Newborns with Congenital Malformations

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Abbreviations

AD	Autosomal dominant
AR	Autosomal recessive
CM	Congenital malformation
MRI	Magnetic resonance imaging
NIPT	Noninvasive prenatal testing
NS	Noonan syndrome

3.1 Introduction

Congenital malformations (CMs) are one of the main causes of the global burden of disease. CM may result in disabilities that may be physical, intellectual, or developmental. The disabilities can range from mild to severe. It is quite difficult to define CM in one sentence only. CMs are defined as structural or irreversible functional anomalies of prenatal origin that can affect almost one or more parts of the body, regardless of their cause. CMs may be diagnosed during pregnancy, at birth, during life, or postmortem. It is generally accepted that 3–4% of children are affected by congenital malformations [1–4].

Some CMs can be treated with surgical or nonsurgical options, such as cleft lip and/or palate, clubfoot, and atresia or stenosis. Others, including heart defects, neural tube defects, and Down syndrome (DS), can cause lifelong impacts. Different degrees of CMs require different surgical approaches: from cosmetic (exeresis of a postaxial polydactyly) to high surgical treatment (heart transplant in severe hypoplastic left heart syndrome and similar extreme forms of congenital heart disease) or with the use of therapeutic treatment for all the person's life (i.e., congenital hypothyroidism) [5–8].

The impact of CMs on clinical and social approaches is high. Almost all birth defect syndromes are rare, and a practicing physician would be expected to see only a limited number of such cases in his professional life. Because of the rarity of some disorders, even a specialist in this field will never gain experience in all of them. The recognition and analysis of various component anomalies are fundamental to reaching a correct diagnosis, with implications on the best way to treat and approach the defects [2, 9, 10].

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3.2 Pathogenetic Mechanism

Four different pathogenetic mechanisms of structural anomalies are indicated by the terms deformation, disruption, dysplasia, and malformation [7]

1. *Deformation*: this is caused by an abnormal external force acting on the fetus during its development. It results in the abnormal growth and formation of fetal structures. Fetuses that grow in a uterine environment where not enough amniotic fluid is present (oligohydramnios) may have a flattened face (Fig. 3.1) due to the compression of the head against the uterine wall, with no room for movement. Similar considerations could be made for positional foot abnormalities, such as calcaneovalgus foot or metatarsus adduct (Fig. 3.2) [4].
2. *Disruption*: this results from destructive processes that alter the fetal structure during organogenesis, i.e., in amniotic bands. The mechanism causing this injury is still unclear, but the resulting lesions range from shallow constricting rings with modifications of the lymphatic and hematological circulation to determine amputation or cutaneous rings, above all, in the distal parts of the fetal body, i.e., hands or feet.
3. *Dysplasia*: it is due to an abnormal cellular organization or function within a specific tissue, resulting in clinically evident structural and anatomical changes. It is a histologic diagnosis and refers to focal diffuse or segmentally arranged primitive structures. An important aspect of most dysplastic conditions is their continued course. Since the tissue itself is abnormal, clinical effects may persist or worsen as long as the tissue contin-

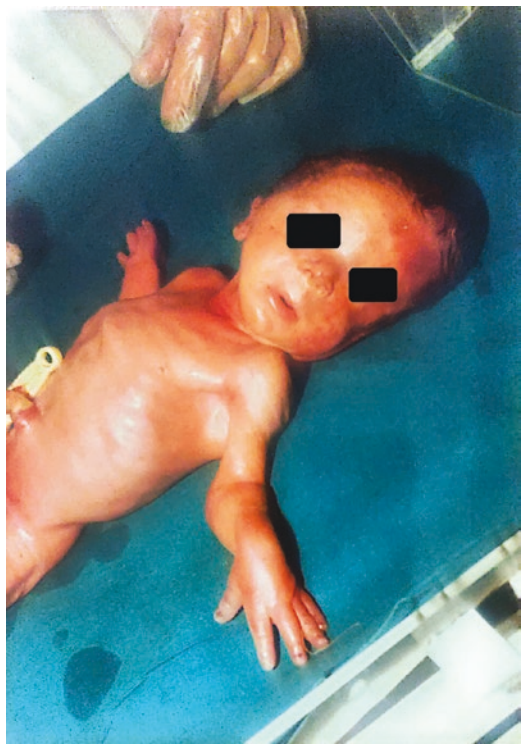

Fig. 3.1 Newborn with a flattened face. Pregnancy was complicated by polyhydramnios, with subsequent compression of the head against the uterine wall with no room for movement

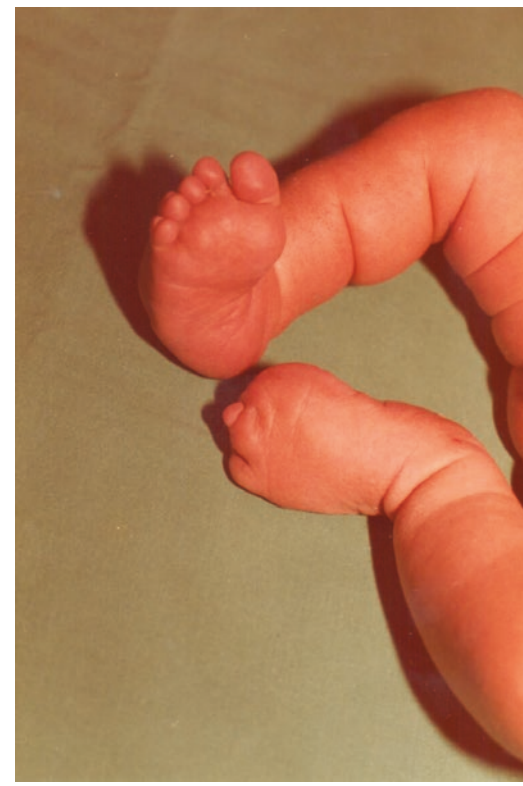

Fig. 3.2 Left finger-foot amputation and right metatarsus adductus foot

ues to grow or function. Almost all the dysplasia forms seem to be caused by a major mutant gene. Examples include metabolic disorders such as storage diseases, i.e., skeletal (achondroplasia) and ectodermal dysplasia (hypohidrotic ectodermal dysplasia XL-R) or renal dysplasia. Dysplasia can continue to produce dysmorphic changes throughout life.

4. *Malformation*: malformations are structural defects in the body due to abnormal embryonic development. They could be consequences of the failure or inadequate completion of embryological processes. As the earliest developmental alteration happens, more important is the damage to the tissue or organ involved. Alterations in the cellular and/or molecular interactions within any particular organ can cause abnormal development, which leads to defective organogenesis till the death of the embryo. The anomaly does not imply any specific etiology but is related to an early error in embryonic development. The result of damage in the fetal period is above all related to the growth and complexity of already differentiated organs, and true malformations arising in this period are quite rare.

3.3 Clinical Classification of Congenital Malformations

The best way to approach the complexity of CMs is to consider the relationship of one defect to another. An anomaly that occurred as isolated has a different significance if the same defect occurs in connection with others [11–15].

(a) Single defects

Malformation occurs only in one single organ or part of the body. In this group are included the majority of birth defects: congenital heart defects, esophageal and gastrointestinal atresia, anorectal atresia, cleft lip/palate, or atresia auris (Figs. 3.3 and 3.4). Most of these conditions are thought to have a multifactorial origin. These may result as a consequence of the impact of environmental factors with multiple genes not able to determine the effect by themselves. In a few other cases, a genetic cause is recognized not always based on Mendelian inheritance patterns, which leads one to think of the role of minor genes. Rarely do the single-system defects, however, show a high degree of concordance in monozygotic twins, which supports the hypothesis of nongenetic factors in their origin.

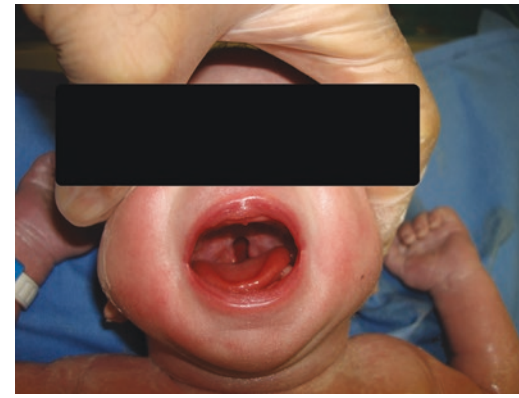

Fig. 3.3 Hard and soft cleft palate

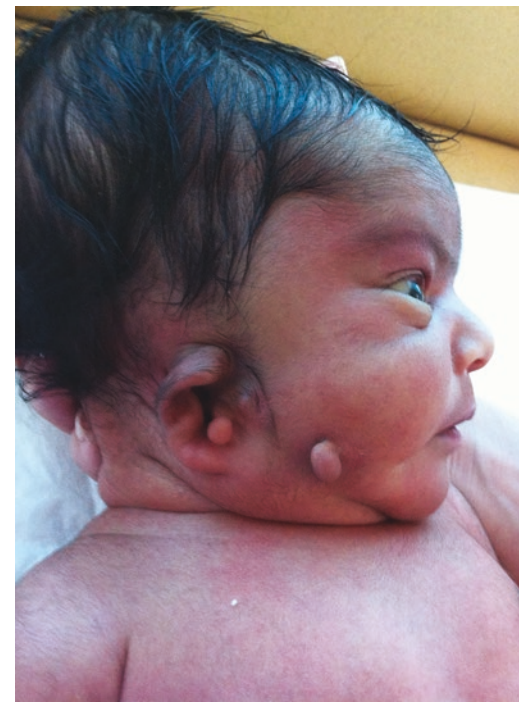

Fig. 3.4 Right mandibular hypoplasia, microtia and accessory prearicular tags. (Hemifacial Microsomia)

(b) Sequences

A sequence is a group of related anomalies that generally originate from a single initial major anomaly that alters the development of other surrounding or related tissues or structures [4]. Malformation sequences may be caused by genetic as well as environmental factors. The primary anomaly interferes with regular embryologic developmental processes, and at birth, the neonate seems to show multiple defects. The oligohydramnios sequence (Potter sequence) is a well-known example where agenesis of the kidneys or other urinary tract anomalies leads to pulmonary hypoplasia and deformations on the fetus, like a dysmorphic face. Spina bifida, for example, is frequently associated with clubfoot, which is closely related to spinal cord injury. The Pierre-Robin sequence, too, is an example in which a set of abnormalities affecting the head and face, consisting of hypoplasia of the mandibular area (micrognathia), glossoptosis (an incorrect placement or displacement of the tongue), that can result in an obstruction of the airways. Early mandibular retrognathia is the primary anomaly that can explain the cascade of events. Most neonates affected by the Pierre-Robin sequence show cleft palate, even though it is not generally considered necessary for the diagnosis of the condition [5, 11, 14, 16].

(c) Syndromes

When multiple congenital anomalies, which are not part of one sequence but may involve several sequences, are thought to be due to a single cause, this is called a syndrome (from Greek "syn" and "drome," in other words, "running together") [4]. When the etiology of a syndrome is detected, the initial designation, known as eponymous, should be abandoned in favor of the specific etiological origin. For chromosomal anomalies, the definitive name should arise from the altered chromosome: for example, Down syndrome, by the eponymous John Langdon Down, who in 1866 described for the first time the condition, should be better defined as trisomy 21 (T-21) for the presence of chromosome 21 triplicate. In the same way, DiGeorge syndrome, reported by DiGeorge in 1965 (also known as conotruncal anomaly face syndrome, described by Takao in 1976, and velocardiofacial syndrome, described by Shprintzen in 1978), should be better described as CATCH 22 syndrome due to the variable deletion of genetic materials by the long arm of chromosome 22. In the case of monogenic disorders, which are caused predominantly by a lesion of a single gene, the phenotypic manifestation may depend, to various extents, on additional genetic variants in the same or other genes, on epigenetic changes, and on environmental factors. In the Noonan syndrome (NS), the most frequent monogenic disorder occurring approximately in 1000–2500 children, the first most common genetic cause is still PTPN11 mutations, observed in 42.5% of NS patients, but many other mutations are described to be associated with NS. All these related disorders are defined as a group of rare conditions caused by mutations in the genes of the Ras-MAPK pathways, better known as RASopathies [14]. Mutations in the alpha-L-iduronidase lead to a deficiency in the glycosidase alpha-L-iduronidase; known as Hurler syndrome, it should be defined as mucopolysaccharidosis type 1 (MPS-1). In some other cases of multiple congenital anomalies, the pattern should be recognized while the etiology and pathogenesis are unknown. In this case, we should speak of association.

(d) Associations

Associations are usually sporadic conditions with a very low risk of recurrence. They are related to each other as a group of anomalies whose occurrence is explained by chance. These conditions emphasize the lack of uniformity in clinical presentation from case to case. VACTERL association comprises varied anomalies that are used as an acronym of the conditions shown at birth as anomalies of vertebrae (V), anal atresia (A), cardiac defects (C), tracheoesophageal atresia (TE),

renal anomalies (R), and limb defects (L). Most children with this condition, however, do not present all these anomalies at the same time but rather show a varying combination of these from this list. The condition is often sporadic with a low risk of recurrence. Until now, it is not possible to identify a common etiology, and a great deal is to be learned about this type of congenital abnormality. Another method that is useful in the presence of one of these malformations is to try and exclude the presence of some other defects. In presence of anal atresia or limb defects, it is necessary to exclude cardiac, renal, spine, and esophageal malformations. The prognosis is related to the severity of the malformation that the newborn presents and the possibility of surgical treatment [2, 17, 18].

3.4 Etiology of Congenital Malformations

For many CMs, the cause is unknown. Most of them are caused by multiple factors, yet at the same time, they are related to each other. Kalter and Warkany (1983) reviewed the knowledge of the etiology of major congenital malformations [11]. CMs are divided into five categories, and the relative contribution of each causal category was estimated:

1. Genetics: one or more genes might undergo a change or mutation that can lead to genetic disorders or illnesses. Some genetic conditions are caused by mutations in a single gene. These conditions are usually inherited in one of several patterns of Mendelian inheritance, depending by the gene involved. Different patterns of Mendelian inheritance—autosomal dominant (AD), autosomal recessive (AR), X-linked dominant (X-LD), and X-linked recessive (X-LR)—are principal examples of genetic patterns of inheritance. In other conditions, a gene or a part of a gene might be missing.
2. Chromosomal abnormalities: in some cases, a chromosome (Turner syndrome: 45, X0) or a part of a chromosome (CATCH 22 syndrome) might be missing. In other cases, such as with Down syndrome, chromosome 21 is triplicate (trisomy 21).
3. Environmental causes: exposure to drugs, chemicals, or toxic substances, i.e., alcohol exposure, can cause fetal alcohol spectrum disorders; exposure to antiepileptic drugs (valproic acid, hydantoin) can determine specific features, i.e., fetal valproate syndrome or fetal hydantoin syndrome. Exposure to maternal infections can produce infectious embryofetopathy too: maternal infection early in pregnancy, i.e., the *rubella virus*, can cause a miscarriage or serious birth defects [congenital rubella syndrome (CRS)]. *Toxoplasma gondii* and, Zika virus can determine teratogenic effects as eye-related manifestations of disease, other organ-related manifestation of disease as microcephaly.
4. Multifactorial disorders: these are due to a combination of the effects of multiple genes or the interactions between hereditary tendencies and nongenetic, usually undefined, factors, like the environment. This group of disorders includes a broad range of congenital birth defects, including cardiac malformations, neural tube defects, and cleft lip and/or palate. The underlying mechanisms by which the genes and the environment interact to cause these conditions are largely unknown.
5. Unknown causes: the dividing line between the categories multifactorial malformations and malformations of unknown etiology is not clear-cut. For multifactorial disorders, the genes and the environmental factors involved are often unknown. On the other hand, for malformations of unknown etiology, it is often assumed that genetic as well as environmental factors might be involved. The attribution of the 70% of malformations of multifactorial or unknown etiology to either one of these two categories is more or less a matter of subjective estimation. Family and twin studies have shown that these diseases have a genetic component, however. It is also clear that there are environmental contributors.

Knowledge of the etiology of congenital malformations is increasing gradually through the continued research of geneticists, embryologists, teratologists, pathologists, epidemiologists, and several other professionals. The estimate, however, that 70% of congenital anomalies are of unknown or multifactorial etiology still seems to be true [6, 7, 19].

3.4.1 Patterns of Inheritance

The diagnosis of a genetic disorder is based on a particular clinical pattern of symptoms and/or signs characteristic of the condition or by laboratory confirmation of the altered gene or gene products associated with the disorders [6]. It is important to distinguish between diseases that are genetic and those that are familial. A genetic disorder is determined completely or partially by altered genetic material. A familial disorder is one that is more common in the relatives of an affected individual than in the general population: some familial disorders are genetic, and others are caused by environmental exposure. The recognition of the pattern of inheritance not only assists in clinical diagnosis but also provides essential information for counseling family members about a recurrence risk in future pregnancies [4, 7].

3.4.2 Autosomal Dominant Inheritance

In an AD disorder, the mutated gene is a dominant gene located in one of the autosomes. Only one mutated gene is necessary to determine this type of disorder. AD disorders present some peculiarities in most circumstances: (1) any child of an affected parent has a 50% chance of inheriting the disorder, (2) phenotypically normal family members do not transmit the condition to their offspring, (3) there is no difference in impact between males and females, and (4) a significant proportion of cases involves new fresh mutation. An example of AD is Marfan syndrome.

3.4.3 Autosomal Recessive Inheritance

AR disorders are those in which two copies of the mutant gene in a homozygous state are necessary to cause the condition. The affected child inherits one copy of the mutated gene from each parent. The parents of a child with an AR condition usually do not have the condition. Unaffected parents are called carriers because they carry one copy of the mutant gene and can pass it to their children. An example of an AR condition is cystic fibrosis.

3.4.4 X-Linked Inheritance

The X chromosome has many genes that are important for growth and development. The Y chromosome is much smaller and has fewer genes. Females have two X chromosomes (XX); therefore, if one of the genes on an X chromosome has a change, the normal gene on the other X chromosome can compensate for the changed copy. If this happens, the female is usually a healthy carrier of the X-linked condition. In some cases, females show mild signs of the condition. Males have X and Y chromosomes (XY); therefore if one of the genes on the male's X chromosome has a mutation, he will be affected by the condition. Conditions that are inherited in this way are called X-linked recessive conditions [18].

(a) X-Linked Dominant Inheritance

Even though the most X-linked conditions are recessive, X-linked conditions can rarely be passed on in a dominant way. X-linked dominant disorders are seen more commonly in females than in males or, in the case of some diseases, affect only females. This means that even though a female inherits one changed copy of the gene, the

changed gene will be enough to cause the condition. In males, it is thought that the hemizygous are so severely affected that they likely do not survive. This may be reflected in the familial pedigree of multiple miscarriages or male infant deaths. An affected female has a 50% chance of having affected children (sons and daughters). An affected male will have all daughters affected, but all sons will be unaffected. Examples of X-linked dominant disorders include X-linked lissencephaly, oral-facial-digital syndrome type I, and Rett syndrome [8, 17, 20].

(b) X-Linked Recessive Inheritance
If a female carrier has a son, she will pass on either the X chromosome with the normal gene or the X chromosome with the changed gene. Each son, therefore, has a 50% chance of inheriting the changed gene and being affected by the condition. There is also a 50% chance that the son will inherit the X chromosome with the normal gene, and for this, he will not be affected by the condition. This chance remains the same for every son. If a female carrier has a daughter, she will pass on either the X chromosome with the normal gene or the X chromosome with the changed gene. Each daughter therefore has a 50% chance of inheriting the changed gene. If this happens, the daughter will be a carrier, like her mother. There is also a 50% chance that the daughter will inherit the normal gene. If this happens, she will not be a carrier and will be totally unaffected by the condition. This chance remains the same for every daughter. If a male who has an X-linked condition has a daughter, he will always pass on the changed gene to her. All his daughters will therefore be carriers; they will usually not have the condition, but they are at risk of having affected sons. If a male who has an X-linked condition has a son, his son will never inherit the condition. Some examples of X-LR include hemophilia, Duchenne muscular dystrophy, and Fabry disease [17].

3.5 Prevention of Congenital Anomalies

Primary prevention represents the protection of the health of every person and of the community by activities that limit risk exposure or increase the immunity of individuals at risk. This could be achieved by preserving a good nutritional state, immunizing against infectious diseases of all community members, and making the environment as safe as possible. Those measures prevent the onset of illness or injury before the disease process begins [1, 16, 21]. Primary prevention is aimed at reducing the occurrence of new cases of the disease. Examples of successful primary prevention programs in the field of congenital malformations are the reduction of the prevalence of congenital rubella syndrome by vaccination and decreased prevalence of neural tube defects, both primary and recurrent, by the use of folic acid supplementation. Often, primary prevention is possible if the etiology of the defect is known. For most congenital malformations, this is impossible. One relevant aspect is the precocious detection, through the different techniques of prenatal diagnosis, of malformation and trying to identify and detect the severity and possibility of some kind of pharmacological or surgical treatment to find the best solution.

3.6 Prenatal Diagnosis

Until the early 1970s, the prenatal diagnosis of congenital anomalies focused on detecting chromosomal abnormalities by amniocentesis. Over the last two decades, prenatal diagnosis has benefited from advances in ultrasound technology. Now, fetal and postnatal ultrasound is a well-established technique for the early detection of abnormalities, and a precocious diagnosis may have important implications for the following:

(a) Obstetric and neonatal management: women carrying fetuses with identified or suspected malformations move to tertiary centers for further evaluation, counseling, and manage-

ment. The task is to differentiate between lesions that could be incompatible with postnatal life, lesions that will necessitate a supporting person for the life of the patients, and lesions that are correctable through surgery or not.

(b) Morphologic anomalies detected by ultrasound could be associated with other defects and sometimes are components of syndromes that are difficult to identify in prenatal life. For these cases, genetic counseling is crucial. It is possible to associate specific genetic analysis to detect microscopic and submicroscopic chromosome abnormalities, like single-gene disorders, leading to relevant improvements in detection, such as congenital anomalies.

Invasive prenatal diagnosis continues to be the gold standard for pregnancies at increased risk for chromosomal and other genetic diseases. Chorionic villus sampling is the procedure of choice for the first trimester, whereas amniocentesis is the most common procedure during the mid-trimester. Prenatal diagnostic testing is available for an ever-increasing number of disorders. At first, prenatal tests focused on Down syndrome, while, actually, prenatal genetic testing can now detect a far broader array of conditions. Advances in genetic and genomic medicine have led to a dramatic increase in the availability of genetic testing, including in the prenatal period. At the same time, prenatal screening has also seen improvements, with the development of cell-free deoxyribonucleic acid (DNA) screening, like expanded carrier screening for a broad array of inherited conditions. This technique has extended fetal screening despite maternal age.

Patients should have pretest counseling that explains the benefits and limitations of invasive prenatal diagnostic testing, the conditions that will and will not be detected, and the risks of the procedures. Prenatal genetic testing has many benefits, like providing reassurance when there are no anomalies or identifying cases that will benefit from proper in utero or neonatal management. One of the goals is to guarantee the appropriate location and staffing for the delivery of affected infants and to provide the option of pregnancy termination for individual families that make that choice.

A new methodology for determining the risk of a fetus being affected by chromosomal and genetic disorders is noninvasive prenatal testing (NIPT). This testing analyzes small fragments of DNA that are circulating in pregnant blood. DNA fragments are free-floating, and they are called cell-free DNA (cfDNA). These small fragments usually contain fewer than 200 DNA building blocks (base pairs) and arise when cells die off and get broken down, and their contents, including DNA, are released into the bloodstream. These fragments originate from placenta cells that have the same fetus DNA. NIPT is used to check chromosomal disorders, such as aneuploidy (presence of an extra or a missing chromosome). Examples of extra chromosomes for autosomes are Down syndrome (T-21), Edward syndrome (T-18), and Patau syndrome (T-13), while for gonosomes, one well-known condition is Klinefelter syndrome (47, XXY). Another example of a missing copy for gonosomes is Turner syndrome (45, X0). All autosomes' monosomy is incompatible with life. The accuracy of the NIPT test varies for each disorder. NIPT can include screening for additional chromosomal anomalies, such as deletion (i.e., del 22q11) or duplication (i.e., mosaic tetrasomy 12p or Pallister–Killian syndrome).

NIPT is beginning to be used to test for genetic disorders caused by variants (changes in single genes). As technology improves and the cost of testing decreases, researchers expect that NIPT will become available for many more genetic conditions. In the low-risk population, prenatal diagnosis generally consists of screening procedures using ultrasound and maternal serum biochemistry.

Ultrasound technology continues to advance. Three-dimensional ultrasound imaging and the development of new markers should help improve diagnostic accuracy. Routine ultrasound screening does appear to reduce adverse outcomes in fetuses diagnosed with congenital anomalies.

However, limitations include operator variability, fetal position, gestational age effects

(poor visualization, skull ossification), and tissue definition. Early studies using magnetic resonance imaging (MRI) in the evaluation of fetal morphology were hindered by fetal motion. Current software and hardware for MRI now allow the performance of MR examinations with high-quality images, permitting fetal imaging without maternal or fetal sedation. Although fast MRI techniques are widely available, few practitioners have knowledge of fetal anatomy and pathology with this technique.

Preliminary studies suggest that MRI may improve diagnostic accuracy and change counseling for many fetal central nervous system lesions and not as fetal abdominal, lung, and pelvic masses or congenital diaphragmatic hernia [22–24].

3.7 Communicating Diagnosis

Nowadays, fetal medicine provides reliable medical data about congenital abnormalities, and intrauterine diagnostic techniques are increasingly safe. The diagnosis that was not feasible a few decades ago can be elaborated with safety and certainty, generating ethical and legal responsibilities for the doctor who recognizes a malformation and communicates a specific diagnosis or the suspect of a diagnosis. When the mother and the couple are informed that the child is affected by a condition with a high risk of a congenital defect, fear and anxiety are increased. The "idealized child," after the communication of bad news, will be replaced by the "real child," who may be affected by some abnormalities as well as some defects that can require postnatal surgical or long-term pharmacological treatment, as well as the association to some degree of cognitive disability. The reactions go through shock, disbelief, denial, frustration, anger, and even irritation directed at the doctor who is to relay the bad news. The sudden change in the expectations of the desired pregnancy and the replacement with this news generates an emotional reaction in the mother above all and the couple too, which can range from the total protection of their baby to the rejection of the pregnancy and asking the for termination of the pregnancy. The communication becomes critical and can worsen by a low or incomplete preparation of the doctor who is in charge of communicating the clinical conditions of the child. Frequently, the parents have negative memories of the moment they receive them, not only because of their content but also because of the way they were informed—with inability, little empathy, and insensitivity [4, 5]. However, the way to report bad news must be learned and improved to understand how it can interfere with the physician-patient relationship. The communicating doctor must clarify, as much as possible, the aspects of the condition and, consequently, keep confidential the information obtained in the medical practice. Therefore, communication is one of the main critical aspects of this phase as it is a fundamental condition of human relations. In the same context, parents should be informed about all possible care attitudes and outcomes, such as the possibility of treatment and taking care of assistance after the birth of the baby by a team of doctors who are specifically involved in the clinical surveillance of the neonate with congenital malformations.

In the diagnosis communication phase, it is necessary to avoid words that can be related to the negative development of the baby and try not to give vague and approximate information. At the same time, it is not helpful to provide a long list of possible complications and comorbidities that a child could encounter over time, which only leads to parents feeling overwhelmed and powerless [15]. It is better to summarize the main features of the condition in a brief but clear way, keeping the focus on the child: every baby is unique, and it is wrong to consider him as a sum of symptoms. The discussion of the condition and the possible comorbidities should be accompanied, every time, by a description of the therapeutic possibilities that exist today and the achievable outcomes. Overall, it should be emphasized that the child will be included in follow-up programs of surveillance in a specialist center to verify the growth and identify any possible problems at an early stage to supply appropriate measures and treatments as soon as possible. In the same way, it is not necessary to

give all the information at the first meeting; it is important to give more time to the couple to face problems and questions that will be debated in other subsequent meetings, where parents will be progressively informed about what they should pay attention to during the different phases of their child's life [1, 6, 7, 9].

3.8 Neonatal Care at Birth

The birth of a baby with congenital malformations is the starting point of a clinical process to reach a precise diagnosis. This leads to appropriate clinical planning and definition of prognosis and counseling to the parents. Different causal pathways may lead to a similar phenotype, and the diagnosis process may be long and difficult, requiring a follow-up survey to establish the natural history of the condition. Frequently, the evaluation process of a neonate affected by congenital malformations must proceed rapidly since decisions regarding intervention and treatment hinge on an accurate diagnosis. The diagnosis of these conditions, as said before, could be prenatally detected, but sometimes it is discovered at the moment of birth either by obstetricians on call or by the neonatologist during the first postnatal control or in connection with the resuscitation approach. All neonates have to undergo a thorough physical examination, and to reach a possible diagnosis, it is necessary to follow multiple sources of information. The methodology to approach the pathological aspects observed at birth is divided into some steps, starting from collecting as much information as possible about maternal medical history, pregnancy reproductive and delivery history, and family history, and an accurate description of the phenotype, with appropriate imaging and laboratory tests, is a relevant step too [6, 13, 25].

3.9 Maternal Medical History

Clear links exist between maternal diseases, including some specific conditions, such as myotonic dystrophy, autoimmune conditions, and diabetes mellitus type I. The incidence of major congenital anomalies among infants of diabetic mothers is four to five times higher than in the general population. It is fundamental to reach information about maternal exposure to drugs, cigarettes, alcohol, and infectious diseases. Medicament exposure during pregnancy may cause adverse pregnancy outcomes, including congenital anomalies, spontaneous abortion, fetal growth restriction, and low birth weight. It is estimated that 2–3% of birth defects are due to drug exposure during pregnancy. Ever since the thalidomide disaster occurred in the 1960s, increasing attention to medication safety in pregnancy has been paid. The proportion of pregnancies involving medication varied dramatically from 27% in the United States to 93% in countries in France. The phenomenon is more common than before because of the higher proportion of pregnancies complicated by chronic diseases and inadvertent drug use after conception. Assisted reproductive technologies (ART) are the treatment of choice for infertile couples. However these procedures are generally considered safe, children conceived by ART show a higher risk of prenatal and perinatal complications as congenital imprinting disorders like Beckwith–Wiedemann syndrome and Silver–Russel syndrome. The incidence of these syndromes in these infants is higher than general population. Human epigenome studies have generally revealed the enrichment of alteration in imprinted regions in children conceived by assisted reproductive technologies [2, 4, 11].

3.10 Pregnancy History

The pregnancy history can provide important information regarding the prenatal onset of congenital abnormalities, including information about the following

1. *Length of gestational age* (*GA*): it includes alteration in GA both before and after maturity.
2. *Fetal activity*: this includes alteration in the onset of fetal activity, which increases from

the 19th and 20th weeks of gestation and reaches a maximum between the 29th and 38th weeks and then decreases somewhat until delivery. Some structural defects are often associated with delayed onset and/or decreased intensity of fetal movement as well as the localization of fetal activity to one particular quadrant of the abdomen.

3. *Amniotic fluid* (*AF*): this includes abnormalities in the amount of AF, such as oligohydramnios and polyhydramnios. During the third trimester of gestation, AF, under physiological conditions, is in a constant state of dynamic equilibrium between its production and resorption. AF is influenced by fetal urine, bronchopulmonary efflux, fetal swallowing and intramembranous and intravascular absorption. Polyhydramnios occurs if the fetus shows difficulty in swallowing AF, as in gastrointestinal or neurological abnormalities. Oligohydramnios is usually present following chronic leakage of AF or anomalies in the urinary system, as in renal agenesis, a polycystic kidney, or urethral obstruction.
4. *Ultrasound findings*: the prenatal detection of abnormalities on routine fetal ultrasound may identify abnormalities and can lead to suspect some genetic or chromosomal disorders. This detailed information regarding the pattern of events can help suspect or reach a diagnosis, also with the contribution of some prenatal genetic tests.
5. *Finding of prenatal screening*: nuchal translucency (NT) scan can detect about 80% of fetuses with trisomy 21 and other major aneuploidies, for a false positive rate of 5%. The combination of NT and maternal biochemical markers can help reach a safer diagnosis. Specifically, the dosage of maternal serum-free beta-hCG and PAPP-A improve detection to 90%. There is now evidence that the detection rate can increase to about 95%, and the false positive rate can be reduced to 3% by also examining the nasal bone, ductus venous flow, and tricuspid flow [2, 22].

3.11 Delivery History

1. *Presentation*: Breech presentation occurs in 3% of normal-term deliveries. However, it occurs much more frequently in some disorders that affect the form and/or function of the fetus. Structural anomalies such as hydrocephalus would be less compatible with vertex presentation because of the large head and joint dislocation (fetal akinesia and fetuses with multiple congenital contractures or arthrogryposis), which may reduce the ability of the fetus to modify its position. Defects of function include some conditions associated with neuromuscular disorders, such as trisomy 18, Prader–Willy syndrome, and Steinert myotonic dystrophy, among others.
2. Type of delivery: In the management of pregnancy complicated by fetal malformation, the choice of delivery method may be made on obstetrical grounds or in the belief that one method offers the fetus benefit over the other. Clear evidence of benefit from cesarean delivery is not available in the case of many malformations that are often considered for abdominal delivery. The choice must be based on the knowledge of individual malformations, fetal maturity, and presentation.
3. Growth deficiency: Growth deficit is another sign that may bring the child to the attention of the neonatologist. Small size at birth, disproportionate to gestational age, is frequently an important clue to prenatal dysmorphic processes. There is an increased incidence of malformation as the weight for gestational age decreases. In addition, there is a marked increase of disabilities in small for gestational age children who had some structural abnormalities.
4. Neonatal adaptation: The immediate postpartum period is a time of significant physiological adaptation for the baby. The neonate must adapt from being completely dependent on his mother for life-sustaining oxygen and nutrients to an independent being, a task accomplished over a period of hours to days. Successful transition from fetal to neonatal

life requires a complete interaction among the various systems: respiratory, cardiovascular, thermoregulatory, endocrinologic, and immunologic. Establishing respiration is critical to the neonate's transition as the lungs become the organs of gas exchange after separation from maternal uteroplacental circulation. Over 90% of neonates make the transition from intrauterine life to extrauterine life without difficulty, requiring little to no assistance. However, for the 10% of neonates who do require assistance, about 1% require extensive resuscitation measures to survive. Neonates with prenatal onset of structural defects frequently have problems with postnatal respiratory adaptation, which may be secondary to altered development of fetal lung or brain structure.

3.12 Family History

A careful, thorough, and fully recorded history, complete with pedigree, forms the foundation for the diagnostic process. Family history can provide a good quality of information and represent the first clue regarding the possible genetic etiology of congenital malformations. Consanguinity in the parents increases the chance of having autosomal recessive conditions as well as multifactorial disorders in their progeny.

3.13 Physical Examination

The critical aspect of a dysmorphology evaluation lies in the recognition or confirmation of major and minor structural anomalies, and therefore, a physical examination of the neonate with congenital abnormalities is the most important step. The clinical assessment of the neonate must be thorough and accurate. Some abnormalities may be quite prominent or involve large areas, while others may be rather subtle. Selected measurements of physical features are extremely useful in confirming a clinical appearance of abnormality. Standard tables and graphs by gestational age norms for many of such physical dimensions are available with the aim of providing standards, both for comparison and for improved definition of normal patterns of human development and growth at birth and late in life [26]. From the primarily qualitative description, it is necessary to pass a new step where accuracy and quantitation must be necessary. Careful documentation by measurement, in well-known conditions, will allow one to distinguish heterogeneity, learn more about natural history, and provide a basis for the future application of techniques and concepts from developmental biology and molecular genetics. The real value of a single measurement lies in a comparison with a standard, which can be either age related or familial and ethnic related.

With the parents' permission, it is useful to take photographs of the baby because photographic documentation often can be of great value and can be used to observe changes in time and to compare with other babies with a similar phenotype. A neonatologist should take care to continue to search for the less obvious anomalies even when a major malformation is present. It could be of some help to ask for advice and expertise from the geneticist with experience in the neonatal age. Peculiar phenotype change can be observed in each individual during the years from neonate to child and to adolescent to adult too. A common pitfall to avoid is the tendency to make an erroneous diagnosis of a well-known syndrome, usually not completely supported by the abnormalities observed at birth. The description of the clinical association should include, moreover, the structural defects, even neuromotor evaluation, growth development, the disorder of sexual differentiation, or pubertal development.

3.14 Surveillance After Birth

Transitional care from hospital to home represents a very critical moment. Returning home with a malformed baby can result in an emotional burden that is very challenging, not only for the parents and family but also for the family pediatrician, territorial doctors, and nursing care, who are required to acquire in a short time new knowledge and skills. Consequently, it is necessary to arrange the complexity of the care, before discharge, organizing care pathways that are in favor of the transition and integration between hospital and home. A consensus statement on birth defect surveillance (2019) proposes, among other things, "to establish a holistic, multidisciplinary and multi-sectorial approach that adequately meets the health the educational, occupational, rehabilitation and social needs of people with birth defects. Many infants with severe birth defects experience lifelong disability requiring long-term treatment or rehabilitation" (World Health Organization 2019). There are promising models for rehabilitation services for children with birth defects. These models are found in communities: hospitals, schools, other institutions, and primary health care. The more comprehensive models are in the primary care system and are centered on rehabilitation strategy. Some reports focus on the care of infants and children with birth defects and on rehabilitation programs, which are required for lifelong conditions. In many cases, appropriate education and rehabilitation for children substantially increase their ability to function independently and contribute to family and community responsibilities. The assumption is that children with disabilities have the right to live a good life. It is mandatory to offer to them and their family the clinical and the social support required their usual way of living. They should have an education like everybody else and should be able to go to school and follow a course of study, like other children. In Italy, school inclusion was regulated in 1977 (National Law n. 517, 1977), with the abolition of differential classes. Even if people learn very slowly, have problems seeing or hearing, or find it hard to move about, they still should be respected for being girls and boys. Nobody should be looked down on or treated badly because of their disability. Houses, shops, and schools should be built in such a way that everyone can easily go in and out and make use of them.

A practical example of a follow-up service to a child born with birth defects could be represented by the surveillance over time of neonates affected by trisomy 21 (T-21), well known as Down syndrome. DS is by far the most common and the best-known aneuploidy due to the nondisjunction, translocation, or mosaicism of chromosome 21. In 94–97%, the extra chromosome may be maternal or, less frequently, paternal in origin. In 3%, there is D/G translocation. Trisomy/normal (mosaicism) occurs in 1–2%. DS occurs approximately in one in every 800 live births in the Emilia-Romagna region.

Physical examination is the first step within the first hours of life, in which it is possible to feel there are enough criteria to advance the diagnosis of DS. The phenotype is characterized by several clinical features, of which the most constant and typical are neuromotor disability and craniofacial dysmorphisms, together with other variable signs and symptoms, such as cardiac malformations and growth delay. Physicians can suspect DS based on some characteristic physiognomic features of infants, and physical examination is the first essential step to reach a diagnosis Neonatologists can also use score system as Hall's ten cardinal signs or Jackson's checklist, which is a more complex scoring system, that could guide them in making diagnosis of DS. The diffusion of these scoring systems is an excellent way to bring attention to clinical and phenotypic signs of DS, contributing to a better understanding of the role of the excess chromosome 21.

When recording the history from the parents of a child with T-21, the clinician should include the following information: parental concern about hearing, vision, developmental delay, respiratory infections, and other problems. Delay in the child's cognitive abilities and motor and language development is the most frequent question from parents and the family, too, and the usual reason for their great anxiety and concern. The clinician must support the family since a diagnosis of DS is made, also if it is done during pregnancy, and has to reassure them about the great possibility for these patients to reach as well as a level of autonomy in life. To reach this result it is necessary to inform about the opportunity to assure and the necessity to implement on one hand all the best assistance for possible clinical problems in the development of the child and on the other hand to underline the strength of early surveillance of neuromotor and neuro-sensorial maturation. All this is to activate the health service of precocious sensorial and motor enabling when clinicians observe a delay or an impaired maturation. Starting from birth it is important and basic to follow the child in a longitudinal survey of all pediatric ages. Neonatologists are now referred to early intervention programs shortly after birth and inform the parents about the best way to follow and foster the growth and development of their child. The goal of intervention programs for children with Down syndrome is to maximize each child's developmental potential and improve the quality of his/her life. In the past few decades, advances in medical care have resulted in improved health and life expectancy for individuals with DS. Each clinical center involved in the clinical assistance of the child has to implement specific protocols, which are internationally defined and useful. Guidelines, produced by the American Academy of Pediatrics (AAP) and recently published (Pediatrics 2022), are a useful guide to follow and to help practitioner doctors and institutions to take care of these children starting from prenatal diagnosis, if there was, to adolescence [24]. Children with DS often have multiple health needs. It makes sense, from the family's perspective, to reduce the number of hospital visits by having multidisciplinary clinical and coordinated appointments. The Center for Rare Disease of Bologna University Hospital uses a care protocol for the survey of children with Down syndrome, which was proposed in 1984. Time after time, the survey was adopted, and the protocol used is shown in Table 3.1. During the first and subsequent visits, it is recommended to pay attention to the child's strengths and achievements, helping parents focus on the child's potential rather than weaknesses. It is also essential to keep parents in touch, if they so wish, with other families with children with DS so they can share information and experiences and expand the support network for both the family and the child.

Table 3.1 Follow-up protocol applied for Down-syndrome-specific care at the Center for Rare Disease Neonatology Dept. Bologna University Hospital

	Birth	3 m	6 m	9 m	12 m	18 m	24 m	36 m	Yearly
Anamnesis	•	•	•	•	•	•	•	•	•
Health maintening visit	•	•	•	•	•	•	•	•	•
Neurological ev.	•	•	•	•	•	•	•	•	•
Neurophiasic ev.		•			•		•	•	
Blood test + TAM	S		•		•	•	•	•	•
NBS	•								
TSH			•		•		•		•
Cerebral US	•	•							
EEG + MRI (1)			•						
Abdominal US	•								
Cardiological Ex.	•				•				
Pneumological Ex (2)									•
Gastro-enter. Ex (3)					•				
ENT Ex. + BAER	S	•	•		•			•	
Ophthalmic ex.	S	•		•				•	
Dental visit			•		•		•	•	•

Cervical X-ray at 9 years (atlantoaxial stability control)
S screening, *TAM* transient abnormal myelopoiesis, *NBS* newborn screening, *TSH* thyroid stimulating hormone, *EEG* electroencephalogram, *MRI* magnetic resonance imaging, *ENT* ear nose throat, *BAER* brainstem auditory evoked response
(1) If cerebral US is pathological
(2) + Pulse-oximetric for OSAS control
(3) + Screening for celiac disease

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