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Review Article

Approach to Prenatal Fetal Malformations

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Abstract

Major fetal malformation affects approximately 3% of births and is leading cause of perinatal morbidity and mortality. Some of these conditions are incompatible with long-term postnatal survival and hence warrants preventive measures by introducing second trimester prenatal ultrasound. Prenatal ultrasound has become an essential practice of antenatal care in urban India. Although the vast majority of the ultrasound examinations performed in antenatal period provide reassurance to pregnant women and their obstetric care providers, however some of these scans may reveal fetal anomaly thus causing stress to parents as well as caregivers. Since many fetal anomalies may be associated with perinatal morbidity and/or mortality as well as risk of recurrence in next pregnancy it is important to provide accurate information about the findings i.e., accurate diagnosis as this is the basis for subsequent counseling and management. Thus obstetric caregivers must refer these cases to a good level II fetal ultrasound clinic or fetal medicine center or tertiary perinatal care unit as first steps for proper re-evaluation of fetal anomalies and subsequent course of management. As fetal anomalies are associated with increased risk of chromosomal and/or sub-chromosomal anomalies, many experts may offer karyotype analysis and/or array comparative hybridization (aCGH) as the second step of management. A malformation (structural anomaly) with normal karyotype and/or aCGH requires classification as either isolated event or as part of a defined syndrome/ sequence/ association as third step of management and for this requires consultation with medical geneticist, dysmorphologist and genetic counselor. With thousands of syndromes listed in the OMIM and Winter-Baraitser Dysmorphology database, medical genetics health professionals can often be overwhelmed in refining the diagnosis, counseling and management however this prenatal assessment may be incomplete and for overcoming this deficiency there is a need for re-assessment after delivery/termination (fourth step of management). This is important today as many of the malformations/developmental defects are yet to be categorized etiopathologically, and hence immediate need is to start clinical registry along with bio-repository of developmental defects cases for research work on informative families, in particular with multiple affected fetuses/sibs, using genomics, epigenomics, proteomics, etc platforms bedsides detailed autopsy by a team of perinatal pathologist and medical geneticist. This write up will provide a framework for managing fetal anomalies detected prenatally during routine ultrasound diagnosis.

keywords: *Prenatal; Fetal malformation; Karyotype; Ultrasonography*

Introduction

Fetal malformations are structural defects in the fetus due to abnormal embryonic or fetal development. It affects different organ systems and etiologically heterogeneous. Fetal malformations could be multifactorial (both genetics and environmental contribution), predominantly genetic (chromosomal or copy number variations/microdeletion or micro duplication syndrome or monogenic) or predominantly environmental (teratogenic exposure). The prevalence of congenital malformation at birth varies between 1-5%, depending on the inclusion criteria. The prevalence of prenatal detection is 2-3.5% and mostly by ultrasonography [1-3]. It is estimated that each year

7.9 million children are born worldwide with major birth defects (The Global Report on Birth Defects is available at www.marchofdimes.com). Among them, at least 3.3 million die before age 5 years and 3.2 million survive with a disability. Congenital malformation is also a significant cause of morbidity and mortality in India. In a multi-centric study (Mumbai, Delhi and Baroda) on 94,610 newborns major malformation frequency was found to be 2.03% and the commonest one was neural tube defects [4]. The frequency for Down syndrome was reported as 0.87 per 1000 births [4]. Congenital malformation is a global problem, but their impact is severe in low and middle-income countries, where the conditions for prevention, treatment, and rehabilitation are more difficult [5]. World Health Assembly has stressed the importance of addressing birth defects [6]. Reduction in malformation could be achieved through primary preventive measures (periconceptional multivitamins or folic acid treatment or preconception rubella vaccination or preimplantation genetic diagnosis) or secondary preventive measures (prenatal detection and selective termination of affected fetus). Second trimester (16-20 weeks) ultrasound scan is an important tool in present day obstetrics practice and this helps in early diagnosis of fetal malformations although not all malformations are detectable [7]. Routine ultrasound screening for fetal malformations is justifiable because they are relatively common and overall detection rate by prenatal ultrasound in a tertiary care unit is over 60% [8]. However, the sensitivity of routine second trimester fetal ultrasound scan vary considerably, ranging from 10% to 80%, average 27.5% [9,10]. The detection rate of fetal malformations varies with competence of sonologist/fetal medicine specialist but may be much less during routine prenatal care. The discrepancy may be attributed to variations in the quality of equipment. This can be improved by efficient systematic approach of mid-trimester fetal malformation scan using integrative mid-trimester anomaly chart [11]. Now prenatal fetal echocardiography, 3D ultrasonography and ultrafast magnetic resonance imaging (MRI) are frequently used as an adjunct to ultrasound for the characterization of fetal malformations (cardiac defect, facial dysmorphology, open fetal defect, CNS defect, skeletal defect, genitourinary defect, etc). Although conventional ultrasound is the standard first tier test for fetal structural evaluation, certain factors like low amniotic fluid volume or maternal obesity may limit the ultrasound assessment. In these situations, fetal MRI is more useful. Prenatal detection of fetal malformations also helps health care providers to plan for birth in appropriate place to avail special postnatal care for the malformed fetus and these includes diagnosis, management and counseling. The most challenging area in fetal malformation is accurate diagnosis, accurate counseling and early prediction and prevention and for this, it is very important to examine & investigate post-delivery or post termination fetus and preserve bio-resources. The flow chart given below describes a framework for managing fetal malformations detected prenatally during routine ultrasound diagnosis and there after each point will be described briefly.

General Approach

History and Examination

When a fetal malformation (structural anomaly) is identified during prenatal ultrasound examination (as part of standard antenatal care practice or targeted viz., following abnormal maternal screening, family history/previous affected pregnancy, etc) a detailed family history, in particular genetic disease and parental physical examination should be performed, keeping in mind the possibility of autosomal dominant traits such as tuberous sclerosis, myotonic dystrophy, velocardiofacial syndrome/22q11.2 microdeletion, skeletal dysplasia, single incisor tooth, polydactyle, etc [12]. The obstetric history should be reviewed, including exposure to teratogens such as medication/drugs (warfarin, ACE inhibitors, isotretinoin, phenytoin, valproic acid, trimethadione, thalidomide, aminopterin, diethylstilbestrol, etc), infection (toxoplasma, rubella, cytomegalovirus, chickenpox, parvovirus, etc), heavy metals (mercury), radiation and lifestyle (alcohol, cocaine, marijuana, etc). Finally, a detailed family history (three generation pedigree) should be obtained from both parents and particular attention should be paid to children born with congenital malformations, early deaths, and to the possibility of consanguinity between the parents. A physical examination should focus on identifying evidence of the detected fetal malformation in the parents to rule out an autosomal dominant trait. For example, a fetus with a cardiac conotruncal anomaly may unveil a familial 22q11.2 deletions, and one of the parents may present with the typical facial features associated with the syndrome only. Similarly, fetus with holoprosencephaly may unveil a familial single incisor tooth.

Prenatal Imaging

All prenatal ultrasound detected fetal malformations must be re-assessed in a tertiary perinatal care or fetal medicine unit for detailed

ultra-sonographic assessment using best available ultrasound probe (at least 8 MHz) in an attempt to obtain targeted/non-targeted structural anomalies so that proper counseling and accurate management possible. It is also important to reassess false positive reports, which are often reported with mild/borderline ventriculomegaly, hydronephrosis, short limbs, cysts (renal, pulmonary, abdominal, or cerebral), etc [13,14]. These may be true false positive or spontaneous resolution of the condition, hence repeat examination and follow up ultrasound is important to prevent mistake. The 3-D ultrasound of fetus may provide additional information in many cases, particularly in assessing facial dysmorphism or hand/foot (digits) anomalies [15]. Similarly, fetal echocardiography is required to evaluate fetal heart in case of suspected cardiac malformation or dysfunction. The newest addition in fetal imaging is ultrafast magnetic resonance imaging. It is useful in the assessment of brain, lung, skeletal dysplasia, open fetal defect or any complex malformation or when oligohydramnios/ maternal obesity or when fetal ultrasound examination is difficult [16].

Non-invasive Testing

Parental blood testing sometimes may be valuable in identifying etiology of fetal malformation. For example, the finding of sonographic signs of echogenic bowel raises the potential diagnosis of fetal cystic fibrosis, an autosomal recessive disorder for which mutation testing identifies carrier states of parents. Testing a parent with physical signs of a microdeletion (e.g., 22q11.2) for that disorder may facilitate pregnancy management. A history of infectious exposure or a constellation of ultrasound findings suggestive of a congenital infection should encourage maternal blood testing for evidence of recent exposure to infectious agent (for example maternal specific antibodies for rubella, toxoplasma, cytomegalo virus, etc). Maternal blood testing using next generation sequencer for aneuploidy and copy number variation (noninvasive prenatal screening/NIPS) may be offered in high risk doubtful cases or cases with multiple malformations.

Invasive Testing

Invasive testing (amniocentesis, chorionic villous sampling, placental biopsy, fetal blood sampling, etc) is carried out to assess the fetal cytogenetics (conventional cytogenetics, DNA microarray, fluorescence in situ hybridization, etc), mutation analysis (PCR/sequencing methods), enzyme estimation, biochemical parameters, etc. DNA microarray may be offered as first-tier prenatal cytogenetics test as diagnostic yield is better than conventional karyotyping. Amniotic fluid may also be used to test for biochemical disorders (17-hydroxyprogesterone for the diagnosis of congenital adrenal hyperplasia), for infections (PCR for viral DNA/RNA) when a congenital infection (toxoplasmosis, rubella, cytomegalo, parvovirus, etc) is a possibility, or for other malformation (alpha-fetoprotein or acetyl cholinesterase in neural tube/ open fetal defect).

Postnatal evaluation and/or Autopsy

The major objective of the malformed perinatal autopsy is to detect additional congenital abnormalities, determine diagnosis and find out recurrence risk. A trained perinatal pathologist and medical geneticist as a team should perform malformed fetal/perinatal autopsy. Autopsy should ideally be an essential part of full investigation of fetal losses associated with non-chromosomal fetal malformations. This must in case of multiple malformations without detectable underlying cause. Genetic syndromes must be identified if present through autopsy and related investigations so that it benefits the parents and treating physician to understand and counsel about the etiology for the disorder. This should include storage of fetal tissues for future specialized investigations, including screening genome. The autopsy may provide valuable explanations, and it allows care providers to offer more accurate genetic counseling to the family and helps in planning for the management of future pregnancies. Post-mortem studies have shown that prenatal diagnosis by ultrasound often misses associated anomalies in fetus [17,18]. Furthermore, the prenatal ultrasound diagnosis varies with the experience of the sonologist, time spent on the ultrasound examination and quality of the equipment used, in particular transducer beside feto-maternal conditions like maternal obesity or oligohydramnios. Hence an examination of the terminated fetus for associated anomalies is essential for providing accurate diagnosis and genetic counseling. Genetic counseling should be preferably based on the post-autopsy diagnosis and not on ultrasound examination alone.

Counseling

Counseling should start as soon as a fetal malformation (structural anomaly) is detected by fetal sonography. However, decision making prenatal counseling should be by fetal medicine/medical genetics expert with/without consultation with pediatric (medical/surgical) or system related subspecialties. This counseling is to provide family with accurate information (including diagnosis, prognosis, etc if possible) to make appropriate decisions about pregnancy management. Despite advances in prenatal diagnosis and knowledge of etiologies, uncertainty may remain until delivery and assessment. Early postnatal management may require additional consultations from pediatric cardiologists, pediatric surgeons, pediatric neurologist, etc in case of live birth. It is essential to invest to find out diagnosis because reliable counseling (prognosis and recurrence risk) depends on the accuracy in diagnosis. Postnatal evaluation should include dysmorphism assessment as prenatal facial dysmorphism evaluation often unsuccessful [19].

Specific Disorders

Fetal Open defect

Common fetal open defects are neural tube defect/NTD (anencephaly, iniencephaly, spina bifida, encephalocele, cranioraschisis, etc), abdominal wall defect (ompalocele, gastroschisis, extrophy of bladder, cloacal extrophy, etc), amniotic band syndrome, etc. The diagnosis of open fetal defect is made during routine sonography or following findings of elevated level of alpha-fetoprotein during maternal serum screening. The diagnosis can be made as early as 12 weeks of gestation by ultrasound examination. Prenatal magnetic resonance imaging can be considered as an additional fetal imaging technique for prenatal diagnosis, counseling and management strategy.

Figure 1: NTD.

NTDs are a group of malformations of fetal brain and spinal cord that originate from failure of closure of neural groove in early embryonic period. NTD is the commonest lethal developmental defects. NTDs can be divided into open NTD (result from failure of primary neurulation; no coverings for nerve tissue, leaving nerve tissue exposed and destroyed e.g., anencephaly, open spina bifida/ meningomyelocele, craniorachischisis, anen-iniencephaly, etc) or closed NTD (defective secondary neurulation; skin covered viz., spinal dysraphism, iniencephaly, etc) [20]. Other NTD malformations, such as encephalocele, are likely to be post neurulation disorders. NTDs can also be divided as isolated NTDs (anencephaly, spina bifida, encephalocele, iniencephaly, craniorachischisis, etc) or syndromic NTD (NTD with trisomy 18 or 13, with Sirenomelia or with Meckel syndrome, or with amniotic band syndrome, etc) [21].

Recurrence risk of isolated NTDs after one affected child is 3-5%, which is 10 times higher than the general population. It increases to 10% after two affected children and 25% after three such births. After birth of one child with NTD a couple should be counseled about prevention in subsequent pregnancies; primary prevention by periconceptional folic acid supplementation and secondary prevention by antenatal maternal serum alpha fetoprotein (MSAFP) and ultrasound examination along with selective termination of affected pregnancy. However, syndromic NTDs have different recurrence risk (sporadic as with amniotic band syndrome to 25% as with Meckel syndrome). Hence, for accurate counseling gross examination and radiography may not be adequate in cases of NTD with multiple malformations. In these cases, an expert opinion from geneticist with specialized tests is required. MSAFP and ultrasound at 10-12 weeks (to exclude anencephaly) and again 16-20 weeks (to exclude all other types of NTD) should be advised in subsequent pregnancy. MSAFP (taking cut-off > 2.5 multiple of median using BPD for estimating gestation age) has a detection rate of 85% at 16-17 weeks. In skilled hand and in high-risk women ultrasound has a detection rate of 98% for NTD malformations.

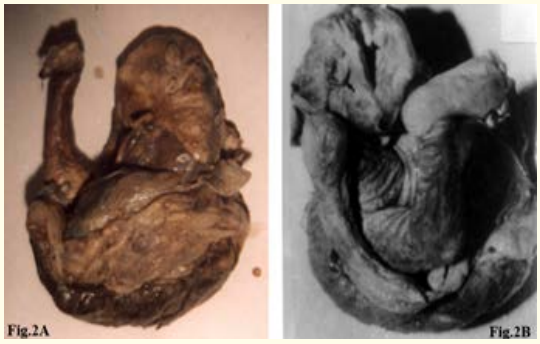

Figure 2: *Amniotic band syndrome.*

Amniotic band syndrome and/or limb body wall complex is accepted to be caused by rupture of the amnion with secondary effects on the fetus producing malformation due to interruption of normal morphogenesis, deformation due to distortion of established structures and disruption of structures already formed [22]. It is commonly associated with loss of amniotic fluid, leading to oligohydramnios and producing secondary effects due to compression. It is under diagnosed and its presentation is so variable that no two cases are exactly alike. Pathogenesis of this defect is probably heterogeneous. Mechanisms proposed are germ disc disruption, genetic disruption, vascular disruption and amniotic disruption. The diagnosis is based on two out of three manifestations viz., craniofacial clefts; limb body wall defects and amniotic band attachment. Single phenotype (resulting from placenta/ membrane attachment with embryo followed by effects due to fetal movement that result in pulling, disruption, and entanglement, with oligohydramnios leading to compression effect as well as pulmonary hypoplasia) with different terminology by different investigators, indicates only etiopathologic heterogeneity.

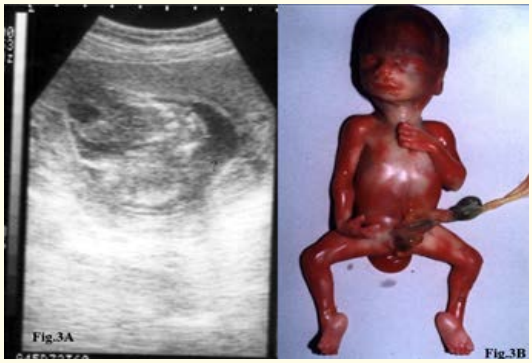

Figure 3: *Omphalocele, gastroschisis, exstrophy, etc.*

These are congenital defects of the anterior abdominal wall of embryo/fetus. In omphalocele a membranous sac covers the herniated viscera, which protrude through a relatively large abdominal wall defect at umbilicus. The intestines and liver remain morphologically and functionally normal however usually associated with other malformations. In gastroschisis bowel does not have any cover and is usually damaged, with short, thick or fibrous. Abdominal wall defect in gastroschisis does not involve umbilicus. Chromosomal anomalies are commonly associated with omphalocele [23], but rare with gastroschisis. Bladder and cloacal extrophy are rare and occur as a result of failed closure of the anterior abdominal wall at the ventral end of the cloacal membrane. Bladder extrophy is often associated with other genitourinary anomalies whereas cloacal exstrophy is usually accompanied by an omphalocele, imperforate anus, diastasis of the pubis, and absent genitalia. Bladder exstrophy may be recognized sonographically by absence of the bladder. Prenatal diagnosis of bladder or cloacal exstrophy should lead to a careful search for associated chromosomal and structural anomalies. OEIS complex is a combination of severe congenital anomalies of the cranial anomalies suggestive of oculo-auriculo-vertebral sequence and caudal anomalies resembling the omphalocele-extrophy of bladder, imperforate anus, and spine defects (OEIS) that suggests a defect during blastogenesis. Oculo-auriculo-vertebral sequence is known to be variable in its clinical presentation, the mildest of which may be the presence of a unilateral ear tag only. The caudal anomalies may resemble the caudal deficiency sequence or the OEIS complex or defect of blastogenesis. A generalized alteration in mesodermal cell migration during the primitive streak period has been postulated to cause the malformations described as axial mesodermal dysplasia and OEIS. However, these malformations can also be adequately explained as defects of blastogenesis [24].

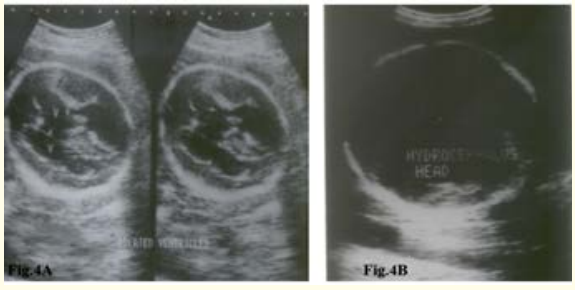

Figure 4: *Ventriculomegaly.*

Ventriculomegaly is often associated with numerous CNS abnormalities. It can be divided as mild (10-12 mm), moderate (12-15 mm), or severe (>15 mm). The causes are many, but usually divided into 3 categories viz., obstructive, dysgenetic or destructive. Obstructive causes lead to enlargement of a normally formed ventricles and falx is seen as midline structures. Destructive causes of ventriculomegaly

are hemorrhage, ischemia, infectious, etc. Here, ventricular enlargement may be asymmetric, focal or diffuse.

Arnold-Chiari (Type II) Malformation (obstructive) is usually secondary to open myelomeningocele. The spinal defect causes downward displacement of the cerebellum through the foramen magnum leading to obliteration of cisterna magna. This obstructs flow of CSF through the fourth ventricle and posterior fossa leading to classical hydrocephalus.

Dandy-Walker malformation (obstructive) is characterized as cystic dilatation of the fourth ventricle, agenesis of the cerebellar vermis, and an enlarged posterior fossa with upward displacement of the tentorium. Many structural abnormalities are frequently associated with this.

Aqueductal Stenosis (obstructive) is due to the blockage of normal CSF flow through the aqueduct of Sylvius, and results in severe obstructive hydrocephalus.

Agenesis of the Corpus Callosum (dysgenetic) can be partial or complete. Ventriculomegaly is due to dilatation of the posterior portion (with normal anterior portion) of the lateral ventricles leading to a teardrop configuration. The ventricular walls are smooth and cortex and falx are intact. Schizencephaly (dysgenetic) is secondary to abnormal neuronal migration. At imaging, it is seen as a CSF cleft extending from the ventricle to the pial surface through the cortex. This may involve a large portion of the cortex.

Holoprosencephaly (dysgenetic) is resulted from failure of normal separation of the midline intracranial structures. The common types are alobar, semilobar, and lobar. The cavum septum pellucidum is absent. Sonographic findings with alobar holoprosencephaly are large mono ventricle, intact cortical mantle, absent falx and cavum septum pellucidum, fusion of the thalami and choroid, and a dorsal cyst. The posterior fossa is normal.

Intracranial Hemorrhage (destructive) is an uncommon prenatal occurrence. Typically, it presents in the third trimester. The hemorrhage frequently involves intraventricular and parenchymal components. Ventriculomegaly is frequently present, initially due to obstructive hydrocephalus from the hemorrhage and later as a result of porencephalic change. The ventricular wall is abnormally echogenic. Midline structures and the posterior fossa are normal.

Periventricular leukomalacia (destructive) is secondary to ischemic injury to the periventricular white matter, most commonly in peri trigonal region and frontal horns. This may be secondary to infection. Early findings are increased periventricular echogenicity and later ventriculomegaly. More severe cases may manifest as multiple cysts in a periventricular location. The ventricular walls are smooth. Midline structures and posterior fossa are normal in appearance.

Hydranencephaly is the most extreme form of destructive insult leading to complete liquefaction of the cerebral hemispheres. Various causes like occlusion of the internal carotid arteries, massive hypoxia and thromboembolism are implicated. Depending on the timing of the insult, remnants of cerebral cortex may persist or the head may appear completely replaced with fluid. The classic appearance is complete absence of the cortical mantle. Differentiation from severe hydrocephalus is critical, because each diagnosis carries a significantly different prognosis for the fetus. The falx is present due to blood supply from the external carotid artery. Structures supplied by the posterior circulation viz., thalami, choroid, brainstem, portions of occipital cortex, and posterior fossa are preserved.

CCAM is a rare developmental abnormality of the lung. It is characterized as benign hamartomatous or dysplastic lung tumors secondary to overgrowth of terminal bronchioles. It is usually unilateral and involves single lobe of the lung. There are 3 types of CCAM viz., macrocystic or microcystic or solid cystic adenomatoid malformations. The antenatal diagnosis of CCAM has become more frequent with higher resolution ultrasound imaging platforms. The outcome of CCAM is good, probably because of the high spontaneous regression rate of this tumor in the last trimester of pregnancy and in the early years of life. Maternal betamethasone administration also induces regression and may reverse fetal hydrops associated with CCAM.

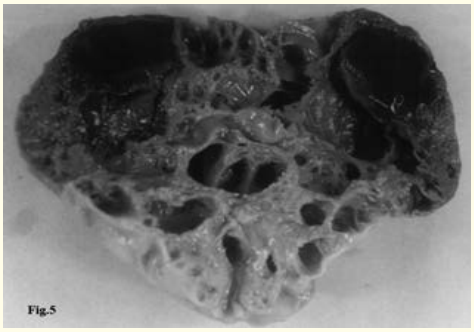

Figure 5: *Congenital cystic adenomatoid malformation (CCAM).*

Figure 6: *Cleft lip and palate or isolated cleft palate.*

Cleft of lip and palate is more common than isolated cleft palate. Often these could be part of chromosomal abnormality (trisomy 13; Figure 6A) or recognized syndrome or amniotic band syndrome (Figure 6B). This can be diagnosed prenatally by ultrasound particularly by 3D or by MRI.

Debatable ultrasound markers

Some ultrasound soft markers are seen during the scan and create confusion in appropriate interpretation, counseling and management due to a knowledge gap between these markers and their clinical significance. Example of these markers are echogenic focus in the heart, echogenic bowel, renal pyelectasis, mild ventriculomegaly, polydactyle, choroid plexus cyst, single umbilical artery and so on.

Echogenic focus of the heart

An echogenic focus of the heart is an echogenic area located in papillary muscles, move with the atrioventricular valve and can occur in either cardiac ventricles [25]. This may be associated with increased (5X) incidence with Down syndrome, however amniocentesis is not warranted in isolated cases [26]. When an echogenic focus in heart is identified then a detailed fetal scan is warranted to search for any associated anomalies. Amniocentesis should be considered in high-risk cases, such as > 35 years of age, associated abnormalities, other soft markers or history of previous chromosomally abnormal pregnancies, etc.

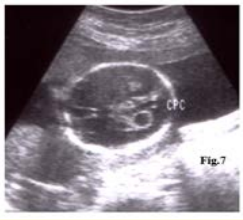

Figure 7: *Choroid plexus cyst.*

Choroid plexus cyst is seen in the choroid plexus of ventricles. They can be single or multiple, unilateral or bilateral and occur with an incidence of approximately 1%. Over 95% of these cysts resolves by the end of the second trimester [27]. The presence of a choroid plexus cyst is associated with increased risk of aneuploidy, in particular trisomy 18 and rarely with Down syndrome [23,28]. Most trisomy 18 fetuses have choroid plexus cysts in addition to other associated sonographic abnormalities [23,29]. American College of Obstetricians and Gynecologists recommends offering amniocentesis in isolated choroid plexus cyst only if the maternal age is >35 years or abnormal serum marker screen result [30]. It is suggested that a careful level II ultrasound examination should be advised on detailed fetal anatomy for any additional abnormalities in hands and feet, omphalocele, etc. In absence of risk factors parents should be advised that most of these cysts will disappear during pregnancy and that they are not associated with any long-term effects like mental retardation, cerebral palsy, or delayed development.

Echogenic bowel

The echogenic bowel on ultrasound examination is bright. It is reported in 0.2-1.4% of 2nd trimester fetal ultrasound and can be either diffuse or focal. When present it can be associated with aneuploidy (trisomy 21), congenital infection (CMV, toxoplasmosis, parvovirus), cystic fibrosis, intra amniotic bleeding and thalassemia [31]. The diagnosis is made by comparing the echogenicity of the bowel to that of the liver and adjacent bone. The prognosis of echogenic bowel depends mostly on whether or not it is associated with other fetal abnormalities. A study with 682 cases of echogenic bowel has shown birth of normal healthy baby in over 65% cases [32]. However, amniocentesis is required even in isolated case. Presence of ecogenic bowel in fetus warrants testing of parents for cystic fibrosis, CMV & toxoplasma infections.

Mild Ventriculomegaly

Ventriculomegaly is dilatation of cerebral ventricles beyond 10 mm. The mild ventriculomegaly ranges between 10-15 mm [33]. It can be an isolated finding or be associated with an underlying anomaly such as agenesis of the corpus callosum. Isolated ventriculomegaly may be associated with karyotype abnormality [34] and therefore need for karyotype analysis. The implication of mild ventriculomegaly without other underlying abnormality is confusing due to the lack of good quality postnatal follow-up studies. This makes antenatal counseling for this abnormality is very difficult, in particular in borderline cases.

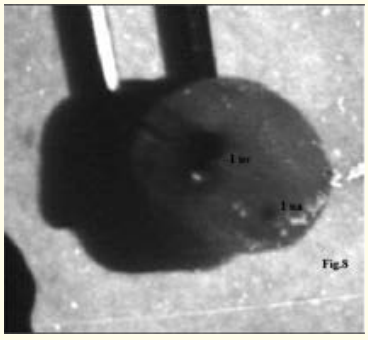

Figure 8: *Single umbilical artery.*

Prevalence of single umbilical artery is about 1% at birth [35]. It may result from primary aplasia of one of the two umbilical arteries or as a consequence of atrophy of one artery. It is more common in the left artery and more in twin gestation. It is sometimes accompanied with abnormal cord insertion in the placenta, i.e. marginal and velamentous cord insertions [35]. The sonographic diagnosis can be made either by visualizing a transverse section of cord or by color Doppler to identify both arteries on both sides of the bladder. Multiple segments of cord should be examined to exclude fusion of the two arteries. Single umbilical artery is associated more frequently with

chromosomal anomalies (in particular trisomy 18) [36], fetal anomalies and worse pregnancy outcome [37]. The most common associated anomalies are cardiac and genitourinary [37].

Renal pyelectasis

Dilatation of the renal pelvis is a common prenatal ultrasound finding. It is more common in male fetuses, and is often bilateral; however, if it is unilateral it is more likely to present on the left side. The pyelectasis may be associated with aneuploidy, mainly trisomy 21 in high-risk pregnancy [38], more so if associated with other anomalies [39]. In low-risk pregnancies, isolated mild pyelectasis does not increase aneuploidy [40] and does not justify amniocentesis [41]. Pyelectasis, in particular moderate to severe, can be a marker for possible urinary tract abnormality.

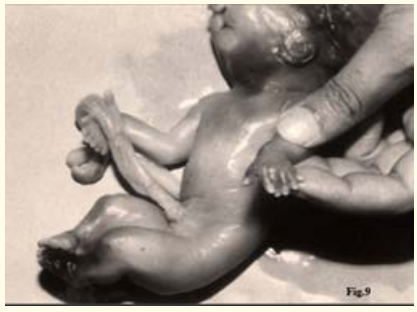

Figure 9: *Polydactyle.*

Polydactyle is the presence of extra finger or toe. Extra digit is either well developed or rudimentary with only soft tissue and no skeletal structure. The extra digit can be preaxial (radial or tibial side) or postaxial (ulnar or fibular side). Polydactyle may be present as part of a syndrome (Figure 9) or as an isolated finding. It is sometimes familial, so family history is very helpful to exclude the association with other abnormalities. Chromosomal study may be offered if there is no familial history of polydactyle. Patients should be informed that fetuses with an isolated finding of polydactyle usually have a favorable outcome, however, possibility of a rare anomaly, such as Bardet-Biedl syndrome cannot be excluded.

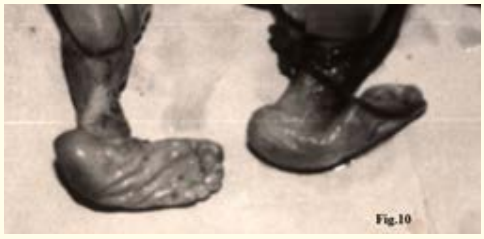

Figure 10: *Club foot/Talipes equinovarus.*

In talipes equinovarus deformity foot is excessively planter flexed with the forefoot bent medially and the sole facing inward. It occurs in 0.1-0.4% of pregnancies and is bilateral in 60% of cases. This may occur in isolation or in association with numerous conditions, such as general musculoskeletal disorders, arthrogryposis, genetic syndromes, neural tube defects and spine defects [42]. The risk of a subsequent pregnancy being affected by clubfoot is 2% if a previous male fetus was affected and 5% if the previous affected fetus was

female [43]. In 6-22% of cases it is associated with aneuploidy, in particular trisomy 18 [44]. Most cases of clubfoot with chromosomal anomalies also have other structural abnormalities. Therefore, chromosomal analysis is recommended in case of other additional structural anomalies. In the absence of other structural anomalies or oligohydramnios or IUGR isolated clubfoot is not associated with adverse pregnancy outcomes.

Controversies in Decision

Physician's approach to comply with parent requests for intervention between nonaggressive and aggressive fetal management varies widely. The other controversy is the limit of gestational age restrictions on the termination of severe malformation. Although many practitioners are limited by legal restrictions, others act solely on medical opinion. Expert opinion in this area generally agree that termination beyond the currently accepted gestational age of viability is ethical as the nature of these anomalies make these fetuses non-viable at any gestational age and may cause maternal morbidity and/or parental stress. Furthermore, in these circumstances there is no benefit to the fetus so an autonomy-based justification exists for offering termination at any gestational age in most nations. This has become acceptable due to availability of better medical methods of termination of pregnancy (anti-progesterone and prostaglandins). Another aspect of controversy is non-directive vs directive counseling. The issue of counseling strategies remains a subject of debate as demographic variables influence counseling, with experts advocating for both approaches depending on situations.

Conclusion

The cause of malformation is unknown in majority of cases at present. Systematic approach to fetal malformation including autopsy and biorepository will certainly improve detecting underlying etiology in near future. The possible association between environmental contaminants and malformation is an important concern, besides chromosomal, genomic (microdeletion/duplication), monogenic, epigenomic and multifactorial disorders. Without etiologic diagnosis, there is no way to provide accurate counseling and management, most importantly predictive & preventive medicine approach. Therefore, research is essential in this field to identify underlying etiology. Research with families affected by several pregnancies is absolute essential as these likely to provide positive associations. Studying (morphologic, genomic, epigenomic, proteomic, etc) embryos from the period when most developmental defects arise will be an important step towards understanding and perhaps eventually predicting and preventing fetal abnormality in future. Malformed fetal repository (whole, tissue, organ, blood, etc from affected, parents, unaffected, etc) as well as clinical details is first step towards achieving this goal. When a major malformation is identified in pregnancy, the parents should be referred to a tertiary ultrasound unit for repeat assessment and attempt to detect other anomalies, and if required then should be offered all other imaging techniques such as fetal echocardiography, ultrafast fetal MRI, etc. Every effort should be ensured for prenatal diagnosis from parental and fetal testing, even if involves invasive testing (chromosomal, specific molecular, etc). Then parents should be offered counseling and should be encouraged for complete fetal autopsy as well as biorepository in case of termination or perinatal death. Finally, but most importantly, family with multiple affected fetus should be referred to a genetic center to find out underlying genetic cause which is most likely contribute for better future (prediction and prevention) in this field.

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