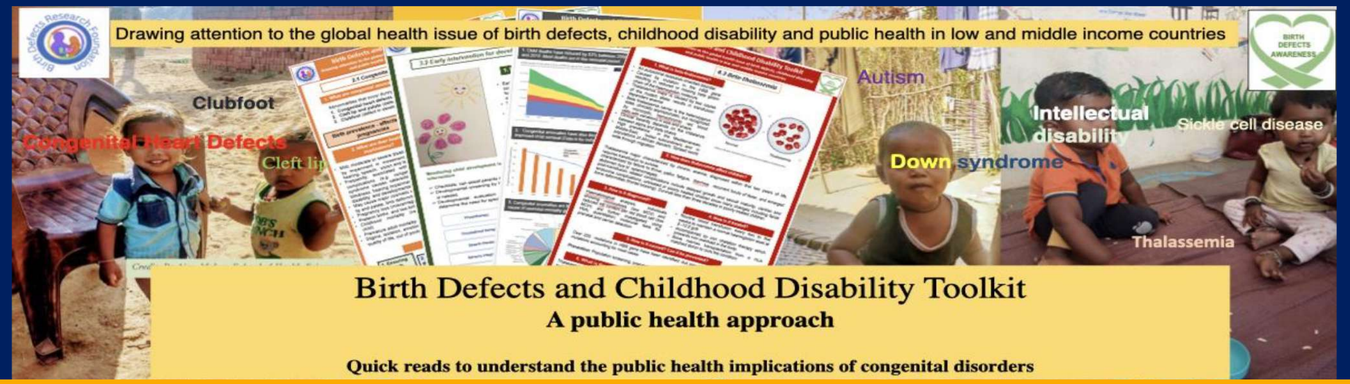


Birth Defects and Childhood Disability Toolkit

Section 5 - Prevention and risk factors

Birth Defects Research Foundation, Pune, India

A research NGO working for evidence based policies and advocating for the rights of children with disabilities caused by congenital, developmental and genetic disorders

www.birthdefectsindia.com

anita_kar

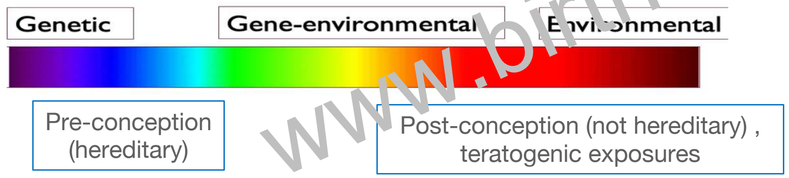
Contact us : birthdefcent@gmail.com WhatsApp+91 9172959236

Birth Defects and Childhood Disability Toolkit

Drawing attention to the global health issue of birth defects, childhood disability and public health in low and middle income countries

5.1 Risk factors and prevention of congenital anomalies

1. The aetiology of most congenital anomalies are unknown
2. Majority caused by, as yet unidentified genetic and environmental factors
3. Less than 20% are caused by single gene and chromosomal disorders (see poster on Recurrence Risks)
4. Teratogenic environmental exposures in the post-conception period cause congenital anomalies,
5. ***Risk factors/exposures during the preconception, prenatal, perinatal and post-natal periods are targets for preventive interventions***



6. Primary prevention

Preconception interventions including

- Education: Awareness about birth defects and their prevention including:
- Lifestyle factors, i.e. benefits of healthy preconception weight; avoidance of alcohol, tobacco; risks of self-medication
- Nutrition intervention : Provision of folic acid supplements/fortified foods, iodized salt use
- Screening and management of maternal pre-existing conditions like epilepsy, thyroid disorders, and diabetes mellitus; TORCH infections, syphilis
- Rubella immunization
- Management of high risk women reporting history of affected pregnancy/living child, family history of disorder, bad obstetric history, and demographic factors like advanced parental age, ethnicity and consanguinity

Prenatal period

- Awareness about protection from teratogenic occupational and environmental exposures, infectious teratogens during pregnancy;
- Regulation of teratogenic occupational and environmental chemical exposures
- Abstinence from alcohol, tobacco, recreational drugs
- Awareness about risks of using non-prescription medications

7. Secondary Prevention

Prenatal tests, genetic testing, ultrasound scans, elective termination of pregnancy

Studies to measure the impact of a package of interventions on prevention of birth defects and improvement of the quality of child survival are unavailable

References: Lee, K. S., Choi, Y. J., Cho, J., Lee, H., Lee, H., Park, S. J., ... & Hong, Y. C. (2021). Environmental and genetic risk factors of congenital anomalies: an umbrella review of systematic reviews and Meta-analyses. *Journal of Korean Medical Science*, *36*(28). Durkin, M. (2002). The epidemiology of developmental disabilities in low-income countries. *Mental retardation and developmental disabilities research reviews*, *8*(3), 206-211.

5.2 Risk factors for developmental disabilities

Condition	Risk factors
Cerebral palsy	Preterm birth, birth complications (neonatal encephalopathy, birth asphyxia, trauma), breech position, mechanical ventilation, post-natal administration of steroids for lung maturation, systemic inflammation in premature born infants, low birth weight, foetal hypothyroxinaemia, genetic factors, multiple births, disadvantaged populations, pre-pregnancy obesity, maternal pre-eclampsia, foetal growth restriction, maternal infections, cerebral malformations, perinatal stroke, kernicterus.
Congenital hearing loss	Low birth weight, preterm birth, admission to a neonatal intensive care unit, medical interventions (assisted ventilation, venous access and aminoglycoside use), single gene disorders, congenital infections (primarily cytomegalovirus infection, rubella), socioeconomic factors
Congenital vision impairment (VI) and blindness	Congenital anomalies (uveal coloboma, anophthalmos, microphthalmos, infantile glaucoma, retinal dystrophies, Leber's congenital amaurosis, congenital cataract, retinoblastoma, opthalmia neonatorum, retinopathy of prematurity, optic nerve lesions, cerebral visual impairment.
Autism Spectrum Disorders	Genetic factors : older sibling with ASD, (approximately 40-90% heritability), environmental risk factors (neonatal hypoxia, maternal obesity, short interval between pregnancies, gestational diabetes mellitus, paternal age >50, maternal age >40, valproate use during pregnancy). Not associated with vaccination, prolonged labour delivery by caesarean section or assisted vaginal delivery, premature rupture of membranes and the use of assisted reproductive technologies.
Attention Deficit Hyperactivity Disorder	Genetic factors (70-80% heritability), male sex, ethnicity and low socioeconomic status, prenatal and perinatal factors, such as maternal smoking and alcohol use, low birth weight, premature birth and exposure to environmental toxins, such as organophosphate pesticides, polychlorinated biphenyls, zinc and lead.
Intellectual disability	Genetic (chromosomal abnormalities, single gene disorders, inherited metabolic disorders), non-genetic (advanced maternal age, maternal black race, low maternal education, third or more parity, maternal alcohol use, maternal tobacco use, maternal diabetes, maternal hypertension, maternal epilepsy and maternal asthma, preterm birth, male sex and low birth weight)

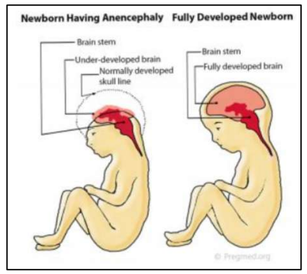
Limited research on the prevalence of maternal, child and health service-related risk factors for congenital disorders and disabilities ; these studies are necessary to inform a birth defects prevention programme

References Ansari, H (2021) Magnitude of Developmental Disabilities in India. . In: Kar, A. (eds) Birth Defects in India. Springer, Singapore. https://doi.org/10.1007/978-981-16-1554-2_1 Centers for Disease Control and Prevention Developmental Disabilities https://www.cdc.gov/ncbddd/developmentaldisabilities/causes-and-risk-factors.html

5.3 Folic acid for prevention of neural tube defects

1. Folate

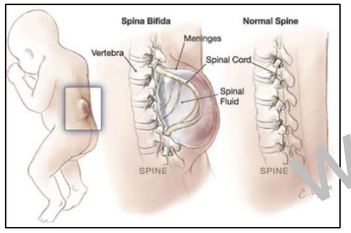
- Folate, that is vitamin B9 is a water-soluble B vitamin that acts as a cofactor in the synthesis of purine nucleotides required for DNA synthesis, and in amino acid metabolism including the synthesis of the methyl group of methionine.
- It is required for nucleic acid synthesis and generation of new cells.



2, Folate deficiency and NTDs

NTDs like anencephaly and spina bifida *(refer to poster 2.4)* are caused by incomplete formation of the brain, skull (cranium) and spinal chord.

Folate deficiency increases the risk of neural tube defects (anencephaly and spina bifida)



3. Laboratory measurement for maternal folate levels

- Serum folate measures are are sensitive to dietary intake, does not indicate long term folate status ((>3 ng/mL indicates folate sufficiency)
- Erythrocyte folate indicates long term folate status and is a more reliable source of measurement of folate levels (>140 ng/mL indicates folate sufficiency).

4. Sources of dietary folate

Naturally present in seafood, liver, meat, milk, eggs, green leafy vegetables, fruits, nuts, beans, peas. Highest folate levels are found in spinach, liver, peas, beans, grains.

Supplements :Folic acid is the synthetic form of folate. It is a fully oxidized monoglutamate form of the vitamin and not naturally available from the diet.

5.Causes of folate deficiency

- Folate deficiency occurs with other nutritional deficiencies, caused by poor diet, alcoholism, malabsorption, increased metabolism,
- Folate antagonist medications (eg cotrimoxazole such as trimethoprim, dapsone, anti-epileptic medications, methotrexate
- Genetic factors – gene polymorphisms affecting folate metabolism, especially with M*THFR*677C>T polymorphism. Genetic testing is not recommended.

6. Recommendations during pregnancy

Women intending a pregnancy need to take 400 mcg folic acid at least 90 days before pregnancy to first 3 months of pregnancy

Pregnant women reporting a previous NTD affected birth is recommended to take a higher dose of 4000 mcg of folic acid from at least 90 days before pregnancy to first 3 months of pregnancy as the recurrence risk of spina bifida is 20-50% in the next pregnancy.

The neural tube closes between day 21 and 28th day after conception when the woman may not be aware of the pregnancy.

This is why it is important to counsel women to start folate supplements when they are considering a pregnancy

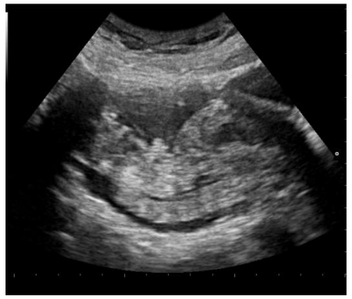
References
Wilson, R. D., & O'Connor, D. L. (2021). Maternal folic acid and multivitamin supplementation: International clinical evidence with considerations for the prevention of folate-sensitive birth defects. *Preventive Medicine Reports*, *24*, 101617.
Bhide, P. (2021). Neural Tube Defects and Folate Status in India. In: Kar, A. (eds) Birth Defects in India. Springer, Singapore. https://doi.org/10.1007/978-981-16-1554-2_4

5.4 Prenatal Genetic Screening and Diagnostic Tests

1. Prenatal screening tests

Identify at risk pregnancies. As screening tests are associated with false positive and false negative results, positive screening tests need to be followed up with *diagnostic tests*.

1. ***Ultrasound scans*** are conducted to identify the risk of congenital malformations (spina bifida, anencephaly, some types of congenital heart defects, abdominal wall defects, major skeletal deformities, orofacial clefts)

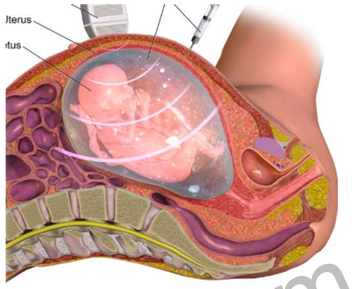


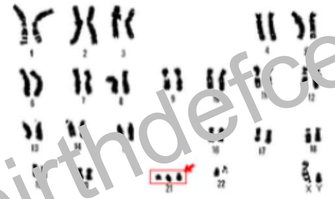
- First trimester scan – conducted between 10 to 13 weeks of pregnancy; nuchal translucency test checks the thickness of space at the back of the neck of the fetus. Abnormal test is indicative of increased risk of Down syndrome and trisomy 18 (Edwards syndrome)
- Second trimester anomaly scan conducted between 13 to 22 weeks detects major anomalies of the brain and spine, face, abdomen, heart and limbs

2. Blood tests

- First trimester maternal serum protein tests : Elevated levels of pregnancy associated plasma protein A (PSPP-A) and human chorionic gonadotropin (hCG) at 10-13 weeks are indicative of chromosomal abnormality
- Second trimester - Quadruple blood test measures levels of four substances [human chorionic gonadotropin (hCG), Alpha-fetoprotein (AFP), Inhibin A, Unconjugated Estriol (UE)] ; identifies risk of Down syndrome, spina bifida, abdominal wall defects
- Blood tests are used in conjunction with nuchal screening to estimate risk

2. Prenatal diagnostic tests

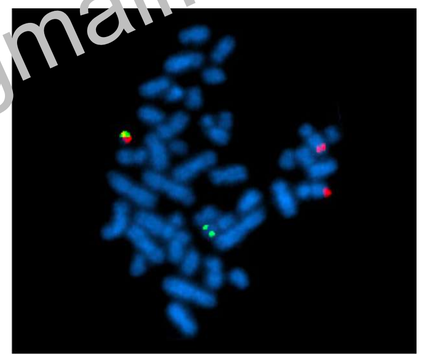




Prenatal diagnostic tests--confirmatory diagnostic testing for women positive through prenatal screening tests.

- *Amniocentesis* (conducted between 15-20 weeks of pregnancy) is an ultrasound guided prenatal procedure for withdrawing amniotic fluid with foetal cells.
- *Chorionic villus sampling* (can be conducted earlier between 10-13 weeks of pregnancy) derives a sample for the placenta. Cells derived by these procedures are used for
- *Karyotyping* ie. Examining chromosomes for chromosomal anomalies (extra, missing, or changes in the structure of chromosomes)
- *FISH (fluorescence in situ testing)* - molecular cytogenetic test to detect chromosomal anomalies
- *Chromosome microarray* a more sensitive analysis for chromosomal anomalies
- *DNA testing* for specific genetic disorders (eg haemophilia, thalassemia, muscular dystrophy) use different molecular methods

3. Carrier screening and testing



- A carrier is a healthy individual without signs or symptoms of the condition, but at risk of transmitting the condition to the next generation.
- Carrier screening uses tests to identify all potential carriers, eg camps to screen carriers of sickle cell disease
- Carrier screening needs to be followed up with diagnostic testing for individuals testing positive;
- positive diagnostic test confirms carrier status
- Carrier screening may be offered during the preconception (before pregnancy) or prenatal (during pregnancy)
- Provides the opportunity for informed decision making

Reference : WorldHealth Organization (2006) Medical genetic services in developing countries: the ethical, legal and social implications of genetic testing and screening. https://www.who.int/genomics/publications/GTS-MedicalGeneticServices-oct06.pdf.

5.5 Molecular Tests

1. Congenital anomalies have a genetic etiology, but very few are not hereditary conditions
2. Molecular genetic tests help clarify the aetiology and inform diagnosis
3. **Results of these tests may not alter patient management decisions, but may provide an insight into the possible cause of the disorder;**

Judicious use of diagnostics, with full parental consent, and ensuring that parents understand the utility of the test is very important, keeping in mind that these tests are paid through personal expenditure

Testing genetic variation	Single gene testing	Test used for a suspected single gene disorder (eg beta-thalassemia or sickle cell disease); carrier testing of relatives	Diagnostic test
	Targeted gene panel	Multigene panels, these tests test genes related to a specific condition eg congenital myopathy	May yield benign, pathogenic variants, or Variants of unknown significance (that is a variant for which a disease association has not been demonstrated).
	Whole exome sequencing	This test examines the protein coding parts of the DNA, where 85% of pathogenic variants are located.	
	Whole genome sequencing	Includes exons (protein coding parts of DNA) plus non coding DNA, Can identify CNVs - Copy Number Variations, which are associated with some disorders	
	Gene expression testing	Mostly used in oncology, eg panel testing for breast cancer	
Chromosome structure	Karyotype	For detecting large chromosomal rearrangements, eg trisomy 21 (Down syndrome)	Yields results on any chromosomal aberrations
	FISH	Used when specific disorder is suspected, or patient has family history eg common fetal aneuploidies;	
	Chromosomal microarray	More sensitive than karyotyping, can be used for detecting smaller chromosomal rearrangements,	

References Verma, R. P. (2021). Evaluation and risk assessment of congenital anomalies in neonates. *Children*, *8*(10), 862.