

Fetal Dysmorphology: An Indispensable Tool for Synthesis of Perinatal Diagnosis

Shagun Aggarwal

Department of Medical Genetics, Nizam's Institute of Medical Sciences, Hyderabad &

Centre for DNA Fingerprinting and Diagnostics, Hyderabad

Email: shagun.genetics@gmail.com

Introduction

Dysmorphology is the science (and art!) of studying abnormal form, with special emphasis on subtle findings which provide clue to an underlying diagnosis, mostly a genetic syndrome. It has been the prime tool of the geneticist enabling a syndromic diagnosis on basis of patient's gestalt with findings like a white forelock, heterochromia iridis, broad thumb, asymmetric crying facies and many other subtle features acting as decisive tools in the genetics clinic. Most individuals with dysmorphism are affected with genetic syndromes, which can be due to chromosomal abnormalities, copy number variations or single gene defects. However, various environmental factors can also lead to dysmorphism, many times mimicking specific genetic syndromes due to involvement of a common biological pathway. A dysmorphological evaluation typically involves a head to toe examination looking for malformations, and minor features showing deviation from the expected norm as per sex, age, family background and ethnicity. This often forms the first and most crucial step in establishing a genetic diagnosis and is subsequently followed by relevant genetic testing for confirmation. In the era of next generation sequencing when the rate of gene discovery has surpassed the clinical recognition of a new genetic syndrome and reverse phenotyping has become commonplace, dysmorphology still remains an important tool in the hands of an experienced geneticist.

Although as a discipline dysmorphology evolved in the paediatrics setting, it can be extended to the fetal life to enable the diagnosis of a genetic syndrome in the fetus. The recognition of a genetic syndrome in particular, has important implications

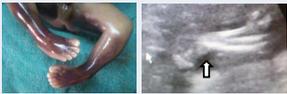
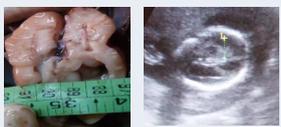
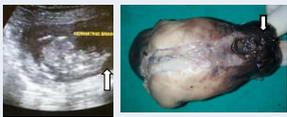
for pregnancy management as it aids in accurate prognostication and communicating the possibility of intellectual disability and other co-morbidities in such children, helps in decision-making regarding termination or continuation of pregnancy, facilitates appropriate postnatal management and also provides recurrence risk estimates for subsequent conceptions. In the postnatal scenario, such a diagnosis facilitates emotional closure, recurrence risk counseling and early, definitive prenatal diagnosis in subsequent pregnancies.

Any morphological or growth abnormality in the fetal life can be an isolated abnormality of multifactorial origin, the consequence of environmental etiologies like a teratogenic insult, intrauterine factors, maternal illness, etc. or a component of a genetic syndrome. In such a scenario, it is important to be aware of these possibilities, and perform a complete dysmorphological evaluation with an aim to distinguish between these different situations with varied prognosis and recurrence risks. Figure 1 shows some common fetal abnormalities and respective etiologies.

Setting of fetal dysmorphology

There are two main settings where syndromic diagnosis in the fetus is a possibility and should be actively looked for:

- a. Abnormal antenatal ultrasound.
- b. Postmortem evaluation of an unexplained fetal demise or morphologically abnormal fetus.
 - **Abnormal antenatal ultrasound:** Abnormalities on antenatal ultrasound can be found in 5-10% of pregnancies. These can vary from growth abnormalities, major or minor malformations, soft

Fetal abnormality		Acquired etiologies	Genetic etiologies
	Naso-maxillary hypoplasia/Binder facies	<ul style="list-style-type: none"> Fetal warfarin syndrome Vitamin K deficiency 	<ul style="list-style-type: none"> Brachytelephalangi chondrodysplasia punctata Keutel syndrome Vitamin K metabolism defects
	Talipes-equinovarus	<ul style="list-style-type: none"> Oligohydramnios Uterine malformations Multiple pregnancy 	<ul style="list-style-type: none"> Chromosomal disorders: sex chromosome aneuploidy Neuromuscular disorders Skeletal dysplasias
	Cleft lip	<ul style="list-style-type: none"> Multifactorial Fetal hydantoin syndrome 	<ul style="list-style-type: none"> Isolated Mendelian* Syndromic- chromosomal disorders, copy number abnormalities or Mendelian disorders#
	Ventriculomegaly	<ul style="list-style-type: none"> Fetal infections Intracranial hemorrhage Associated with neural tube defect (multifactorial) 	<ul style="list-style-type: none"> Isolated Mendelian* Syndromic- Chromosomal disorders Copy number abnormalities Mendelian disorders#
	Hydrops fetalis	<ul style="list-style-type: none"> Blood group antigen isoimmunisation Fetal infections esp. Parvovirus Hypothyroidism Congenital heart block, fetal arrhythmias Cardiac defects 	<ul style="list-style-type: none"> Chromosomal disorders: Turner syndrome, Down syndrome Mendelian disorders#: Noonan syndrome, primary lymphatic dysplasias, alpha thalassemia, lysosomal storage disorders, others
	Neural tube defect	<ul style="list-style-type: none"> Maternal diabetes Maternal hyperthermia Folate deficiency 	<ul style="list-style-type: none"> Isolated Mendelian* Syndromic- Chromosomal, Mendelian# eg. Meckel-Gruber syndrome, Spondylocostal dysostosis

*Isolated Mendelian: Isolated defect due to mutation in single gene
 #Syndromic Mendelian disorder: A spectrum of multiple defects arising due to mutation in single gene

Figure 1 Common fetal abnormalities and their etiologies.

markers and liquor or placental abnormalities. At least 10-30% of prenatally detected malformations are due to a genetic etiology (Beke et al., 2005). This figure is much higher for specific abnormalities like omphalocele, holoprosencephaly and cystic hygroma where 50-90% cases can be attributed to genetic abnormalities involving the chromosomes. In each of these scenarios, the antenatal ultrasonography should be performed by a fetal medicine specialist with a dysmorphology or clinical genetics knowledge. Alternatively, a clinical geneticist consultation should be sought,

along with relevant images to enable recognition of dysmorphic facies, recognize the pattern of abnormalities and elicit a detailed family history, which would help in synthesis of a syndromic diagnosis. The advent of 3D ultrasound technology provides opportunity for facial dysmorphism recognition, and can be used as an adjunct to the conventional 2D ultrasonography.

- **Postmortem evaluation/ Fetal autopsy:** Post-mortem evaluation is an important modality for establishing the cause of unexplained fetal

deaths as well as a medically terminated morphologically abnormal fetus. At least 15-30% of stillbirths are reported to be due to genetic causes (Reddy et al., 2012). Besides the histopathological examination of the placenta which provides evidence of acquired insults like utero-placental insufficiency and perinatal infections, dysmorphological evaluation by a geneticist or perinatal pathologist with expertise in dysmorphology is essential for syndrome recognition. Various studies indicate that autopsy provides additional findings or modifies the antenatal diagnosis in 20-50% cases (Rodriguez et al., 2014). Antenatal series have also shown that at least 50% syndromic diagnoses are possible only after an autopsy (Stoll et al., 2003). Hence, all cases with abnormal ultrasound findings should undergo a post-mortem evaluation.

Practical approach to fetal dysmorphology

The evaluation of the fetus in-utero and/or post-mortem for syndrome recognition involves the following steps (depicted in figure 2):

- Antenatal and medical history
 - Family history
 - Ultrasonographic findings
 - Reports of serum aneuploidy screen
 - Postmortem evaluation
 - Genetic testing
- **Antenatal history:** The woman should be asked about history of potential teratogenic exposure in the form of prescription drugs, high grade fever, exposure to environmental toxins and infection with teratogenic pathogens like rubella, cytomegalovirus, etc. History of decreased fetal movement perception and malpresentations is important in cases with arthrogryposis, polyhydramnios and small stomach bubble, where these finds can provide a clue regarding a primary neuromuscular disorder in the fetus. History of previous pregnancies is also important, as previous pregnancy losses, pregnancy terminations due to similar or overlapping findings, neonatal deaths or previous live abnormal offspring all indicate possible segregation of a genetic disorder in the family.
 - **Medical history:** History of maternal illness like uncontrolled diabetes, phenylketonuria, thyroid disorders, etc. needs to be elicited as they can play an important role in fetal growth and devel-

opment. Maternal drug use especially antiepileptic drugs, coumarin derivatives, ACE inhibitors and some rarer drugs like retinoic acid derivatives, thalidomide, etc. needs to be ascertained as these are known to be potent fetal teratogens. Some of these can result in fetal malformations which mimic genetic disorders involving defects in the common biological pathway. An example is fetal warfarin syndrome, arising due to exposure to warfarin in the first half of pregnancy. Warfarin inhibits the activity of Vitamin K, and its fetal effects are similar to a genetic disorder brachytelephalangi chondrodysplasia punctata which is caused by a mutation in the *ARSE* gene, important for Vitamin K metabolism in the body.

- **Family history:** A three-generation family pedigree forms the cornerstone of the family history ascertainment. This can provide important information like consanguinity, which increases the risk of autosomal recessive disorders; previous fetus or child with similar or overlapping phenotype; other family members with pregnancy losses, infertility or abnormal offspring indicating possibility of a chromosomal rearrangement or single gene etiology; and at times a parent with milder manifestation of the same condition as the fetus.

- **Ultrasonographic findings:** Various ultrasonographic findings may be a manifestation of an underlying genetic syndrome in the fetus and a high degree of suspicion as well as careful search for associated abnormality(ies) is important to recognise these.

- a. **Structural/ morphological abnormality:** These most commonly are malformations i.e. intrinsic defects in the formation of a structure, but can also be deformations due to compressive effects on a normally formed structure e.g. varus deformity in oligohydramnios, or disruptions due to sudden insult, traumatic or vascular on a normally formed structure e.g. amputation due to amniotic band. Malformations or intrinsic defects are likely to be of genetic etiology. They may be isolated or may be associated with other malformations and/or growth problems which indicate an underlying genetic syndrome. A specific spectrum of abnormalities may be characteristic of a specific genetic syndrome e.g. Meckel Gruber syndrome presents with encephalocele, polydactyly and multicystic dysplastic kidneys; trisomy 13 presents with holoprosencephaly, midline cleft, polydactyly and multicystic dysplastic kidneys; and similarly many other patterns of malformations indicating a par-

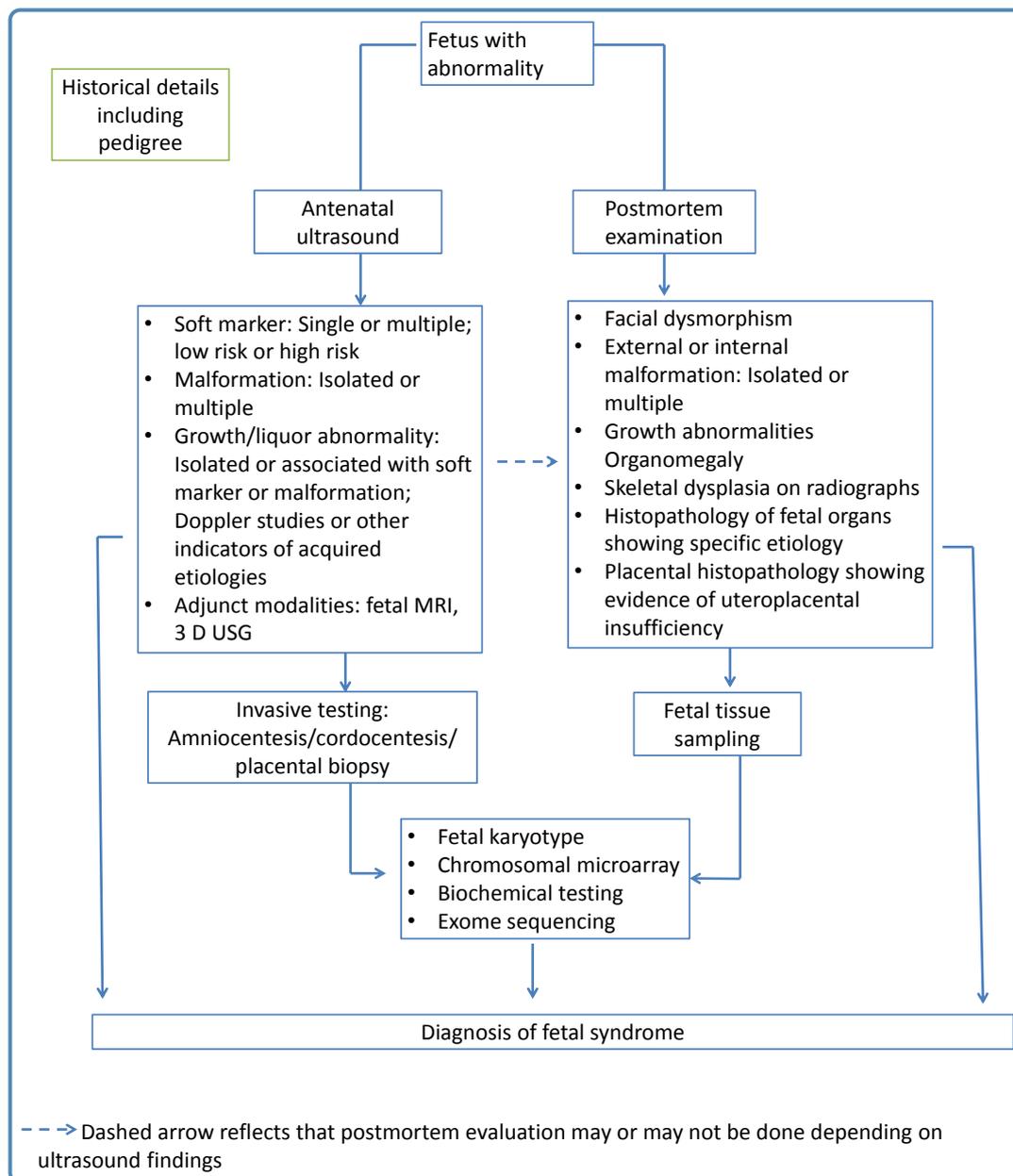


Figure 2 Practical approach to fetal syndrome diagnosis.

ticular diagnosis. As a rule, multiple abnormalities per se indicate possibility of a genetic syndrome, whereas a single malformation may or may not be genetic in etiology.

b. Soft markers: These are ultrasound findings, which may be seen in many normal fetuses, but are also indicators of underlying syndromic etiology, primarily chromosomal disorders in some fetuses. Many soft markers have been described and the risk of chromosomal disorders associated with

each has been statistically quantified. These risks are integrated with the maternal demographics and serum screening risks to provide a final aneuploidy risk, which is then used for decision-making regarding invasive testing and fetal karyotyping. Similar to malformations, presence of multiple markers increases the risk of chromosomal aneuploidy more significantly.

c. Growth abnormalities: Both fetal growth restriction as well as fetal overgrowth can be due

Fetal abnormality		Genetic syndromes reported to be associated
	Increased nuchal fold thickness	<ul style="list-style-type: none"> • Trisomy 21 • Other trisomies • Noonan syndrome • Skeletal dysplasias: Achondrogenesis, osteogenesis imperfecta
	Absent nasal bone	<ul style="list-style-type: none"> • Trisomy 21 • Skeletal dysplasias: asphyxiating thoracic dystrophy, brachytelephalangi chondrodysplasia punctata
	Short long bones	<ul style="list-style-type: none"> • Skeletal dysplasias: Various with distinctive features like fractures, bending, macrocephaly, polydactyly • Syndromes with primordial short stature
	Multicystic dysplastic kidney	<ul style="list-style-type: none"> • Trisomy 13 • Meckel-Gruber syndrome and other ciliopathies

Figure 3 Common ultrasound abnormalities and associated genetic syndromes.

to maternal and utero-placental factors or due to an intrinsic fetal abnormality. Besides chromosomal disorders, various single gene disorders like microcephalic osteodysplastic dwarfism, Seckel syndrome, Smith-Lemli Opitz syndrome (SLOS), Russel-Silver syndrome, etc. can present with intrauterine growth restriction (IUGR). Another important group of disorders presenting with short bones and mimicking IUGR is the skeletal dysplasia group, which includes at least 100 different single gene conditions presenting in the prenatal period. Fetal overgrowth may also be due to primary overgrowth disorders like Beckwith-Wiedemann syndrome(BWS), Pallister-Killian syndrome and Weaver syndrome, among others. Hence, it is important to look for additional findings like facial dysmorphism and malformations in all cases of fetal growth abnormalities, where no acquired etiology is apparent. At times, maternal serum screen results can provide clues to the un-

derlying genetic etiology, such as low estriol levels in SLOS and high alfa-fetoprotein in BWS.

d. Liquor abnormalities: Both excess and scanty liquor can be due to underlying genetic etiologies, eg Bartter syndrome in polyhydramnios and autosomal recessive polycystic kidney disease in oligohydramnios. At times, these could be indicators of other underlying morphological abnormalities, indicating a syndromic diagnosis.

Figure 3 depicts some common ultrasound abnormalities and associated genetic syndromes.

- **Maternal serum screen:** These are biomarkers in the maternal serum which are assayed with the primary aim to screen for common fetal chromosomal abnormalities. Both first and second trimester screening protocols are available, which in combination with ultrasonic soft markers aid in screening of low risk women for fetal chromosomal disorders with high sensitivity and low false positive rates. However, these markers are primarily useful

for a few specific conditions, and the detection of most fetal genetic syndromes are on basis of

ultrasound findings and historical data as detailed above.

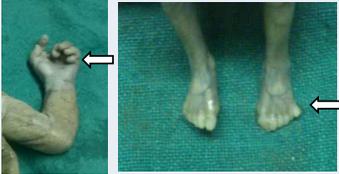
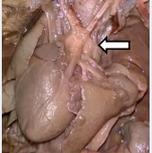
Postmortem external or internal abnormality		Genetic syndromes reported to be associated
	Radial ray defect	<ul style="list-style-type: none"> • Trisomy 18 • VACTERL association • Fanconi anemia • TAR syndrome • SALL4 mutation • Rothmund-Thomson syndrome
	Polydactyly	<ul style="list-style-type: none"> • Trisomy 13 • Meckel-Gruber syndrome and other ciliopathies • Orofaciodigital syndrome • Pallister-Hall syndrome and other GLI3 disorders • At least 400 different disorders
	Overlapping fingers	<ul style="list-style-type: none"> • Trisomy 18 • Distal arthrogryposis • Otopalatodigital syndrome
	Arthrogryposis multiplex congenita	<ul style="list-style-type: none"> • Trisomy 18 • Multiple pterygium syndrome • Neuromuscular disorders • Skeletal dysplasias • Connective tissue disorders • At least 300 different disorders
	Cleft Palate	<ul style="list-style-type: none"> • 22q11.2 deletion • Stickler syndrome • Smith-Lemli-Opitz syndrome • Otopalatodigital syndrome • Orofaciodigital syndrome
	Congenital diaphragmatic hernia	<ul style="list-style-type: none"> • Fryns syndrome • Simpson-Golabi-Behmel syndrome • Pallister-Killian syndrome • Donnai-Barrow syndrome
	Truncus arteriosus	<ul style="list-style-type: none"> • 22q11.2 deletion • Trisomies • Holt-Oram syndrome • Townes-Brocks syndrome
	Dandy-Walker malformation	<ul style="list-style-type: none"> • Walker-Warburg syndrome • Trisomies • Ritscher-Schinzel syndrome • Meckel-Gruber syndrome • Congenital disorder of glycosylation • Orofaciodigital syndrome

Figure 4 Common postmortem dysmorphic findings and associated genetic syndromes.

- **Postmortem evaluation/fetal autopsy:** This involves a comprehensive and step-wise evaluation of the fetus in a post-mortem setting and forms the single most important modality for diagnosis of a genetic syndrome. Typically, autopsy encompasses an external examination or dysmorphological evaluation of the fetus, similar to the approach in a clinical genetics clinic; internal dissection to look for gross morphological abnormalities of fetal organs and structures; whole body radiogram, both antero-posterior and lateral views; and histopathological evaluation of fetal organs and placenta. A standard autopsy proforma helps in maintaining record of the findings. Briefly, the following are the steps, relevant findings and implications during an autopsy:

a. Radiographs: A complete fetal radiograph is essential for diagnosis of a skeletal dysplasia and in distinguishing the various types from each other. Cardinal features like platyspondyly, flaring of ends of femur, bent femur, fractures, absent ossification, epiphyseal stippling, etc. all help in providing diagnosis of a specific condition. A radiograph can also provide ancillary information like joint dislocations, spine deformities, missing or supernumerary bones, etc., which may help in diagnosis of a specific genetic syndrome.

b. External/Dysmorphological examination: This involves assessment of anthropometric parameters like crown rump length, crown heel length, head circumference, chest circumference and foot length. Other parameters like inter-orbital distance, hand length, philtrum length, phallus length, and limb segment length may also be assessed as required. All the parameters should be compared to available centile charts and recorded. This is followed by a head to toe examination with special attention to dysmorphic features. The head, face, neck, spine, chest, abdomen, external genitalia, extremities, joints and skin are assessed for shape, size and appearance, and any deviation from normal searched for and noted. The placenta, membranes and umbilical cord are also examined for appearance and any abnormality. The weight of the placenta and number of cord vessels are recorded. Figure 4 provides some dysmorphic features and the corresponding genetic syndromes associated with these.

c. Internal examination: This involves the examination of the intra-abdominal, intra-thoracic and intra-cranial structures for any abnormalities, in size, shape or morphology. Incision is made on the anterior aspect of the trunk and the skull following

standard techniques. It is important to be aware of some normal gestation-dependent findings, like the lobulated appearance of fetal kidney, the relative large size of adrenals, thymus and liver, the developing internal genitalia and lung fissures and the smooth brain surface in early gestation among others. Gestation-specific photographs should be used for comparison before concluding a structure as abnormal. Figure 5 provides some normal gestation-dependent findings. Figure 4 depicts some internal organ abnormalities and respective associated genetic syndromes.

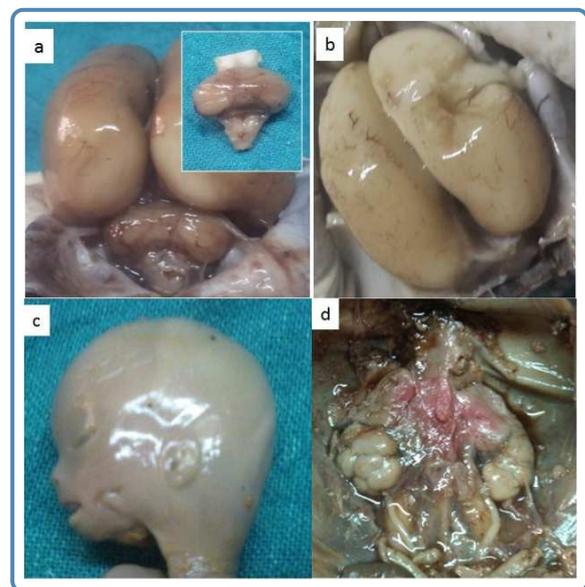


Figure 5 Some gestation-dependent normal morphological findings in fetal life a: Blake pouch cyst with normal cerebellum (inset) at 19 weeks; b: Smooth brain at 19 weeks gestation; c: Low set and poorly formed ear placode in a first trimester fetus; d: Lobulated fetal kidneys similar in size to fetal adrenals at mid-trimester.

d. Gross examination and histopathology of fetal organs: All fetal organs are weighed and compared with gestation-dependent percentiles. A detailed histopathological evaluation is performed, using H&E staining, and if necessary special stains and immunohistochemistry. Many renal and brain pathologies can be well delineated following histopathology and in many instances this forms the sole basis for diagnosis. An example being cystic diseases of kidney, where histopathology can distinguish between autosomal recessive,

dominant polycystic kidneys, multicystic dysplastic kidneys and glomerulocystic kidney disease, all of which can have a similar gross appearance and clinical presentation. Similarly, brain pathologies like neuronal migration disorders can be well delineated and classified on histopathology. Placental histopathology can provide evidence of uteroplacental insufficiency and fetal infections.

This comprehensive approach to an abnormal fetus, using historical, imaging and postmortem findings provides important diagnostic information and often leads to the diagnosis of a specific dysmorphic syndrome or identification of an acquired etiology. However, final confirmation of a genetic etiology depends on laboratory testing and identification of the underlying genetic aberration.

Genetic testing for the dysmorphic fetus

Genetic disorders can broadly be classified into three different types, and each of these require a specific laboratory diagnostic approach.

a. Chromosomal disorders: These are disorders arising due to numerical or structural abnormalities in chromosomes. The common ones with well described prenatal phenotypes are Down syndrome (Trisomy 21), Patau syndrome (Trisomy 13), Edward syndrome (Trisomy 18), Turner syndrome and triploidy. A karyotype from the amniotic fluid (following amniocentesis), cord blood (following cordocentesis or at birth), intra-cardiac blood (post mortem) or skin fibroblasts, is the gold standard for the diagnosis of this group of disorders. These on average constitute 10-30% of fetuses with an antenatal malformation (Beke et al., 2005). Since karyotyping requires the presence of viable cells, it is essential to obtain suitable samples antenatally or soon after birth for this investigation.

b. Single gene disorders/ Mendelian disorders: These are diseases arising due to mutations in individual genes. At least 6000 single gene disorders have been described and for 4500 of them the molecular basis is known. Many of these disorders present in the prenatal period with fetal abnormalities, some common examples being Meckel-Gruber syndrome, Noonan syndrome, short rib polydactyly syndromes, lysosomal storage disorders, etc. The exact estimate of such disorders in the prenatal period is not known, however some recent studies employing Next generation sequencing-based novel technologies have found single gene defects in 20-30% of fetuses with antenatal malformations (Drury et al., 2015). The diagnosis of these dis-

orders is challenging in the laboratory as many conditions have overlapping features and genetic heterogeneity is common. Conventionally, most often the diagnosis was made following a post-mortem evaluation, and then subsequent targeted testing was done by Sanger sequencing of the causative gene in the fetal DNA. However, availability of the Next generation sequencing technology has made it easier to provide molecular testing, as this enables the parallel sequencing of multiple genes enabling interrogation of overlapping phenotypes as well as genetically heterogeneous conditions. An example would be the skeletal dysplasias, with at least 100 different single gene disorders presenting with short bones on antenatal ultrasound. Exact diagnosis is often not possible antenatally, and fetal sampling followed by a NGS-based testing of all skeletal dysplasia genes can be done to arrive at a final diagnosis and provide accurate prognostication to the family.

c. Genomic disorders: Another group of genetic diseases are caused by copy number abnormalities in the genome i.e. small, submicroscopic microdeletions or microduplications involving part of the genome. These conditions require special molecular cytogenetic techniques for diagnosis, and often in the antenatal period, where a specific diagnosis is not apparent, a chromosomal microarray is the most common testing modality used. Various antenatal series have found that chromosomal microarray studies from fetal DNA of a morphologically abnormal fetus indicate a copy number abnormality in 6-10% (de Wit et al., 2014). Presently, microarray studies are recommended as first tier test in case of morphological abnormalities on ultrasound. Postnatal studies have also found 2-10% of stillbirths as having copy number abnormalities, indicating the significant contribution of this group of genetic aberrations to fetal abnormalities (Reddy et al., 2012).

d. A relatively rarer type of genetic disorders known as imprinting disorders can also present with fetal abnormalities, primarily affecting growth. Examples being Beckwith-Wiedemann syndrome presenting with overgrowth, organomegaly, omphalocele and polyhydramnios; and Russel-Silver syndrome presenting with fetal growth restriction. Testing for these conditions requires methylation studies on fetal DNA.

Unlike samples for karyotyping, which require viable cells, fetal DNA can be obtained from any fetal sample, including an umbilical cord segment, either antenatally or post-mortem. The

only prerequisite for suitable DNA sample is that the concerned sample should not be exposed to formalin, which can lead to cross linkage, adduct formation and fragmentation of DNA, precluding further molecular studies. Hence, to facilitate laboratory testing and confirmation of a genetic diagnosis, suitable fetal sample should be obtained and stored if immediate testing is not possible. Storage for purpose of DNA extraction can be done at 2-8°C for few weeks and at -20°C for long term. For karyotyping, sample can be stored at 2-8°C and be transferred to the laboratory as soon as possible, and at least within 48 hours.

Genetic counseling

Appropriate genetic counselling is possible after an accurate diagnosis has been made following the clinical and laboratory evaluations. Counseling typically addresses the following issues:

1. *Prognosis*: This is relevant in the antenatal setting when a couple is faced with an ultrasound diagnosis of a fetal abnormality. Besides the morbidities of the abnormality and outcome of postnatal surgery in structural abnormalities, the recognition of a syndrome has various implications. Most genetic syndromes are associated with intellectual handicap, which does not have a satisfactory therapy. Additionally, there can be growth issues, presence of other internal malformations not detectable by imaging, and occasionally premature lethality. This information needs to be communicated to the couple as it helps in decision making regarding pregnancy termination, obstetric management as well as neonatal management.

2. *Recurrence risk*: There is an increased recurrence risk associated with genetic etiologies, which is 25% for autosomal recessive disorders, 50% for an autosomal dominant disorder with affected parent and 50% for male offspring of a carrier female for X-linked recessive disorders. The risk is low for chromosomal disorders, unless they arise due to a parental chromosomal rearrangement and for autosomal dominant disorders with normal parents. This risk estimate helps the couple in availing prenatal diagnosis services in subsequent pregnancies, and the need and availability of the same should be communicated.

3. *Prenatal diagnosis*: The pre-requisite to definitive prenatal diagnosis in subsequent pregnancies is identification of the underlying genetic aberration

in the affected fetus. Hence, laboratory genetic testing and confirmation of the clinical diagnosis plays an important role in fetal dysmorphism. Once the exact mutation or chromosomal abnormality or biochemical defect in the index case is known, early and definitive prenatal diagnosis is possible by chorionic villus sampling at 11-12 weeks in subsequent conceptions. In absence of a laboratory diagnosis, prenatal diagnosis can be attempted by ultrasound, however this may not be of utility till later in pregnancy, and milder or discordant manifestations may not be detected. These issues need to be discussed with the family prior to pregnancy termination, so that appropriate fetal samples can be obtained.

Conclusion

Fetal dysmorphism plays an important role in evaluation of an abnormal fetus with far reaching implications for the current as well as future pregnancies. A multi-disciplinary approach, with clinical geneticist playing a pivotal role is integral to optimising the care of these special patients and their families.

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