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Review Article

### A SYSTEMATIC REVIEW ON CONGENITAL ANOMALIES

**Mangesh Z. Sangle<sup>1</sup>, Mr. Pramod M. Bhosale<sup>2</sup>**

\*<sup>1</sup>Student Ojas College of Pharmacy, Jalna-431203, Maharashtra, India.

\*<sup>2</sup> Guide & Assistant Professor, Department of Pharmaceutics, Ojas College of Pharmacy,  
Jalna-431203, Maharashtra, India.

**Article Received:** January 2023**Accepted:** February 2023**Published:** March 2023**Abstract:**

*Congenital anomalies are a major cause of stillbirths and neonatal mortality. The pattern and prevalence of congenital anomalies may vary over time or with geographical location. In addition to examining maternal and perinatal risk factors, the goal of this study is to ascertain the prevalence and kinds of congenital abnormalities in live babies. Depending on the exact birth defect, birth defects can be detected either during pregnancy or after the infant is delivered. Neural tube defects (NTDs), including spina bifida and anencephaly, are severe birth defects of the central nervous system that originate during embryonic development when the neural tube fails to close completely. The causes of human NTDs are multifaceted and include both genetic and environmental elements. Several nongenetic risk factors have been identified as having potential for protection by maternal folic acid supplementation, despite the fact that the genetic foundation is still poorly understood.*

**KEYWORD'S:** Congenital Anomaly, Diagnosis of Birth Defects, Neural Tube Defect, Treatment of NTD's,

**Corresponding author:****Mangesh Zanakrao Sangle,**

Student, Ojas College of Pharmacy, Jalna,  
Maharashtra- 431203, India

Email: [mangeshsangle2001@gmail.com](mailto:mangeshsangle2001@gmail.com)

QR code



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**INTRODUCTION:**

Congenital anomalies, also commonly referred to as birth defects, congenital disorders, congenital malformations, or congenital abnormalities, are conditions of prenatal origin that are present at birth, potentially impacting an infant's health, development and/or survival. We will use the term congenital anomalies in this report. Congenital anomalies encompass a wide array of structural and functional abnormalities that can occur in isolation (i.e., single defect) or as a group of defects (i.e., multiple defects). Multiple defects may occur as part of well-described associations, such as the non-random co-occurrence of Vertebral anomalies, Anal atresia, Cardiac defects, Tracheoesophageal fistula, and/or Esophageal atresia, Renal and Radial anomalies, and Limb defects (VACTERL). Congenital anomalies vary substantially in severity. Some congenital anomalies are associated with spontaneous abortion, stillbirth, or death in the early postnatal period. Global deaths due to congenital anomalies decreased from 750.6 thousand in 1990 to 632.1 thousand in 2013, with respective age-standardized death rates of 11.0 and 8.7 per 100,000. Subtypes of fatal congenital anomalies (with estimated number of global deaths in 2013 in thousands) are congenital heart anomalies (323.4), neural tube defects (68.9), Down's syndrome (36.4), and chromosomal unbalanced rearrangements (17.3). [1] Other congenital anomalies may have little impact on survival. Anomalies which affect an infant's life expectancy, health status, physical or social functioning may be described as "major" anomalies. In contrast, "minor" anomalies are those with little or no impact on health or short-term or long term function. We have chosen to focus on major anomalies for this case definition due to their impact on public health and preexisting structure for surveillance and reporting by large national and international organizations. [1] Congenital anomalies are defined as abnormalities of body structure or function that are present at birth and are of prenatal origin. [2] Synonymous terms that are often used are "birth defects", "congenital abnormalities" and "congenital malformations", although the latter has a more specific meaning. For the purposes of this manual, the term "congenital anomalies" will be used throughout. According to the World Health Organization (WHO), in 2010, an estimated 270,000 deaths globally were attributable to congenital anomalies during the first 28 days of life, with neural tube defects (NTDs) being one of the most serious and most common of these anomalies. In an effort to decrease the number of congenital anomalies worldwide, the Sixty-third World Health Assembly adopted a Birth defects resolution. Among other objectives, this resolution

encourages countries to build in-country capacity related to the prevention of congenital anomalies and raising awareness about their effects [3].

**❖ OCCUPATION OF EXPOSURE:**

Around 2–3% of pregnancies in Europe are affected by a major congenital anomaly (European Surveillance of Congenital Anomalies, 2017). The etiology of most congenital anomalies is not fully understood, but genetic factors as well as environmental factors are involved. To decrease the prevalence of congenital anomalies, it is important to identify modifiable environmental factors and prevent maternal exposure to harmful factors. Examples of environmental factors known to increase the risk of having a child with a congenital anomaly include smoking during pregnancy and increased body mass index (BMI). Air pollution is another factor that has been associated with development of congenital anomalies, in particular with congenital heart defects. One important environmental factor that has been associated with development of congenital anomalies is maternal exposure to chemicals in the workplace prior to and during pregnancy. Most studies that have investigated maternal occupational exposure have focused on exposure to solvents, pesticides and metals. Epidemiological studies that have investigated the association between maternal occupational exposure and congenital anomalies in the offspring have conflicting results. [4]

**❖ INCIDENCE AND PREVALENCE:**

According to the World Health Organization (WHO) document of 1972, the term congenital malformations should be confined to structural defects at birth. However, as per the more recent WHO fact-sheet of October 2012, congenital anomalies can be defined as structural or functional anomalies, including metabolic disorders, which are present at the time of birth. Congenital anomalies are an important cause of neonatal mortality both in developed and developing countries. It accounts for 8-15% of perinatal deaths and 13-16% of neonatal deaths in India. It is not only a leading cause of fetal loss, but also contributes significantly to preterm birth, childhood and adult morbidity along with considerable repercussion on the mothers and their families.[5] Such services would lead to appropriate management of intrapartum related complications] premature births, low birth weight babies, and infections, resulting in increasing contribution of congenital anomalies to neonatal deaths. The possibility of transition in causes of mortality in urban areas of LMICs argues for the need for data on the magnitude and types of congenital anomalies, and the proportionate mortality due to

congenital anomalies in LMICs. Another reason to investigate congenital anomalies in LMICs is that not all congenital anomalies are lethal. Babies born with several types of non-fatal anomalies would survive with disability or need lifelong care, often leading to out-of-pocket and catastrophic expenditure for affected families. There is scant data on the number of live born children with birth defects. Data on the healthcare needs of babies affected with congenital anomalies remains unavailable.[6]

#### ❖ RISK FACTOR ASSOCIATED WITH CONGENITAL ANOMALIES:

Intrauterine development can be considered as normal development as well as abnormal development. Abnormal development occurs because of the interference of normal development from genetic disorders, environmental factors, and the combination of both genetic and environmental factors during the critical period of embryogenesis. This leads to abnormal cytogenesis, histogenesis and morphogenesis with which the neonate born with a defect known as a congenital anomaly (CA). Environmental factors that are considered as being potential risk factors in causing congenital malformation include maternal infection, maternal age and maternal drug intake during the critical period of embryogenesis and substances such as, caffeine, nicotine, commonly used medicines, maternal nutritional and health status, maternal exposure to hazardous waste and maternal alcohol intake during early pregnancy. Chemical substances such as mercury, lead and arsenic are known to lead to the development of congenital abnormalities. Multifactorial inheritances linked to the causation of CAs in humans include gene-gene and gene-environment interactions and have been demonstrated in mouse models of neural tube defects. [7]

#### ❖ MULTIDIMENSIONAL ETIOLOGIC CLASSIFICATION:

To systematically capture the clinical presentation and etiology in the study cohort we developed and implemented a multidimensional classification with three axes: etiology (known, unknown), morphology (isolated, multiple majors, minors only), and pathogenesis (sequence, developmental field, or pattern). Summarizes the system and definitions. Briefly:

- Known etiology was assigned based on specific and conservative criteria and could be either genetic, environmental (teratogenic), or due to twinning:

- Genetic—cases were classified as having a known genetic etiology if there was documentation of abnormal chromosomal number (trisomy) or

structure (insertion, deletion) or a single gene condition (such as Noonan syndrome)

- Environmental—this required documentation of exposure to a recognized human teratogen<sup>8</sup> (for example, medication, such as valproic acid, or pregestational diabetes with abnormal hemoglobin A1c concentration during the periconceptional period or early pregnancy).
- Twinning—abnormalities in twinning included either a cardiac or conjoined twins.[8]

#### ❖ MORPHOLOGY:

A case with a single major birth defect (with or without a minor birth defect) was considered isolated. This definition includes isolated sequences. Infants without a major birth defect were included if they had a chromosomal anomaly (such as trisomy 21 with no reported major birth defect, normal echocardiogram, and none of the selected list of objective minor defects) or eligible genetic condition (such as skeletal dysplasia). Only a selected list of minor defects was classified and analyzed; these were selected because they can be considered as objective findings with limited variation in reporting and classification. This list included mainly discontinuous traits such as preauricular tags or single umbilical artery, rather than continuous traits such as hypertelorism, which require careful measurements and chart based decision criteria.

#### ❖ PATHOGENESIS:

Three groups were created and defined by mechanism based on embryology, not ICD-9 BPA codes (sequence, developmental field defect, or known pattern of birth defects, table 1 ). An example of a “known pattern” is the VATER/VACTERL association. This association was operationally defined as the presence of three or more VACTERL defects (vertebral defects, anal atresia, cardiac anomaly, esophageal atresia or tracheoesophageal (TE) fistula, renal malformation, radial limb malformation) with at least one being either esophageal atresia/TE fistula or anal atresia.<sup>12</sup> To further promote consistency, the same clinical geneticist (JCC) reviewed and classified all cases of potential VACTERL association. Implementation of multidimensional classification For this study, the clinicians together developed a systematic process for the re-review of all cases. In general, each case was reviewed by one clinician, and the accuracy of the classification was further enhanced by assigning certain phenotypes to the clinician with the greatest expertise in that specialty. [8]

#### ❖ DIAGNOSIS OF BIRTH DEFECTS:

Birth defects can be diagnosed during pregnancy or after the baby is born, depending on the specific type of birth defect.

### 1) DURING PREGNANCY:

#### ❖ PRENATAL TESTING:

##### A. SCREENING TESTS:

A screening test is a procedure or test that is done to see if a woman or her baby might have certain problems. A screening test does not provide a specific diagnosis—that requires a diagnostic test (see below). Less often, a screening test result can be normal and miss a problem that does exist. During pregnancy, women are usually offered these screening tests to check for birth defects or other problems for the woman or her baby. Talk to your doctor about any concerns you have about prenatal testing.

#### i. FIRST TRIMESTER SCREENING:

First trimester screening is a combination of tests completed between weeks 11 and 13 of pregnancy. It is used to look for certain birth defects related to the baby's heart or chromosomal disorders, such as Down syndrome. This screen includes a maternal blood test and an ultrasound.

- ✓ Maternal Blood Screen
- ✓ Ultrasound

#### ii. SECOND TRIMESTER SCREENING

Second trimester screening tests are completed between weeks 15 and 20 of pregnancy. They are used to look for certain birth defects in the baby. Second trimester screening tests include a maternal serum screen and a comprehensive ultrasound evaluation of the baby looking for the presence of structural anomalies (also known as an anomaly ultrasound).

##### ➤ MATERNAL SERUM SCREEN

It is also known as a “triple screen” or “quad screen” depending on the number of proteins measured in the mother's blood. [9,10, 11]

##### ➤ FETAL ECHOCARDIOGRAM

A fetal echocardiogram is a test that uses sound waves to evaluate the baby's heart for heart defects before birth. This test can provide a more detailed image of the baby's heart than a regular pregnancy ultrasound. Some heart defects can't be seen before birth, even with a fetal echocardiogram. [12]

##### ➤ ANOMALY ULTRASOUND

An ultrasound creates pictures of the baby. This test is usually completed around 18–20 weeks of pregnancy. The ultrasound is used to check the size of the baby and looks for birth defects or other problems with the baby. [13]

### B. DIAGNOSTIC TESTS

If the result of a screening test is abnormal, doctors usually offer further diagnostic tests to determine if birth defects or other possible problems with the baby are present. These diagnostic tests are also offered to women with higher risk pregnancies, which may include women who are 35 years of age or older; women who have had a previous pregnancy affected by a birth defect; women who have chronic diseases such as lupus, high blood pressure, diabetes, or epilepsy; or women who use certain medications. [12, 14]

#### a. HIGH RESOLUTION ULTRASOUND

An ultrasound creates pictures of the baby. This ultrasound, also known as a level II ultrasound, is used to look in more detail for possible birth defects or other problems with the baby that were suggested in the previous screening tests. It is usually completed between weeks 18 and 22 of pregnancy. [15]

#### b. CHORIONIC VILLUS SAMPLING (CVS)

CVS is a test where the doctor collects a tiny piece of the placenta, called chorionic villus, which is then tested to check for chromosomal or genetic disorders in the baby. Generally, a CVS test is offered to women who received an abnormal result on a first trimester screening test or to women who could be at higher risk. It is completed between 10 and 12 weeks of pregnancy, earlier than an amniocentesis. [16]

#### c. AMNIOCENTESIS

An amniocentesis is test where the doctor collects a small amount of amniotic fluid from the area surrounding the baby. The fluid is then tested to measure the baby's protein levels, which might indicate certain birth defects. Generally, an amniocentesis is offered to women who received an abnormal result on a screening test or to women who might be at higher risk. It is completed between 15 and 18 weeks of pregnancy. Below are some of the proteins for which an amniocentesis test.

- **AFP:** AFP stands for alpha-fetoprotein, a protein the baby produces.
- **AChE:** AChE stands for acetylcholinesterase. [18]

### 2) AFTER THE BABY IS BORN

Certain birth defects might not be diagnosed until after the baby is born. Sometimes, the birth defect is immediately seen at birth. For other birth defects including some heart defects, the birth defect might not be diagnosed until later in life. When there is a health problem with a child, the primary care provider

might look for birth defects by taking a medical and family history, doing a physical exam, and sometimes recommending further tests. If a diagnosis cannot be made after the exam, the primary care provider might refer the child to a specialist in birth defects and genetics. A clinical geneticist is a doctor with special training to evaluate patients who may have genetic conditions or birth defects. Even if a child sees a specialist, an exact diagnosis might not be reached. [19]

#### ❖ Recent Advances In The Diagnosis And Subsequent Management Of Congenital Anomalies

The fetus has become a distinct patient, accessible with an ever-increasing array of imaging techniques, diagnostic procedures, and even in-utero interventions. Ultrasound (US) has been the mainstay of prenatal imaging since the 1970's when techniques were originally developed for imaging the gravid uterus. Techniques have progressed such that 3-D imaging, vascular and cardiac Doppler, and ultrasound-guided invasive procedures, are all commonly performed for prenatal diagnosis. We can now identify the majority of congenital anomalies before birth, and this ability has provided valuable insight into the natural history of these defects. This level of information also raises the anxiety level of the expectant parents. Prenatal consultation is valuable to help alleviate this anxiety, and to create plans for the special needs of the baby and mother at birth, including the mode and location of delivery. Neonatal and Pediatric specialists can develop treatment strategies in advance, and review them with the parents. Rarely, an anomaly will even require a prenatal intervention. This rapidly growing field is constantly evolving as increasingly subtle antenatal findings are correlated with post-natal outcomes. This review will provide an update on some of these advances. We will explore fetal MRI as a new diagnostic modality. Then, we will discuss recent recommendations about two of the most common prenatal diagnoses, hydronephrosis and congenital heart disease.

#### ➤ FETAL MRI

Even with the tremendous versatility of contemporary prenatal US techniques, there are still some diagnoses that elude delineation by sonography. As early as the mid 1980's, fetal MRI demonstrated promise in improving anatomic visualization compared to US, but fetal motion and long imaging times limited the diagnostic

quality of early studies. Mothers required sedation to quiet the fetus in order to achieve adequate images, severely limiting utilization of MRI. With the development of ultra-fast imaging techniques in the mid to late 1990's, however, fetal MRI has grown rapidly. Moreover, MRI cine techniques can evaluate fetal motion and swallowing. In general, fetal central nervous system (CNS) abnormalities are the most frequent indications for MR imaging. and specific imaging parameters. Tissue heating is limited to less than one degree. Experience with fetal exposure to MRI is much less than with US, but no adverse outcomes have been reported thus far from fetal exposure to MRI in the second and third trimesters.

#### ➤ FETAL HYDRONEPHROSIS

Urological abnormalities, specifically hydronephrosis, are commonly discovered during routine fetal ultrasound. It is estimated that 1 of every 100 fetal sonograms will demonstrate some degree of hydronephrosis. Over the last 25 years, there has been much emphasis on the postnatal evaluation of these patients, with the ultimate intent of preventing renal deterioration in the postnatal period which could result from obstruction or infection of the affected kidneys. The usual approach in the past has been to start the neonate on antibiotic prophylaxis, usually amoxicillin, and then obtain a postnatal ultrasound and a voiding cystourethrogram (VCUG) looking for vesicoureteral reflux (VUR), a condition that has been associated with UTI and renal damage. It is estimated that 50% of children who experience a febrile UTI are found to have reflux, and when children with prenatal hydronephrosis are evaluated postnatally, reflux can be detected in 7 to 35% of patients (average: 16%). The ideal prophylactic agent should be well tolerated, have a favorable risk profile, be excreted preferentially in the urine, and have minimal effect on the gastrointestinal bacterial flora.. The recommended dose for prophylaxis is 2 m/kg/day. This antibiotic should not be used in cases of neonatal jaundice. [20]

#### Types Of Congenital Anomalies

Congenital anomalies comprise a wide range of abnormalities of body structure or function that are present at birth and are of prenatal origin.



Table No. 1 Selected Major Congenital Anomalies

Selected Major Congenital Anomalies	
External	Internal
<ul style="list-style-type: none"> <li>Neural tube defects               <ul style="list-style-type: none"> <li>Anencephaly</li> <li>Craniorachischisis</li> <li>Iniencephaly</li> <li>Encephalocele</li> <li>Spina bifida</li> </ul> </li> <li>Microcephaly</li> <li>Microtia/Anotia</li> <li>Orofacial clefts               <ul style="list-style-type: none"> <li>Cleft lip only</li> <li>Cleft palate only</li> <li>Cleft lip and palate</li> </ul> </li> <li>Exomphalos (omphalocele)               <ul style="list-style-type: none"> <li>Gastroschisis</li> <li>Hypospadias</li> </ul> </li> <li>Reduction defects of upper and lower limbs</li> <li>Talipes equinovarus/club foot</li> </ul>	<ul style="list-style-type: none"> <li>Congenital heart defects               <ul style="list-style-type: none"> <li>Hypoplastic left heart syndrome                   <ul style="list-style-type: none"> <li>Common truncus</li> <li>Interrupted aortic arch</li> </ul> </li> <li>Transposition of great arteries                   <ul style="list-style-type: none"> <li>Tetralogy of Fallot</li> </ul> </li> <li>Pulmonary valve atresia</li> <li>Tricuspid valve atresia</li> </ul> </li> <li>Esophageal atresia/tracheoesophageal fistula               <ul style="list-style-type: none"> <li>Large intestinal atresia/stenosis</li> <li>Anorectal atresia/stenosis</li> <li>Renal agenesis/hypoplasia</li> </ul> </li> </ul>
Chromosomal	
Trisomy 21 (Down syndrome)	

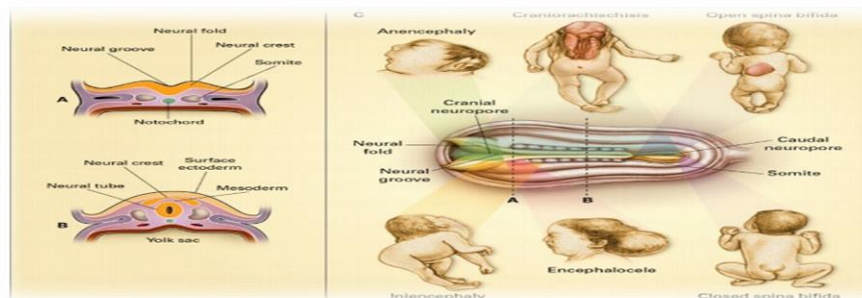


Fig. No.1: Congenital Anomalies of Nervous System

Classification by developmental mechanism or clinical presentation can be important in surveillance, because the same congenital anomaly can have

different etiologies. Furthermore, the distinction may be important both clinically and in etiological studies. Please refer to Appendix C for more information about

the causes of congenital anomalies and their classification according to developmental mechanism and clinical presentation. [21]

#### ❖ NEURAL TUBE DEFECT

Neural tube defects (NTDs) are severe birth defects of the central nervous system that originate during embryogenesis and result from failure of the morphogenetic process of neural tube closure (see sidebar). In higher vertebrates, the neural tube is generated by the processes that shape, bend, and fuse the neural plate, and fusion in the dorsal midline progressively seals the neural tube as it forms. The type and severity of these open NTDs vary with the level of the body axis affected. Thus, failure of closure in the prospective brain and spinal cord results in anencephaly and open spina bifida (myelomeningocele), respectively. [22]

#### ❖ EPIDEMIOLOGY

Neural tube defects resulted in 71,000 deaths globally in 2010. It is unclear how common the condition is in low-income countries. Prevalence rates of NTDs at birth used to be a reliable measure for the actual number of children affected by the diseases. However, due to advances in technology and the ability to diagnose prenatally, the rates at birth are no longer reliable. Maternal age has not been shown to have a huge impact on prevalence rates, but when there has been a relationship identified, older mothers along with very young mothers are at an increased risk. While maternal age may not have a huge impact, mothers that have a body mass index greater than 29 double the risk of their child having an NTD. Studies have also shown that mothers with three or more previous children show moderate risk for their next child having an NTD. [23], [24]

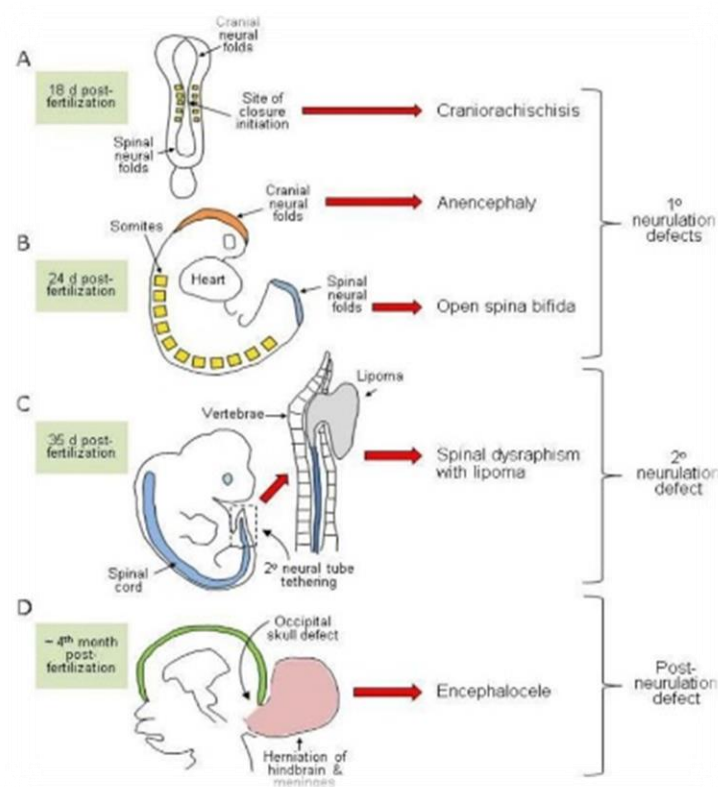


Fig. No. 2: Diagrammatic representation of the developmental origin of malformations

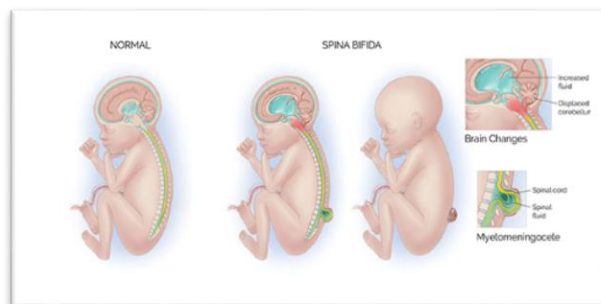


Fig. No. 3: Neural Tube Defect

### ❖ CAUSES OF NTDS

NTDs are among the most common birth defects worldwide with a prevalence that varies from 0.5 to more than 10 per 1,000 pregnancies. This variance likely reflects differing contributions from risk factors such as nutritional status, prevalence of obesity and diabetes, usage of folic acid supplementation and/or fortification, the presence of environmental toxicants, and differing genetic predisposition among ethnic groups. In most populations, there is also a striking gender bias: Anencephaly is more prevalent among females than males. Many NTD mouse strains also show a female preponderance among cranial NTDs, apparently reflecting a fundamental higher sensitivity of cranial neural tube closure to disturbance in female embryos. Overall, although studies have identified numerous risk factors, these may account for less than half of NTDs, suggesting that additional genetic and nongenetic factors remain to be identified.

- Genetics Of NTDS
- Gene-Gene Interactions And Effect Of Modifier Genes
- Genes Implicated Through Experimental Models
- Nutritional Factors And Folate
- Environment Factors

### ❖ PREVENTION OF NTDS

Neural tube defects (NTDs) are severe birth defects, occurring in 0.5 to 2 per 1000 pregnancies. The neural tube is the embryonic structure that develops into the brain and spinal cord; the defects arise from failure of embryonic neural tube closure by the fourth week of pregnancy (28<sup>th</sup> day after conception), causing malformations of the brain and spine, most commonly anencephaly and (myelo)meningocele or spina bifida, less frequently craniorachischisis (involving the posterior body axis) and encephalocele (involving the closure of the cranial neural tube). Periconceptional folate intake can prevent about 70% of NTDs.

However, correct NTDs prevention using periconceptional folate supplementation is rarely accomplished, as folinic acid (5-formyltetrahydrofolate) is commonly considered as an equivalent substitute of folic acid, while timing and dose of folate supplementation are often randomly approached. Following the WHO recommendations, some simple and practical rules are reviewed hereafter, with the aim to improve the efficiency of folate supplementation in preventing NTDs. [28, 29]

### ❖ TREATMENTS FOR NTDS

There is no treatment for anencephaly or iniencephaly. Infants with these conditions usually die shortly after birth.

#### ➤ ENCEPHALOCELES

People with encephaloceles—sac-like bulges where the brain and surrounding membranes protrude through the skull—are sometimes treated with surgery. During the surgery, the bulge of tissue is placed back into the skull. Surgery also may help to correct abnormalities in the skull and face.

#### ➤ SPINA BIFIDA

Treatment for spina bifida (/health/topics/spina-bifida) depends on the severity of the condition and the presence of complications. For some people, treatment needs may change over time, depending on the condition's severity or complications.

- ✓ **OPEN SPINA BIFIDA:** An infant with myelomeningocele, in which the spinal cord is exposed, can have surgery to close the hole in the back before birth or within the first few days after birth. [26, 27]

### CONCLUSION:

Congenital anomalies are a broad category of structural or functional abnormalities of the body that are apparent at birth and have a prenatal cause. Major structural abnormalities are frequently the focus for efficiency and practicality. These are characterized as



structural alterations that significantly impact an individual's health, well-being, or appearance and usually call for medical attention. To avoid neural tube abnormalities, congenital heart malformations, and orofacial clefts, clinicians should advise women before to conception about employment exposure to solvents. Future studies should concentrate on particular chemicals, employ exposure assessment based on expert opinion, and conduct dose-response analysis.

## REFERENCE:

1. M. DeSilva et al. /Vaccine 34 (2016) 6015-6026. 0264-410X/© 2016 Published by Elsevier Ltd. <http://dx.doi.org/10.1016/j.vaccine.2016.03.047>.
2. Congenital anomalies [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/mediacentre/factsheets/fs370/en/index.html> , accessed 12 February 2020).
3. Resolution WHA63.17. Birth defects. In: Sixty-third World Health Assembly, Geneva, 17–21 May 2010. Geneva: World Health Organization; 2010
4. N Spinder, J R Prins, J E H Bergman, N Smidt, H Kromhout, H M Boezen, H E K de Walle, Congenital anomalies in the offspring of occupationally exposed mothers: a systematic review and meta-analysis of studies using expert assessment for occupational exposures, Human Reproduction, Volume 34, Issue 5, May 2019, Pages 903–919, <https://doi.org/10.1093/humrep/dez033>.
5. Sarkar S, Patra C, Dasgupta MK, Nayek K, Karmakar PR. Prevalence of congenital anomalies in neonates and associated risk factors in a tertiary care hospital in eastern India. J Clin Neonatol 2013;2:131-4
6. Bhide P, Gund P, Kar A (2016) Prevalence of Congenital Anomalies in an Indian Maternal Cohort: Healthcare, Prevention, and Surveillance Implications. PLoS ONE 11(11): e0166408. doi:10.1371/journal.pone.0166408
7. Abebe S, Gebru G, Amenu D, Mekonnen Z, Dube L (2021). Risk factors associated with congenital anomalies among newborns in southwestern Ethiopia: A case-control study. PLoS ONE 16(1): e0245915. <https://doi.org/10.1371/journal.pone.0245915>.
8. Marcia L Feldkamp, John C Carey, Janice L B Byrne, Sergey Krikov, Lorenzo D Botto (2017). An overview on Etiology and clinical presentation of birth defects: population based study. the bmj | BMJ 2017;357:j2249 | doi: 10.1136/bmj.j2249.
9. Thacker SB, Berkelman RL. History of public health surveillance. In: Halperin W, Baker EL, editors. Public health surveillance. New York: Van Norstrand Reinhold; 1992:1–15.
10. Centers for Disease Control and Prevention. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. MMWR Morb Mortal Wkly Rep. 2001;50(RR-13):1–30 (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5013a1.htm>, accessed 12 February 2020).
11. Surveillance of antiretroviral drug toxicity in pregnancy and breastfeeding. Geneva: World Health Organization; 2013 ([http://www.who.int/hiv/pub/arv\\_toxicity/technical-brief-maternal/en/index.html](http://www.who.int/hiv/pub/arv_toxicity/technical-brief-maternal/en/index.html) , accessed 12 February 2020).
12. Massachusetts Birth Defects Surveillance Reports. Massachusetts Birth Defects Monitoring Program reports and fact sheets [online database]. Boston: Commonwealth of Massachusetts; 2020 (<https://www.mass.gov/lists/massachusetts-birth-defects-surveillance-reports> , accessed 12 February 2020).
13. Bower C, Rudy E, Callaghan A, Quick J, Nassar N. Age at diagnosis of birth defects. Birth Defects Res A Clin Mol Teratol. 2010;88(4):251–5. doi:10.1002/bdra.20658.
14. Sever LE, editor. Guidelines for conducting birth defects surveillance. Atlanta: National Birth Defects Prevention Network, Inc.; 2001.
15. Leite IC, Koifman S. Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil. Braz Oral Res. 2009;23(1):31–7. doi:10.1590/s1806-83242009000100006.
16. Khalid Y, Ghina M, Fadi B, Fadi C, May K, Joseph R, et al. Consanguineous marriage and congenital heart defects: a casecontrol study in the neonatal period. Am J Med Genet A. 2006;140(14):1524–30. doi:10.1002/ajmg.a.31309.
16. Nabulsi MM, Tamim H, Sabbagh M, Obeid MY, Yunis KA, Bitar FF. Parental consanguinity and congenital heart malformations in a developing country. Am J Med Genet A. 2003;116A(4):342–7. doi:10.1002/ajmg.a.10020.
17. Ramegowda S, Ramachandra NB. Parental consanguinity increases congenital heart diseases in South India. Ann Hum Biol. 2006;33(5–6):519–28. doi:10.1080/03014460600909349.
18. Ravichandran K, Shoukri M, Aljohar A, Shazia NS, Al-Twajiri Y, Al Jarba I. Consanguinity and occurrence of cleft lip/palate: a hospital-based registry study in Riyadh. Am J Med Genet A. 2012;158A(3):541–6. doi:10.1002/ajmg.a.34432.

19. Rittler M, Liascovich R, Lopez-Camelo J, Castilla EE. Parental consanguinity in specific types of congenital anomalies. *Am J Med Genet A*. 2001;102A(1):36–43. doi:10.1002/1096-8628(20010722)102:13.0.co;2-m.
20. Sharon W. Gould, MD, T. Ernesto Figueroa, MD, FAAP, FACS, Bradley W. Robinson, MD, FAAP, FACC, and Kirk W. Reichard, MD, MBA, FACS, FAAP. Recent Advances in the Prenatal Diagnosis and Subsequent Management of Congenital Anomalies. Published in *The Journal of Lancaster General Hospital* • Spring 2011 • Vol. 6 – No. 1.
21. Centers for Disease Control and Prevention (2020). Congenital Anomalies Definitions & Types. <https://www.cdc.gov/ncbddd/birthdefects/index.html>
22. Greene ND, Copp AJ. Neural tube defects. *Annu Rev Neurosci*. 2014;37:221-42. doi: 10.1146/annurev-neuro-062012-170354. PMID: 25032496; PMCID: PMC4486472.
23. Zaganjor, Ibrahim; Sekkarie, Ahlia; Tsang, Becky L.; Williams, Jennifer; Razzaghi, Hilda; Mulinare, Joseph; Snizek, Joseph E.; Cannon, Michael J.; Rosenthal, Jorge (2016-04-11). "Describing the Prevalence of Neural Tube Defects Worldwide: A Systematic Literature Review" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827>)
24. PLOS ONE. 11 (4): e0151586. Bibcode:2016PLoSO..1151586Z (<https://ui.adsabs.harvard.edu/abs/2016PLoSO..1151586Z>)  
doi:10.1371/journal.pone.0151586 (<https://doi.org/10.1371/journal.pone.0151586>).ISSN 1932-6203 (<https://www.worldcat.org/issn/1932-6203>) . PMC 4827875 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827875>) . PMID 27064786 (<https://pubmed.ncbi.nlm.nih.gov/27064786>) .
25. Frey, Lauren; Hauser, W. Allen (2003). "Epidemiology of Neural Tube Defects" (<https://doi.org/10.1046%2Fj.1528-1157.44.s3.2.x>) . *Epilepsia*. 44 (s3): 4–13. doi:10.1046/j.1528-1157.44.s3.2.x (<https://doi.org/10.1046%2Fj.1528-1157.44.s3.2.x>) . ISSN 1528-1167 (<https://www.worldcat.org/issn/1528-1167>) . PMID 12790881 (<https://pubmed.ncbi.nlm.nih.gov/12790881>).
26. National Institute for Neurological Disorders and Stroke. (n.d.). Spina bifida information page. Retrieved February 23, 2017, from <https://www.ninds.nih.gov/Disorders/All-Disorders/SpinaBifida-Information-Page> (<https://www.ninds.nih.gov/Disorders/All-Disorders/Spina-BifidaInformation-Page>)
27. Centers for Disease Control and Prevention. (2015). Birth defects: Facts about anencephaly. Retrieved February 23, 2017
28. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. *Lancet* 1991;338(8760):131-7.
29. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. *Lancet* 2001;358(9298):2069-73.