconomic standing, access to healthcare, exposure to the environment, and cultural norms. For a thorough knowledge of the association between maternal risk factors and congenital abnormalities among different ethnic groups in Karachi, it is crucial to close this contextual gap.

1.2.3 Methodological Gap: N/A

1.3 PROBLEM STATEMENT

Globally, congenital malformations have varied incidence rates and are one of the leading causes of newborn death and morbidity. According to data from the World Health Organization (WHO) approximately 6% of infants worldwide are born with a congenital disease, with variations based on ethnicity, region and other variables. Cardiac and neural tube abnormalities are the most common types of congenital abnormalities, which can have substantial morbidity and mortality effects. Genetic and chromosomal abnormalities, teratogenic exposures during pregnancy, environmental pollutants, maternal illnesses during pregnancy, and maternal age more than 35 are all risk factors for the development of congenital malformations.

Congenital abnormalities can have significant impact on newborns, their families, and society as a whole. Physical burdens, parental stress and financial challenges are a few examples of these repercussions. Preventive measures, environmental factor research, early detection methods, intervention strategies, and support for those affected are all required.

1.4 HYPOTHESIS OF STUDY

A) Null Hypothesis

There is no association of congenital malformations with maternal risk factors.

B) Alternate Hypothesis

There is an association of congenital malformations with maternal risk factors

1.5 OBJECTIVES OF STUDY

The following are the study's objectives:

To determine the association of congenital malformations with maternal risk factors in different ethnicities.

To determine the association of craniofacial congenital malformations with anomalies of other systems.

1.6 SIGNIFICANCE OF STUDY

To the best of our knowledge, this is the first study in the country to determine the association of congenital malformations with maternal risk factors in different ethnicities. Only a few studies have been conducted in Pakistan to indicate an association between congenital malformations and maternal risk factors. This study will also provide a pattern of congenital malformations in our country which would enhance motivation to explore more about the subject and promote adoption of health care strategies for prevention.

CHAPTER 2

LITERATURE REVIEW

Forci et al. (2020) conducted a descriptive epidemiological study in Morocco in which cases were diagnosed prenatally by ultrasound. Fetal deaths in utero (FDIU), which had an incidence of 5.58 per 1,000 live births and a 19.2% rate, were revealed. With 470 anomalies, polymalformative syndrome was seen in 26.5% of the patients. Musculoskeletal defects dominated (33%), and neurological abnormalities (18%) were the next most common, including hydrocephalus (31%), anencephaly (26.2%), and spina bifida (20.24%) among them. In 12% of the patients, deformities of the eye, ear, neck, and face were found and in 8.5% genetic problems were discovered with 87.5% of these cases confirming Down syndrome. In 28.6% of instances, prenatal diagnosis of congenital anomalies was conducted. However, the incidence of congenital abnormalities as well as their etiologies have not yet been proven due to the absence of an interstate congenital surveillance system. As a result, it was recommended that congenital abnormalities be registered and monitored across the nation as a component of the national health information system.

Qadir et al. (2017) conducted a descriptive cross-sectional study on all congenitally abnormal newborns delivered between May 1, 2016, and April 30, 2017, in Mardan, Pakistan. It was observed that 117 (1.23%) of the 9,453 newborns had congenital abnormalities. The most prevalent abnormalities were encephalocele (9.4%), meningomyelocele (11%), hydrocephalus (27.3%), and anencephaly (18%). The average mother's age was 25.597.6 years. 66 (56.4%) mothers were between the ages of 21 and 30, and 66 (56.4%) were multigravidas. In 83 (71%) cases, there was a deficiency in folic acid intake, and consanguinity was present in 72 (61.5%) cases. Antenatal care was provided to 33 (28.2%), but not to 84 (71.8%). According to the study, pregnant women of childbearing age should be informed about the need of getting enough folic acid before

and throughout the first trimester. It also emphasized avoiding cousin marriages. Prenatal care must be considered since it is crucial for the early detection, prevention, and treatment of congenital abnormalities.

In Brazil, a prospective, observational, case-control study was conducted on hospital patients. In all, 357 women were pregnant, with 223 (case group) having fetuses diagnosed with structural abnormalities and 134 having structurally normal fetuses. A history was taken before to the prenatal consultation, and structural congenital abnormalities (CAs) were found using ultrasonography. Central nervous system anomalies were the most common structural CAs (30.94%), followed by genitourinary system anomalies (23.80%), and then multiple CAs (16.60%), according to the data supplied. The background of preceding children with CAs, as well as consanguinity between the progenitors and family history, all had an influence on the development of structural CA. The data described can help in the formulation of programs to enhance CA patient care, genetic counselling, and rehabilitation, as well as the implementation of public health efforts to identify risk factors. (De Moraes, Melo & Amaral, 2020)

To ascertain the incidence and forms of congenital defects, their impact on infant mortality, the necessity for monitoring, and the availability of healthcare for early detection and treatment, India's first cohort study observed 2107 women till the conclusion of the pregnancy. It was found that there were 230.5 major congenital anomalies per 10,000 live births among 1822 babies. The most frequently seen anomaly in the group occurred in 65.86 out of every 10,000 newborns and was congenital heart abnormalities. While being somewhat common (27.44/10,000 babies), neural tube abnormalities were 2.5 times less common than congenital heart problems. The second most common reason for neonatal deaths in this group was congenital diseases. 10.98/1000 live births had a prenatal diagnosis of a congenital abnormality, and 4.39/1000 live births had a congenital anomaly pregnancy termination rate. Suggestions for prevention and surveillance were made in the form of a well-defined program. (Bhide, Gund & Kar, 2016).

At Eastern India's neonatal care centre between September 2011 and August 2012,

cross-sectional descriptive research (Sarkar et al., 2013) looked into the incidence of birth defects in newborns and the risk variables associated with them. It was demonstrated that 12,896 infants were born throughout the research period, and 286 of them had congenital abnormalities, for a frequency of 2.22%. The majority of the female population (55.7%) was between the ages of 21 and 30. Contrary to primiparas (1.8%), congenital abnormalities were more frequently observed in multiparas (3.3%). Most often impacted (33.2%) was the musculoskeletal system, followed by the gastrointestinal (GI) system (15%). The most prevalent musculoskeletal condition was talipes (17.1%), while the most prevalent Gastrointestinal condition was cleft lip and palate. Low birth weight, preterm, multiple pregnancies, consanguinity, and cesarean section had higher odds of being linked to congenital abnormalities.

Man et al. (2017) evaluated the prevalence of congenital malformations, its risk variables, and its immediate prognosis in Bida, the northern part of Nigeria. Over the research period, 46 infants with congenital defects were identified and all of them were included in the investigation. Neonatal prevalence at the hospital was 111/1000 newborns. The digestive system was the most often impacted (50.0%), then the central nervous system, then head and neck anomalies. The distribution of abnormalities among the different ethnic communities did not differ significantly. 8.7% of moms were older than 35, and about 22% of consanguineous households were made up of first cousins alone. Congenital abnormalities had a case fatality rate of 2.2%, and 60.9% of patients were sent to other institutions for further treatment. To prevent issues, particularly financial and social ones, and to introduce timely and suitable help, it was proposed that there be support available for families of children with these diseases. The high rate of congenital abnormalities in this study (111/1000 admissions of newborns) emphasizes the need for local capacity building for the treatment of these diseases in facilities with comparable congenital abnormality statistics.

From July 2010 to June 2011, prospective study was conducted at Gian Sagar Medical College in Banur on congenital malformations in 1554 successive deliveries. Prenatal ultrasonography or a neonatologist's clinical assessment of the infant was used to make the congenital malformations diagnosis. According to the data provided by the

study, the prevalence of congenital malformations was 4.44% and 49 (71.01%) of the newborns with congenital malformations were stillborn. Significant anomalies were present in 68.11% of cases. The most often affected systems were the brain and urogenital system, and 8.6% of infants had many abnormalities. Advanced age, parity, consanguineous marriage, poor obstetric history, unintentional medication consumption all contributed to this, however, radiation exposure and prenatal infections had no influence. To reduce suffering and successfully control the related morbidity and mortality, suggestions were developed for the early diagnosis and proper therapy of life-threatening abnormalities. Premarital counseling is indicated, especially if there are consanguineous parents and a family history of congenitally deformed children. By avoiding consanguineous marriages, the prevalence of such unions may be significantly reduced. Hence, widespread health education will go a long way towards raising public understanding of the etiological causes of prenatal abnormalities that may be avoided (Marwah et al., 2014).

Francine, Pascale & Aline (2014) evaluated the prevalence, kinds, and correlations of congenital abnormalities (CA) in stillborn and liveborn newborns at two Lebanon-based hospitals in Mount Lebanon. 24 (2.4%) of the 1000 single newborns were found to have congenital malformations. Anomalies of the limbs and the cardiovascular system (4/1000) were most often seen, followed by abnormalities of the genitourinary (2/1000), neurological (2/1000), respiratory (2/1000), and chromosomal (1/1000) systems. Parents' consanguinity and the pregnant mother's alcohol consumption were linked to higher CA rates. It was determined that educational programs must be established to prevent these difficulties in the kids due to the higher frequency of CA in situations of parental consanguinity.

Hussain et al. (2014) conducted a prospective hospital-based study in Kharian, Pakistan in which the neonatal congenital malformations frequency and pattern were identified. The data showed that 226 of the 3,210 total hospitalizations were newborns with congenital malformations. Of them, 96 females were and 130 were males. Anomalies affecting the various body systems included 46 related to the central nervous system, 42 musculoskeletal, 34 related to the genitourinary system, 30 cardiovascular

systems, 27 related to the ear, eye, face, and neck, 19 related to the digestive system, and 14 each for syndromes and skin. To reduce the percentage of congenital abnormalities that are avoidable, it was advised that healthcare management place a strong emphasis on primary prevention through immunization, diet, and medications.

A cross-sectional analytical research was carried out in Kohat, Pakistan, from January to December 2011. According to the data provided, 9558 infants were delivered, and 93 of them had different congenital malformations. The most frequent congenital malformations were anencephaly followed by hydrocephalus, hydrocephalus with meningocele, and hydrops fetalis. Mothers were 26.10 ±7.406 years old on average. 75 (or 80.6%) of the 93 moms were in the 20–40 age range. There were 25 (26.9%) grand-multigravida moms among the 54 multigravida mothers. 63 (67.7%) moms did not get a prenatal checkup before receiving the final diagnosis, and the majority (65.6%) had low socioeconomic levels (SES). 33.3% of moms consumed prenatal folic acid, and the consanguinity rate was 61.3% (57/93). In 5.3% of the patients, toxoplasmosis was found, while syphilis was found in one instance. Eight (8.6%) of the cases had a family history of congenital abnormalities. Furthermore, three (3.2%) of the mothers had a history of maternal passive smoking throughout pregnancy. To gauge the problem's size and determine the causes of these congenital malformations in our setup, a large-scale population-based investigation on diverse congenital malformations is needed (Gul, Jabeen & Khan, 2012).

At Fortaleza, Ceará, Brazil, three public newborn facilities underwent prospective, quantitative research. The central neurological and musculoskeletal system anomalies outnumbered the other categories, according to data gathered from the medical records of 159 malformed newborns. There were statistically significant correlations between a variety of variables and the different types of abnormalities, including gender, gestational age, birth weight, drug usage, mother age, family income, educational attainment, and number of children. This kind of malformation has strong correlations with maternal and neonatal variables, and these findings reinforce the need for newborn nursing care (Fontoura & Cardosa, 2014).

In Finland, a population-centered case-control (1:5) study was conducted on the entire country. The "Finnish Registry of Congenital Malformations" issued by the "Finnish Institute for Health and Welfare" recorded congenital limb abnormalities. Live births, stillbirths, fetuses from spontaneous abortions, and pregnancy terminations due to severe fetal abnormalities were all included in the database. Based on the residence and pregnancy year, 2,520 controls were matched to 54 cases to identify 534 children with limb impairments. Longitudinal, transverse, intercalary, mixed, and unknown defects were classified as non-syndromic instances. Pregestational diabetes, male sex, early maternal age, and primiparity have all been demonstrated to increase the incidence of congenital limb deficiency. The use of antiepileptic drugs during the 1st trimester has been connected to limb deficit. Therefore, this study suggests that any action taken to prevent congenital limb abnormalities begins even before conception. This can involve teaching people about the risks associated with using drugs while pregnant in the first trimester. (Syvänen et al., 2021).

Abdolahi et al. (2014) performed a study in which epidemiological aspects of congenital abnormalities were assessed in rural regions of northwest Iran. According to the study, congenital abnormalities were the major diagnosis in 254 out of 22,500 live births, for a prevalence rate of 112.89/10,000 live births. 24% of all birth defects were nervous system anomalies, followed by heart-related malformations. The southwestern area had the greatest occurrence of birth abnormalities with 386 per 10,000 births, while the northwestern region had a rate of 15 per 10,000 births. Although there were few birth abnormalities in Iran's northwest, it was discovered that the region's significant regional variances in the prevalence of birth disorders may be due to a highly polluted industrial zone. As a result, a greater etiological study in this area was suggested.

Tayebi, Yazdani & Naghshin (2010) conducted a cross-sectional study at Shahid Sadoughi Hospital, Yazd, Iran which determined the relationship between the inbreeding coefficient and abnormalities and the impact of consanguinity on congenital anomalies. The data demonstrated that 300 of the 1195 neonates were from consanguineous unions, whereas 895 came from non-familial unions. Just 11 of the 45 instances with abnormalities were from non-familial marriages, compared to 34 cases from familial

marriages. The incidence of abnormality and parental marriages were significantly correlated. According to the study, consanguinity should be considered while offering genetic counselling in Iran since it may have a significant role in the high frequency of malformation in babies. Thus, it was advised that genetic counseling be performed before marriage for potential prevention, not just for couples who are related by blood, but for all couples who could have genetic issues.

A retrospective, observational population study was undertaken from 1995 to 2012 utilizing data from the "California Office of Statewide Health Planning and Development's Linked Birth Database" to determine trends in prevalence, risk factors, and consequences of gastroschisis. It was observed that among 10,000 live births, there were 2.7 occurrences of gastroschisis. Although not specifically alcohol, cocaine, opioids, or hallucinogens, people suffering from gastroschisis have a higher exposure to illegal drugs or other toxic chemicals. Low/very low birthweight and preterm delivery were linked to gastroschisis. In comparison to white patients, a reduced risk was seen among Asian/Pacific Islander, Hispanic, and black individuals. Rural locations presented a greater risk. With increasing maternal age, the risk is reduced in comparison to women aged 20 (Anderson et al., 2018).

A multicentre cohort study in a hospital population in Vietnam was conducted to investigate the incidence of FA supplement usage and associated maternal factors. Throughout 2015 and 2016, the effects of FA supplementation were evaluated in 2030 singleton pregnant women. Among the 654 women who admitted to taking supplements with FA alone or with multivitamins, 505 (24.9%) did so correctly. The remaining 654 women (32.2%) stated they only used supplements with FA. Less likely to use FA supplements were women over the age of 30, with low levels of education, formal employment, and current pregnancies that were either their first or unexpected. Suggestions were provided for the implementation of educational initiatives that support FA supplementation while taking pregnancy into account (Ha et al., 2019).

Pace et al. (2019) investigated the relationship between the mother's body mass index (BMI) before conception and newborn mortality, as well as the 1st year survival of

neonates born with spina bifida. Information on spina bifida was provided by the National Birth Defects Prevention Study (NBDPS), a population-based, multi-state study of more than thirty severe structural birth defects. The study's findings revealed that infant mortality was 4.4% higher in babies with spina bifida. Infant mortality was increased by premature birth, multiple gestations, severe spina bifida lesions, non-Hispanic Black mothers, and infants with several co-occurring abnormalities. Obese or underweight pregnant women were more likely to lose their unborn infants than healthy-weight mothers. The findings also highlighted the relevance of a woman's healthy weight before pregnancy in lowering the risk of adverse newborn and neonatal outcomes. More research is needed to completely understand the various causative processes through which maternal BMI before conception increases the risk of death in spina bifida neonates.

Adane et al. (2020) assessed the frequency and risk variables for birth abnormalities in sub-Saharan African nations in unpublished as well as published studies. A literature study using Medline (PubMed), Excerpta Medica Database (EMBASE), Health Inter-Network Access to Research Initiative (HINARI), Google Scholar, Science Direct, and other sources turned up a total of 43 qualified papers. According to 25 studies from 9 countries, the total incidence of birth defects was 20.40/1,000 births. Southern Africa had the greatest incidence in the sub-group analysis, with a frequency of 43/1000. The pooled frequency of birth abnormalities in the musculoskeletal system was 3.90 per 1000, whereas the pooled incidence of Down syndrome was 0.62/1000. Birth abnormalities were strongly associated with the absence of folic acid supplementation, the prevalence of chronic illness, and drug usage during pregnancy. These findings led to recommendations for folic acid supplementation for women both before and during pregnancy. Pregnant women should only be given drugs with prudence and their chronic diseases must be correctly managed to lower the probability of birth abnormalities. It was also advised that the countries set up fetal medicine units considering the high rate of birth abnormalities revealed in this analysis.

In Utah, United States, a population-based case-cohort was undertaken. The study's data source was the “Utah Birth Defect Network” (UBDN). In 20.2% of cases, a clear etiology was identified. Teratogens accounted for 4.1% of cases, hereditary

anomalies (94.4%), and conjoined or acardiac twins (1.4%). The remaining 79.8% were categorized as having an unknown cause, and 88.2% of them were isolated birth abnormalities. 4.8% of the population had family history information (first-degree relative similarly afflicted). The cohort had 92.1% births (isolated and non-isolated birth issues), with isolated birth disorders accounting for 75.3%. (unknown or known etiology). The results highlighted the gaps in the understanding of the causes of birth abnormalities. More collaboration between researchers, clinicians, and epidemiologists was recommended as better techniques for the aspects that are yet unknown. They included improved means to objectively evaluate fetal exposures and closer to the critical phases of organ development (Feldkamp et al., 2017).

289,365 babies were screened for anomalies at Boston's Brigham and Women's Hospital over 41 years (1972-2012). Reviewing the findings of the pediatricians' and specialists' examinations, diagnostic tests for live-born infants, and fetal autopsies in cases of elective abortion and stillbirth allowed researchers to identify the anomalies. The following apparent etiologies were found in 26.6% of the total number of 7020 (2.4%) babies and fetuses with one or more malformations: Mendelian problems, such as monozygotic twinning issues, vascular disruption, chromosomal abnormalities, postaxial polydactyly, type B newborns, and environmental variables. There were a lot more abnormalities with an unclear origin. According to the study's findings, causal heterogeneity of common malformations can be identified through malformation surveillance programs. The prevalence of several reasons, including identical twin problems, chromosomal abnormalities, vascular disruption, and deformities caused by mutations with Mendelian inheritance, was verified. Formerly referred to as demonstrating multifactorial inheritance, modern technologies, such as chromosomal microarray and genome sequencing, uncover the genetic defects present in newborns with deformities (Toufaily et al., 2018).

In a research by Skuladottir et al. (2014), data from the National Birth Defect Prevention study (NBDPS), a population-based, multicenter case-control study of birth defects, were utilised. Information on births that occurred between October 1997 and December 2009 was provided by the ten NBDPS research centres (Arkansas, California,

Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Data from 5922 control neonates born between 2003 and 2009 and 2372 cases of orofacial clefts were evaluated to see whether there is an association between corticosteroids and orofacial clefts. According to the newly released data, there is a 1.0 (95% CI, 0.7-1.4) overall relationship between CL/P and corticosteroids. There was just a weak correlation between clefts and specific corticosteroid components or time. Based on the data gathered, it was determined that in the NBDPS, maternal usage of corticosteroids is not linked to the delivery of a baby with an orofacial cleft. Additionally, these findings may help with the clinical risk-benefit analysis of giving corticosteroids to pregnant women during the 1st trimester. A meta-analysis was performed to determine if beta-blockers are teratogenic during the 1st trimester of pregnancy. Through the use of Cochrane Clinical Trials, EMBASE, PubMed, and a manual search, an in-depth literature review was conducted. Random-effects models based on odds ratios (ORs) were used for meta-analyses. To evaluate heterogeneity, analyses of specified subgroups were carried out. The risks of congenital abnormalities related to exposure to beta-blockers during the first trimester were compared to those related to no exposure in randomized controlled trials or observational studies. 13 population-based case-control or cohort studies were discovered. There is no association between first-trimester-blocker exposure and an increase in congenital abnormalities overall, according to a meta-analysis of the information that was made available. Nevertheless, organ-specific studies revealed mouth clefts, NT deficits, and the likelihood of CV issues all increased by more than three times each, respectively. Because of the small number of studies that have been published, the differences in the research, and various biases, it is challenging to determine the degree and source of this link. It was suggested that in the future, more precise and thorough data on the usage of -blockers, the length of being exposed, and confounding variables should be gathered to further study this, ideally within the context of significant observational studies, if practicable. Beta-blockers should be compared to other antihypertensives in future studies, and by using untreated hypertensive controls as a comparison group, researchers may try to separate the effects of beta-blocker treatment from the influence of underlying hypertension (Yakoob et al., 2013).

In a meta-analysis of observational data, it was determined if mothers who had experienced a viral infection in their early pregnancies were more likely than mothers who had not to have children with congenital heart disease (CHD). 'PubMed', 'Embase', 'Google Scholar', 'Cochrane Libraries', and 'Chinese databases' were all searched without restrictions. Analysis of 17 case-control studies with 67 233 women was done. Women with a history of viral infection during the first trimester of pregnancy had a substantially increased risk of CHD in their children, according to both random-effects and fixed-effects models. While other maternal viral infections in the first trimester did not significantly enhance the risk of CHD in the offspring, rubella and cytomegalovirus (CMV) infections during pregnancy significantly increased the risk of CHD in the children. (Ye et al., 2019).

Between 2009 and 2013, a population-based study was conducted in three regions in southern Thailand to determine the prevalence of mouth clefts from the congenital malformations database and the relationship between the risk of oral cleft and mother age. Oral cleft data and mother details, such as live births, stillbirths, and pregnancies terminated after a prenatal checkup, were generated using the birth defects registry of 467 hospitals in three southern Thai provinces. An average incidence of 1.44/1000 births was observed in cases of oral cleft out of a total of 186,393 births. CL/P (45.0%), CP (29.0%), and syndromic cleft (15.6%) were the three most prevalent types of clefts. The average age of the mother was 28.0±6.4 years. The incidence of oral clefts did not differ between mother age groups. Nevertheless, children with syndromic clefts were linked to older mothers (35+ years). According to the study, there are 1.44 oral clefts for every 1000 live births, 15% of cases had a congenital abnormality or recognized condition, and higher age of the mother is associated with a higher incidence of syndromic clefts (Jaruratanasirikul et al., 2016).

Research by Loane et al. (2013) studied trends and geographic variations in the prevalence of trisomies 21, 18, and 13 in total and live births in Europe about an aging maternal population and prenatal diagnosis. Between 1990 and 2009, There were 6.1 million births registered by the 21 population-based EUROCAT registries. Trisomy instances include live births, fetal deaths before twenty weeks of pregnancy, and

miscarriages brought on by congenital abnormalities. Early terminations were corrected to twenty weeks' gestational age to account for differences in overall frequency induced by artifactual screening. The percentage of births to women aged 35 or older in the population was recorded by the participating registries and ranged from 13% in 1990 to 19% in 2009. Trisomy 21 had a total frequency of 22.0, trisomy 18 had a frequency of 5.0, and trisomy 13 had a frequency of 2.0. The frequency of trisomy 13 was 0.48, while trisomy 21 was 11.2. The three trisomies' overall and total adjusted prevalence all rose with time, largely due to an older mother population. There was a threefold disparity in the prevalence of trisomy 21 among countries. Almost 13% of all births in the 12 nations of Europe considered in the research occurred in 2007. In terms of screening for pregnancy and termination of pregnancy for fetal anomaly (ToPFA), the areas differed from other regions in these countries, but they were representative of European statistics in terms of mother age, particularly after the year 2000. The conclusion reached was that national disparities should be interpreted with considerable care. To evaluate screening programs, provide healthcare, and determine the effects of postponed childbearing, trisomy 13, 18, and 21 must be continuously monitored. The overall incidence of T21, T18, and T13 has increased over time, which is partially due to the increase in older mothers giving birth. The total prevalence of these trisomies has remained virtually constant, despite the increasing acceptance of prenatal screening and consequent abortions.

In Mashhad, North-Eastern Iran, Kianifar et al. (2015) investigated the incidence of CL/P in live neonates as well as the risk factors that contribute to it. Three major hospitals in Mashhad's birth registers for 28,519 newborns from March 1982 to March 2011 were examined for oral clefts. Date of birth, gender, birth weight, maternal age, pregnancy statistics, kind and location of the cleft, and the presence of other congenital abnormalities were clinical and demographic data associated with recognized cases that were noted for examination. The incidence of CL/P/1,000 live births was 1.9 overall. Following isolated cleft lip (35.2%) and isolated cleft palate (14.8%) as the most prevalent types of clefts, respectively, came CLP. Oral clefts affected 92.6% of participants, with the right side accounting for 5.5%. Additionally, the birth ratio of males to females was 2:3, which has been shown to increase the risk of clefts in male newborns. 37% of babies

with CL/P had congenital abnormalities that were connected with them. Except for CLP, which was considerably more common between 2002 and 2011, there were no substantial differences in the occurrence of mouth clefts across the 3 decades of investigation. Over the study's three time periods, there were no discernible variations in the afflicted neonates' mother's age, related abnormalities, or season of delivery. Moreover, no obvious variations in the 3 different types of clefts were seen in terms of maternal age or number of pregnancies. The difference between neonates with a single cleft palate and those with the other two types of clefts was shown to be insignificant by statistical analysis, despite the fact that the former group had much lower mean birth weights. According to the statistics, this research showed an incidence of CL/P that was higher than that of some studies from Persian, European, and American nations and more similar to those in East Asian nations. Therefore, the differences seen across groups may be influenced by genetic features associated with ethnicity.

Rasheed, Ahmed & Yar. (2009) conducted a prospective study to ascertain the prevalence of NTDs among all newborns at Rahim Yar Khan Teaching Hospital, Pakistan, and to understand the probable etiology of neural tube abnormalities in Rahim Yar Khan, Pakistan. All expectant moms registered for the research, however only those who had been identified as cases of NTDs either during pregnancy or after birth were chosen. A total of 52 instances out of 6701 live births had NTDs diagnoses. The data was gathered through the history-taking process, ultrasound results, and biochemical analysis which included blood sugar level and hemoglobin concentration. The estimated incidence ranged from 2 to 8 per 1000 live births. The mother's average age was 28.9 years, with 33% primigravida and 30% grand multigravida predominating. 75.3% of the women in this category had low incomes and did not consume a healthy, balanced diet. 80% of women were housewives and lived in joint families. During a mean gestation of 21.66 weeks, ultrasonography found 96% of instances with neural tube defects. The most frequent neural tube defects were anencephaly, which was present in 67% of cases. Spina bifida was second, with 29% of cases, and encephalocele was third, with 4% of instances. Female newborns outnumbered male babies by 23, 74% of women had hemoglobin levels below 10, and 20 women had macrocytic-hypochromic anemia. It was determined that poor food, low socioeconomic position, and poverty may all contribute to a greater

prevalence of neural tube abnormalities. To avoid neural tube abnormalities, recommendations on how to enhance health facilities and how to use them as well as folic acid and iron supplements for all women of childbearing age were made.

Gole, Meshram & Hattangdi (2014) examined Anencephaly and its associated malformations. The "Lokmanya Tilak Municipal Medical College and General Hospital," a sizable tertiary care maternity facility in western India, served as the study's setting. The instances were caused by spontaneous abortion, stillbirth, and medical abortion. 16 to 34 weeks was the range for gestational age. In the study, pregnant women without a history of diabetes, obesity, or infections were examined. No teratogenic medications were administered. The prescribed 0.5mg of folic acid supplements had been given to all moms. External inspection, photography, and inside inspection were used to get the results. Only the genitourinary and abdominal viscera underwent an internal examination. Approximately 80% of fetuses had related abnormalities. Nine fetuses had spina bifida, and eight had cleft palate. There were significant gastrointestinal and skeletal malformations present in female fetuses with cleft palate. Anencephaly is caused by several etiological entities, as demonstrated by cleft palate, clubbed foot, clubbed hands, gastroschisis, and spina bifida. To determine its relationship to other illnesses, suggestions on molecular research were provided.

According to research (Edwards & Hui, 2018) conventional prenatal care has included ultrasound-based screening for many years. Up to 3% of fetuses were found to have fetal structural abnormalities. Prenatal fetal abnormality detection enables the best perinatal care by giving pregnant parents access to further imaging, genetic analysis, and information about prognosis and treatment alternatives. Nearly half of all serious structural abnormalities, including acrania/anencephaly, holoprosencephaly, cystic hygromata, and abdominal wall malformations may now be found within the first trimester of pregnancy. Other abnormalities, however, won't be visible until later in the pregnancy since some organ systems are still developing. For this purpose, professional associations advise using second-trimester anatomy as the standard inquiry for finding prenatal structural defects. The stated structural anomaly detection rates rely on several variables, including the sonographer's expertise and the organ system being evaluated, in

addition to the equipment settings. The position of ultrasonography as the principal imaging modality throughout pregnancy has been supported by technological advancements over the past 20 years, and its safety for the growing baby is widely known. With growing knowledge and skill, it is now feasible to examine the heart and neurological system in detail, and specialized tests like fetal echocardiography and fetal neurosonogram are now routinely carried out at tertiary hospitals.

Pre-surgical planning before prenatal spina bifida repair and lung volume measurement are two other possible reasons for fetal MRI. The use of fetal MRI in evaluating prenatal brain abnormalities is widely established. The better genomic resolution of chromosomal microarray genetic testing over conventional karyotype is advised when a significant structural problem is discovered during pregnancy (Edwards & Hui., 2018).

(Sunitha et al. 2017) assessed the prevalence, kinds, and distribution of distinct congenital malformations as well as the precise risk variables associated with diverse obstetric histories. A total of 3301 high-risk pregnant women (HRP) were recruited. The diagnosis was made using 3D/4D ultrasonography. An enzyme-linked immunosorbent assay (ELISA) was used to detect the existence of IgG and IgM antibodies against TORCH in serum. It was discovered that 11% of expecting moms were carrying fetuses with congenital malformations. The Central Nervous System (CNS) and renal abnormalities were the two main congenital malformations found. Age of the mother, the father, consanguinity, and primigravida was found to be risk factors for HRP women who were currently pregnant with fetal congenital malformations. While consanguinity was related to congenital malformations in high-risk pregnant women with a poor obstetric history (BOH), maternal age under twenty-five and paternal age under thirty were linked to an almost two-fold greater risk of congenital malformations in primigravida women. Toxoplasmosis had a significant influence on pregnant women with congenital malformations in both their current and past healthy pregnancies. Congenital malformations continue to be a major factor in morbidity and death, particularly in poor nations. As a result, enhanced screening approaches for early HRP identification may aid in the management and treatment of congenital abnormalities.

In order to investigate the relationship between the incidence of congenital anomalies in Iran and different maternal and neonatal characteristics during pregnancy, Daliri et al. (2019) carried out an in-depth research and meta-analysis. Between 2000 and 2016, all Iranian research was retrieved from internal and external databases, including Medlib, Medline, Pubmed, Web of Science, Google Scholar, Scopus, Magiran, SID, Cochrane, Irandoc, and all Iranian publications. There were 30 trials in all, with a total enrollment of 928,311 patients. Congenital malformations risk was strongly correlated with the mother's chronic illness status and with the mother's chronic disease. By modifying or controlling the aforementioned factors, a health and education intervention approach can lower the birth rate of children with congenital abnormalities.

OPERATIONAL DEFINITIONS

Congenital malformations: CMF or birth defect is a structural or functional abnormality that occurs during the development of the embryo or fetus (Forci et al., 2020).

Organogenesis: Six through eight weeks of the human fetus are characterized by the development and organogenesis of cells. During the prenatal stage, which lasts from weeks three to eight, this procedure is called organogenesis (Embryology, Weeks 6-8 - StatPearls - NCBI Bookshelf, n.d.).

Neural tube defects (NTDS): Are severe birth disorders of the CNS caused by the incomplete fusion of neural tubes during embryonic development (Greene & Copp, 2014).

Hydrocephalus: It is the disturbance of CSF circulation with imbalanced CSF flow (Thomale, 2021).

Anencephaly: A serious birth defect in which the baby is born without part of their skull and brain. (Greene & Copp, 2014)

Conotruncal defects: These are a group of congenital heart defects affecting the major arteries and outflow pathways (Brooks, 2019).

Down syndrome: Trisomy of chromosome 21 (Coppedè, 2016).

Gastroschisis (GS): A full-thickness abdominal wall deformity in which the fetal gut herniates into the intrauterine chamber alongside the umbilical cord, causing an intestinal injury of varying degrees (Al Maawali & Skarsgard, 2021).

Spina Bifida: A congenital abnormality caused by inadequate neural tube development (Brea & Munakomi, 2023).

Hydronephrosis (HN): Kidney collecting system enlargement brought on by a blocked urinary discharge (Alshoabi et al., 2021).

Gastroesophageal Reflux Disease (GERD): The retrograde movement of stomach contents into the oesophagus causes GERD. Either erosive esophagitis or non-erosive reflux disease might appear as manifestations (Antunes; Aleem & Curtis, 2022).

Aneuploidy: Aneuploidy, defined as chromosome counts that are not a multiple of the diploid set, has been associated with cell function, including cancer, as well as developmental disorders such as Down syndrome (DS) and mosaic variegated aneuploidy (Orr, Godek & Compton, 2015).

Maternal Serum Alpha-fetoprotein: In the 2nd trimester, the molecular marker for prenatal screening is maternal serum alpha-fetoprotein (MS-AFP). MS-AFP levels are connected with either open neural tube abnormalities or genomic aneuploidy (Hu et al., 2020).

Chorionic villus sampling: A technique used to sample placental cells for fetal DNA testing between 10 and 13 weeks of gestation (Jones & Montero, 2021).

Antenatal care (ANC): It is the care provided by an experienced healthcare professional to women throughout their pregnancy (Miltenburg et al., 2017).

Consanguineous marriage (CM) or cousin marriage: The marriage of two blood relatives who happen to be 2nd cousins or closer is a kind of interfamilial relationship that takes place among two families (Anwar et al., 2020).

CHAPTER 3

METHODOLOGY

3.1 STUDY DESIGN

This case-control research included pregnant women aged 18 to 45 years. The research was carried out over a six-month period. An association was sought between craniofacial congenital malformations and abnormalities in other systems.

3.2 SUBJECTS

Participants fulfilling the inclusion criteria

3.3 SETTING

Jinnah Post Graduate Medical Centre (JPMC), a government-funded medical centre in Karachi, and Tanveer Ultrasound Clinic (TUC), a private ultrasound facility, both participated in the study. Both institutions have the most modern ultrasound equipment and qualified staff.

3.4 INCLUSION CRITERIA

- Pregnant women between the ages of 18-45 years
- Cases: Pregnant women carrying fetuses with congenital malformations
  Controls: Pregnant women carrying fetuses without any congenital malformations

3.5 EXCLUSION CRITERIA

- Pregnant women with gestational age less than 11 weeks
- Women with missed abortion
- Women with intrauterine death of the fetus
- Pregnant women who were not Balochi, Pashtun, Punjabi, Sindhi or Urdu Speaking

3.6 DURATION OF STUDY

- Individual study period: 1 hour per subject
- Total period of study: 6 months

3.7 SAMPLE SIZE ESTIMATION

The sample size for the current study, "Association of Congenital Malformations with Maternal Risk Factors," was calculated by considering the parameters used in article (Nosheen et al., 2019). It was determined using population prevalence and the open-source calculator www.openepi.com, version 3.01-SSPropor.

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1) +p*(1-p)]$

3.8 SAMPLING TECHNIQUE

A purposive sampling technique was used. The study included all pregnant women who came for prenatal ultrasounds at or after 11 weeks of gestation, and it eliminated all participants who met the exclusion criteria. The fetuses were examined using ultrasonography, and fetal biometry measures of the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) were also obtained. Fetal examinations of the head, spine, heart, pulmonary system, anterior wall of the abdomen, stomach bubble and its location, urinary bladder, kidneys, and skeletal system were also done.

3.9 HUMAN SUBJECTS & CONSENT

Pregnant Pakistani women between the ages of 18 and 45 who were at least 11 weeks along in their pregnancies were included in the study. After the principal investigator had thoroughly explained the study's parameters and its rationale to the patients, in either English or Urdu, they each signed or left a thumb impression on a printed form indicating their informed permission. The research subjects had the option of discontinuing participation at any time or choosing not to participate at all.

3.10 MATERIALS USED

On a subject evaluation form, all the study's parameters were filled out. All scans were conducted using the Sonoscape S22 ultrasound system (Figure1.15), a Toshiba Aplio 500 ultrasound system, and a convex transducer with a frequency range of 1 to 7 MHz. A height and weight scale was used to ascertain the height and estimate the weight of the pregnant women. (Figure 3.1). Using a sphygmomanometer, the blood pressure of the pregnant women was measured. (Figure 3.2)

3.11 PARAMETERS OF STUDY

The study's parameters comprised the following:

• Ethnicity • Maternal age at conception • Educational level • Family income • Multiple pregnancies • Parity • BMI • Blood pressure • Co morbidity - Diabetes - Hypertension - Thyroid diseases - Cardiac diseases – Epilepsy – Asthma – Psychiatric diseases – Kidney diseases • Maternal use of folic acid • Maternal use of antenatal supplements (antenatal vitamins, iron supplements) •Use of medications (other than antenatal supplements) • Exposure to rubella • History of (H/O) stillbirth/miscarriage • H/O consanguinity • H/O birth defects/NTDs • H/O of birth defects/NTDs in the family • Fetal biometry

Figure 3.1: Height & weight scale

Figure 3.2: A photograph showing measurement of blood pressure by digital sphygmomanometer in the current study

Fetal biometry parameters included the following:

Biparietal Diameter (BPD):

On the ultrasonography console, the biometry program was chosen. After choosing the BPD option, a caliper displayed on the monitor. The caliper was placed about at the level of the thalami, where the skull is broader, on the proximal parietal bone's periphery. The second caliper was placed symmetrically on the inner side of the distal parietal bone so that the midline falx and the line connecting the two calipers were at an angle of 90^{o}. The BPD measurement was made sure to be the broadest and parallel to the midline falx (Figure 3.3).

Head Circumference (HC):

On the ultrasonography console, the biometry program was chosen. After selecting the HC option, a caliper displayed on the monitor. On the proximal parietal bone's periphery, the caliper was placed. The second caliper was symmetrically placed on the outside of the distal parietal bone such that the line connecting the two calipers met the midline falx at an angle of 90^{o} (Figure 3.3).

Abdominal Circumference (AC):

On the ultrasonography console, the biometry program was chosen. When the AC option was chosen, a caliper showed on the monitor. The caliper was placed about at the level of the rib end on the proximal side of the fetal abdomen, along the outside edge of the skin line. The second caliper was placed symmetrically on the skin line's distal surface such that the line connecting the two calipers was at an angle of 90^{o} to the midline. By moving the trackball on the console in a sideways direction, the ellipse was expanded until it was exactly overlaying the skin shape. It was made certain that the measurement included the outer margin of the skin contour (Figure 3.4)

Femur Length (FL):

To find the femur bone, the fetal abdomen was examined. Once the femur bone was found, the calipers were put at the most proximal and distal parts of the bone on the

ultrasound screen. Using calipers, the distance between these two spots was determined. (Figure 3.4).

Head Anatomy:

Three axial sonographic planes are necessary to analyse the head's anatomy: One at the lateral ventricle level, one at the BPD level, and one at the posterior fossa level (Figure 3.5, 3.6 & 3.7).

Facial Anatomy:

By assessing the orbits, upper lip, and philtrum on sonograms of the face, the basic sonographic anatomy of the face was accomplished (Figure 3.8).

Chest Anatomy:

In order to assess the heart and lungs, an axial image of the chest at the level of the heart was required. (Figure 3.9).

Abdominal anatomy:

On the transverse view, which was used to estimate the AC, the stomach was observed (Figure 3.10).

Skeletal Anatomy:

In the coronal, transverse, and sagittal planes, the spine was seen and assessed. Long bones of the four limbs were clearly seen. Additionally, an effort was made to visualize the feet and hands (Figure 3.11, 3.12 & 3.13).

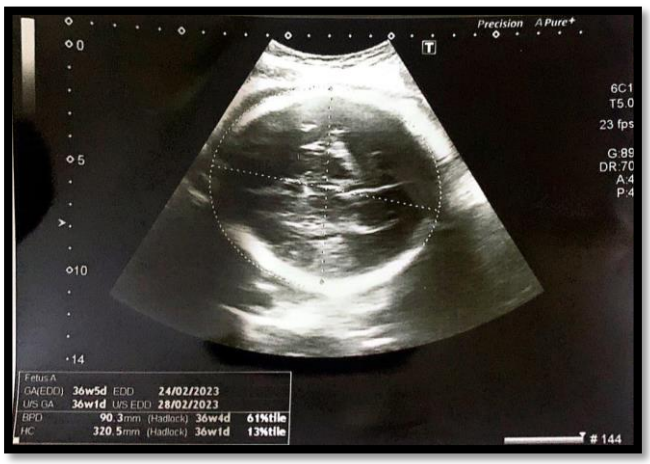


Figure 3.3: A 2 – D ultrasonography of the fetal head at 36 weeks and 5 days of gestation demonstrating biparietal diameter (BPD) and head circumference (HC) in the current study

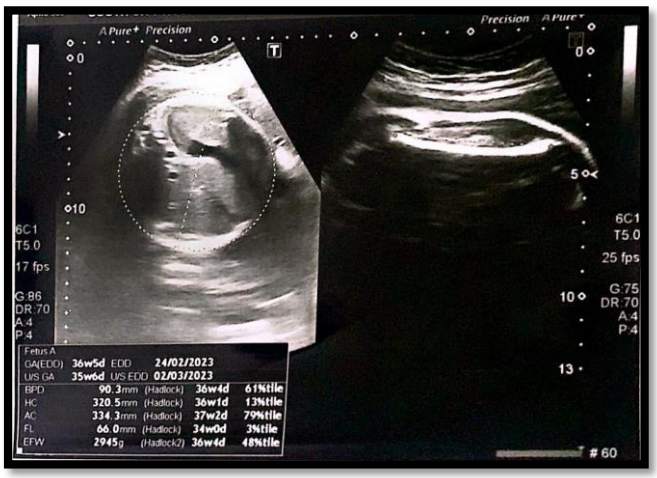


Figure 3.4: A 2 – D ultrasonography of the fetal abdomen at 36 weeks of gestation depicting the measurement of the abdominal circumference and femur length in the current study

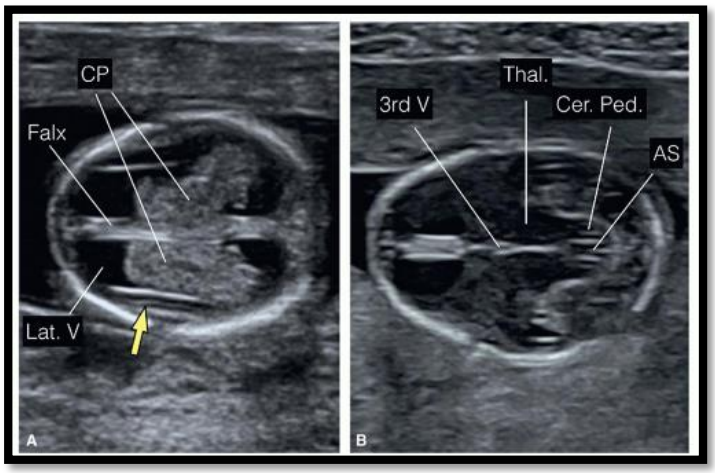


Figure 3.5: A 2 – D ultrasonography of the fetal head at 13 weeks of gestation obtained superiorly at the level of the lateral ventricles **(A)** and inferiorly at the level of the thalami **(B)**. (The Fetal Central Nervous System | Radiology Key, n.d.)

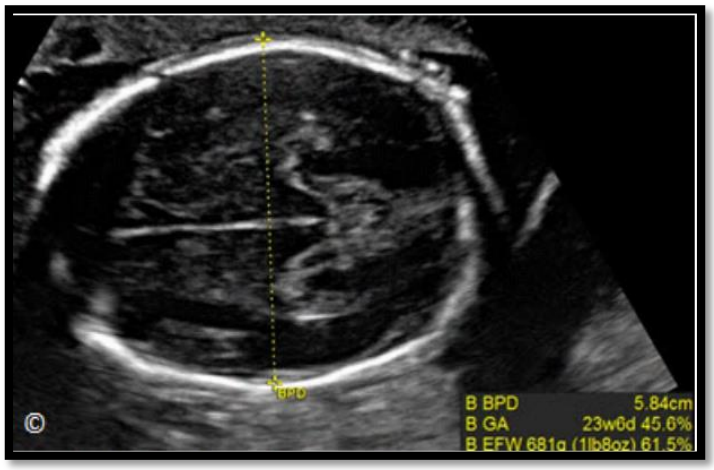


Figure 3.6: A 2 – D ultrasonography of the fetal skull at 23weeks, 6 days of gestation at the biparietal diameter (BPD) level (Ultrasound in Obstetrics and Gynecology: A Practical Approach | Textbook | GLOWM, n.d.)

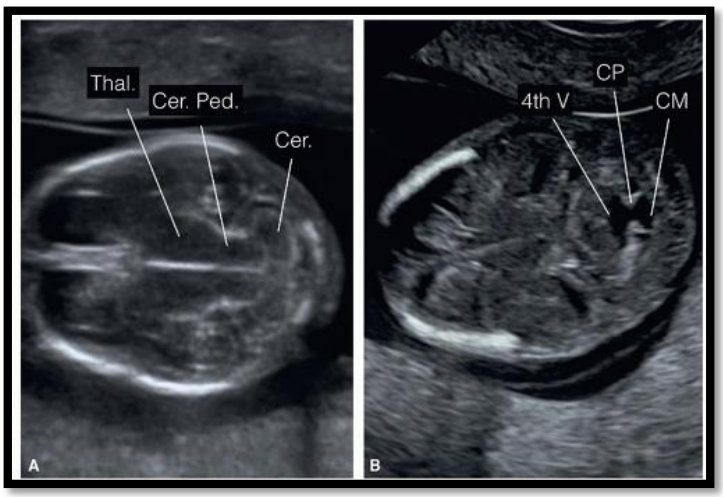


Figure 3.7: A 2 – D ultrasonography of the fetal head at 13 weeks of gestation obtained at the level of the posterior fossa **A:** At the level of the developing cerebellum (Cer.) and cerebral peduncles (Cer. Ped.). **B:** An oblique, slightly more inferior plane demonstrating the open fourth ventricle (4th V) connecting to the future cisterna magna (CM). (The Fetal Central Nervous System | Radiology Key, n.d.)

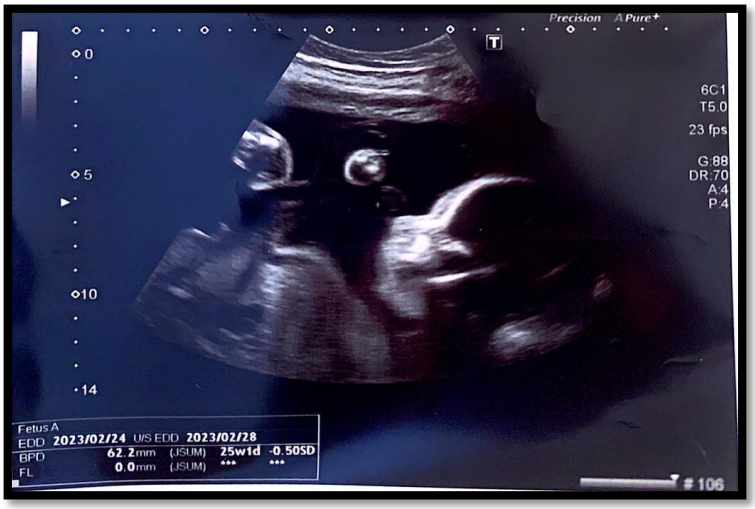


Figure 3.8: A 2 – D ultrasonography of the fetal head at 25 weeks of gestation showing the profile with the forehead in the current study

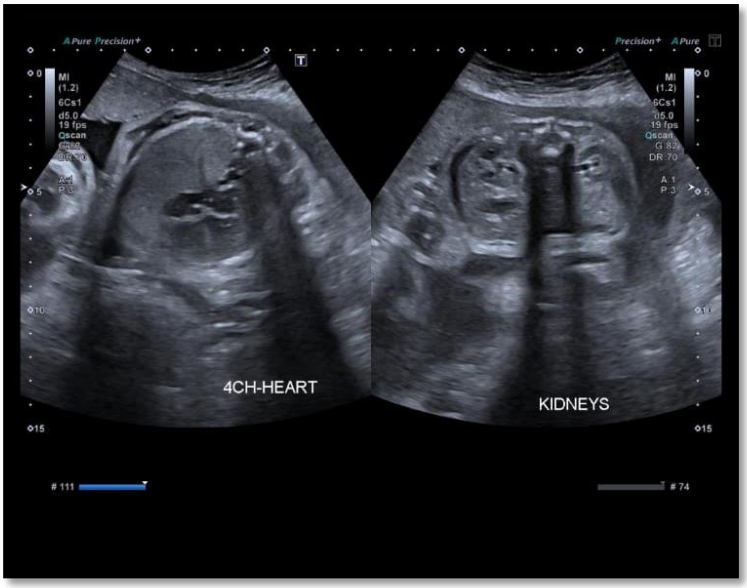


Figure 3.9: A 2 – D ultrasonography showing fetal heart at 30 weeks of gestation in the current study

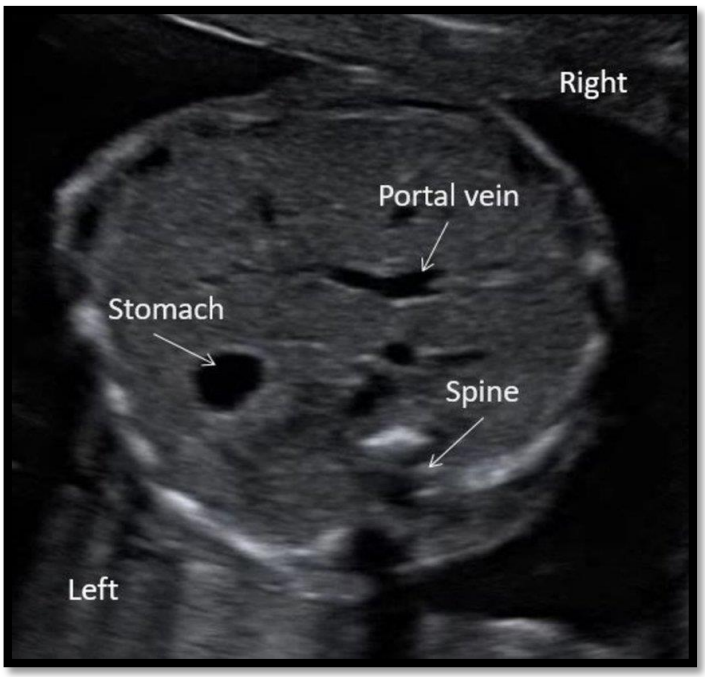


Figure 3.10: A 2 - D ultrasonography of the fetal abdomen at 22-weeks of gestation, with the stomach visible as a cystic mass in the left upper quadrant (Tawk et al., 2018)

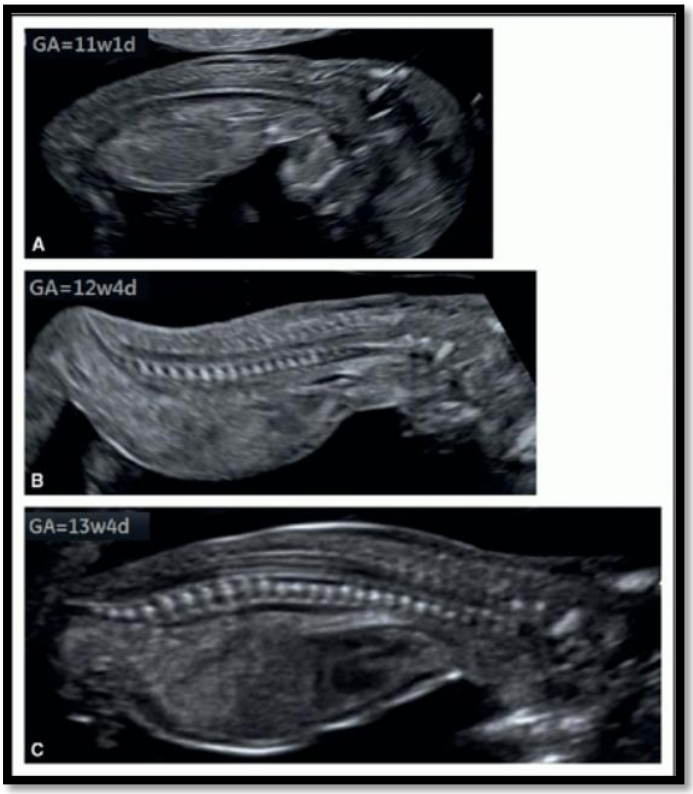


Figure 3.11: 2 - D ultrasonography of the fetal spine in three fetuses at (A) 11, (B) 12, and (C) 13 weeks of gestation. (The Fetal Skeletal System | Radiology Key, n.d.)

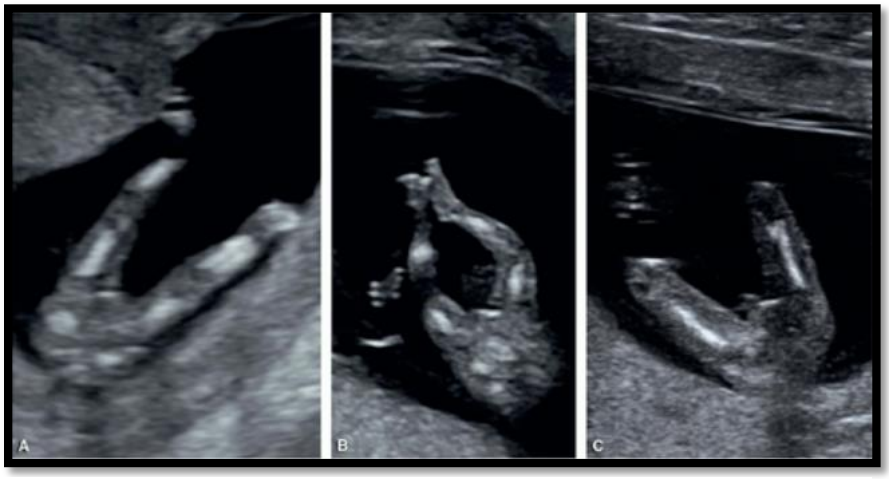


Figure 3.12: A 2 - D ultrasound of the fetal lower extremities at 13 weeks of gestation (The Fetal Skeletal System | Radiology Key, n.d.).

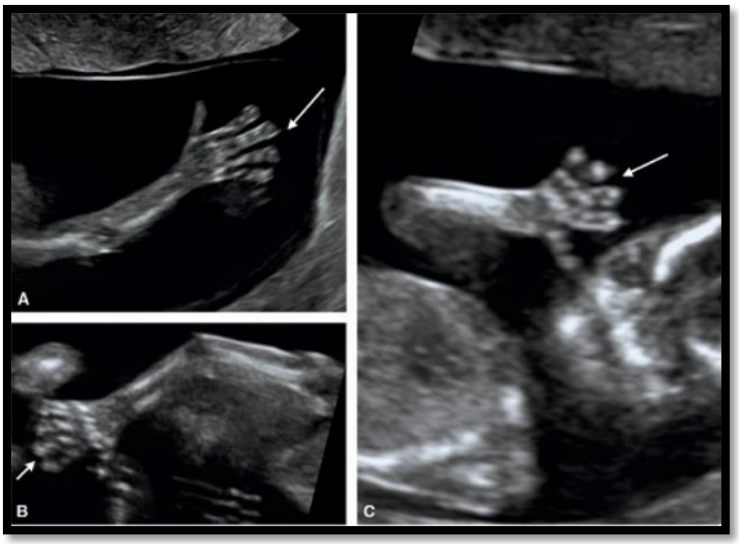


Figure 3.13: A 2 - D ultrasound of the fetal upper extremities at 13 weeks of gestation (The Fetal Skeletal System | Radiology Key, n.d.)

3.12 PROTOCOL OF STUDY

The research was conducted at JPMC and TUC, Karachi from December 2022 to May 2023. The study's population comprised the pregnant women who visited the radiology department, TUC, and JPMC for prenatal obstetrics ultrasonography and had fetuses with structural anomalies (case group) or with structurally normal fetuses (control group).

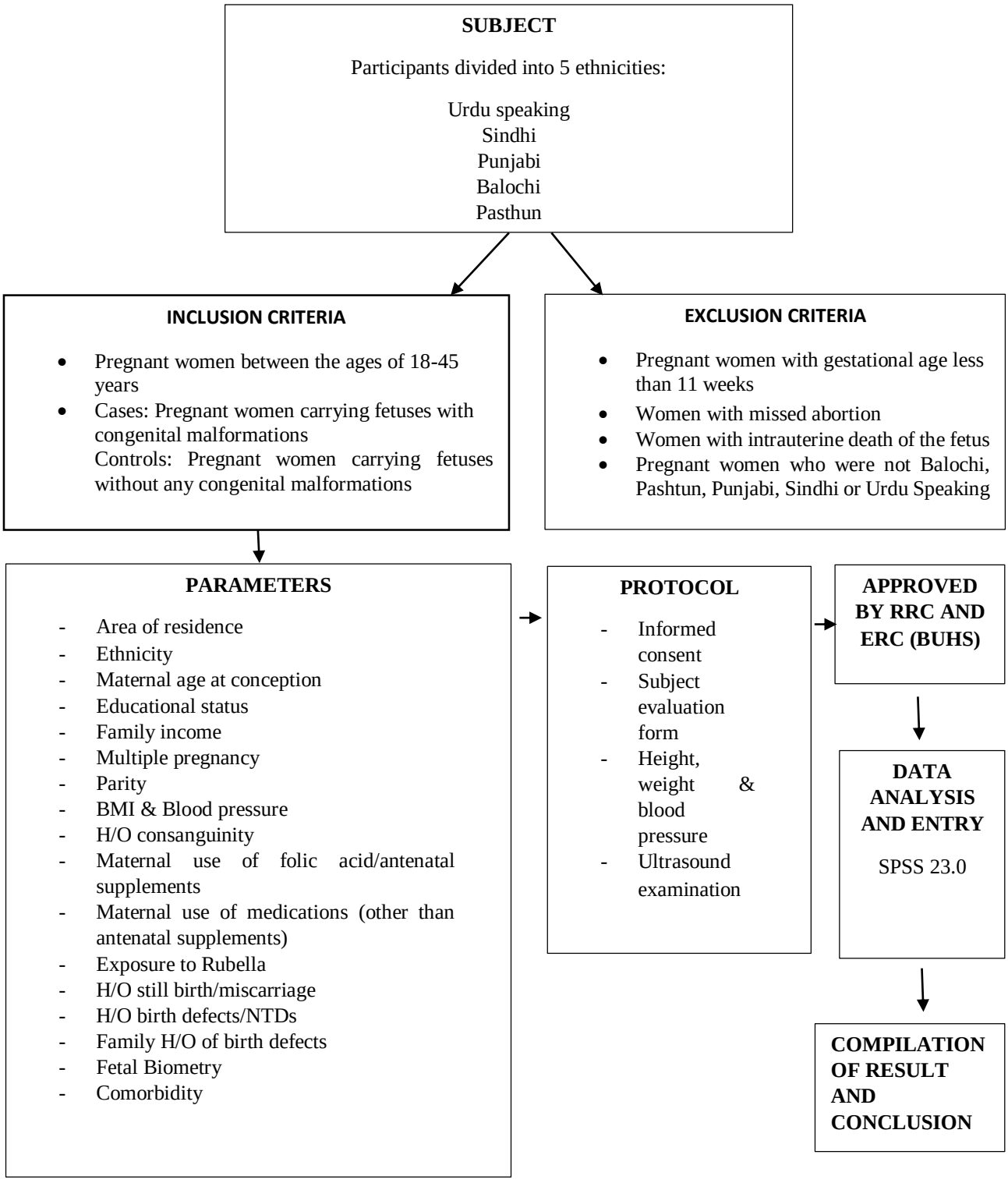
Following informed and understood consent from participants, a thorough history was collected. The subject's height, weight and blood pressure were noted. A comprehensive obstetric ultrasound was conducted by a consultant radiologist utilizing a Sonoscape S22 ultrasound system, a Toshiba Aplio 500 ultrasound system, and a convex transducer with a frequency range of 1 to 7 MHz

Fetal biometry was performed, including measurements of the biparietal diameter, head circumference, and femur length following the application of the coupling gel to the abdomen. Fetal examination of the brain, spine, heart, lungs, anterior wall of the abdomen, stomach bubble and its location, urinary bladder, kidneys, and skeletal system was also performed.

All the findings were documented on the subject evaluation form

Only those pregnant women who met the inclusion criteria became part of the study.

3.13 ALGORITHM OF STUDY



3.14 STATISITCAL ANALYSIS

SPSS version 23.0 was used to analyse all of the data. Descriptive statistics were generated, and the Chi-square and Fisher's exact tests were employed to determine the association of congenital malformations with maternal socio – demographic and risk factors. In order to determine the strength of association between congenital malformations and maternal characteristics, binary logistic regression was performed. The level of statistical significance (P value) was set at < 0.05.

CHAPTER 4

RESULTS

This case-control study was conducted at Bahria University Health Sciences Campus, Karachi, and the samples were collected from the radiology department of Jinnah Postgraduate Medical Centre and Tanveer Ultrasound Clinic.

The sample in the current study included 120 pregnant women. Of them, 50% (60/120) were expecting fetuses with structural abnormalities (case group) and 50% (60/120) were expecting fetuses with normal structural development (control group).

4.1 DISTRIBUTION OF MATERNAL SOCIODEMOGRAPHIC AND RISK FACTORS:

The maternal age ranged from 20 – 39 years. Of the 60 participants in the case group, about 1.7% (1) of the mothers were under the age of 20, whereas, 18.3% (11) were in the age group of 20 and 24, 15% (9) were between the ages of 25 and 29. 26 mothers, or 43.3%, were between the ages of 30 and 34. Lastly, about 21.75% (13) of the mothers were ≥ 35 years old. However, in the control group, 5% (3) were under the age of 20, 13.3% (8) were in the age group of 20 and 24, and 45% (27) were between the ages of 25 and 29. 17 mothers, or 28.3%, were between the ages of 30 and 34. and about 8.3% (5) of the mothers were ≥ 35 years old (Table 4.1). About 38.3%(23) of the cases went to primary school, and 36.7%(22) had received secondary education. 6.7% (4) had completed higher secondary education, and 18.3% (11) were graduates, whereas 10% (6), 76.7% (46), 10% (6), and 3.3% (2) of the controls had completed primary, secondary, higher secondary, and graduation education, respectively (Table 4.1).

The majority of mothers without any congenital malformations came from lower socioeconomic status 91.7% (55), followed by middle class which was 8.3% (5). Pregnant

women who visited the facilities with congenital malformations tended to come from lower socioeconomic positions, accounting for 76.7% (46), followed by individuals from the middle class, who made up 23.3% (14) (Table 4.1). In terms of ethnicity, there were 20% (12) cases of each of the five ethnic groups (Balochi, Pashtun, Punjabi, Sindhi and Urdu-speaking) as well as 20% (12) controls from each of these groups.

In the case group, 4 (6.7%), 37 (61.7%), 18(30%), and 1(1.7%) individuals fit into the underweight (BMI 18.5), normal (BMI 18.5-24.9), overweight (BMI 25-29.9), and obese (BMI >30) BMI categories, respectively. In the control group, the corresponding numbers were 4 (6.7%), 47 (78.3%), 9(15%), and 0(0%). Most women in both the case (58.3%, 35) and control groups (66.7%, 40) had normal systolic blood pressure. The diastolic blood pressure in the case and control groups was seen to be 55% (33) and 66.7% (40), respectively. High systolic blood pressure was observed in 15% (9) of the cases and 16.7% (10) of the control, whereas 15% (9) of the cases and 18.3% (11) of the controls demonstrated high diastolic blood pressure. Diastolic high blood pressure stage 1 was discovered in 23.3% (14) of cases and 11.7% (7) of controls, whereas systolic high blood pressure stage 1 was observed to be 16.7% (10) in cases and 13.3% (8) in controls. Furthermore, 10% (6) of patients and 3.3% (2) of controls had stage 2 systolic high blood pressure, whereas stage 2 diastolic high blood pressure was seen in 6.7% (4) of cases and 3.3% (2) of controls.

In terms of parity, 16.7% (10) of the mothers expecting fetuses with congenital malformation and 31.7% (19) without any fetal abnormalities were found to be primiparous, whereas 20% (12) with fetal malformation and 23.3% (14) without fetal defect were found to have 2 children. Lastly, 63.3% (38) and 45% (27) of the cases and controls respectively had more than 2 children (Table 4.2).

61.7% (37) of mothers of cases and 71.7% (43) of mothers of controls supplemented their diets with folic acid, 90% (54) of mothers of cases and 96.7% (58) of mothers of controls took prenatal drugs to ensure the healthy growth and development of the fetus. In the first, second, and third trimesters, 45% (27), 6.7% (4), and 6.7% (4) of the cases, respectively, took medications; however, 41.7% (25) of the cases did not take any medications. Similar to how 3.3% (2) did so in the first trimester, 50% (30) did so in the second, and 0% (0)

did so in the third, 46.7% (28) of the controls did not utilise any medication. About 1.7% (1) of the cases as compared to 0% (0) of the controls were tested positive for rubella, 43.3% (26) of the cases and 28.3% (17) were tested negative, however, 55% (33) of the cases and 71.7% (43) of the controls did not get themselves tested. 25% (15) of the mothers of controls and 53.3% (32) of the mothers of cases had a history of consanguinity (Table 4.2). Approximately 45% (27) of the women with fetal anomalies and 35% (21) of the mothers without any identified fetal abnormalities had a history of stillbirth or miscarriage (Figure 4.1). A birth history of congenital abnormalities/neural tube defects was found in 30% (18) of the cases and 18.3% (11) of the controls (Figure 4.2). A family history of congenital anomalies was also present in 28.3% (17) of cases and 6.7% (4) of controls (Table 4.3).

Diabetes mellitus was discovered in 40% (24) of controls and 18.3% (11) of cases. In addition, 23.3% (14) of the control group and 31.7% (19) of the cases had hypertension. 20% (12) of the controls and 3.33% (2) of the cases had hypothyroidism whereas 5% (3) of the controls and 1.7% (1) of the cases had hyperthyroidism. Mothers of cases were found to have incidences of 5% (3), 5% (3), 10% (6), 5% (3), and 1.7% (1) of cardiac disease, epilepsy, asthma, psychiatric disease, and kidney disease, respectively. About 1.7% (1), 3.3% (2), 30% (18), 3.3% (2), and 1.7% (1) of individuals in the control group had cardiac, epilepsy, asthma, psychiatric, and kidney diseases. (Table 4.4).

Congenital abnormalities are classified as either single or multiple system malformations. Single system malformations were 36.7% (44) more common than those of multiple system malformations, which were 13.3% (16) (Figure 4.3). The most frequent abnormalities diagnosed were those of the central nervous system (CNS), which comprised 26.7% (32) of all cases, followed by 17.5% (21) of the genitourinary system, 9.2% (11) miscellaneous anomalies, 6.7% (8) craniofacial abnormalities, 5% (6) musculoskeletal abnormalities, 2.5% (3) anomalies of GIT, 1.7% (2) anomalies of abdominal wall and 0.8% (1) cardiovascular defects. (Figure 4.4).

Ventriculomegaly (7.5%, 9) was the most prevalent CNS anomaly followed by anencephaly (3.3%, 4), encephalocele (3.3%, 4), hydrocephalus (3.3%, 4), Arnold Chiari syndrome (2.5%, 3), spina bifida (1.7%, 2), holoprosencephaly (1.7%, 2), dandy walker

malformation (0.8%, 1), cisterna magna (0.8%, 1), meningocele (0.8%, 1) and finally microcephaly (0.8%, 1) (Figure 4.5). The most frequent craniofacial defect was facial deformity (2.5%, 3), followed by a cleft lip (1.7%, 2)., cleft lip & palate (0.8%, 1), cleft palate (0.8%, 1), and micrognathia (0.8%, 1) (Figure 4.6). Only one (0.8%) abnormality was discovered in the cardiovascular system, which was congenital heart defects (Figure 4.7). There was a greater frequency of club foot (2.5%, 3) in the musculoskeletal abnormalities, followed by skeletal dysplasia (0.8%, 1), rhizomelia (0.8%, 1), and club hand (0.8%, 1) (Figure 4.8). The most common genitourinary defect was hydronephrosis (11.7%, 14), followed by multicystic dysplastic kidney (1.7%, 2), polycystic kidney (1.7%, 2), fetal megacystitis (0.8%, 1), bladder exstrophy (0.8%, 1), and dilated renal pelvis (0.8%, 1) (Figure 4.9). There were two anomalies in the GIT and anterior abdominal. Oesophageal atresia (1.7%, 2) and duodenal atresia (0.8%, 1) were the most common GIT abnormalities (Figure 4.10), whereas gastroschisis (0.8%, 1) and omphalocele (0.8%, 1) (Figure 4.11) were the most common anterior abdominal wall anomalies. There were additional cases of hydrops fetalis (1.7%, 2), fetal pleural effusion (1.7%, 2), sacrococcygeal teratoma (1.7%, 2), fetal ascites (1.7%, 2), rocker-bottom feet (1.7%, 2), and cystic hygroma (0.8%, 1). (Figure 4.12)

4.2 ASSOCIATION OF CONGENITAL MALFORMATIONS WITH MATERNAL RISK FACTORS

When case group and control group comparisons were made the data analysis showed a statistically significant difference in the mother's age ($p = 0.003$), education level ($p = 0.000$), family income ($p = 0.024$) (Table 4.1), use of medications ($p = 0.000$) consanguinity ($p = 0.001$) (Table 4.2) family history of congenital malformations ($p = 0.002$) (Table 4.3) diabetes mellitus ($p = 0.009$) (Table 4.4) hypothyroidism ($p = 0.004$) (Table 4.4) and asthma ($p = 0.006$) (Table 4.4). Fisher’s exact test was used for use of medications while the Chi square test was applied for age, education level, family income, history of consanguinity, family history of congenital malformations, diabetes mellitus, hypothyroidism and asthma.

4.3 BINARY LOGISTIC REGRESSION WITH FACTORS ASSOCIATED WITH CONGENITAL MALFORMATIONS

In binary logistic regression, 25 – 29 year-old mothers (OR = 7.800, 95% CI = 0.649 – 93.807), secondary education (OR = 11.500, 95% CI = 2.345 – 56.393), family income (OR = 3.348, 95% CI = 1.122 – 9.994), use of medications in the 2nd trimester (OR= 6.696, 95% CI = 2.069 – 21.671), history of consanguinity (OR = 3.429, 95% CI =1.582 – 7.433) and family history of birth defects (OR = 5.535, 95% CI = 1.736 – 17.646) were associated with an increased risk of congenital malformation, however, diabetes mellitus (OR = 0.337, 95% CI = 0.146 – 0.775), hypothyroidism (OR = 0.138, 95% CI = 0.029 – 0.647) and asthma (OR = 0.259, 95% CI = 0.095 – 0.710) were associated with decreased risk of congenital malformations. (Table 4.5)

4.4 ASSOCIATION OF TYPES OF CONGENITAL MALFORMATIONS WITH ETHNICITY

The Fisher's exact test demonstrated an association between the kind of congenital abnormalities and the ethnicity of the mother (Table 4.6). While there was no association between mothers of Balochi, Pashtun, Punjabi, or Sindhi ethnicity and any other type of congenital malformation, there was a statistically significant association between central nervous system malformations among Urdu-speaking mothers (p = 0.016).

4.5 ASSOCIATION OF TYPES OF CRANIOFACIAL CONGENITAL ANOMALIES WITH ANOMALIES OF OTHER SYSTEMS:

Table 4.7 demonstrated that there was no association between craniofacial anomalies and types of other system anomalies, such as those affecting the cardiovascular, genitourinary, gastrointestinal and abdominal wall system. However, there was a significant association between the central nervous system, musculoskeletal system, and miscellaneous congenital abnormalities.

Table 4.1: Distribution & Association of Congenital Malformations with Maternal Sociodemographic Factors

Maternal Sociodemographic Factors	Population				p-value
	Case		Control		
	N	%	N	%	
AGE					
< 20	1	1.7	3	5	0.003**$^{\epsilon}$
20 -24	11	18.3	8	13.3	
25 -29	9	15	27	45	
30 -34	26	43.3	17	28.3	
35 – 39	13	21.7	5	8.3	
EDUCATION LEVEL					
Primary	23	38.3	6	10	0.000** $^{\epsilon}$
Secondary	22	36.7	46	76.7	
Higher Secondary	4	6.7	6	10	
Graduation	11	18.3	2	3.3	
FAMILY INCOME					
50,000 – 99,999	46	76.7	55	91.70	0.024* $^{\epsilon}$
≥100,000 – 200,000	14	23.3	5	8.3	

p – value ≤ 0.05: statistically significant (*)
p – value ≤ 0.01: highly statistically significant (**)
Test applied = $^{\epsilon}$ Chi-square

Table 4.2: Distribution & Association of Congenital Malformations with Maternal Risk Factors

Maternal Risk Factors	Population				p-value
	Case		Control		
	N	%	N	%	
BMI					
< 18	4	6.7	4	6.7	0.128§
18.5 – 24.9	37	61.7	47	78.3	
25 – 29.9	18	30	9	15	
>30	1	1.7	0	0	
SYSTOLIC BLOOD PRESSURE					
< 120mmHg	35	58.3	40	66.7	0.479§
120 – 129 mm Hg	9	15	10	16.7	
130 – 139 mm Hg	10	16.7	8	13.3	
140 – 180 mm Hg	6	10	2	3.3	
DIASTOLIC BLOOD PRESSURE					
< 80 mm Hg	33	55	40	66.7	0.281§
< 80 mm Hg	9	15	11	18.3	
80 – 89 mm Hg	14	23.3	7	11.7	
90 – 120 mm Hg	4	6.7	2	3.3	
PARITY					
1st child	10	16.7	19	31.7	0.090c
2nd child	12	20	14	23.3	
> 2 children	38	63.3	27	45	
MULTIPLE PREGNANCY					
Yes	1	1.7	2	3.3	1.000 §
No	59	98.3	58	96.7	
USE OF FOLIC ACID					
Yes	37	61.7	43	71.7	0.245 c
No	23	38.3	17	28.3	
USE OF ANTENATAL SUPPLEMENTS					
Yes	54	90	58	96.7	0.272§
No	6	10	2	3.3	

Maternal Risk Factors	**Population**				
	Case		**Control**		**p-value**
	N	**%**	**N**	**%**	**N**
USE OF MEDICATIONS					
1st Trimester	27	45	2	3.3	0.000**§
2nd Trimester	4	6.7	30	50	
3rd Trimester	4	6.7	0`	0	
None	25	41.7	28	46.7	
EXPOSURE TO RUBELLA					
Yes	1	1.7	0	0	0.088§
No	26	43.3	17	28.3	
Did not get tested	33	55	43	71.7	
HISTORY OF CONSANGUINITY					
Yes	32	53.3	15	25	0.001**ᶜ
No	28	46.7	45	75	

p – value ≤ 0.05: statistically significant (*)

p – value ≤ 0.01: highly statistically significant (**)

Test applied = ᶜ Chi-square

§ Fisher's exact test

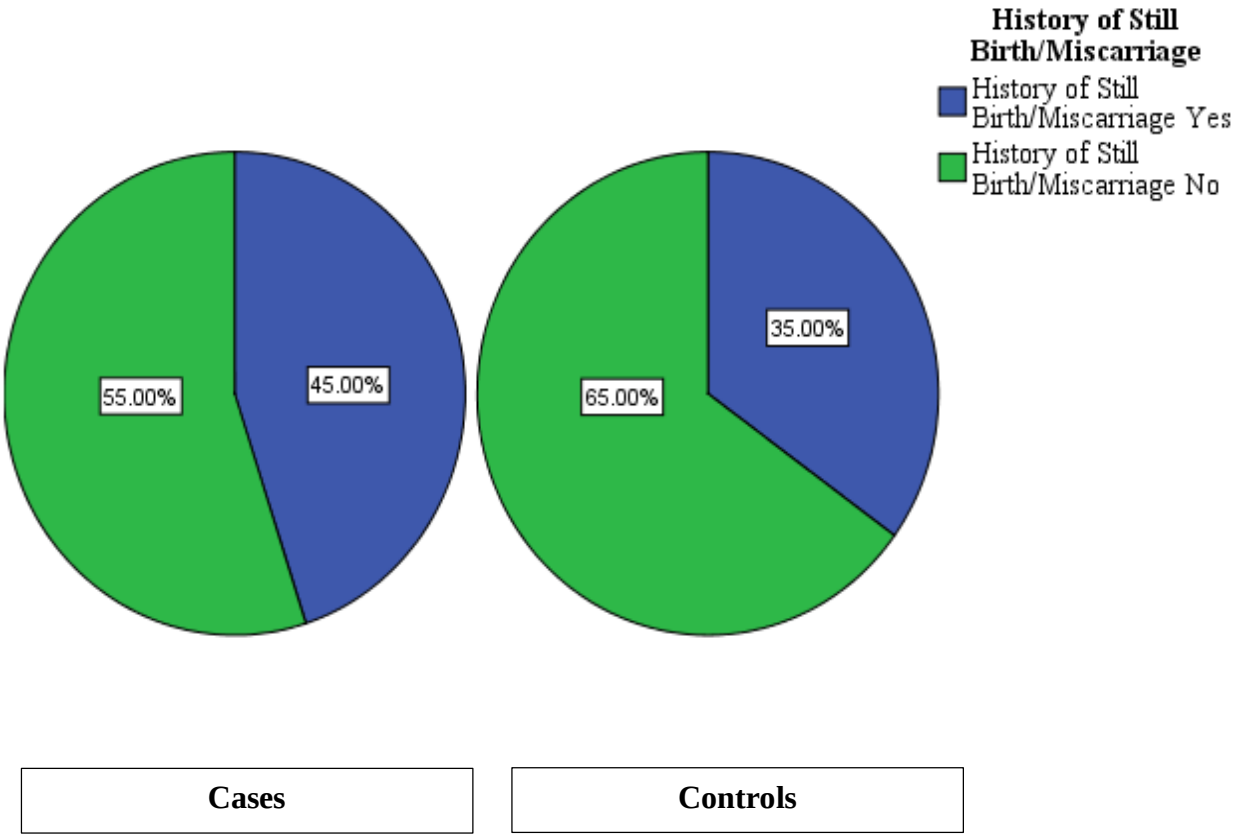


Figure 4.1: Distribution of Congenital Malformations with History of Still Birth/Miscarriage

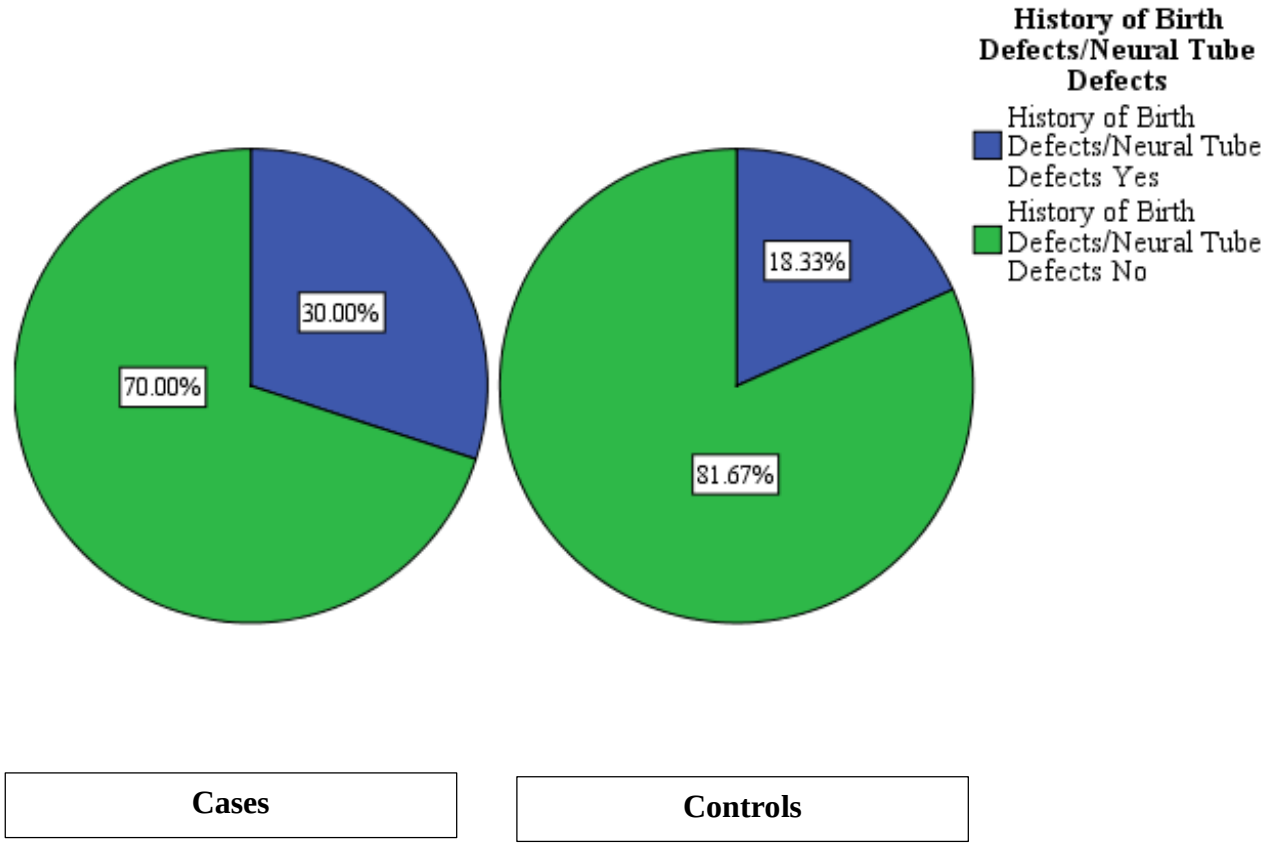


Figure 4.2: Distribution of Congenital Malformations with History of Birth Defects/Neural Tube Defects (NTDs)

Table 4.3: Distribution and Association of Congenital Malformations with Family History of Birth Defects

Maternal Risk Factors	**Population**				**p-value**
	Case		**Control**		
	N	**%**	**N**	**%**	
FAMILY HISTORY OF BIRTH DEFECTS					
Yes	17	28.3	4	6.7	0.002**$^{\epsilon}$
No	43	71.7	56	93.3	

p – value ≤ 0.05: statistically significant (*)
p – value ≤ 0.01: highly statistically significant (**)
Test applied = $^{\epsilon}$ Chi-square

Table 4.4: Distribution and Association of Congenital Malformations with Maternal Co-Morbidity

Maternal Comorbidity		**Population**				**p-value**
		Case		**Control**		
		N	**%**	**N**	**%**	
DIABETES MELLITUS						
Yes		11	18.3	24	40	0.009**$^{\epsilon}$
No		49	81.7	36	60	
HYPERTENSION						
Yes		19	31.7	14	23.3	0.307 $^{\epsilon}$
No		41	68.3	46	76.7	
THYROID DISEASE						
Yes	Hypothyroidism	2	3.33	12	20	0.004** $^{\epsilon}$
	Hyperthyroidism	1	1.7	3	5	0.309 §
No		57	95	45	75	-
CARDIAC DISEASE						
Yes		3	5	1	1.7	0.619§
No		57	95	59	98.3	
EPILEPSY						
Yes		3	5	2	3.3	1.000§
No		57	95	58	96.7	
ASTHMA						
Yes		6	10	18	30	0.006** $^{\epsilon}$
No		54	90	42	70	
PSYCHIATRIC DISEASE						
Yes		3	5	2	3.3	1.000§
No		57	95	58	96.7	
KIDNEY DISEASE						
Yes		1	1.7	1	1.7	1.000§
No		59	98.3	59	98.3	

p – value ≤ 0.05: statistically significant (*)

p – value ≤ 0.01: highly statistically significant (**)

Test applied = $^{\epsilon}$ Chi-square

§ Fisher's exact test

Table 4.5: Binary Logistic regression with factors associated with congenital malformations

Maternal Risk Factors	OR [95% CI]	p-value
AGE		
< 20	7.800 [0.649 – 93.807]	0.106
20 -24	1.891[0.478 – 7.486]	0.364
25 -29	7.800 [2.173 – 27.993]	0.002**
30 -34	1.700 [0.513 – 5.638]	0.386
35 – 39[R]	1	1
EDUCATION LEVEL		
Primary	1.435 [0.248 – 8.291]	0.687
Secondary	11.500 [2.345 – 56.393]	0.003**
Higher Secondary	0.643[0.172 – 2.405]	0.512
Graduation[R]	1	1
FAMILY INCOME		
50,000 – 99,999	3.348 [1.122 – 9.994]	0.030*
≥100,000 – 200,000 [R]	1	1
USE OF MEDICATIONS		
1st Trimester	0.066 [0.014 – 0.307]	0.061
2nd Trimester	6.696 [2.069 – 21.671]	0.002**
3rd Trimester	0.000 [0.000]	0.999
None[R]	1	1
HISTORY OF CONSANGUINITY		
Yes	3.429 [1.582 – 7.433]	0.002**
No[R]	1	1
FAMILY HISTORY OF BIRTH DEFECTS		
Yes	5.535 [1.736 – 17.646]	0.004**
No[R]	1	1
DIABETES MELLITUS		
Yes	0.337 [0.146 – 0.775]	0.010*
No[R]	1	1
HYPOTHYROIDISM		
Yes	0.138 [0.029 – 0.647]	0.012*
No[R]	1	1
ASTHMA		
Yes	0.259 [0.095 – 0.710]	0.009*
No[R]	1	1

p – value ≤ 0.05: statistically significant (*)
p – value ≤ 0.01: highly statistically significant (**)
Test applied = Binary logistic regression; OR: Odds ratio, CI: Confidence interval
R: Reference category
1: Reference

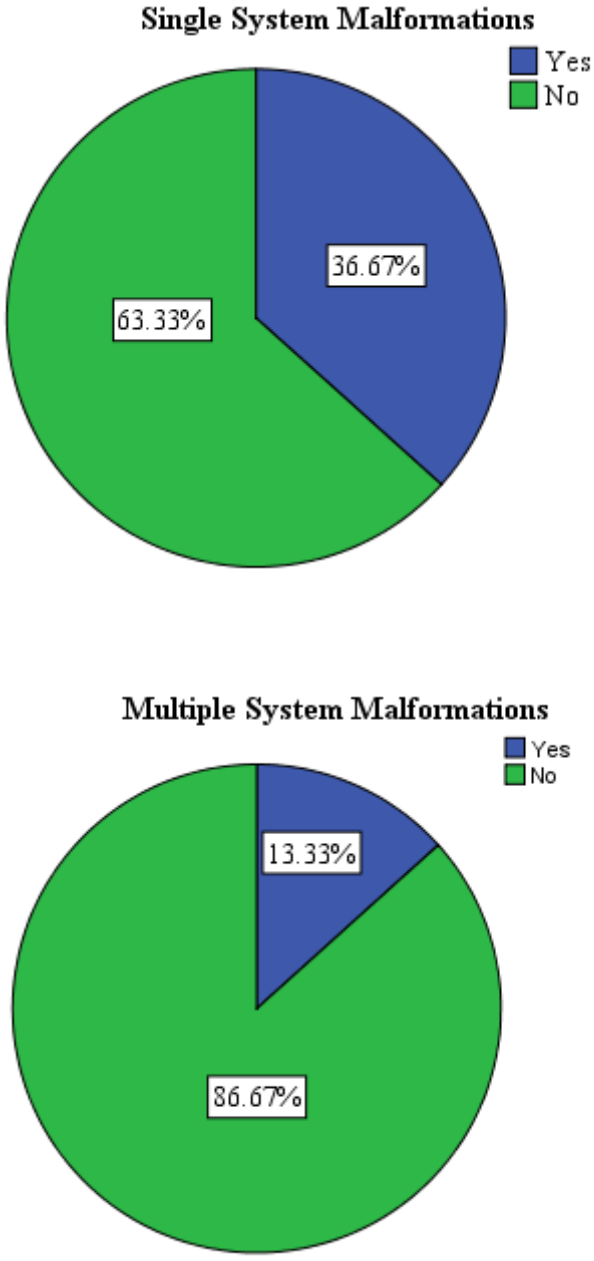


Figure 4.3: Distribution of Single-System and Multiple-System Congenital Malformation

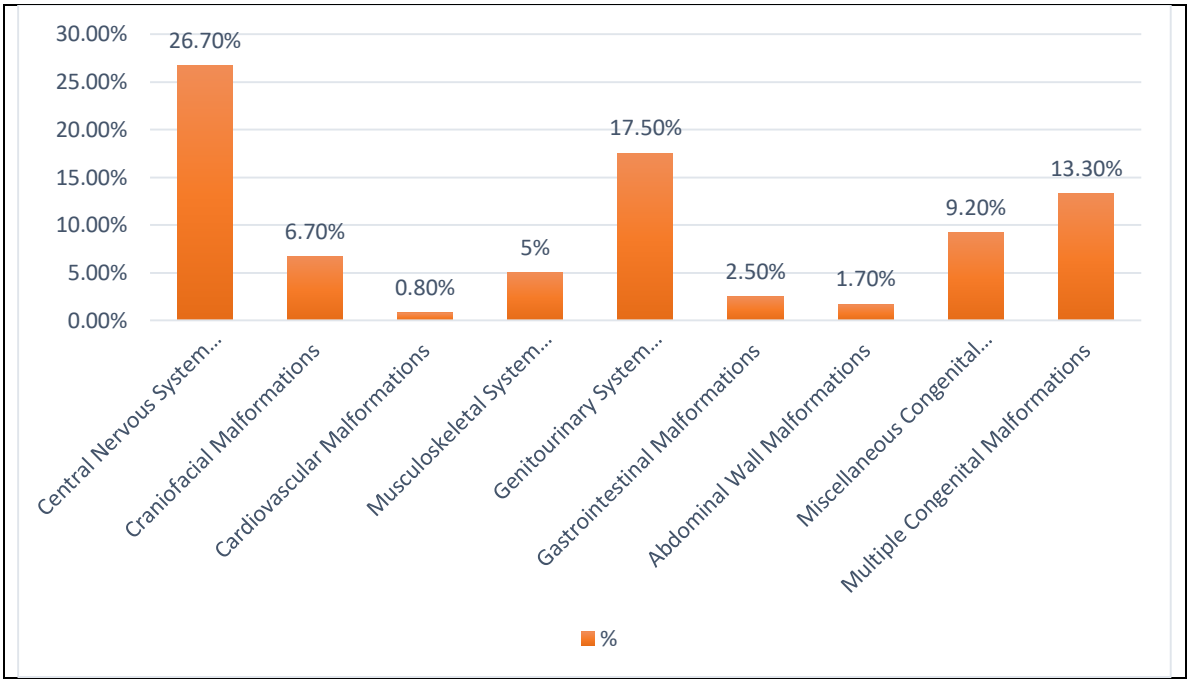


Figure 4.4: Distribution of Congenital Malformations

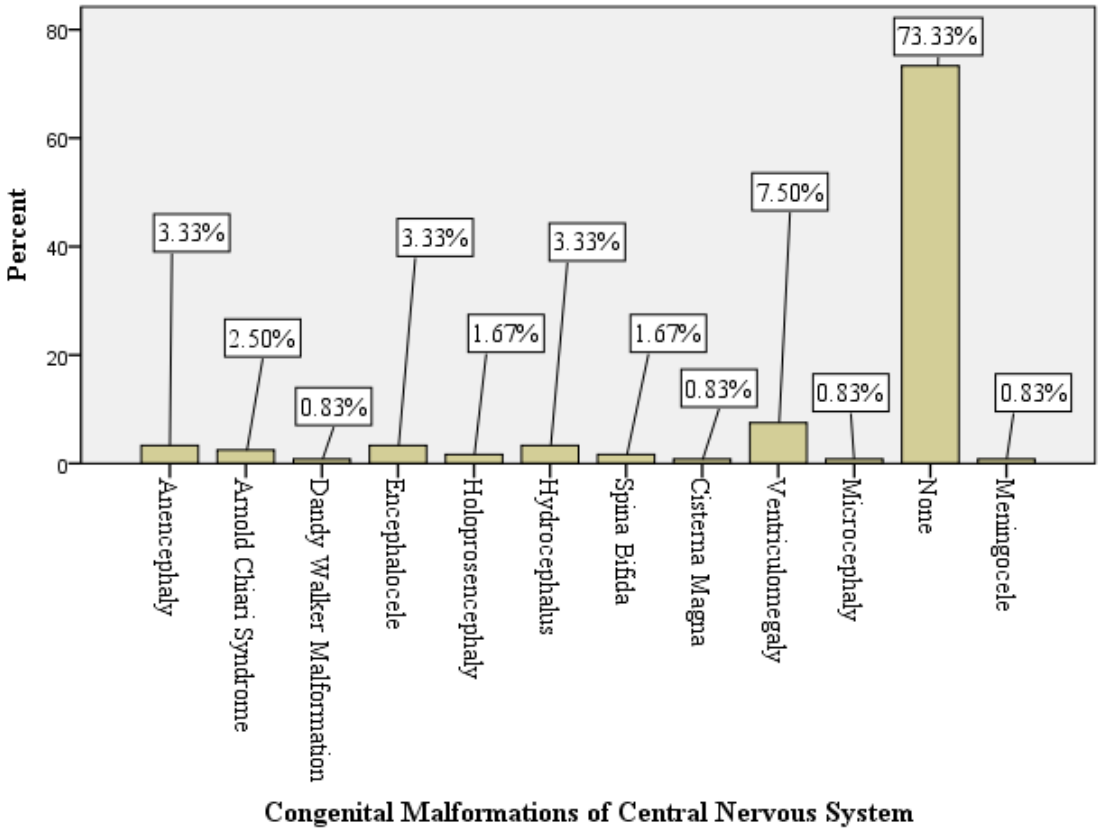


Figure 4.5: Distribution of Congenital Malformations of the Central Nervous System

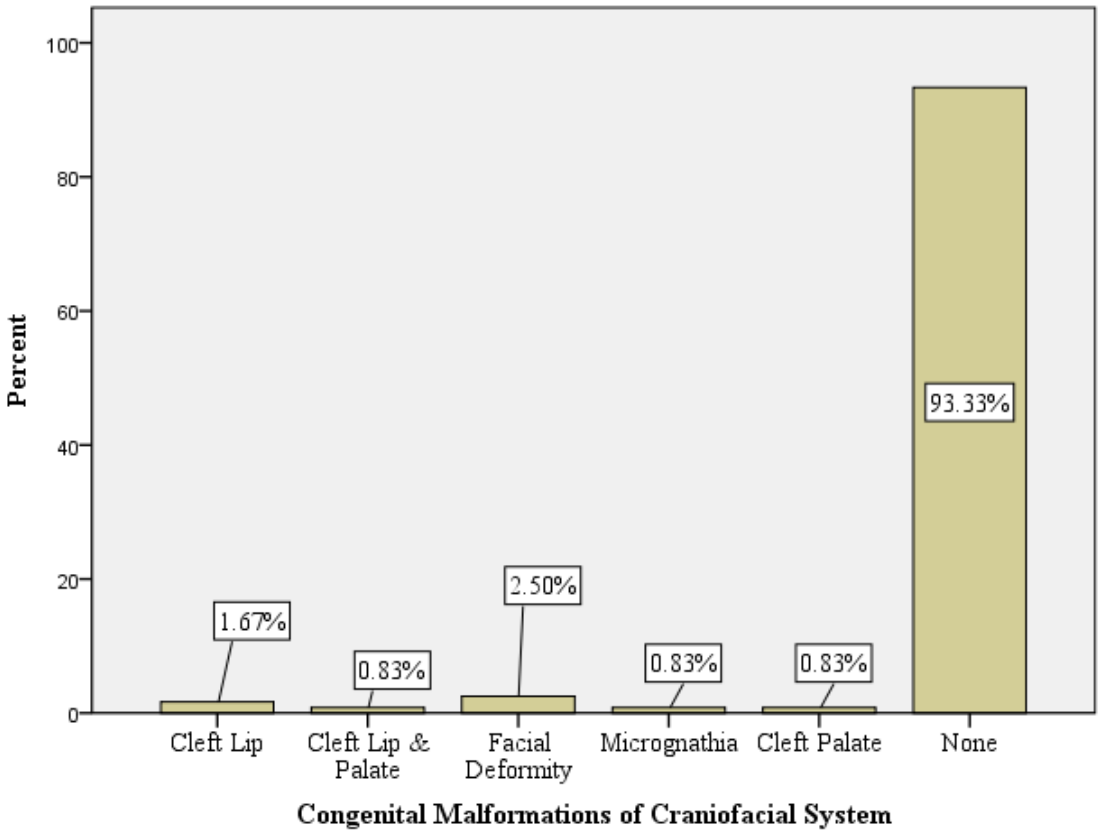


Figure 4.6: Distribution of Congenital Malformations of Craniofacial System

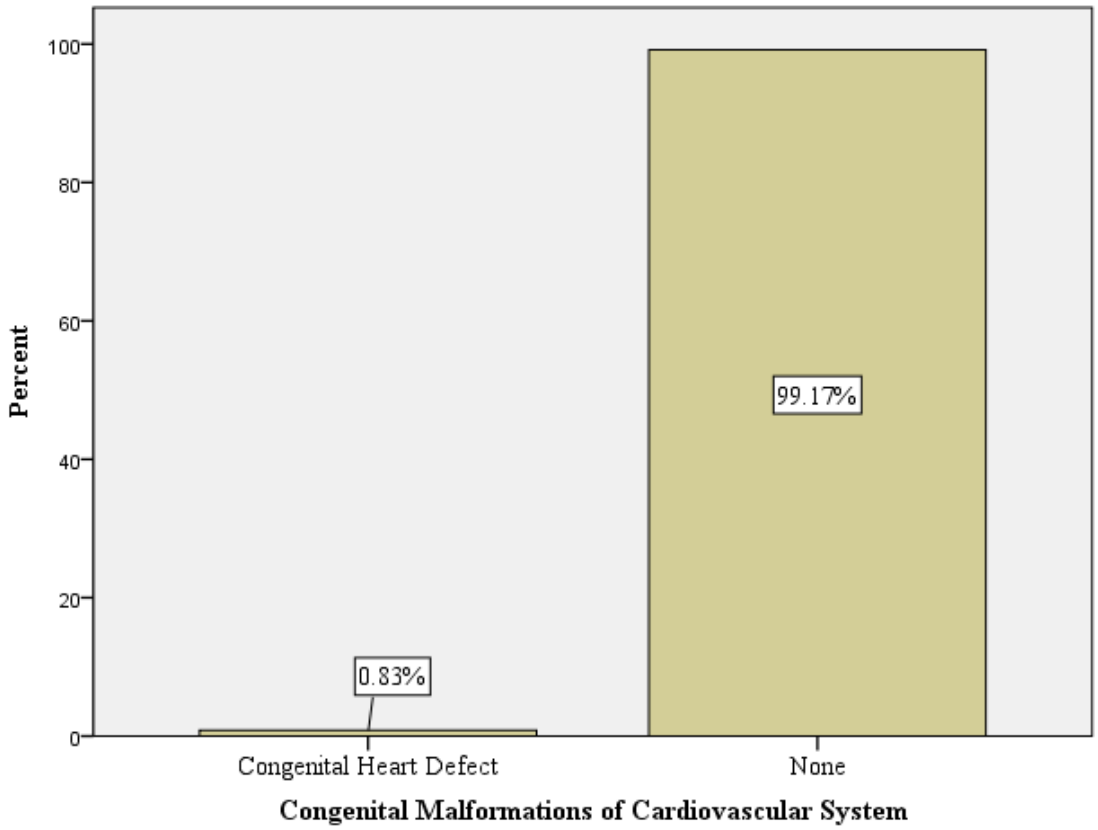


Figure 4.7: Distribution of Congenital Malformations of Cardiovascular System

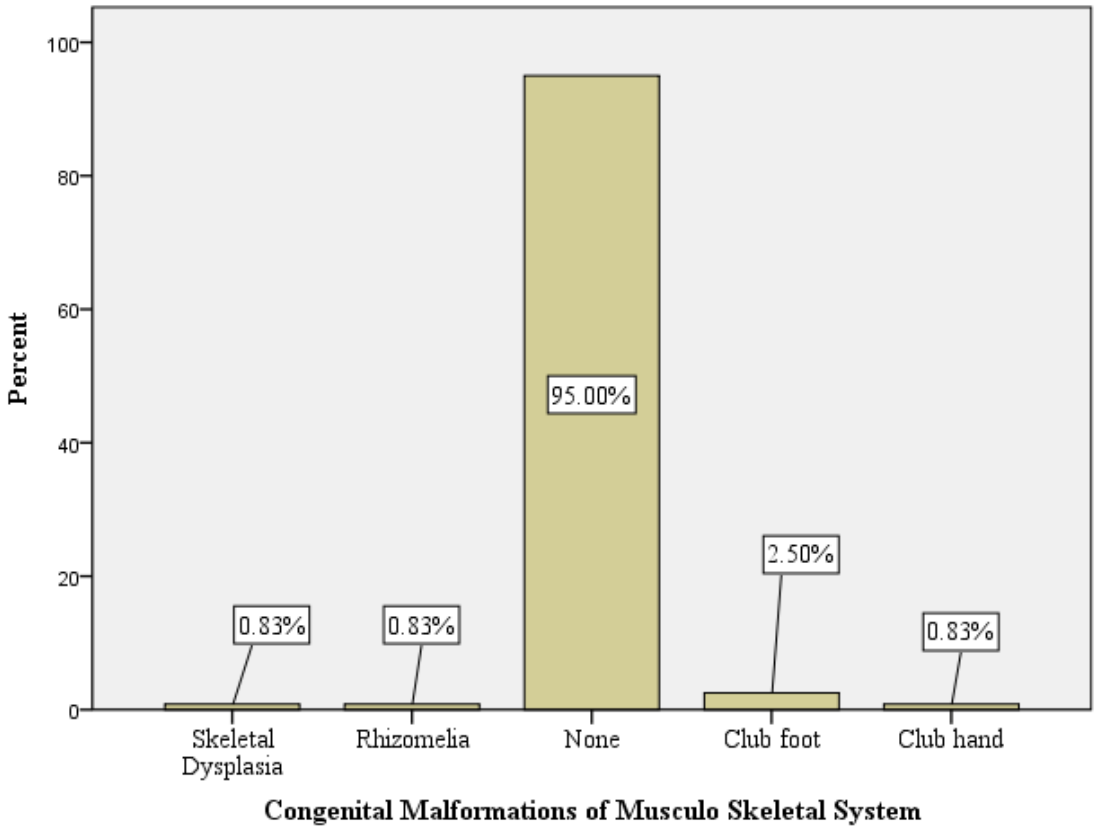


Figure 4.8: Distribution of Congenital Malformations of Musculoskeletal System

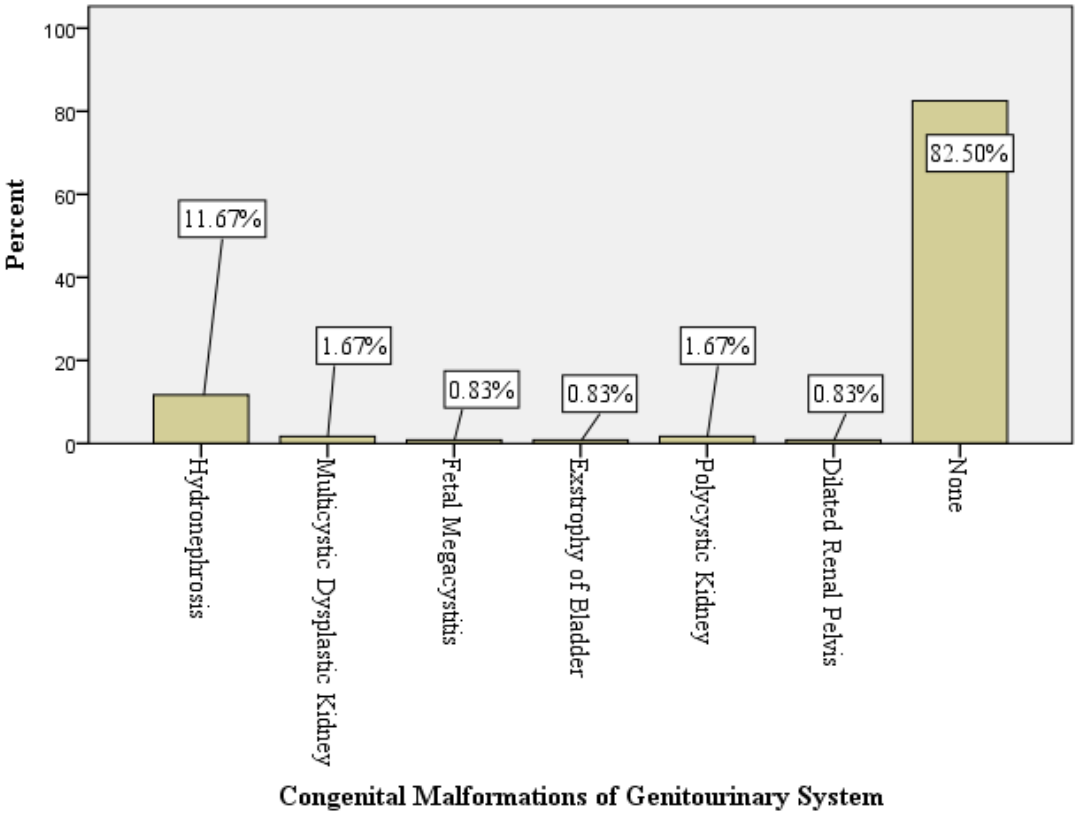


Figure 4.9: Distribution of Congenital Malformations of Genitourinary System

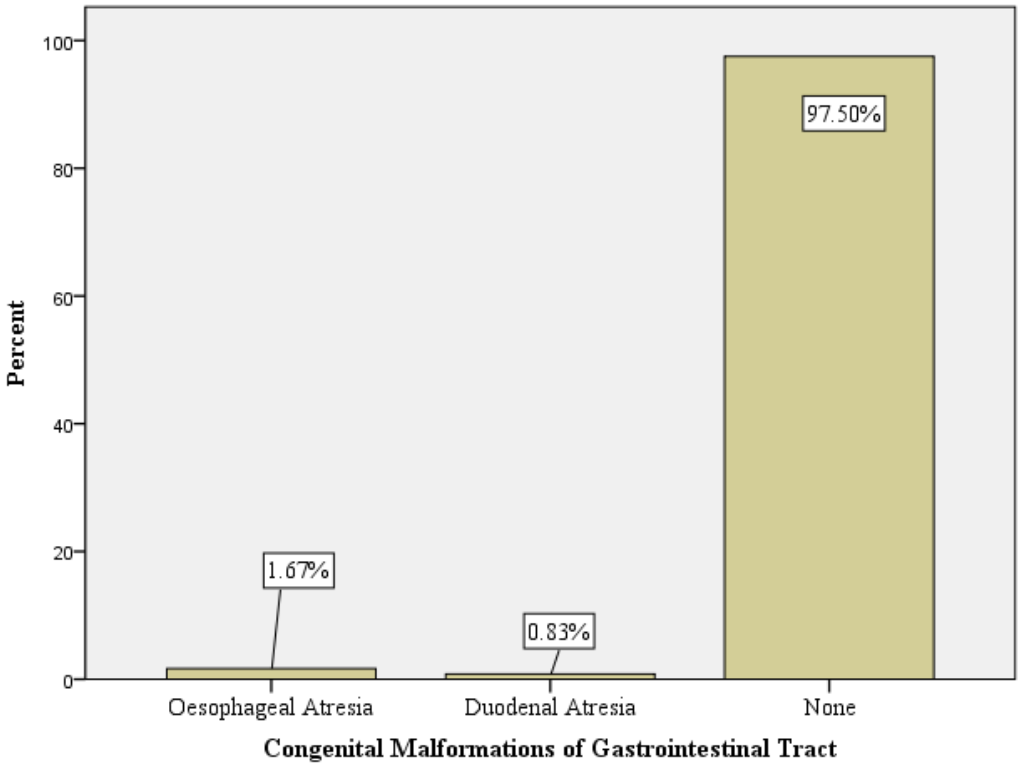


Figure 4.10: Distribution of Congenital Malformations of Gastrointestinal System

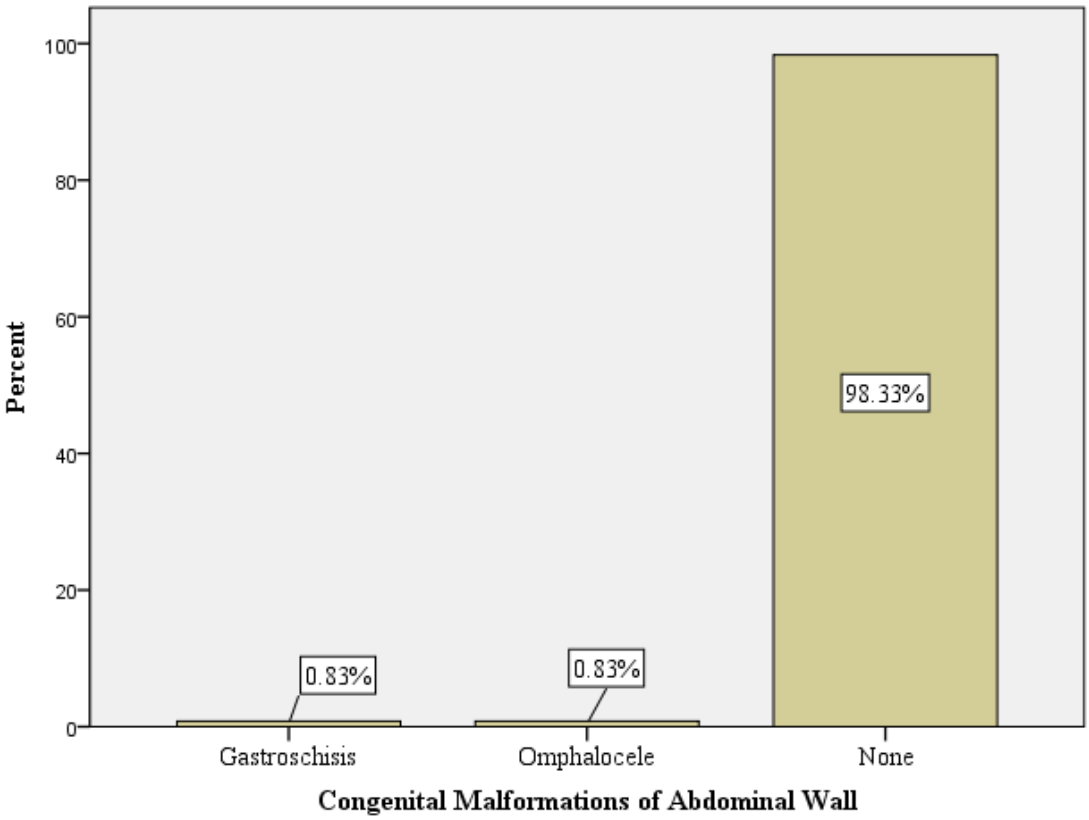


Figure 4.11: Distribution of Congenital Malformations of Abdominal Wall

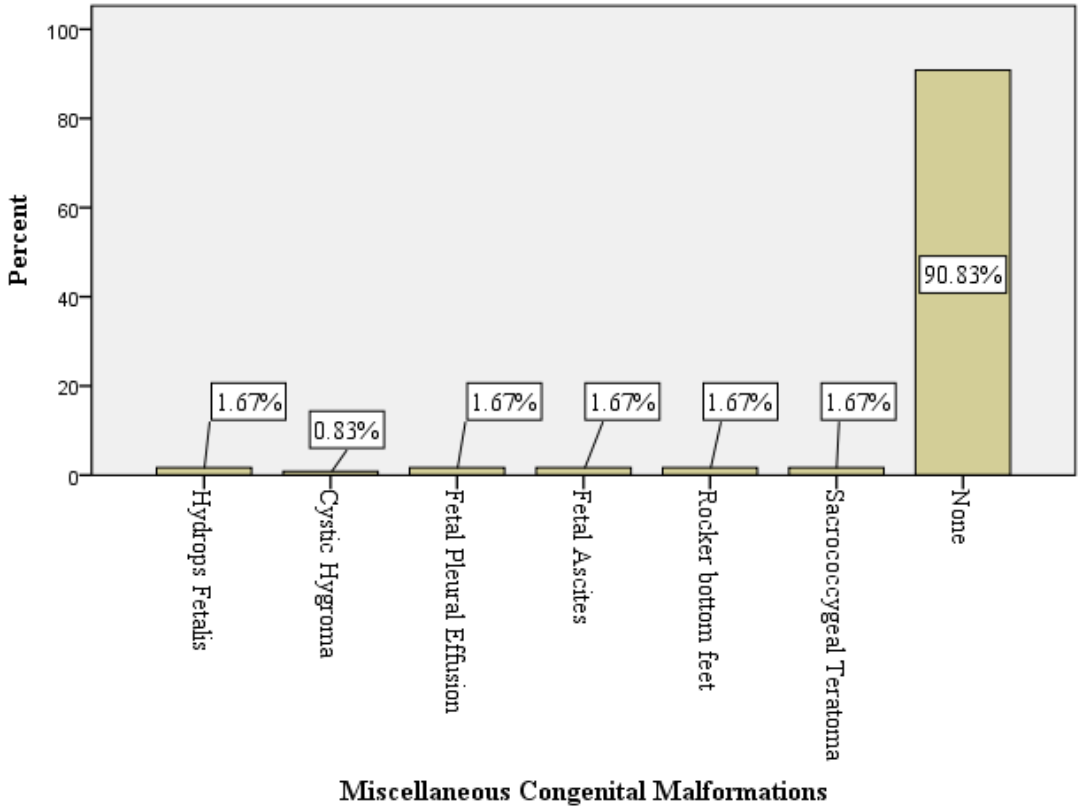


Figure 4.12: Distribution of Miscellaneous Congenital Malformations

Table 4.6: Association of Types of Congenital Malformations with Ethnicity

Congenital Malformations	Balochi	Pashtun	Punjabi	Sindhi	Urdu Speaking
	p-value				
CNS malformations	0.169	0.862	0.408	0.690	0.016*
Craniofacial malformations	0.255	1.000	0.458	0.121	0.062
CVS malformations	1.000	1.000	0.192	1.000	1.000
Musculoskeletal malformations	0.746	0.232	0.729	1.000	0.345
Genitourinary malformations	0.634	0.393	0.072	1.000	0.801
GIT Malformations	0.231	0.088	1.000	1.000	1.000
Abdominal wall malformations	0.361	0.388	1.000	1.000	1.000
Miscellaneous malformations	0.298	0.323	0.914	0.712	0.924

p – value ≤ 0.05: statistically significant (*)

p – value ≤ 0.01: highly statistically significant (**)

Test applied = [§] Fisher's exact test

Table 4.7: Association of Type of Cranio Facial Congenital Malformations with Anomalies of Other Systems

Congenital Anomalies of Other Systems	**Craniofacial congenital Malformations (N=8)**	**p – value**
Central nervous system congenital anomalies	7	0.000**§
Cardiovascular congenital anomalies	0	1.000
Musculoskeletal system congenital anomalies	3	0.004**§
Genitourinary system congenital anomalies	2	0.548§
Gastrointestinal congenital anomalies	1	0.093§
Abdominal wall congenital anomalies	1	0.082§
Miscellaneous congenital anomalies	2	0.030*§

p – value ≤ 0.05: statistically significant (*)
p – value ≤ 0.01: highly statistically significant (**)
Test applied = § Fisher's exact test

CHAPTER 5

DISCUSSION

5.1 SEQUENCE OF DISCUSSION EXPERIMENT/HYPOTHESIS WISE

According to the World health organization, congenital malformations are conditions that are present at birth and are either structural or functional, including metabolic abnormalities. Malformations, dysplasia, and deformations are the three categories into which structural disorders of prenatal origin are divided.(Baruah Kusre & Bora, 2015). Pattern and congenital malformations related characteristics help plan and analyze prenatal screening, especially in high-risk populations, and for establishing baseline rates, documenting changes over time, and identifying information for etiology.

The central nervous system had the most abnormalities found in the current investigation. Additionally, it was shown that China (Zhang et al., 2012), Iran (Golalipour Mirfazeli & Mobasheri, 2013), and Tanzania (Mashuda et al., 2014) were the countries with the highest prevalence of central nervous system malformations. One of the most common congenital illnesses, the etiology of CNS abnormalities is multifactorial and includes complex relations between environmental and genetic variables. (Singh et al., 2017, Sunitha et al., 2017). The high prevalence of central nervous system abnormalities might be explained by a shortage of folic acid-fortified foods, extremely low conventional folic acid consumption, insufficient dietary intake of folic acid-rich foods, such as vegetables and inadequate awareness regarding preconception care. Better prenatal care may have allowed for the early detection of these abnormalities. Studies have demonstrated that daily maternal folic acid intake, either by itself or as part of multivitamin supplements, from conception through the 1st trimester of pregnancy, can assist to prevent the development of neural tube abnormalities and their recurrence (Ameen et al., 2018). The most common CNS defects identified in the current study were

ventriculomegaly followed by anencephaly, encephalocele, and hydrocephalus, which is comparable to earlier studies that also identified hydrocephalus and anencephaly as the most common anomalies (Marwah et al., 2014). However, Aziza, Kandasamy & Shazia (2011) found facial cleft to be more common. This may be related to food habits and geographical variation. (Alakananda, Choudhury & Neiting, 2015). Another study conducted in Uganda by Ndibazza et al. (2011) demonstrated anomalies of the musculoskeletal system to be highly prevalent. This could be due to certain teratogens that may have an impact on the developing fetus, resulting in irreversible postnatal harm, changes in morphology, or changes in function. These agents can include chromosomal problems, radiation, medications like thalidomide, infections like rubella, and dietary inadequacies (Agrawal et al., 2014). A greater incidence of gastrointestinal abnormalities was discovered in Nigeria by Ekwere et al.'s (2011) research. This might be caused by biological, genetic, hormonal, and environmental variables, to name one potential explanation (Wu et al., 2022). Additionally, it has been demonstrated that the occurrence of congenital deformity varies through time and from one place (region) to another (Chimah et al., 2022).

Our study identified multiple malformations in 13.3% of cases, which is comparable to the Nigerian study by Singh & Gupta (2009) but differs from the Egyptian study, which discovered a 28% frequency of multiple malformations.(El Koumi et al., 2013).

In our study, socio-demographic factors such as mother age, educational level, and family income were found to have a significant association with the occurrence of congenital abnormalities.

The age of the mother is an important factor linked to a higher risk of congenital malformations. Ageing women are thought to be the sole non-genetic risk factor for trisomy in humans, contributing to an increase in chromosomal meiotic errors (Khan et al., 2015). The present study found that anomalies were more common among young women, which may be related to poor nutrition, insufficient prenatal care, and limited access to medical services. Our results supported Rehan, Farooqui, and Farooqui's (2019), Goetzinger et al. (2016) and Hollier et al. (2002) findings that congenital abnormalities were more prevalent in younger women. In Turkey, research has shown that 5.2% of

women (35 years of age or older) had 8.7% more anomalies, albeit this was not statistically significant. Malik, Khanna, and Verma (2019) and Taksande et al. (2010), on the other hand, revealed that mothers above the age of 30 are associated with a greater overall risk of significant birth abnormalities.

Pevandi et al. (2020) population-based study in California demonstrated that it is difficult to distinguish between the two main factors that determine health—socioeconomic status and environmental contaminants—and the detrimental effects of social disadvantage on health. According to their findings, those with the lowest levels of social status are most likely to be exposed to dangerous substances. Environmental injustice stems from disparities in racial and social vulnerability to pollutants. The highest percentage of pregnant women with abnormalities belonged to the lowest socioeconomic class in the present study. Comparable research done by Vrijheid et al. (2000) found that the risk of structural abnormalities was higher in populations with higher socioeconomic challenges (Alakananda, Choudhury & Neiting, 2015). Similar results were obtained by studies conducted by Enders et al. (2019). However, Abebe as al. (2021) discovered no link between maternal age, mother's education level, and monthly income.

Maternal education levels are a known risk factor for pregnancy complications and less adherence to advice, and they are often associated with poorer socioeconomic situations (Anele et al., 2022). Our research found an association between CA and a lower level of education, indicating that the mother's own decisions like following advice more closely may have a greater impact than the socioeconomic context in which she lives.

In many countries nowadays, obesity (body mass index (BMI) < 30 kg/m^2) during pregnancy is considered the most significant avoidable risk factor for unfavourable pregnancy outcomes. Risks of serious fetal problems, such as abnormalities, are linked to maternal obesity. About one-third of all severe congenital abnormalities are congenital heart problems, making them the most prevalent kind of abnormality. Congenital cardiac abnormalities range in severity, but they are frequently associated with higher chances of death and long-term morbidity. Although the exact cause of congenital cardiac abnormalities is not fully understood, it is most likely the consequence of intricate interactions between environmental and genetic variables (Van der Bom et al., 2011). Maternal obesity is the most common environmental factor linked to higher risks of

congenital cardiac abnormalities. Umesa et al (2019) conducted a research in Sweden which showed prevalence rates and ratios of distinct and complex cardiac problems over the whole range of BMI categories, including severe obesity. The study found that whereas PRRs of aortic arch anomalies increased with the degree of maternal obesity, PRRs of ASD and PDA rose with maternal overweight and obesity severity (Persson et al., 2019). Research conducted by Mezzasalma et al. (2022) and Cynthia & Leslie (2010), which revealed maternal obesity as a risk factor for the development of congenital malformations in newborns, supported the idea that BMI and congenital anomalies are positively associated. Nevertheless, no association between congenital abnormalities and BMI was found in the current investigation.

Pre-eclampsia or eclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension, and gestational hypertension are together referred to as hypertensive disorders in pregnancy (HDP), a collection of maternal illnesses marked by elevated blood pressure throughout pregnancy. Worldwide, the prevalence of HDP in pregnancy was estimated to be between 5 and 8% (Umesawa & Kobashi, 2017). According to earlier research, HDP may create an unfavourable condition in utero environment, raising the possibility of untoward pregnancy outcomes (such as low birth weight, neonatal mortality, intrauterine growth restriction, congenital abnormalities, and so on) (Li et al., 2021). These suggested that children of women with HDP may be more susceptible to cardiac abnormalities. It is yet unknown what possible processes might underlie the link between a mother's exposure to HDP and her offspring's risk of CHD. Nonetheless, a number of underlying theories have been proposed to attempt and explain the link between maternal HDP and the risk of CHD. The most plausible hypothesis is that early vasculogenesis damage caused by maternal HDP may result in aberrant placental development. Placental dysplasia has been linked to changes in protein expression, oxygen concentration, and placental genes, according to earlier research (Sanapo et al. 2020) The aforementioned modifications may result in modified antioxidant enzyme activity, elevated apoptosis, decreased angiogenic factors, an irregular growth factor balance, hypoxic stress, and finally, an aberrant development of the fetal cardiovascular system (Boyd et al. 2017). Bellizzi et al. (2016) and Bánhidy et

al. (2012) reported similar findings, however our investigation revealed no evidence of a significant association between congenital abnormalities and hypertension.

The current study found that 63.3% (38) of women with parity greater than two had congenital abnormalities. Marwah et al. (2014) also discovered that moms with parity 4 had a much higher prevalence of congenital abnormalities than did anomalous newborns with a birth order of one or two. However, our investigation did not find any association between parity and congenital malformations. A plausible rationale for the observed higher birth order is that women who are susceptible to unfavourable pregnancy outcomes, including severe congenital abnormalities, could persist in trying to conceive until they give birth to normal children. Nevertheless, as poor socioeconomic groups are more likely to have high parity, the impact of this parameter on fetal death cannot be separated from the confounding effects of socioeconomic factors.

There is evidence that multiple births have an increased risk of CA relative to singleton births. The excess in CAs has been associated with the splitting of the zygote and with vascular accidents as a result of blood clots or other debris moving across a shared or joined placenta in monozygotic twins (Boyle et al., 1984 – 2007). A favorable association was discovered in research undertaken by Dawson et al. (2017), Kshitija et al. (2020), and Piro et al. (2020). Twin pregnancy was 2.5% in our research, with no significant association between multiple births and congenital malformations found.

Folic acid-containing multivitamin supplements given during pregnancy have been found to reduce the prevalence of neural tube anomalies and orofacial clefts. (Mashuda et al., 2014). 66.7% (80) of the mothers in our study utilized folic acid, although congenital abnormalities were still found in 61.7% (37) of the fetuses. To reduce the development of neural tube defects, it is recommended that all pregnant women consume 400 µg of folic acid daily. (Centers for Disease Control and Prevention CDC, 2007). According to a research conducted in Atlanta, pregnant women who did not take multivitamin supplements around the time of conception had an increased chance of giving birth to a neonate who had a cardiovascular abnormality (Botto, Molinari & Erickson., 2003). Despite having antenatal care at some point in the antepartum period, some of the mothers were still engaged in customs that may prevent the maintenance of

adequate folic acid stores, such as the use of customary herbal mixtures whose unidentified ingredients may be antagonistic to folic acid functions. (Chimah et al., 2022).

The most commonly used drugs in the current study were antibiotics, anti-asthmatic, anti-epileptic, anti-hypertensive, anti-psychotic, anti-thyroid, and renal medications. Congenital defects and the drugs used were shown to have a substantial association. Studies by Agrawal et al. (2022), Yang et al. (2019), and Ellfolk et al. (2021) also demonstrated a high association between drug use and congenital malformations. There was just one case of rubella exposure in the current investigation, and no statistically significant relationship was discovered. In contrast, research by Wang et al. (2022) and Gupta et al. (2021) discovered a strong association between rubella exposure during the first trimester and congenital heart abnormalities.

Birth abnormalities are linked to a number of maternal disorders. For example, insulin-dependent diabetes mellitus increases the chance of congenital malformations, such as spina bifida and congenital heart disease, by two to three times. Congenital heart disease, intellectual impairment (mental retardation), and microcephaly are linked to maternal phenylketonuria. The fetus may be impacted by maternal antibodies that readily cross the placenta (Malik, Rizwan and Latif, 2018). In the current research diabetes, hypothyroidism, and asthma were found to be linked to a lower incidence of congenital abnormalities. A study by Ameen et al. (2018), discovered a link between maternal glycemic control and the occurrence of congenital anomalies. Shawky and Sadik (2011) demonstrated that offspring of diabetic mothers were more likely to have mild congenital abnormalities (18%) than serious congenital deformities (11%). Kiran et al. (2021) discovered a direct link between maternal risk factors and hypothyroidism in a research on neonatal outcomes and congenital abnormalities in hypothyroidism affected pregnancies. The same results were seen in the study done by Andersen et al. (2019) and Chen et al. (2014). Furthermore, Murphy, Clifton, and Gibson (2006) discovered an association between asthma and poor pregnancy outcomes.

Consanguineous marriages are thought to contribute significantly to the chance of congenital defects. The probability of a child inheriting a recessively inherited disorder is greater among related parents, and this risk rises as the connection grows closer. Our study reported a strong relationship between consanguineous marriage and congenital

defects. In the current study, 39.2% of the parents were related. Furthermore, the rate of abnormalities in consanguineous and non-consanguineous marriages was 53.3% and 46.7%, respectively. The incidence of abnormalities had a significant association with the inbreeding coefficient and was greater in couples who were consanguineous than in non-consanguineous marriages. Francine et al. (2014), Kurdi et al. (2019), and (Majeed-Saidan et al. (2015) discovered similar findings. Despite the high rate of consanguinity among people with malformations Mehrabi & Zeyghami (2005) found no connection between parental relationships and deformity. Furthermore, Bromiker et al. (2004) discovered no statistically significant difference in the prevalence of congenital abnormality in a research conducted in Palestine. Another research by Córdova Neira et al. (2015) found no instances of consanguinity among the parents of babies with birth defects.

The outcomes of our investigation found no statistically significant association between previous experiences of miscarriage or stillbirth and history of congenital abnormalities. The results of a study by Shawky and Sadik (2011) revealed similar results. However, a study by Malik, Khanna, and Verma (2019) revealed that mothers with a history of congenital malformations (8.3%) and abortions (13.6%) had a higher incidence of congenitally malformed newborns and had odds of having a malformed baby that was 2.6 and 4 times greater.

Of the mothers in this study, 28.3% (17 cases) and 6.7% (4) of the controls had a family history of congenital abnormalities. The results of the study indicate an association between the occurrence of fetal anomaly in one or more family members and the development of CAs. Pregnant women with a family history of CAs are 6.03 times more likely to give birth to fetuses with a structural abnormality (Marwah et al., 2014). Correia et al. (2016) found that one or more family members had CAs in 16% of Portuguese families with recorded instances of fetal malformations. The findings were comparable to those of studies by Abebe et al. (2021), De Moraes , Melo and Do Amaral (2020), El Koumi, Banna, and Lebda (2013), and Madi et al. (2005). Moreover, studies indicate that some different CAs, such those pertaining to the heart and kidney, have the capacity to group together into families (Dias, Sairam and Kumarasiri, 2014).

According to WHO statistics, around 20% of newborns born with orofacial clefts have additional congenital abnormalities. The study of related abnormalities is beneficial in detecting pathogenetically homogeneous patterns of malformations, as well as in determining etiologic research and improving public health monitoring. The current investigation discovered a significant association between different forms of craniofacial anomalies and central nervous system abnormalities, musculoskeletal anomalies and miscellaneous anomalies. In research done by Farhan et al. (2020), the prevalence of internal abnormalities linked to craniofacial anomalies was discussed. Congenital heart disease was found to be the most prevalent condition, which may be explained by its high relationship with dysmorphic facial anomalies. This group may also include cases of Down syndrome, which is known to be associated with congenital heart illnesses. According to a 2008 study on congenital heart disease and its associated malformations in countries like Jordan, the majority of cases involved congenital heart disease, followed by skeletal malformations and renal malformations, whereas in the current study, the majority of craniofacial anomalies cases were linked to CNS congenital anomalies. According to the study done in Jordan by Rawashdeh & Jawdat Abu-Hawas, (2008), 2.3% of instances of craniofacial anomalies were associated with GIT abnormalities, which was in accordance with the findings of the current study's 2.5% of cases that were linked to the condition. There is absolutely no research on these connections between craniofacial anomalies and other congenital abnormalities coming from Saudi Arabia.

The recent study showed an association between congenital malformations and ethnicity in Karachi. All the cases (60) and controls (60) were equally divided into 5 ethnic groups that are Balochi, Pashtun, Punjabi, Sindhi, and Urdu speaking. Although an association between Urdu speaking mothers and central nervous anomalies was found, the results cannot be generalized due to the small sample size and time constraints. The reasons for the development of CNS anomalies can be related to both hereditary (consanguineous marriage) and environmental variables (being exposed to toxins, infections during pregnancy, and poor maternal nutrition), however, no research has been done in which CNS anomalies have been linked with Urdu speaking individuals, so it cannot be compared with other studies.

Peake et al. (2021) conducted a study in England and Wales to determine neural tube defects prevalence by mother ethnicity. Neural tube defects prevalence was found to be much greater among Indian and Bangladeshi women, particularly in anencephaly and spina bifida affected pregnancies.

Asians, Caucasians, and aboriginal peoples have orofacial cleft anomalies more frequently than non-white ethnic groups do. Although orofacial clefts are a complex disorder, the genetic element has become extremely important. This feature was included because of the high rate of orofacial clefts among infants born to consanguineous marriages, a condition that is uncommon in Western nations but common in less developed or emerging nations (such as Iran) (Inchingolo et al., 2022).

According to UK studies, British Asian children had a greater risk of congenital heart disease (CHD), with more complicated cyanotic abnormalities and less obstructive aortic outflow problems. Although consanguinity may raise the incidence of congenital malformations, a meta-analysis predicted an extra abnormality risk of roughly 3%. Because Black and Asian communities have diverse migratory and cultural influences, ethnic disparities in CHD incidence may not be immediately relevant to the UK population. Understanding ethnic variety is critical for avoiding oversimplified categorization (Knowles et al., 2017).

According to a research by Egbe A. C. (2015), Caucasians have birth abnormalities at a rate that is higher than that of African Americans and Hispanics. In general, the chance of having birth abnormalities was the same for Caucasians and Asians. Contrary to Caucasians, African-Americans had a higher prevalence of musculoskeletal abnormalities but a decreased risk of cardiac, genitourinary, and craniofacial malformations. Abnormalities of the gastrointestinal and genitourinary systems were less common in Hispanics. Asians were more prone to suffer from craniofacial and musculoskeletal issues. Numerous potentially harmful exposures, such as socioeconomic position, food, stress, and access to healthcare, might be concealed by race and ethnicity. Currently, it is unclear if the observed racial differences in the incidence of birth defects are caused by any potential underlying genetic susceptibilities, various mother ages among races, various prenatal teratogen exposures, or any combination of these factors.

5.2 IMPLICATIONS OF THE STUDY

5.2.1 THEORETICAL IMPLICATIONS

The intricate interactions between genetics, environment, and maternal health behaviors that lead to birth abnormalities can be better understood with the aid of this kind of study. Researchers can establish theories regarding the underlying biological pathways that might be involved in the development of congenital abnormalities by identifying certain risk factors that are more frequent in certain ethnic groups. This research may also help to establish new theoretical models for understanding the etiology of birth abnormalities. It might be possible, for instance, to develop models that include both genetic and environmental aspects, as well as potential interactions between these components. This might lead to more precise estimates of the likelihood of birth abnormalities in various groups, as well as more effective prevention methods.

5.2.2 PRACTICAL IMPLICATIONS

The practical implications of studying the association between congenital malformations and maternal risk factors in different ethnicities in Pakistan are significant. The development of useful therapies targeted at lowering the risk of birth abnormalities in certain groups can be guided by this kind of study. For example, healthcare practitioners might utilize this data to establish targeted screening and counseling programs for pregnant women from high-risk ethnic groups. These programs can assist women in identifying and addressing possible risk factors for birth abnormalities, such as inadequate diet, toxic exposure, and specific hereditary characteristics. Furthermore, the findings of this study can help to shape public health policies and programs focused on reducing birth abnormalities and improving maternal and fetal health outcomes. Policymakers, for example, might utilize this data to create targeted public health initiatives to raise awareness about the significance of prenatal care and good mother behaviors among certain ethnic groups. They may also utilize this knowledge to create

policies that promote access to nutritious food and clean drinking water while limiting exposure to environmental contaminants. In general, research on the association between maternal risk factors and congenital anomalies in various ethnic groups has important practical implications for enhancing maternal and fetal health outcomes. Healthcare practitioners and policymakers may collaborate to lower the prevalence of birth abnormalities and enhance the health of mothers and newborns in Pakistan by identifying specific risk factors and implementing focused treatments.

5.2.3 POLICY IMPLICATIONS

The creation of policies aiming at enhancing maternal and fetal health outcomes, decreasing the prevalence of birth abnormalities, and promoting health equality among various ethnic groups can be informed by this kind of study. One key policy conclusion is the necessity for focused public health initiatives in certain ethnic groups to raise awareness about the need for prenatal care and good mother behaviors. This might involve targeted health education programs and outreach initiatives to ensure that women of various ethnic groups have access to the knowledge and services they require for safe pregnancies. Another policy aspect is the requirement for measures to lessen exposure to environmental contaminants and to promote access to healthy food and clean water. This can include laws aimed at limiting the use of pesticides and other dangerous chemicals, as well as policies aiming at increasing access to nutritious and affordable food alternatives for women of various ethnic groups. Furthermore, this research can help shape policies targeted at enhancing access to healthcare services for women of diverse ethnic groups, such as prenatal care and genetic counseling. Policymakers may utilize this data to create policies and programs that reduce disparities in health services and promote health equity across ethnic groups.

5.3 LIMITATIONS AND STRENGTHS OF STUDY

(A) LIMITATIONS

- Limited time duration did not allow a more detailed analysis of specific congenital malformations groups.
- Gender of the fetus should have been identified in order to determine which types of malformations were more common in male and female fetuses

(B) STRENGTHS

- The first study of its kind in Pakistan aimed to determine the relationship between congenital abnormalities and maternal risk factors in various ethnic groups
- Ethnic representation was equal in the study

5.4 FUTURE RESEARCH DIRECTIONS / RECOMMENDATIONS

Based on the study of the association between congenital malformations and maternal risk factors in different ethnicities in Pakistan, the following recommendations can be made:

1. Additional research is needed to better understand the complicated interplay between genetics, environmental variables, and maternal health behaviors that lead to birth abnormalities among Pakistan's many ethnic groups.
2. Policy makers should design tailored screening and counseling programs for expectant mothers from high-risk ethnic groups. These programs should concentrate on identifying and correcting potential risk factors for birth abnormalities, such as inadequate nutrition, chemicals in the environment, and specific genetic variables.

3. The government should create public health campaigns to spread awareness of the value of prenatal care in middle and lower socio economic income groups. These advertisements should be attentive to cultural differences and customized to the demands of various ethnic communities.
4. Policies and programs should be implemented to increase access to healthcare services for women, particularly prenatal care and genetic counseling.
5. Policies should be devised to limit the use of pesticides and other dangerous chemicals and to encourage access to healthy and inexpensive food alternatives for women.

5.5 CONCLUSION

Young age, secondary level of education, low income, use of medication in the 2nd trimester, history of consanguinity and family history of birth defects were risk factors that were significantly linked to an increased risk of congenital malformations, while diabetes mellitus, hypothyroidism and asthma were significantly linked to a decreased risk. As compared to Balochi, Pashtun, Punjabi, and Sindhi mothers, our study also found a significant association between congenital malformations of the central nervous system abnormalities and Urdu-speaking mothers; however, the results cannot be generalized to the general population due to the small sample size and time constraints. Craniofacial congenital anomalies have been associated with the central nervous system, the musculoskeletal system, and miscellaneous congenital abnormalities.

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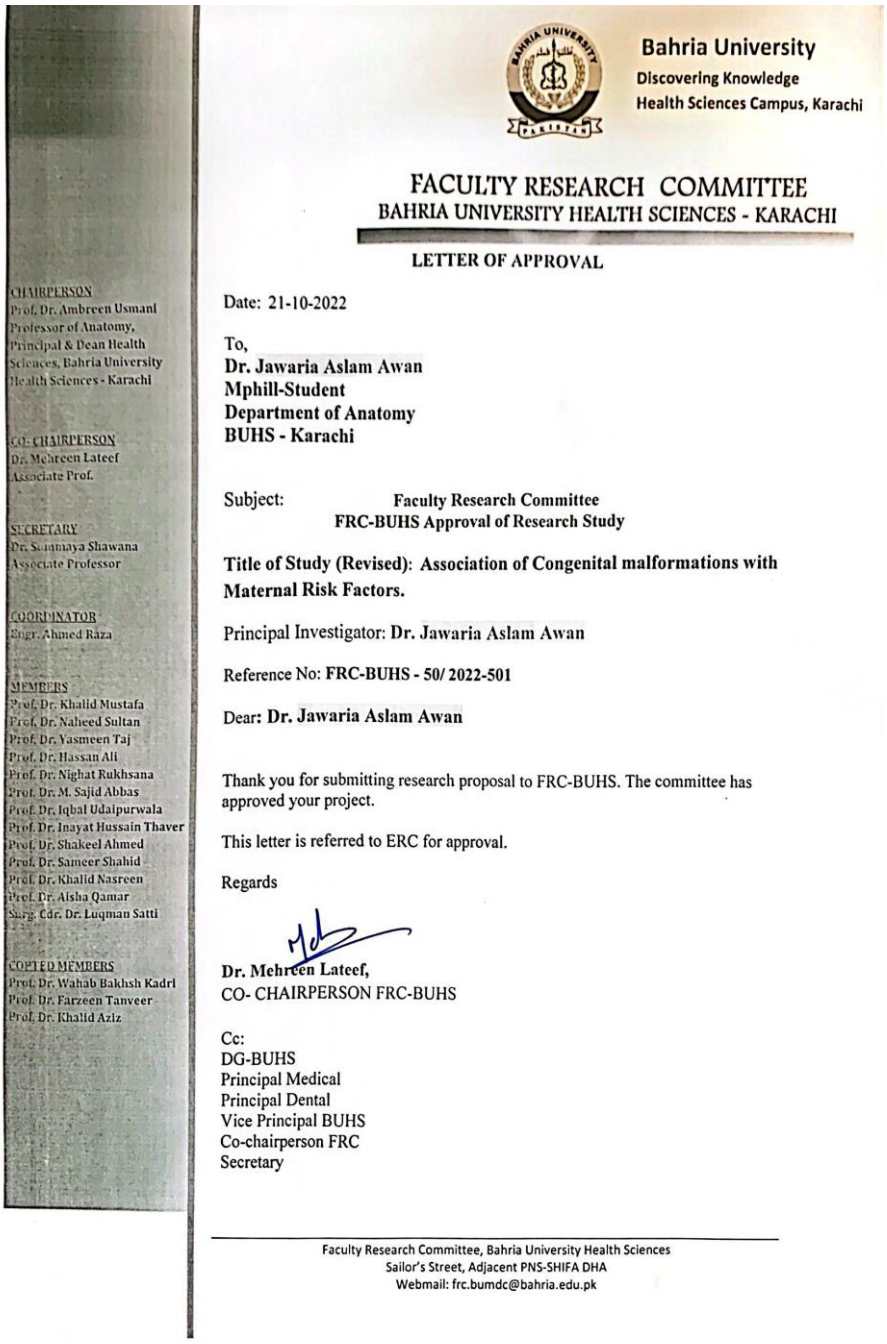
ANNEXURES

ANNEXURE A: FRC



Bahria University
Discovering Knowledge
Health Sciences Campus, Karachi

FACULTY RESEARCH COMMITTEE
BAHRIA UNIVERSITY HEALTH SCIENCES - KARACHI

LETTER OF APPROVAL

CHAIRPERSON
Prof. Dr. Ambreen Usmani
Professor of Anatomy,
Principal & Dean Health
Sciences, Bahria University
Health Sciences - Karachi

CO- CHAIRPERSON
Dr. Mehreen Lateef
Associate Prof.

SECRETARY
Dr. Sumnaya Shawana
Associate Professor

COORDINATOR
Engr. Ahmed Raza

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Prof. Dr. Aisha Qamar
Surg. Cdr. Dr. Luqman Satti

COPTED MEMBERS
Prof. Dr. Wahab Bakhsh Kadri
Prof. Dr. Farzeen Tanveer
Prof. Dr. Khalid Aziz

Date: 21-10-2022

To,
Dr. Jawaria Aslam Awan
Mphill-Student
Department of Anatomy
BUHS - Karachi

Subject: **Faculty Research Committee**
FRC-BUHS Approval of Research Study

Title of Study (Revised): Association of Congenital malformations with Maternal Risk Factors.

Principal Investigator: **Dr. Jawaria Aslam Awan**

Reference No: **FRC-BUHS - 50/ 2022-501**

Dear**: Dr. Jawaria Aslam Awan**

Thank you for submitting research proposal to FRC-BUHS. The committee has approved your project.

This letter is referred to ERC for approval.

Regards

Dr. Mehreen Lateef,
CO- CHAIRPERSON FRC-BUHS

Cc:
DG-BUHS
Principal Medical
Principal Dental
Vice Principal BUHS
Co-chairperson FRC
Secretary

Faculty Research Committee, Bahria University Health Sciences
Sailor's Street, Adjacent PNS-SHIFA DHA
Webmail: frc.bumdc@bahria.edu.pk

ANNEXURE A: IRBC

IRB

NO.F.2-81/2022-GENL/323/JPMC
JINNAH POSTGRADUATE MEDICAL CENTRE
KARACHI.75510.

Dated the 26-12-2022

Dr. Jawaria Aslam Awan,
Department of Anatomy
Bahria University Health Sciences Campus
Karachi.

Subject: Association of congenital malformation with maternal risk factors.

With reference to your application / letter dated 26th October, 2022, on the subject noted above and to say that the Institutional Review Board has approved your subject proposal.

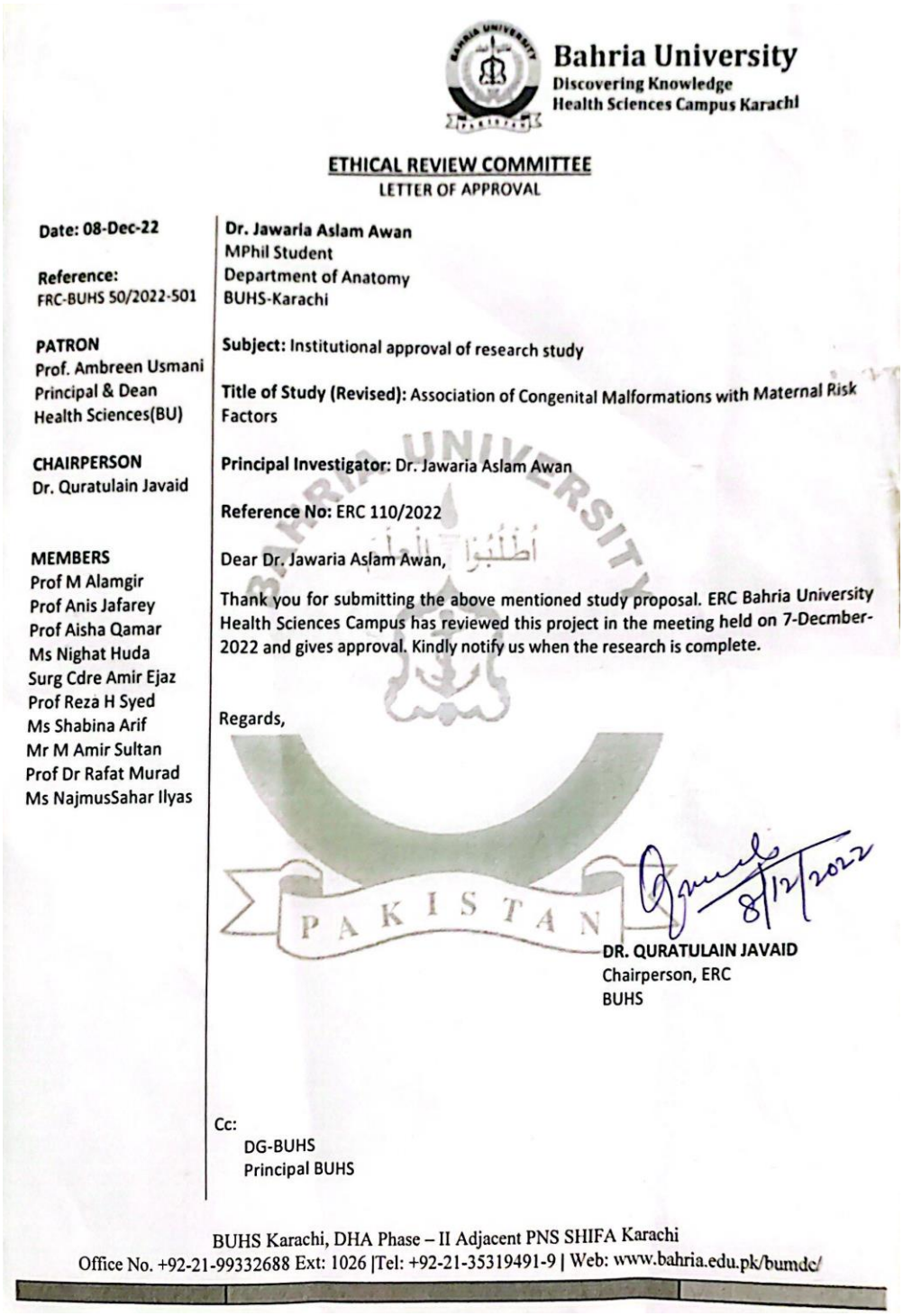
Prof. Dr. Tariq Mehmood, Head Department of Radiology, Cyberknife & Tomotherapy, JPMC, Karachi is the co-supervisor of this study.

Prof. Syed Masroor Ahmed
Prof. of Medicine / Dean and
Chairman, Institutional Review Board Committee
JPMC, Karachi.

Copy forwarded for information and necessary action to:

- Prof. Dr. Tariq Mehmood (T.I) Head Department of Radiology, Cyberknife & Tomotherapy, JPMC, Karachi.
- Prof. Dr. Aisha Qamar, Head Department of Anatomy, Department of Anatomy, Bahria University Health Sciences Campus, Karachi.

ANNEXURE B: ERC



Bahria University
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ETHICAL REVIEW COMMITTEE
LETTER OF APPROVAL

Date: 08-Dec-22

Reference:
FRC-BUHS 50/2022-501

PATRON
Prof. Ambreen Usmani
Principal & Dean
Health Sciences(BU)

CHAIRPERSON
Dr. Quratulain Javaid

MEMBERS
Prof M Alamgir
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Ms Shabina Arif
Mr M Amir Sultan
Prof Dr Rafat Murad
Ms NajmusSahar Ilyas

Dr. Jawaria Aslam Awan
MPhil Student
Department of Anatomy
BUHS-Karachi

Subject: Institutional approval of research study

Title of Study (Revised): Association of Congenital Malformations with Maternal Risk Factors

Principal Investigator: Dr. Jawaria Aslam Awan

Reference No: ERC 110/2022

Dear Dr. Jawaria Aslam Awan,

Thank you for submitting the above mentioned study proposal. ERC Bahria University Health Sciences Campus has reviewed this project in the meeting held on 7-Decmber-2022 and gives approval. Kindly notify us when the research is complete.

Regards,

8/12/2022

DR. QURATULAIN JAVAID
Chairperson, ERC
BUHS

Cc:
DG-BUHS
Principal BUHS

BUHS Karachi, DHA Phase – II Adjacent PNS SHIFA Karachi
Office No. +92-21-99332688 Ext: 1026 |Tel: +92-21-35319491-9 | Web: www.bahria.edu.pk/bumdc/

ANNEXURE C: SUBJECT CONSENT FORM - ENGLISH

INFORMED CONSENT

You are giving consent to participate in a research titled “Association of congenital malformation with maternal risk factors”

You have been explained in detail the nature and significance of participating in the project, and that the ultrasound scan of the baby will help notify you about any possible anomalies, provide time for additional tests and options of surgical termination in case of severe and lethal malformations. Ultrasound is a valuable tool and there is no clinical risk associated with it.

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

You will be participating willingly in the research and will not be provided with any incentive, financial assistance or reimbursement, whereas you do have the right to withdraw from the study at point of time.

I understand and fully agree to participate in the research.

You are advised to contact Dr. Jawaria Aslam Awan on
Mobile number: 0334 -3325420
Signature of Researcher: _____
Date: _____

Name of Participant: _____
Signature of Participant: _____
Date: _____

ANNEXURE C: SUBJECT CONSENT FORM – URDU

موضوع کی رضامندی کا فارم

آپ "زچگی کے خطرے کے عوامل کے ساتھ پیدائشی خرابی کی انجمن" کے عنوان سے ایک تحقیق میں حصہ لینے کے لیے رضامندی دے رہے ہیں۔

آپ کو پروجیکٹ میں حصہ لینے کی نوعیت اور اہمیت کے بارے میں تفصیل سے بتایا گیا ہے، اور یہ کہ بچے کا الٹراساؤنڈ اسکین آپ کو کسی بھی ممکنہ بے ضابطگیوں کے بارے میں مطلع کرنے میں مدد کرے گا، اضافی ٹیسٹ کے لیے وقت فراہم کرے گا اور شدید اور مہلک خرابی کی صورت میں سرجیکل ختم کرنے کے اختیارات فراہم کرے گا۔ . الٹراساؤنڈ ایک قیمتی ٹول ہے اور اس سے کوئی طبی خطرہ وابستہ نہیں ہے۔

آپ کو بتایا گیا ہے کہ تمام نتائج اور آپ کے ذاتی ڈیٹا کو سختی سے خفیہ رکھا جائے گا اور صرف کمیونٹی کی بہتری کے لیے، اشاعتوں اور کاغذی پیشکشوں میں سختی سے استعمال کیا جائے گا۔

آپ تحقیق میں اپنی مرضی سے حصہ لیں گے اور آپ کو کوئی ترغیب، مالی امداد یا معاوضہ فراہم نہیں کیا جائے گا، جبکہ آپ کو وقت پر مطالعہ سے دستبردار ہونے کا حق حاصل ہے۔

میں سمجھتی ہوں اور تحقیق میں حصہ لینے سے مکمل اتفاق کرتی ہوں ۔

آپ کو مشورہ دیا جاتا ہے کہ ڈاکٹر جویریہ اسلم اعوان سے رابطہ کریں۔
موبائل نمبر: 0334 – 3325420
محقق کے دستخط: _____
تاریخ: _____

شرکاء کا نام: _____
شرکاء کے دستخط: _____
تاریخ: _____

ANNEXURE D: SUBJECT EVALUATION FORM

SUBJECT EVALUATION FORM

DEMOGRAPHICS

1.	Name:		
2.	Residence:		
3.	Age:		
4.	Weight:	Height:	Blood Pressure:
5.	Ethnicity:		
6.	Marital status:		
7.	Education:		
8.	Phone no:		

HISTORY OF ANTENATAL CARE:

FAMILY HISTORY:

HISTORY OF COMORBIDITIES:

MATERNAL RISK FACTORS & FETAL BIOMETRY

1.	**MATERNAL AGE AT CONCEPTION** < 20 20 – 24 25 – 29 30 – 34 35 – 39 40 – 45	
2.	**FAMILY INCOME** 50,000 – 99,999 ≥100,000 – 200,000	
3.	**MULTIPLE PREGNANCY** Yes No	
4.	**PARITY** 1st child 2nd child > 2 child	
5.	**BMI** < 18.5 18.5 - 24.9 25– 29.9 ≥ 30	
6.	**HISTORY OF CONSANGUINITY** Present Absent	
7	**MATERNAL USE OF FOLIC ACID** Yes No	
8.	**MATERNAL USE OF ANTENATAL SUPPLEMENTS** Yes No	
9.	**MATERNAL USE OF MEDICATIONS** None 1st Trimester 2nd Trimester 3rd Trimester	
10.	**EXPOSURE TO RUBELLA** Yes No Did not get tested	
11.	**HISTORY OF STILLBIRTH** Yes No	
12.	**HISTORY OF BIRTH DEFECTS/ NEURAL TUBE DEFECTS IN FAMILY**	

	Yes No	
13.	**FAMILY HISTORY OF BIRTH DEFECTS** Yes No	
14.	**FETAL BIOMETRY** Biparietal diameter (BPD) Head circumference (HC) Abdominal circumference (AC) Femur length (FL)	

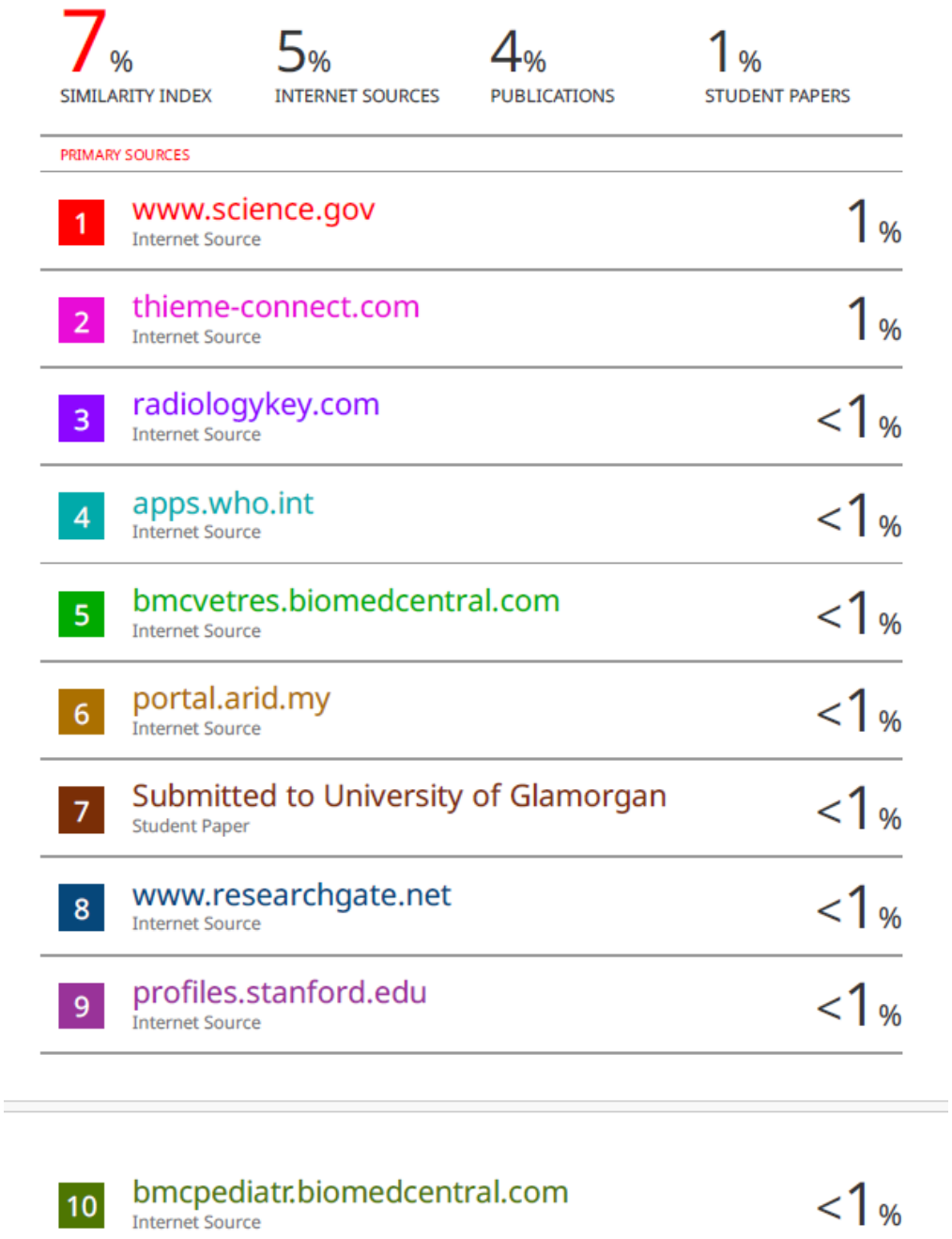
TYPE OF ANOMALY DETECTED

INVESTIGATION PERFOMED

Name of investigation:	
Date of investigation performed:	
Patients ID:	

ANNEXURE E: HOSPITAL / INSTITUTE CARD

ANNEXURE F: TURNITIN PLAGIARISM CHECK REPORT



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