Indian Academy of Pediatrics (IAP)

GUIDELINES FOR PARENTS

Genetic Disorders: How to Prevent Recurrence?

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10 FAQs on GENETIC DISORDERS: HOW TO PREVENT RECURRENCE?

1. If we have one affected child with a genetic disorder. What is the risk of recurrence in subsequent pregnancies?
2. Can we prevent birth of another affected child (recurrence)? If yes, how?
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10. My daughter was born with a spinal defect and had some swelling at the site and weakness of both lower limbs. She could not be saved after surgery. Can this be prevented if we plan another pregnancy?

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Genetic Disorders: How to Prevent Recurrence?

INTRODUCTION

India has a very high birth rate, huge population, and practice of marriages in family relations or same community is favored in certain parts of the country. Due to these reasons, genetic disorders are highly prevalent in our country. Commonly seen genetic disorders include Down syndrome, thalassemia, muscular dystrophy, etc.

The general belief that genetic disorders can only occur in your child if there is a family history of a genetic disorder, is a misconception. There may be a risk of genetic disorder in each pregnancy without anyone else affected in the family or previous baby affected with a genetic disorder. Hence, some *red flags* (other than previous affected child or history of affected individuals in the family) can be picked up which predispose a family for genetic disorders. These include advanced maternal age—35 years or more, multiple pregnancy losses, unexplained death of babies after birth or in-utero, unexplained developmental delay or intellectual disability, loss of attained skills, etc. If any of these are present in any family, then parents should consult a genetic specialist before planning pregnancy. In addition, without any of these red flags also screening for some common genetic disorders before or during early pregnancy is possible. Please consult your obstetrician for more information.

If you already have an affected child, then there is a chance of having another affected child in the next pregnancy. But, the *good news* is that this can be prevented in most situations and this parent guide shall help you understand that. Remember in most situations, you have a good chance of having a normal child.

Q1

If we have one affected child with a genetic disorder. What is the risk of recurrence in subsequent pregnancies?

Let us first understand how genetic disorders are caused. Genetic disorders are caused by defect in chromosomes or a gene or a group of genes. The risk of recurrence in the next child depends on type of genetic disorder.

Broadly, every cell has a nucleus, which contains 23 pair of chromosomes, which includes two sex chromosomes. In females, both are X-chromosomes whereas in males, one is X and another is Y. Genes are present on the chromosomes which are involved in formation of proteins and responsible for all functions in our body **(Fig. 1)**. Abnormalities in the number or structure of chromosomes or

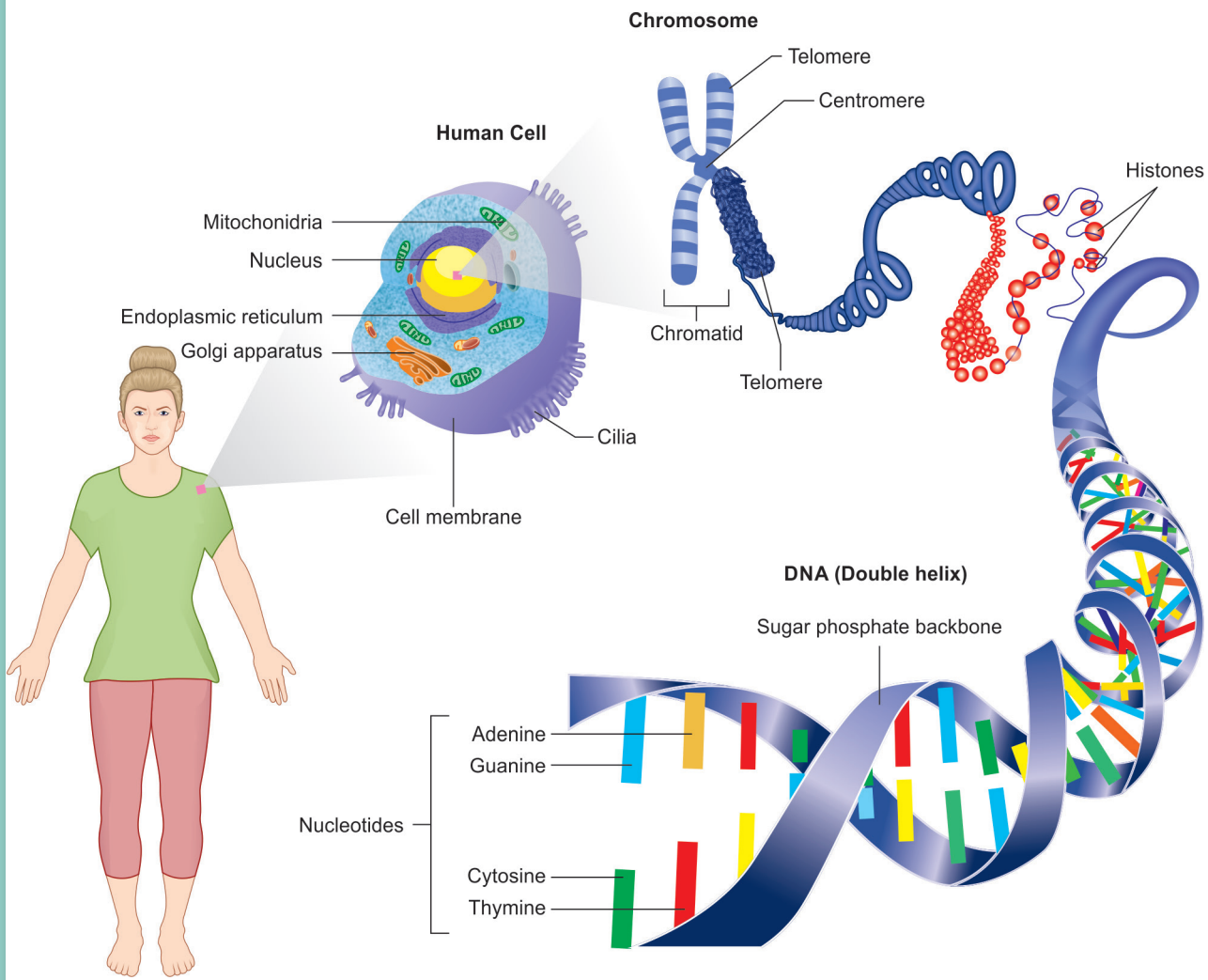

Fig. 1: Chromosomes and genes.

in the gene sequences may cause a genetic disorder. The risk of recurrence will depend on the type of genetic disorder, which may vary from as low to as 1–50% or very rarely 100%.

An abnormal gene may be located on any of these chromosomes. The gene may behave as recessive, which means that unless gene is defective in both pair of chromosome, it will not manifest and remain hidden, and may be passed on to next generation. Other behavior can be dominant—that is even if one of the genes out of two chromosomes is defective, it will give rise to symptoms or manifestations. Sometimes, genes involved may be more than one and may also be influenced by the environment. These are known as "multifactorial disorders" which include some structural birth defects, diabetes, obesity, etc.

The recurrence risk for chromosomal disorders varies from as low as 1% as in common "de novo" cases (which means abnormality only in the baby and parents being normal) to up to 30% if one of parents is a carrier for a balanced chromosomal abnormality. What we mean by balanced chromosomal abnormality is that genetic material of a part of chromosome gets translocated to another chromosome and sum total of genetic material remains same so does not cause any symptoms.

For "autosomal recessive" disorders **(Fig. 2)**, the recurrence risk is 25% in each pregnancy since the abnormality needs to be present on both pairs of chromosomes. Common example is thalassemia in which the child requires frequent blood transfusions. Other examples are sickle cell disease, spinal muscular atrophy, etc.

Autosomal Recessive Inheritance Pattern

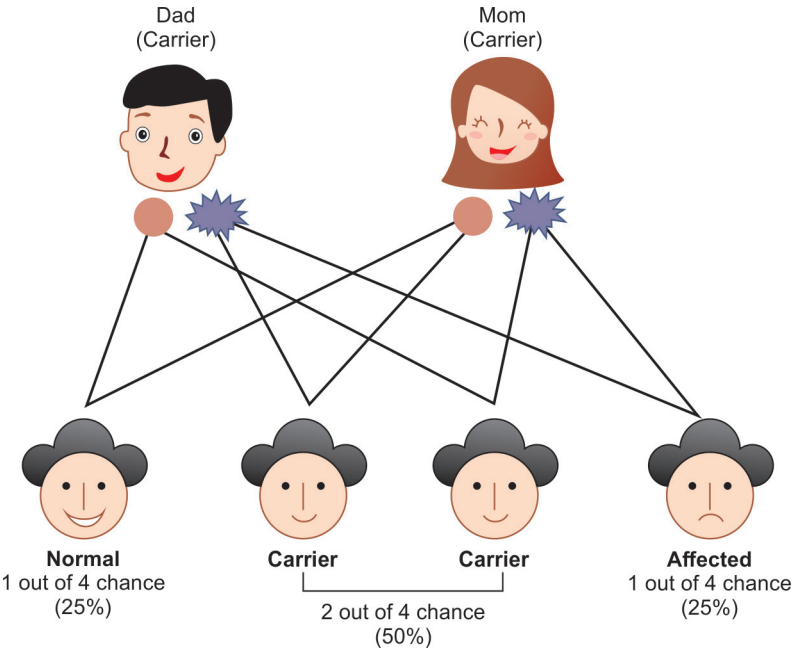

Fig. 2: Autosomal recessive inheritance.

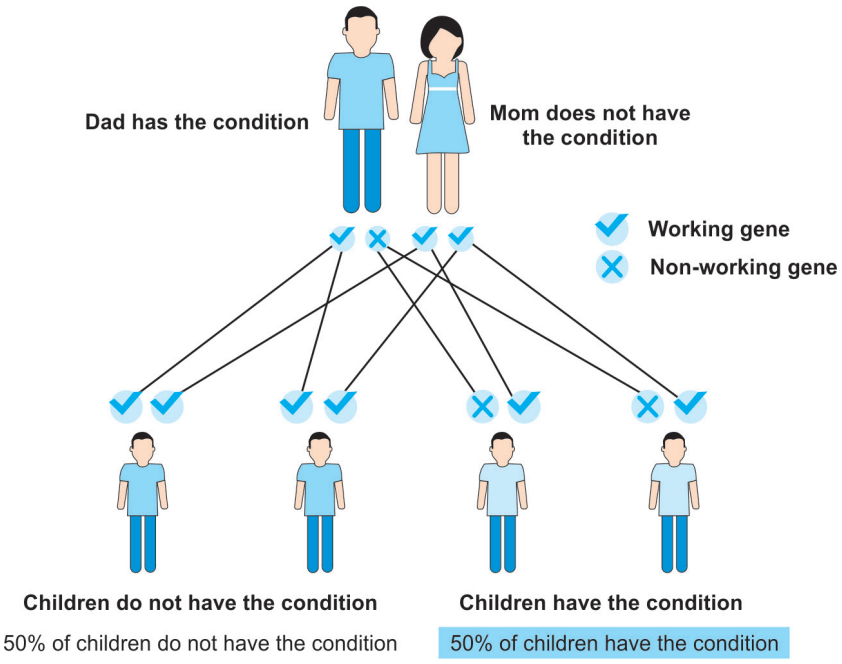

Fig. 3: Autosomal dominant inheritance.

For "autosomal dominant" disorders **(Fig. 3)**, the recurrence risk is 50:50, i.e., chances of getting an affected child is 50% in each pregnancy with affected parent. If none of the parents are affected, then risk of recurrence is low. Examples of autosomal dominant disorders include "achondroplasia" (babies have short stature with large head and other skeletal abnormalities) and "neurofibromatosis" in which skin pigmentary abnormalities and swellings are present.

The third group of disorders is X-linked **(Fig. 4)** recessive in which only boys are affected except in rare situations. This is because females have two X-chromosomes and males have one X-chromosome only. The recurrence risk is 50% for boys getting affected in each pregnancy, if mother is a carrier. If mother is not a carrier, the risk of recurrence is low. Important examples in this group include Duchenne muscular dystrophy (causes progressive muscle weakness) and hemophilia (frequent bleeding episodes requiring specific therapy).

For multifactorial disorders, important examples for babies include neural tube defects, clefts in lip or palate, limb defects, etc. Risk of recurrence is <5% in these situations.

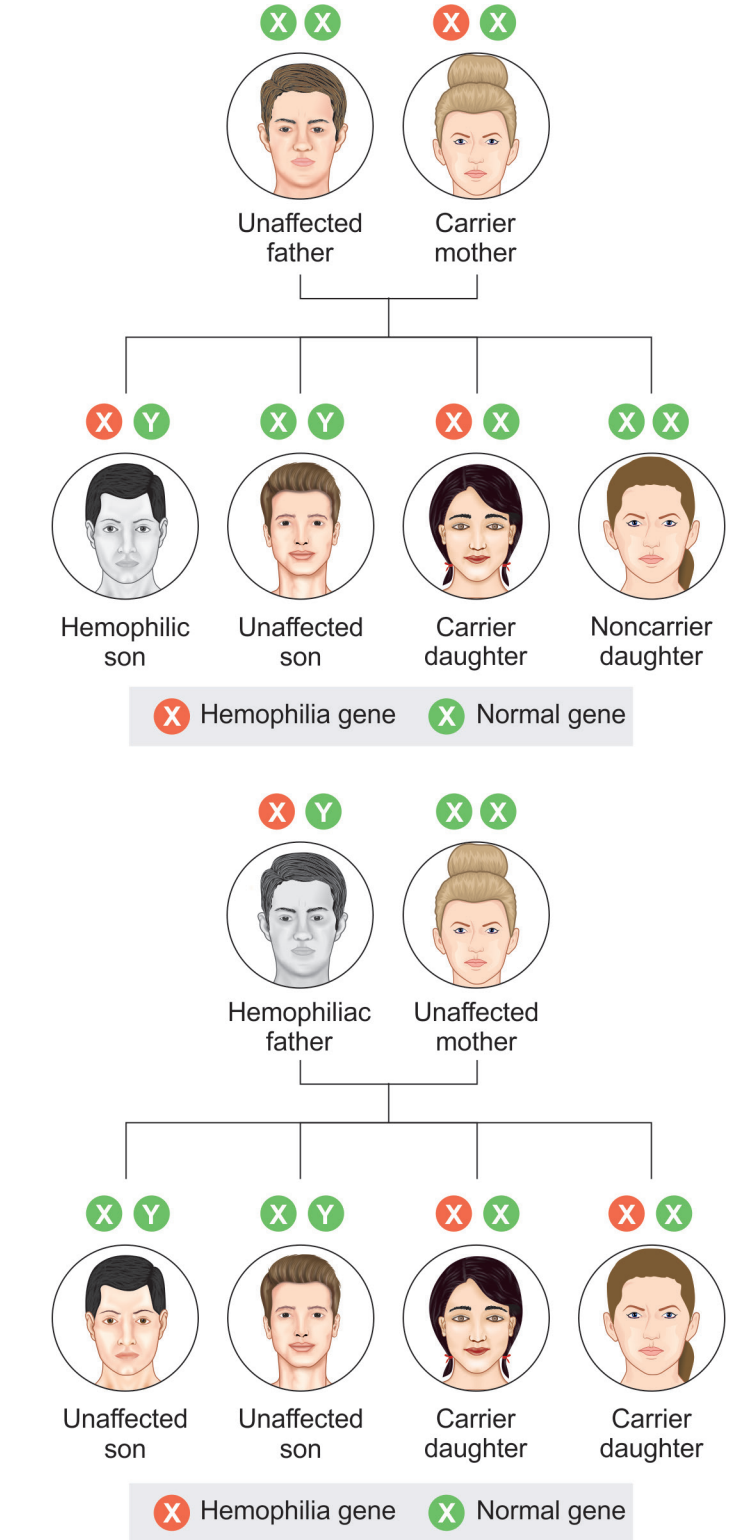

Fig. 4: X-linked recessive inheritance.

Q2

Can we prevent birth of another affected child (recurrence)? If yes, how?

The genetic disease can be tested before the birth of the baby and birth of an affected child prevented if we make a confirmed diagnosis of a condition based on clinical features and genetic testing in the affected child. For this prior consultation with a genetics expert preferably before pregnancy or early in pregnancy is a must so that there is sufficient time to make a confirmed diagnosis in affected child if not done already.

Gross malformations in the fetus can be detected with help of high-resolution ultrasonography (USG) performed by an expert radiologist or obstetrician or fetal medicine expert.

For others like chromosomal or disorders due to defects in genes, a genetic testing has to be performed before 20 weeks of pregnancy by taking a fetal sample and the fetus may be medically terminated, if found to be affected by an incurable or life-limiting disorder, if the parents desire. The whole process requires extensive pre- and post-test genetic counseling. The testing should be completed before 20 weeks as the legal limit for medical termination presently in India is 20 weeks.

Q3

What are the methods by which sample from our unborn baby shall be taken?

There are two common ways to test the fetus for a genetic disease.

Sample can be taken by "chorionic villous" biopsy (CVS) from the placenta and by amniocentesis (fluid which is there in the amniotic cavity). Even cord blood fetal sample can be taken but needs high expertise and is possible only after 18 weeks of pregnancy. Any of these samples can be tested in the laboratory for different genetic disorders **(Figs. 5 and 6)**.

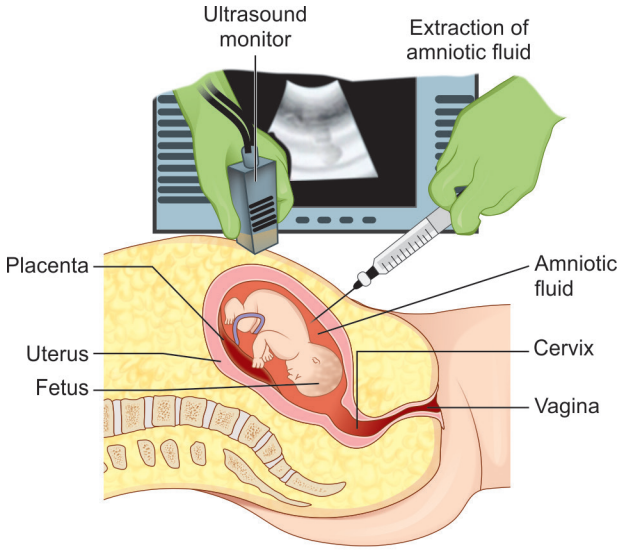

Fig. 5: Amniocentesis.

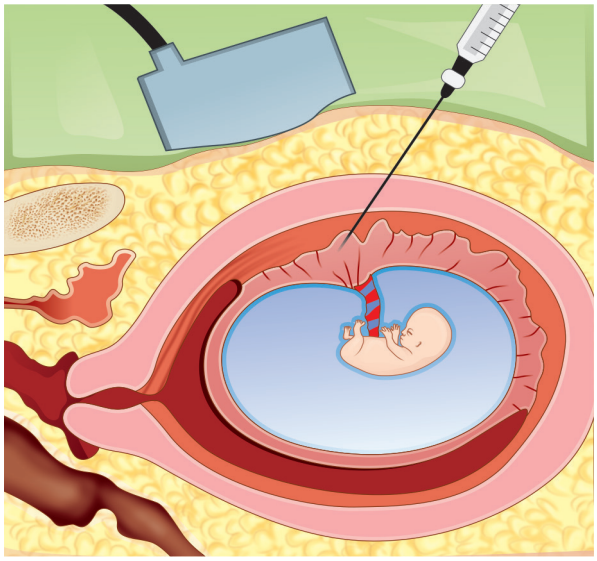

Fig. 6: Chorionic villus biopsy.

Q4

How early these can be performed?

- *Chorionic villus sampling* is generally performed from between 10 and 12 weeks (or later) in pregnancy. This process involves obtaining small pieces of developing placenta that has the same genetic makeup as the baby. This process involves ultrasound examination to check the position of the baby and the placenta followed by administration of a local anesthetic to numb the area from where the needle will be inserted. Under ultrasound guidance, a needle is used to obtain the samples which is then sent to the laboratory for genetic testing. This is done mostly through the abdomen of the woman.
- *Amniocentesis* is performed during 16–20 weeks of pregnancy. The amniotic sac is a bag of fluid in which the baby floats in the womb. Amniotic fluid contains some of the baby's cells which can be examined in the laboratory to check the baby's genes and chromosomes. This process involves taking some of this amniotic fluid from the sac under ultrasound guidance followed by genetic testing on the cells or deoxyribonucleic acid (DNA) extracted from the cells in the fluid.

Q5

How safe are the tests for which fetal sampling is required?

The methods used for prenatal testing are generally considered safe. However, they carry a minimal risk of miscarriage of 0.3% for CVS and 0.1% for amniocentesis. It is expected that the pregnancies would continue normally in most of the cases. Pregnant women undergoing invasive prenatal testing are assured that if such procedures carried out by experienced operators in specialist centers are not associated with increase in miscarriage rate as compared to women who are not undergoing these procedures.

Q6

What is the reliability of these invasive tests?

These tests are considered to be very accurate. Reliability of these invasive genetic testing usually depends on two factors, the procedure and the genetic test in the laboratory. The overall chances for the test being wrong is only 1–2%.

Occasionally, one might fail to obtain sufficient villi during the chorionic villus sampling or sample might contain some maternal cells or tissues. There is a slight chance of 1–2% (1 in 100 samples) for the test to fail due to several reasons. If the test fails due to any reason, it is informed accordingly to the patients and a repeat test is planned.

Q7

My first baby has developmental delay and has been diagnosed to have Down syndrome by chromosome test. Is there a risk that my next baby will also be affected? Can I prevent that?

When a child with Down syndrome having 47 chromosomes (extra chromosome no. 21) has been born, the risk of birth of a second affected child in subsequent pregnancies is only about 1%. This is a very low risk. A small percentage of cases of Down syndrome have a different chromosomal abnormality called translocation. Here the extra chromosome no. 21 is present, but is attached to another chromosome such as no. 13, 14, 15, 21, or 22. In these cases, chromosomal analysis of the parents should be done. If either of the parents have a balanced abnormality, risk of recurrence is higher. Birth of the second baby with Down syndrome can be prevented by testing the fetal tissue (as explained above) by chromosomal studies and some DNA-based rapid tests which are very reliable. Presently, a noninvasive test is also being used in which fetal genetic material is obtained from maternal blood, the test is very reliable, if negative but positive test needs to be confirmed by fetal sampling and testing.

Q8

My first baby has thalassemia and requires blood transfusion every few weeks. Can I prevent the birth of second affected child, how?

Your first baby is affected with thalassemia major and this genetic disorder is a recessive disorder. There will be a defect on both copies of the thalassemia gene in the baby whereas both parents will have abnormal gene on one of the copies, which means that both of you are carriers. In this situation, there is a 25% chance of recurrence for affected child in every pregnancy. You can prevent the birth of a second affected child by testing the genetic defect in the fetus around 10–12 weeks of gestation by CVS and taking a formal decision on continuation of pregnancy. Availability of the report of genetic defect causing thalassemia (tested in parents/affected child] is a prerequisite for prenatal testing.

Q9

My first son has "Duchenne muscular dystrophy" and is wheelchair bound at 13 years. Can I prevent the birth of second affected child, how?

Duchenne muscular dystrophy is a muscle disease inherited as X-linked recessive disorder. Genetic testing by DNA analysis should be done in the affected child to identify the causative defect in the gene. This can be done by multiplex ligation probe amplification (MLPA) test which detects large missing or duplicated portions of the gene (positive in 70% cases) or sequencing of the dystrophin gene (if MLPA is normal). If the defect is identified in the affected child, then mother should be tested for carrier status. If she is a carrier of this defect, then there is a 50% chance that the diseases will affect male children in each pregnancy. However, females will not be affected with disease (except in rare circumstances) and 50% will be carriers of disease. You can prevent the birth of a second affected child by testing the same defect in the fetus around 10–12 weeks of gestation on CVS by prenatal sampling. If mother is not a carrier, then the disease in the affected child is due to new gene defect, which is not inherited and recurrence risk is low (up to 10%) due to the defect in the gonadal cells. Prenatal testing can be offered in this situated also.

Q10

My daughter was born with a spinal defect and had some swelling at the site and weakness of both lower limbs. She could not be saved after surgery. Can this be prevented if we plan another pregnancy?

Your child had a "neural tube defect" **(Fig. 7)**, a very common birth defect seen in our population. Most of the time, this malformation is isolated and not associated with other malformations. Since your child had an isolated neural tube defect, recurrence risk in next pregnancy is up to 5%. The mother should take 5 mg of folic acid daily, orally to reduce the risk of this anomaly by 70% in next pregnancy. For the drug to have its effect, it should be started 2 months before you plan pregnancy till 3 months after pregnancy. This is because the neural tube is formed very early in pregnancy. Moreover, a blood test on mother's blood (increased Alfa-Feto protein) around 16–18 weeks of pregnancy and ultrasound anomaly scan around the same time (even earlier) during next pregnancy will be able to detect the anomaly in most cases. If neural tube defect is associated with other malformations, then baby should be tested for some other genetic disorders in consultation with a genetics expert.

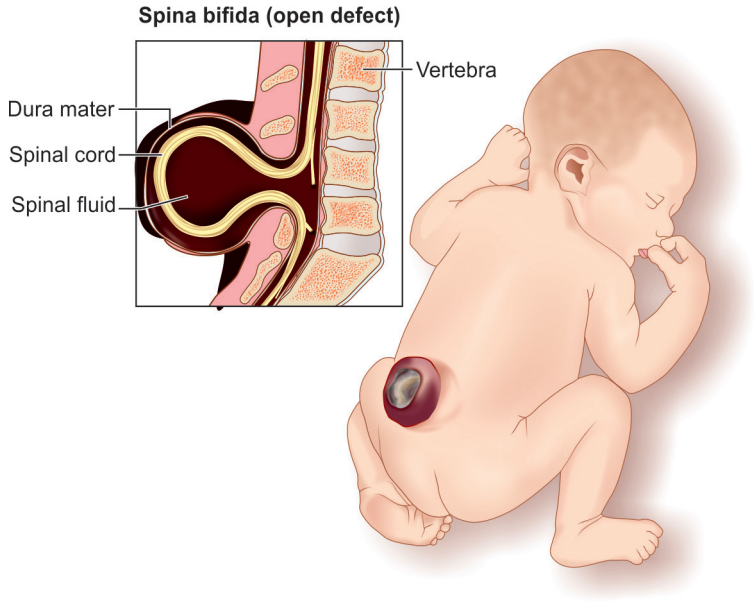

Fig. 7: Neural tube defects.