Contemporary Evaluation of the Neonate with Congenital Anomalies

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Education Gaps

1. There is a need for increased understanding of how state-of-the-art genetic testing, including noninvasive prenatal screening and whole exome sequencing, affects the evaluation of a neonate with congenital anomalies.

2. There is a need for a thorough understanding of the terminology and organization of congenital anomalies of various etiologies for improved communication among health care teams, to optimize care for affected neonates.

Objectives

After completing this article, readers should be able to:

1. Accurately define and organize minor and major congenital anomalies.

2. Compare and contrast congenital anomalies with genetic and environmental etiologies.

3. Evaluate the strengths and weaknesses of newly implemented pre- and postnatal genetic screening and testing for the neonate with congenital anomalies.

4. Implement an approach for the compassionate and thorough evaluation of infants with congenital anomalies, improve communication with consulting services, and improve clinical care.

Abstract

The evaluation of the neonate with congenital anomalies has always been a vital and challenging task. In recent years, many advances and challenges have complicated the process, including noninvasive prenatal screening, Zika virus, assisted reproductive technology, and rapid exome sequencing. This review will provide a context for the general evaluation of a neonate with congenital anomalies, including adaptation of the most precise terminology, definition of major and minor anomalies, and the determination of whether the anomalies are the result of a sequence, deformation, disruption, or malformation. Practical tools, including a concise family history, nutritional implication, pregnancy history, and the effects of assisted reproductive technologies are also
presented. With the advent of Zika virus–associated congenital anomalies, emphasis has also been placed on travel and infection exposures. A particular challenge has been the incorporation of both pre- and postnatal genetic screening and testing into a diagnostic framework. The most common tests will be reviewed, including the practical applications of both a positive and negative result in varying contexts. It has become clear that noninvasive prenatal screening and rapid exome sequencing are having an increasing impact on the evaluation of children with congenital anomalies, and their application and evaluation of their results will be reviewed in detail. The overarching goal of this review is to provide neonatal clinicians the tools to assess, contextualize, and discuss congenital anomalies in neonates to improve communication and the diagnostic process.

INTRODUCTION

Congenital anomalies are a common cause of admission to NICUs, and carry a significant burden of morbidity and mortality worldwide. According to the World Health Organization, worldwide, an estimated 303,000 newborns die within 4 weeks of birth due to congenital anomalies each year. In the United States, congenital anomalies occur in 2% to 5% of live births, and comprise 20% to 30% of neonatal deaths as well as 30% to 50% of infant deaths outside the neonatal period. Many congenital anomalies are isolated and infants with these differences will likely never be admitted to a NICU (eg, cleft lip and palate, isolated limb abnormalities). However, because of the relative frequency with which infants with congenital anomalies are admitted to the NICU, neonatologists should have a working framework with which to evaluate these infants. Recent advances in prenatal genetic screening with noninvasive prenatal screening (NIPS) and prenatal imaging (eg, high resolution ultrasonography, echocardiography, magnetic resonance imaging) have improved detection of anomalies before birth, but can introduce diagnostic confusion for providers not familiar with the limitations of this technology. This review will focus on an approach to children with congenital malformations for neonatologists focusing on when genetics consultations are needed, appropriate first steps before consultation, and the benefits and limitations of new forms of genetic testing, including NIPS, prenatal diagnostic testing, and exome sequencing.

ENHANCING TEAM COMMUNICATION WITH PRECISE TERMINOLOGY

To effectively communicate with consulting services, interact with search engines (eg, Online Mendelian Inheritance in Man; London Dysmorphology Database), or use reference materials (eg, Smith’s Recognizable Patterns of Human Malformation; Elements of Morphology), the use of precise terminology is critical. Often a child will have a known malformation and will be described as “syndromic” or “nonsyndromic,” but a systematic approach to categorization of anomalies will enhance the likelihood of making an accurate diagnosis and of ensuring that accurate information is transmitted to consulting teams. When initiating early conversations with parents and determining the appropriate consulting teams for a child in the NICU with congenital anomalies, it is important to remember that most children with birth defects do not have a genetic syndrome. Approximately 3% of children are born with a congenital malformation, and most of these abnormalities have multiple causes. Environmental exposures, including extrinsic (eg, fetal alcohol syndrome) or intrinsic (eg, diabetic embryopathy), are also important contributors in many cases. It is also important to determine whether environmental factors have contributed, because in many cases, they will be modifiable for future pregnancies. Applying appropriate terminology to describe the type of anomaly/anomalies a child has will help to determine whether a genetic syndrome is likely. The first step is to determine which of a child’s differences are caused by major versus minor anomalies.

- **Major anomalies**: These include malformations that have a significant medical or cosmetic impact, which are never considered part of normal variation (eg, congenital heart disease, cleft lip and palate, ectrodactyly, holoprosencephaly).
- **Minor anomalies**: These include features that are uncommon in the general population, occurring in less
than 4% of individuals, and do not have medical impact (eg, single palmar crease, ear tags and pits, lip pits).

Up to 20% of healthy newborns have at least 1 minor anomaly. Approximately 0.8% of newborns have 2 minor anomalies, with an associated 10% risk of major malformation. Only 0.5% of infants have 3 minor anomalies, and these children have approximately 20% chance of a major anomaly. Therefore, even though minor anomalies have no medical impact on isolation, they can signal that a child has a malformation. Approximately 0.8% of newborns have 2 minor anomalies, and these children have approximately 20% chance of a major anomaly. Only 0.5% of infants have 3 minor anomalies, and these children have approximately 20% chance of a major anomaly. Therefore, even though minor anomalies have no medical impact on isolation, they can signal that a child has an occult major malformation, particularly when more than 1 minor anomaly is seen in a neonate.

For infants with more than 1 major or minor anomaly, the constellation of abnormalities is classified based on the relationship between the differences.

• **Association:** A group of anomalies that occur more frequently together than would be expected by chance, but do not have a predictable pattern of recognition and/or suspected unified underlying etiology (eg, vertebral anomalies, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, limb defects [VACTERL] association).

• **Deformation:** Abnormal formation due to external force on the fetus during in utero development that resulted in abnormal growth or formation (eg, oligohydramnios in an infant with renal anomaly can cause flattened face due to compression against the uterine wall).

• **Disruption:** Growth arrest of a structure that had been developing normally due to an external force (eg, amniotic bands).

• **Malformation:** Abnormal formation of a fetal structure due to an underlying genetic, epigenetic, or environmental factor that alters development.

• **Sequence:** A group of related anomalies that generally stem from a single major anomaly that alters the development of other surrounding or related tissues or structures (eg, Pierre Robin sequence with microretrognathia causing the tongue to impede closure of the embryonal palatal shelves with resulting cleft palate).

• **Syndrome:** Well-characterized constellation of major and minor anomalies that occur in a predictable fashion presumably with a single underlying etiology. Syndromes can have genetic (eg, Down syndrome, Prader-Willi syndrome) or teratogenic (eg, fetal alcohol syndrome) etiologies.

After initial resuscitation and stabilization of an infant born with congenital anomalies, the history and physical examination should focus on the identification of major and minor malformations and classification of the etiology. Possible classifications include association, deformation, disruption, malformation, sequence, or syndrome. Prenatal genetic testing, including NIPS and diagnostic testing (eg, microarray, karyotype), is likely to be informative for infants with malformations whose anomalies are due to syndromes or some sequences (eg, Pierre Robin sequence due to Stickler syndrome), but is unlikely to be informative for neonates with most disruptions or deformations, or malformations due to associations. Although history is critical in determining whether a child was exposed to a teratogenic agent, attribution of a congenital malformation to an environmental exposure remains a diagnosis of exclusion. Therefore, unless an infant has a set of congenital abnormalities that are pathognomonic for an exposure, along with documented history (eg, sacral dysgenesis in the setting of uncontrolled diabetes), children whose anomalies are suspected to be due to an environmental exposure should still undergo a full evaluation to rule out other causes. The classification of an infant to a likely category of “syndrome” or “sequence” does not imply a genetic versus environmental cause. There are examples of syndromes, disruptions, and sequences with both genetic and environmental etiologies. For example, Pierre Robin sequence can be caused by Stickler syndrome (genetic) or constriction of the chin (environmental) during fetal development. Transverse limb defects of the fingers can be due to amniotic bands (environmental) or in the setting of Adams-Oliver syndrome (genetic). Therefore, it is important that suspected genetic or environmental causes are specified when using the terminology listed earlier.

Whenever a genetic syndrome is suspected because of the presence of an uncommon congenital malformation or the presence of more than 1 major and 1 minor malformation, genetics consultation should be obtained. For institutions without clinical genetics, a call should be placed to the nearest referral hospital with a genetics consultation service to help determine whether transfer or outpatient follow-up is most appropriate. In some situations, telemedicine genetics consultations may be available, depending on the institution. The remainder of this review will focus on information that will be helpful to the neonatologist in parallel with consultation with a clinical geneticist for the evaluation of the infant with congenital anomalies in a NICU setting.

**APPROACH TO THE EVALUATION OF A NEONATE WITH CONGENITAL ANOMALIES**

The critical elements in the history of a neonate born with congenital anomalies include a thorough family history, pregnancy history, and the events surrounding the birth, as well as review of any laboratory or radiologic studies.
When discussing aspects of the history with the parents, it can be helpful to list the items for which they need clarification from other family members or physicians. In addition, it is helpful to bring a few copies of consent forms for release of medical records when sitting down with parents so that they can be filled out if the need arises. For example, if they note that a previous child was born with similar abnormalities, it is critical to obtain medical records for review. It is also common for parents to remember that genetic testing was completed and had normal results, but not remember exactly what testing was conducted. In the vast majority of cases, the congenital anomaly will not be linked to any maternal behavior. However, most parents will question or even assume that their actions led to the child’s anomalies. It is helpful to take a thorough history and, when appropriate, reassure them that they did not do anything to cause the anomaly to occur. In many cases, well-meaning family members or friends may suggest things that the mother did during pregnancy that they believe caused the anomaly. It is helpful to elicit what the parent’s beliefs are regarding the etiology of their child’s differences, and to dispel spurious assumptions.

FAMILY HISTORY

When eliciting the family history, it is helpful to take a systematic approach; starting with the parents of the neonate, elicit how many pregnancies have occurred and what happened to each one. Then ask how many brothers and sisters each parent has and whether they have children. Continue this process until a 3-generation pedigree is constructed. Infertility, miscarriages, consanguinity, and major medical problems are all important to include. Even seemingly unrelated information, such as cancers in adult relatives, can be important because many cancer predisposition syndromes have birth defects as their first manifestation. The reason it is important to take this approach is that many parents will be focused on the congenital anomaly at hand, and may not report other types of medical problems or recurrent miscarriages that could give clues as to the underlying etiology of a disorder.

PREGNANCY HISTORY INCLUDING ASSISTED REPRODUCTIVE TECHNOLOGIES AND TRAVEL HISTORY

Pregnancy history should include the method of conception, including any use of assisted reproductive technologies (ART), travel or illnesses within the 6 months prior to conception (especially to Zika virus–endemic areas), pregnancy-related complications, results of ultrasonography, and any prenatal genetic testing. ART history should include information on whether ovarian hyperstimulation was used (because this can be linked to methylation defects); use of donor oocytes, sperm, or embryos; method of in vitro fertilization (IVF; with or without intracytoplasmic sperm injection [ICSI], as there is differential risk); preimplantation genetic screening (PGS) versus preimplantation genetic diagnosis (PGD). The reason for ART use is also important, because different reasons for infertility are linked to different genetic conditions (eg, premature ovarian failure in fragile X premutation carriers, recurrent pregnancy loss in balanced translocation carriers).

DIETARY CONSIDERATIONS

For infants with congenital anomalies linked to inadequate maternal folate consumption, the timing of initiation of maternal prenatal vitamins should be elicited. To be effective at preventing birth defects (eg, neural tube defects), prenatal vitamins should have been initiated in the months before conception. Other unusual dietary issues that can lead to birth defects include malnutrition or specific micronutrient deficiency associated with maternal eating disorders, gastric bypass surgery, or severe hyperemesis gravidarum.

CONSIDERATIONS FOR INFANTS CONCEIVED USING ART

Infertility history, with or without the use of ART, is important to elicit, because of the increased risk of birth defects in couples with a history of infertility even in the absence of ART. The rate of birth defects in pregnancies conceived using ART (8.3%) is higher than that in the normal population. The highest risk is among infants conceived using ICSI (9.9%). Many embryos conceived via IVF with or without ICSI will undergo PGS, in which a limited chromosomal analysis is conducted, or PGD, in which diagnostic testing is conducted for a genetic condition in the family. Both PGS and PGD are performed on a biopsy specimen from an embryo, and can occur on either day 3 (1–2 cells removed at the 8-cell stage) or day 5 (4–5 cells taken from the outer trophectoderm layer of the blastocyst). The use of PGS has increased the likelihood of live birth after IVF significantly. However, it is important to note that PGS does not rule out the possibility of mosaic chromosomal disorder and does not test for single gene disorders or methylation defects. Therefore, a history of a “PGS-normal embryo” with congenital anomalies should still undergo a complete genetic evaluation. There is also an elevated risk of
methylpyrimidines defects after the use of ART; an infant with Beckwith-Wiedemann syndrome is 13 times more likely to have been conceived with IVF than an unaffected infant. Recurrent pregnancy loss anywhere in the pedigree should prompt consideration of a balanced translocation in a parent, leading to an unbalanced translocation in the offspring.

**ILLNESS AND TRAVEL HISTORY**

Maternal illnesses during pregnancy should be interpreted in the context of early pregnancy titers for maternal immunity to cytomegalovirus, varicella zoster virus, toxoplasmosis, parvovirus, and rubella, when they are available. The type of congenital anomalies present in an infant can also guide the type of confirmatory immunologic testing that should be performed. Until recently, travel history was only considered relevant for the pregnant mother during the pregnancy itself. For infants with microcephaly or other brain malformations, travel for both the mother as well as the father to Zika-endemic areas within 6 months before conception should be elicited, because Zika infection can be contracted from mosquitoes or sexually transmitted from an affected man to his partner during the pregnancy. Individuals with Zika infection may not recall having symptoms of infection during the pregnancy, therefore, any infant with suggestive congenital anomalies born to a woman with history of travel to a Zika-endemic region for herself or her partner should contact the Centers for Disease Control and Prevention (CDC) to ascertain next steps in evaluation and treatment.

**REVIEW OF PRENATAL IMAGING**

It is important that congenital anomalies identified on prenatal imaging are confirmed on diagnostic imaging after the birth of a child, when the birth defect is not readily visible. It is common to feel concern on prenatal ultrasonography results of an abnormality that is not detected after birth (eg, hydronephrosis). Postnatal imaging may also identify abnormalities that were not obvious at the time of the anatomy scan (eg, brain malformations, craniosynostosis, congenital heart disease).

**WHEN “NORMAL” DOES NOT MEAN “NORMAL”: CONSIDERATIONS FOR THE NEONATOLOGIST INTERPRETING “NORMAL” GENETIC TESTING PERFORMED DURING PREGNANCY**

An infant’s history commonly includes the statement that genetic testing was performed, and findings were normal. There is often confusion about what type of genetic testing was performed during pregnancy, and what the “normal” testing truly ruled out. It is imperative to obtain copies of the test results to verify the type of testing that was performed to guide appropriate postnatal evaluation.

Types of genetic testing that may have been conducted during pregnancy include:

- **Sequential screening:** This includes a combination of blood tests (α-fetoprotein, human chorionic gonadotropin, unconjugated estriol, inhibin pregnancy-associated plasma protein A) and nuchal translucency to determine the risk of having a child with trisomy 13, 18, 21, or spina bifida. This testing was the standard of care for many years for women with normal risk. A “positive” result means that the risk of having a child with trisomy 21 is greater than 1 in 190. This somewhat arbitrary cutoff was originally selected to be equal to the risk of loss of pregnancy from amniocentesis. It also means that the vast majority of individuals with a “positive” screen will have a false-positive result, with a positive predictive value of approximately 3.4%. The detection rate is approximately 80% to 95%, depending on whether first, second, or sequential screening is performed. This test can identify individuals at risk for trisomy 13, 18, 21 or spina bifida, but has limited diagnostic usefulness for other genetic syndromes. Isolated increased nuchal translucency has also been linked to several syndromes (eg, Noonan syndromes, congenital heart disease).

- **NIPS:** NIPS uses fragments of placental DNA that are circulating in the maternal bloodstream to identify pregnancies affected by trisomy 13, 18, 21, sex chromosome aneuploidies, and certain syndromes associated with copy number variants (eg, 22q11.2 deletion, Wolf-Hirschhorn syndromes). The American College of Medical Genetics and Genomics (ACMG) supports the use of NIPS over sequential screening because of its higher sensitivity and specificity for identification of trisomies. However, ACMG encourages ongoing education to understand the implications and limitations of the testing. Two large studies suggest that the positive predictive value for trisomy 21 is 94% (N=72,382) for “high-risk women” and 50% to 81% (N=55,244) for “low-risk women.” The negative predictive value approached 100%. This is in contrast to the positive predictive value using conventional sequential screening of 3.4%. However, despite widespread use of NIPS for the detection of other copy number variants (eg, 22q11.2 deletion, Wolf-Hirschhorn, 1p36, 5q11.2-13 deletion syndromes), the positive and negative predictive values are substantially worse than for trisomies. Estimates of positive predictive value for copy number variants using NIPS are between 3.8% and 18%. There is very limited information regarding
negative predictive value. With current technology, ACMG does support the idea that NIPS can be used to screen for these pathogenic copy number variants, but recommends substantial pretest counseling regarding the limitations of the test. Therefore, a neonatologist evaluating an infant with clinical features suggestive of one of these microdeletion syndromes should not consider them “ruled out” based on normal NIPS finding; and should not consider a child to have the syndrome who was screened “positive” without confirmatory diagnostic testing. In contrast, it would be highly unlikely, but possible, that a child would be diagnosed postnatally with trisomy 13, 18, or 21 after normal findings on NIPS. Clinicians who wish to determine the positive or negative predictive values for NIPS for their patients may enter the characteristics into an online calculator (eg, perinatalquality.org). Neonatologists should also be aware that a “no-call” result on the testing can indicate an abnormality, including long stretches of homozygosity, which could increase the likelihood of a recessive or imprinting disorder.

- **Karyotype**: Neonatologists should obtain a copy of all prenatal karyotypes performed for infants in their care. It is customary for the term “prenatal karyotype” to refer to both a full karyotype, which would be expected to identify a large number of chromosomal abnormalities, as well as for a limited prenatal karyotype. A limited prenatal karyotype includes fluorescence in situ hybridization (FISH) for chromosomes 13, 18, 21, and chromosomes X and Y. This type of karyotype is not equivalent to a complete karyotype, but it is typically denoted with identical terms in the chart.
- **FISH**: When certain congenital malformations are identified on ultrasonography (eg, congenital heart disease), FISH is often offered to test for classic microdeletion syndromes such as 22q11.2 deletion syndrome. It is critical for neonatologists to understand that a normal FISH result may not be as sensitive as a single nucleotide polymorphism (SNP) array or multiplex ligation probe amplification for the region of interest. These tests should be considered in a patient with signs of a deletion/duplication syndrome even with a normal FISH result.
- **SNP microarray**: Prenatal microarrays are similar to postnatal microarrays, but rules for what variants are reported may differ depending on the specific laboratory. Usually it is not necessary to repeat an SNP microarray postnataally if there is documentation of one that is normal from prenatal testing.

**PHYSICAL EXAMINATION**

The length, weight, and head circumference of the infant should be plotted on a growth chart that accounts for gestational age, and comparisons should also be made with measurements of the parents and siblings at the time of birth. If any of the infants’ measurements are abnormal for gestational age, it is important to note if these measurements are proportional to one another. For example, there would be greater concern for a syndromic form of microcephaly in a neonate whose head circumference is at the 1st percentile but length and weight are at the 50th percentile, compared with a neonate whose head circumference, length, and weight are all at the 10th percentile. In addition, a child whose length and weight are at the 1st percentile but head circumference is at the 75th percentile may need to be evaluated for relative macrocephaly, even though the head circumference is the “normal” measurement.

For minor malformations, it is helpful to take a head-to-toe approach. When confronted with a physical feature that appears unusual but for which the terminology is unclear, a helpful resource is the Elements of Morphology by Hennekam et al. Jones and Adam have also published an excellent review of the types of genetic syndromes associated with specific major and minor malformations. It is important to remember that although some minor malformations will be present at birth (eg, single palmar crease), some minor anomalies will develop at a later age (eg, lip pits in Van Der Woude syndrome); therefore, it is important not to “rule out” a syndrome as a possibility based on the absence of these anomalies at the time of birth. There are also differences in minor malformations based on race—postaxial polydactyly and umbilical hernia are much more common in infants with African ancestry compared to those with European ancestry.

If parents are at the bedside, it is helpful to examine them for the minor anomalies present in the child, particularly growth parameters and minor anomalies of the head and hands.

In general, it is helpful to approach an infant with a known congenital anomaly in the NICU setting with a high index of suspicion for occult medical issues. Careful attention should be given to the neonate’s breathing while supine and prone, any feeding issues, tone, abnormal behaviors or desaturations suggestive of seizure activity and any observations from staff or parents that are unusual. Additional evaluations to assist in unifying the diagnosis or identification of comorbidities may be considered depending on the type of malformation and other concerns. Common additional evaluations to consider include ophthalmologic examination, hearing test, echocardiography, electroencephalography, abdominal ultrasonography, skeletal survey, and head ultrasonography. Head computed tomography and magnetic resonance imaging are typically reserved.
for patients in whom the procedure-related risks (ie, radiation, sedation) are outweighed by clinical suspicion for a medically actionable condition.

RAPID POSTNATAL TESTING: IMPORTANT CONSIDERATIONS

Increasing numbers of institutions are taking advantage of rapid exome sequencing for infants in whom a specific diagnosis is not strongly suspected, and who are felt to have sufficient medical complexity or severity. This testing is similar to exome sequencing, but for increased cost, a verbal result is given in approximately 7 days. Exome sequencing will identify children with single gene disorders caused by variants in known disease-causing genes. As the cost of exome sequencing comes down, it is rapidly becoming a cost-effective option for patients without an obvious diagnosis. Although exome sequencing is a powerful tool that can identify a genetic etiology in 20% to 50% of patients based on clinical features, it is critical for clinicians to understand its limitations. Exome sequencing will NOT identify patients with trinucleotide repeat disorders (eg, myotonic dystrophy), methylation defects (eg, Prader-Willi), balanced translocations disrupting a disease-causing gene, mosaic disorders that are not present in blood (eg, segmental neurofibromatosis), many mitochondrial disorders, diseases associated with pseudogenes (eg, spinal muscular atrophy), or disorders caused by abnormalities in introns or genes that are not yet reported to be disease-causing. It should be emphasized to patients with “negative” exomes that they should follow up with a clinical geneticist because additional methods of genetic testing may be needed, and advances in genetic testing may allow for a diagnosis through future reanalysis of the exome data.

In addition to exome sequencing, it is likely that neonates will undergo newborn screening while they are in the NICU. Although most conditions on the newborn screen will not be associated with congenital malformations, there are exceptions. Congenital hypothyroidism may be associated with macroGLOSSIA, and many states are now expanding newborn screening to include peroxisomal disorders and lysosomal storage disorders, which can be associated with anomalies at birth. Newborn screening based on T-cell receptor excision circles for severe combined immunodeficiency (SCID) can have abnormal findings for many genetic syndromes (eg, coloboma of the eye, heart defects, atresia of the choanae, retardation of growth and development, and ear abnormalities and deafness [CHARGE], 2q21.2 deletion syndrome, ataxia telangiectasia, TP63-associated disorders). If a child with congenital anomalies has an abnormal newborn screening result showing SCID, but is found not to have SCID on confirmatory testing, genetic syndromes that include T-cell lymphopenia should be considered. Despite the standard nature of newborn screening for disorders of intermediary metabolism, hypothyroidism, and hemoglobinopathies, states vary in the newborn screening tests used for SCID and peroxisomal and lysosomal storage disorders. In addition, some states have 1 newborn screen and others have a repeat newborn screen at 2 weeks of age. This is particularly relevant for clinicians who train in one state and move to another state, because it requires them to become familiar with the specific disorders screened for in their state.

In summary, there are multiple frameworks to consider in the evaluation of the newborn with congenital anomalies. Major and minor anomalies should be documented using appropriate terminology, then each patient’s family, pregnancy, and birth history should be obtained, and any results of previous testing should be evaluated in context. Emerging issues of NIPS, Zika virus exposures, ART, and rapid exome sequencing should be considered in these existing evaluation frameworks.

Suggested Online Resources

Online Mendelian Inheritance in Man (Omim.org)
GeneReviews (www.ncbi.nlm.nih.gov/books/NBK1116/)
NORD (rarediseases.org)

American Board of Pediatrics
Neonatal-Perinatal Content Specifications

- Know the rationale, methods, and interpretation of results of first and second trimester screening for aneuploidy (eg, nuchal translucency, choroid plexus cysts) and neural tube defects.
- Know the appropriate cytogenetic evaluation of the family and infant with a structural chromosome abnormality.
- Differentiate between a malformation, a deformation, and a disruption.
- Know the risk of congenital anomalies and chromosomal or genetic abnormalities associated with assisted reproductive technology.
- Know the components of a complete family history for genetic disorders.
- Know the frequency of minor congenital anomalies.
- Know the frequency of major congenital malformations.
Suggested Readings


1. A newborn is noted to have several findings on physical examination including cleft palate, syndactyly, and hypospadias. Which of the following characterizations correctly describes the findings in this patient?
   A. This patient has vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL) association.
   B. This patient has at least 3 minor anomalies.
   C. This patient is best described as "syndromic."
   D. This patient has at least 1 major anomaly.
   E. This patient has 3 deformations.

2. You are considering further evaluation and consultation with specialty services for a patient who has several birth defects. Which of the following statements describing incidence of congenital anomalies is correct?
   A. Up to 20% of healthy newborns have at least 1 minor anomaly.
   B. Approximately 10% of newborns have at least 2 minor anomalies.
   C. When there are 3 minor anomalies seen in a patient, there is a 90% chance that the patient also has a major anomaly.
   D. A minor anomaly is an abnormal course of a single organ’s development that is seen in more than 10% of the general population.
   E. Approximately 10% of term newborns will have 1 major anomaly.

3. A patient with respiratory distress is noted to have inability to pass an orogastric tube past the oropharynx and is diagnosed with tracheoesophageal fistula. On further evaluation, he is noted to have vertebral defects, anal atresia, congenital heart disease, and an absent kidney. VACTERL is suspected. Which of the following terms is most appropriate when describing a patient with VACTERL?
   A. Disruption.
   B. Deformation.
   C. Association.
   D. Syndrome.
   E. Sequence.

4. A neonate with isolated microcephaly is being evaluated. You are concerned about potential environmental exposures during pregnancy. As you obtain historical information from the parents, which of the following aspects of the evaluation is described correctly?
   A. Travel history for both the mother and father to Zika-endemic areas should be obtained.
   B. With regard to Zika infection, the most crucial period of travel in questioning should be about the third trimester.
   C. Unless the mother had symptoms during the third trimester, there is no concern for Zika infection affecting the fetus.
   D. There is no current laboratory testing available to elucidate the potential for Zika transmission from mother to infant.
   E. The most common mode of transmission of Zika virus to the mother is via blood transfusion in a foreign country.

5. A mother enters prenatal care in the second month of her pregnancy. She has a sibling with a genetic syndrome and is considering various screening tests for her fetus. In particular, she is interested in noninvasive prenatal screening (NIPS). Which of the following statements most appropriately describes NIPS?

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A. It is most useful for discovering major anatomic congenital anomalies such as gastroschisis or myelomeningocele.
B. It has a higher sensitivity and specificity than sequential screening for the identification of trisomies.
C. The positive predictive value of NIPS is higher for low-risk women than it is for high-risk women.
D. The negative predictive value of NIPS is 75% to 80%.
E. With regard to specific conditions, NIPS has the highest positive and negative predictive values in screening for 22q11.2 deletion.

Parent Resources from the AAP at HealthyChildren.org
- Congenital Abnormalities: https://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Congenital-Abnormalities.aspx

For a comprehensive library of AAP parent handouts, please go to the Pediatric Patient Education site at http://patiented.aap.org.
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NeoReviews 2017;18:e522
DOI: 10.1542/neo.18-9-e522

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