Indian College of
Obstetricians & Gynaecologists
Academic Wing of FOGSI

ICOG CAMPUS

Birth Defects:

Beyond genetics & ways to minimise!

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From the Desk of President, FOGSI

Dr. Jaydeep Tank
President, FOGSI

FOGSI ICOG Campus on : "Birth Defects: Beyond genetics and ways to minimize"

Birth defects contribute to significant perinatal morbidity and mortality, despite the developments in medical science and technology. Management of birth defects pose complex clinical challenges - both in personal medicine as well as the public health domain.

Iam happy that the ICOG has addressed this topic in the current edition of the ICOG Campus and I congratulate Dr Parul Kotdawala, Chair ICOG and Dr Sarita Bhalerao, Secretary ICOG for conceptualising this very pertinent theme. In the past few decades we have achieved progress in prevention, diagnosis, and management of birth defects but their impact remains profound-shaping the lives of children, families, and communities in countless ways. While much has been discussed in academic forums about prenatal diagnosis and management of birth defects, the concepts of pre conceptional interventions to minimise these conditions and the environmental paradigm has been largely unexplored.

It is heartening to see these topics addressed in this issue. These articles will foster awareness about the different aspects of birth defects and the possible ways of reducing their burden in coming years. The theme for FOGSI this year was "Co ordinate, Communicate, Community" - the three C's which also summarise the plan of holistic care for birth defects. Through evidence-based updates and expert insights, the authors have tried to emcompass this ethos and I hope the readers enjoy this issue.

FOGSI Secretary General's Message

Dr. Madhuri Patel
Secretary General, FOGSI
Editor-in-Chief, JOGI

The birth of a child with any major anomaly spells a kind of gloom for the entire family. Birth defects are major contributors to adverse perinatal outcome. In an era when couples are looking forward to the "perfect baby", there is growing impetus on preventing, predicting, diagnosing and managing birth defects in a manner that will do the greatest good to the greatest numbers.

I am very happy to see this ICOG campus based on topics that address "Birth Defects: Beyond genetics and ways to minimize" and I congratulate DR Parul Kotdawala ICOG Chairpersons and Dr Sarita Bhalerao ICOG Secretary for their efforts in putting together this edition of the ICOG Campus.

The topics are testimony to the importance being laid on understanding the causes of birth defects and looking for methods to prevent the. The fight against birth defects is not confined to the walls of hospitals or laboratories-it is a global effort involving policymakers, healthcare providers, researchers, and advocates. By coming together, we can promote earlier detection, enhance access to specialized care, and strengthen preventive measures.

In the chapters of this ICOG campus the authors have put together very pertinent information ranging from the latest breakthroughs in genetic research and prenatal screening to innovative approaches in rehabilitation and long-term care. As we continue to make strides in addressing birth defects, let us remain committed to compassion, collaboration, and the pursuit of better outcomes for all. Together, we can ensure that every child has the opportunity to thrive.

From the Desk of Chairperson, ICOG

Dr. Parul Kotdawala
Chairperson, ICOG

It is a matter of great pleasure to offer you another new and final ICOG Campus this year, again on a very vital aspect of Birth Defects. It is time to delink a thought that all birth defects are genetic in origin! In fact, a large proportion of them are a result of assault on early development of the embryo and the fetus. These factors can be nutritional, Environmental or toxic exposures. We need to keep in mind the impact and timing of these; as well as detecting them early, developing treatment protocols and above all - preventing them!

In this ICOG Campus we have just 5 contributors, each of them an authority by themselves, sharing with us their knowledge and experience on the topics of;

1. Role of pre conceptional Folic acid in preventing birth defects - Dr Sarita Bhalerao
2. Contemporary challenges with "teratogenicity"; advice following teratogen exposure - Dr Charmilla Ayyavoo
3. Prenatal diagnosis of "birth defects"- appropriate screening protocols - Dr Vandana Bansal
4. Managing birth defects rationally - preventing despair - Dr Chinmayee Ratha
5. The "Environment" paradigm - is that increasing the risk of birth defects? - Dr Uday Thanawala

I congratulate Dr Chinmayee Ratha for conceptualizing and designing this issue of ICOG Campus along with Dr. Sarita Bhalerao. I appreciate and I am very thankful to each of the learned authors for their time & inputs. Their expertise has been instrumental in shaping this book.

I also take this opportunity to thank Mssrs. Aristo Pharma and Mr. Ramnathan in particular, for supporting this publication of ICOG.

I feel very sure that this book will be an excellent reference book for colleagues in dealing with the tricky pathways of managing and preventing the birth defects in caring for Indian women.

ICOG Secretary's Message

Dr. Sarita Bhalerao
Secretary, ICOG

I am delighted that this ICOG campus on Birth Defects is ready and set for release.

Preventing birth defects is the responsibility of all Obstetricians and the role of folic acid in prevention is well known. L-Methylfolate is the biologically active form of folic acid.

Other issues like teratogen exposure, screening for birth defects and managing them are discussed in detail by the authors and carry important practicalpoints.

Finally, Dr Uday Thanawala addresses the issues of environmental factors possibly an important cause of birth defects.

My congratulations to Dr Chinmayee Ratha the editor and the entire team for this effort.

My thanks to Aristo Pharma for their support in this endevours.

Preface

Dr. Chinmayee Ratha
Editor

The life of an Obstetrician is dedicated towards achieving a favorable perinatal outcome with a happy mother and a healthy child. Till almost a century back in time, Obstetricians were focussing largely on the care of the mother in pregnancy and childbirth but they eventually realized that if the outcome of the child is adverse, then their entire hard work goes to the background and they have to deal with the despair of their patient and her family. The advent of the concept of Perinatology included the "child" into the focus of the Obstetrician and with the birth of "Fetal medicine" there was a continuum of care from pre conception to fetal development to childbirth and beyond. As medical science advanced and infectious diseases were managed better, the perinatal morbidity and mortality due to birth defects started occupying the frontlines in clinical challenges. While we have now definitely accepted that birth defects are a cause of great despair, ways and means of minimizing birth defects seem to be a relevant area to focus in the present era.

I thank the ICOG Chairperson Dr Parul Kotdawala and Secretary Dr Sarita Bhalerao for the opportunity to put together the topics for this ICOG Campus which has been very aptly themed on ""Birth defects: Beyond genetics and ways to minimise".

Starting from the role of Folic acid in preventing congenital anomalies, the authors have delved into thought provoking areas like managing Obstetric patients following teratogen exposure which often becomes a daunting challenge to the obstetrician. Timely prenatal diagnosis and management of birth defects have their definite roles in the paradigm of care but exploring the angle of "environmental effects " on the fetus has been an endeavour to look beyond the obvious etiology of fetal anomalies. We hope that the readers find the contents interesting and inspiring as the aim is to extend our efforts in not only direct prediction, diagnosis and management of birth defects but in minimising teratogen exposure by generating pre conception awareness and a better environment around us.

Happy reading

CONTENTS

TOPICS

1 L-Methylfolate and its Role in Prevention of Pregnancy Complications

Dr Sarita Bhalerao, MD
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The Substance

Folate, or vitamin B9, is one of the 13 essential vitamins. It cannot be synthesized *de novo* by the body and must be obtained either from diet or supplementation.

Folic acid is a synthetic dietary supplement that is present in artificially enriched foods and pharmaceutical vitamins.

Metabolism

Neither folate nor folic acid is metabolically active. To become metabolically active, folic acid must first be converted to dihydrofolate (DHF) and then tetrahydrofolate (THF). This step requires the enzyme DHF reductase (DHFR). Thereafter, THF can be converted to the biologically active L-methylfolate by the enzyme methylenetetrahydrofolate. (MTHFR).

This key conversion is necessary to provide L-methylfolate for the one-carbon transfer reactions (methyl donations) needed for purine/pyrimidine synthesis during DNA and RNA assembly, for DNA methylation, and to regulate homocysteine metabolism. MTHFR is the critical enzyme for almost all biologic processes that involve the metabolism of folate and methionine.

Genetic variations (polymorphisms) are common within the human genome. 40 to 60% population has polymorphisms. These can result in the production of proteins with altered biologic activity. Several such MTHFR genetic polymorphisms have been identified in the general population. This can lead to less biologically available L-methylfolate. Therefore, newer research recommends supplementation with L-methylfolate rather than folic acid. 5-MTHF does not require activation, and it is immediately available to mother and foetus. This will ensure that the pregnant women will get the adequate dose of the utilizable form of folate.

Folic Acid and the Prevention of NTDs

There is enough scientific evidence to support dietary supplementation with folic acid before conception and in early pregnancy to reduce the risk of NTD in the offspring.

A dose of 5 mg per day can reduce the risk of NTD by 85%.[1,2,3,4,]

Folic Acid and Prevention of Anemia

Increase in blood volume involving increase in both plasma and red blood cells is normal in pregnancy. Erythropoiesis requires adequate supplies of three key nutrients: folate, cobalamin (vitamin B12), and iron. It needs the transfer of a methyl group from L-methylfolate to homocysteine via methylcobalamin for the regeneration of methionine. Therefore, supplementation with the active form of folate may be useful in improving the red cell production and thereby reducing anaemia.[5]

Folic Acid and Prevention of Preterm Birth

In observational studies, a shorter duration of pregnancy has been associated with low serum folate levels[6,7] and with the absence of folic acid supplementation during pregnancy.[8]

Studies suggest that folic acid supplementation alone may protect against PTB, in both low- and high-risk populations.[8,9,10,11] The authors of the FASTER trial (analysis included 34,480 women with singleton pregnancies) carried out in the United States from 1999-2002, concluded that pre-conceptional folate supplementation for 1 year was associated with a significant reduction in spontaneous PTB and that this association was strong, specific, dose dependent.[11]

Folic acid and Potential additional benefits on pregnancy outcome

Various epidemiologic studies show that pregnancies exposed to folic acid antagonists have significantly higher rates of placenta-related pregnancy complications.[12,13,14,15]

Folic acid antagonists are a broad spectrum of drugs used for a variety of clinical indications, such as treatment of seizure disorders, mood disorders, and urinary tract infections.

In one study, pregnancies exposed to folic acid antagonists were noted to be at increased risk of developing preeclampsia, severe preeclampsia, placental abruption, fetal growth restriction and fetal death.[14]

These adverse events have one thing in common: they all appear to result from abnormalities in implantation and placentation that occur early in gestation. Folic acid has been shown to regulate trophoblast invasion.[16] Therefore it is biologically plausible that folate deficiency may interfere with the early stages of placental development leading to complications later in gestation. Therefore, we may extrapolate and conclude to say that folic acid supplementation may prevent complications related to placentation.

Risks of High-Dose Folate Supplementation

Folic acid supplementation to supraphysiologic levels has demonstrated many benefits to pregnant women and to the fetus. Nevertheless, the potential risk of high-dose folate supplementation must also be considered.

Folate supplementation can mask vitamin B12 deficiency (pernicious anemia) and care must be taken with susceptible individuals to avoid missing this diagnosis. Secondly, there is a concern about the potentially untoward effects of unmetabolized synthetic folic acid with regard to cancer, depression, and cognitive impairment. With all these concerns, data suggest supplementation with L-methylfolate rather than folic acid may mitigate these risks.[17]

Conclusions

Folic acid supplementation has proven benefit in prevention of neural tube defects.

There is some scientific evidence that people with genetic variations in the MTHFR may not be able to complete the conversion of folic acid to its active form. Therefore, it may be beneficial to supplement with L- methyl hydrofolate especially the high-risk group. There is evidence to support that the active form regulates homocysteine metabolism and is readily available in the blood stream for utilization.

Folate supplementation also may have a role in improving placentation and preventing preterm delivery, and low birth weight.

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2 Contemporary challenges with "teratogenicity" - advice following teratogen exposure

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Introduction

The field of teratology deals with the study of the effect of the environment on the development of fetal malformations. It has been developed as a science from the 1930s. Pregnant pigs were fed with a Vitamin A deficient diet. The experiment proved that that there is no complete protection for the fetus from harmful agents when there is maternal exposure. These experiments proved that simple changes in the environment can cause harmful effects in the foetus.

There are many episodes where drugs were seen to cause severe malformations in the foetus. In 1950s, a drug called aminopterin was used as an abortifacient. It was seen to produce severe malformations in the children born when the drug failed to cause a termination. In the 1960s, the thalidomide tragedy highlighted the fact that a drug which causes minimal toxic effects in the mother can cause severe toxicity in the baby. Because of this tragedy, regulatory agencies like the Food and Drug Administration in the United States, brought out guidelines for testing drugs in animals before approval was provided for marketing. Animal testing is also not fool proof because the drugs which were tested, frequently caused side effects in human beings while they were thought to be safe. This was attributed to the difference in maternal metabolism and distribution of the drug which can change the effect of the drug on the foetus. Most of the toxicity studies performed in animals are based on the understanding of the effects of the drug in each species.[1]

The different types of teratogenic agents which can affect during pregnancy are drugs, chemicals, infectious organisms, radiation, heat, and maternal diseases like diabetes, phenylketonuria. Many pregnancies are unplanned and there is a likelihood of inadvertent exposure to teratogens during pregnancy. Some pregnancies have exposures to multiple teratogenic agents and advice on the risk cannot be provided with clarity. Exposure to teratogens can lead to fetal death, fetal structural malformations, fetal growth restriction, or functional defects.

Even though there have been dramatic events associated with teratogens like thalidomide and valproic acid, the congenital defects associated with drug exposures are very rare. When they occur, they have a lasting impact on the medical community and the general population. The defects can be very minimal like a depressed nasal bridge to very severe like cardiac anomalies & mental retardation.

Mechanism of action of drugs on the foetus:[1]

Medications or chemicals taken by the mother will cross the placenta if it is not destroyed or changed during transfer through the placenta.

The size of the molecule and the solubility in lipids will also affect the transfer. The placental transfer of drugs can occur from the fifth embryonic week. If the drug is of low molecular weight, the transfer will depend on the concentration gradient.

According to a study by Finnell et al, malformations due to teratogens are only 2-3% of birth defects seen. The majority do not have a cause identified. Genetic conditions account for 20% of birth defects while chromosomal causes account for 3-5% of birth defects. Maternal infections and metabolic disorders cause very few birth defects.[2]

The USFDA has categorized maternal benefit to fetal risk when there is a drug exposure during pregnancy. The categories are A, B, C, D, X.1

Category A: Studies failed to show any fetal harm when the mother was exposed to the drug in the first trimester. The studies were well conducted and controlled studies.

Category B: Reproductive studies in animals did not show any harm but there are no controlled studies available in pregnant women to show safety. Or reproductive studies in animals showed harm but they were not confirmed in controlled studies conducted in pregnant women in the first trimester.

Category C: Reproductive studies in animals have revealed harm or there are no studies conducted in animals or pregnant women. These drugs should be used only if there is a potential benefit which outweighs the risk involved.

Category D: There is evidence of risk in pregnant women but benefits are present which are more than the risk involved.

Category X: These drugs are not to be used in pregnancy because of confirmed teratogenic effects.

Advice after exposure:

When a patient comes with a history of exposure to teratogens, the couple should be counselled as per the following points: The susceptibility to a drug induced change depends on

- The genetic structure of the foetus,
- The gestational age when the foetus is exposed,
- The mode of action of the drug,
- The accessibility of the drug to the developing tissues, and
- The dosages of the drug used.

It must be remembered that defects induced by teratogens can be prevented if the dose-response and the teratogenic effect of the drug is clearly elucidated.

Fetal surveillance:

After counselling, a protocol for fetal surveillance is instituted.

Early diagnosis will form a key for risk assessment as well as the formulation of a protocol for perinatal and postnatal care. An early scan at 10 weeks is done to establish viability, date the pregnancy and identify chronicity if it is a multiple pregnancy. An anomaly scan in early pregnancy is not informative. A combined test is offered with screening for ultrasound markers and biochemical testing for Trisomy 21, 13 and 18 at 11-14 weeks of pregnancy. A screening for structural anomalies is done at 20 weeks of gestation. In countries like Netherlands, non-invasive prenatal testing (NIPT) using cell free DNA is offered when the combined test shows a high risk or there is a history of a previous child with Trisomy. This protocol has increased the detection rates of congenital defects like neural tube malformations, cardiac anomalies, and anomalies of the urinary tract.[3]

Contemporary challenges in teratogenic exposure:

The changes induced in the foetus may not be structural malformations alone. There can be functional or behavioural changes which may not be identified at birth but may occur later in the child's life.

Women tend to use drugs purchased over the counter for recreational or medical use. A survey by WHO identified that almost 86% of women took medications without prescription during their pregnancy.[4]

In a study by Andrade et al, 50% of prescriptions in pregnancy were for drugs classified as C, D or X. The drugs commonly taken were acetaminophen, ibuprofen, and pseudoephedrine.[5]

The use of herbal medicines and dietary supplements also adds to the teratogenic risk. There is no quality control for these medications and there is less information on the toxicity.[6]

Preventive strategies:[7]

Governments have enacted laws to prevent the prenatal exposures of foetuses to harmful medications. The manufacturers have been advised to implement Risk evaluation and Mitigation strategies for each drug to prevent prenatal exposures. The response is not adequate as only few drugs like isotretinoin and mycophenolate have been risk evaluated. The effects of these measures is also unknown. More needs to be done to provide safety for mothers and children. compared with drugs subject to Risk Evaluation and Mitigation Strategies is unknown. Moreover, the effectiveness of such advanced risk mitigation programs in preventing prenatal exposure is not clear.

Conclusion:

There is no specific group of symptoms ad signs which can develop following drug exposure. Counselling of parents on the effects of the drugs which can cause birth defects is very difficult as literature is very sparse on risk mitigation strategies. Pre-conceptional counselling & care are important to reduce inadvertent exposures and their sequelae.

Key points:

Unintended exposure to teratogenic drugs can occur as there are many unplanned pregnancies and exposure would have already occurred during the crucial embryonic stage.

All drugs may not cause birth defects. The development of defects is dependent on the genetic constitution of the foetus, the

gestational age when the foetus is exposed, the mode of action of the drug, the accessibility of the drug to the developing tissues, and the dosages of the drug used.

Teratogens are the cause in only 2-3% of the babies with birth defects.

Teratogenic exposures can also cause functional or behavioural defects in children which may not be identified at birth.

Pre-conceptional care is very important to reduce unintended prenatal exposures to teratogens.

The challenges of teratogenic exposures are the usage of the over-the-counter drugs in the peri-conceptional period without prescriptions by an increasing group of women which may prove harmful. The Governments need to do more to compel manufacturers to follow risk evaluation and mitigation strategies for every new drug in the market. The use of herbal medicines and food supplements which have not been subjected to controlled trials may prove more harmful for the mother and the foetus. These practices should be curbed to reduce teratogenic exposures.

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3 Prenatal diagnosis of Birth Defects: Appropriate screening protocols

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Introduction

Birth defects, or congenital anomalies, are structural or functional abnormalities present at birth that may result in physical or intellectual disabilities. These can range from minor malformations to severe anomalies affecting multiple organ systems. The causes of birth defects are multifactorial, involving genetic, environmental, and maternal factors.

Congenital malformations occur in 3% of all births globally equating to 1 in every 33 live births. The prevalence can vary geographically, with developing countries reporting higher rates due to limited access to healthcare & higher exposure to teratogens.

Prevalence of birth defects in India is 6-7% contributing to approximately 1.7 million birth defects annually.[1]

Ultrasound is a cornerstone of prenatal diagnosis, offering a non-invasive and detailed evaluation of fetal anatomy and growth. Ultrasound does not involve the use of ionizing radiation and hence is a safe modality that can be repeated as and when necessary.

Early detection of birth defects facilitates timely counselling, detailed evaluation, and informed decision-making for parents and healthcare providers. Screening for birth defects is crucial for identifying anomalies associated with chromosomal abnormalities, syndromic conditions, or isolated structural

defects that might influence management strategies. In certain cases, prenatal diagnosis allows for interventions such as fetal therapy or delivery planning at a tertiary care centre equipped for neonatal and surgical management.

The time lines for offering ultrasound for prenatal diagnosis of birth defects and genetic abnormalities:

- **11-13+6 weeks Nuchal translucency scan** (Figure1) where in addition to focussing on NT, other soft markers like nasal bone, ductus venosus, tricuspid regurgitation are also evaluated as critical soft markers for identifying chromosomal abnormalities such as trisomy 21, 18, and 13. At the same time detection of major malformations early, dating of gestational age of pregnancy, looking at no of fetuses with their chorionicity and screening for preeclampsia and growth restriction by uterine artery dopplers is also done.

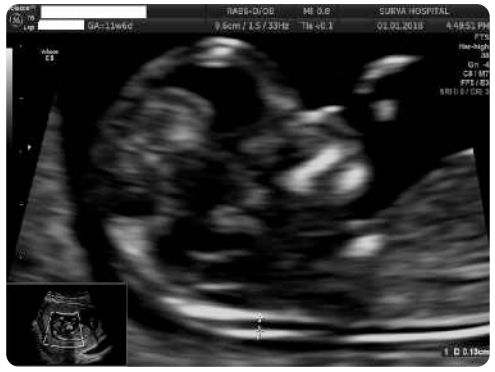


Figure 1

- **18-22 weeks, second trimester anomaly scan** where all structural abnormalities and soft markers are assessed along with cardiac evaluation, screening for preeclampsia by uterine artery dopplers and risk prediction for preterm birth by looking at cervical length is practiced. The ISUOG recommends systematic evaluation of the fetal head, face, spine, thorax, abdomen, extremities, and heart, with an emphasis on detecting anomalies. Amniotic fluid, placental morphology, and cervical length are also evaluated. The second trimester scan serves as the primary tool for structural anomaly detection.[2]
- Later scans after 26-40 weeks are done for assessment of growth and well-being of the fetus and its environment, assessment of fetoplacental blood flow by doppler to monitor complicated pregnancies and sometimes diagnosis of a late onset or evolving anomaly. Few structural anomalies like urinary tract abnormalities, microcephaly and skeletal dysplasia are progressive and late in onset and may not be detectable during the routine 18-22 weeks malformation scan.

Screening tests for Aneuploidy

Aneuploidy screening in pregnancy is offered to all irrespective of maternal age.[3] It is very important to explain the optional nature of all prenatal testing and to emphasize this fact that a low-risk screening test result does not guarantee a healthy child and a high risk screening test result does not mean the fetus has the disorder.

1. First trimester biochemical screening for aneuploidy

Double marker test is a biochemical screen which includes maternal serum free beta human chorionic gonadotropin (β-hCG) and pregnancy associated plasma protein A (PAPP-A), both produced by placenta. It is carried out between 11^{+0} to 13^{+6} weeks gestation.

First trimester screening test (FTS) is a terminology used for a combination of maternal age, dual marker screen along with nuchal translucency at a crown rump length of 45-84mm. This gives a risk assessment for trisomy 21, 13 and 18. The detection rate of this First trimester screen test is > 90% for a 5% false positive rate.

Combined First trimester screening (cFTS) : Effectiveness of this First trimester Screening is improved further if along with nuchal translucency, other first trimester markers such as fetal nasal bone, assessment of blood flow across tricuspid valve, fetal heart rate and ductus venosus flow are included. Addition of these first trimester markers increase detection rate for Trisomy 21 to more than 95% for a false positive rate of 2.5% and 95% with false positive rate of 0.1% for Trisomy 13 and 18.

2. Second trimester screening

Screening test available in the second trimester is a quadruple screen which includes a combination of four biochemical serum markers i.e. free beta HCG, MSAFP and unconjugated estriol (uE3) and inhibin A. This test is used to screen for trisomy 21, 18 and neural tube defects between 15-21 weeks.

Detection rate of quad screen is between 81%- 85.8% for false positive rates of 7-8.3%. Therefore, in cases where first trimester screen could not be done, quadruple test should be offered owing to its good detection rates and low false positive rates. MSAFP levels in the quadruple test are also analysed to give cut off risk for neural tube defects. In pregnancies affected with trisomy 21, elevated levels of HCG, inhibin A and reduced levels of MSAFP, uE3 are observed.

trimester screening

With the aim of improving detection rate, first trimester combined screening is followed by second trimester biochemical screening and results of both trimester screening tests are combined and risk is calculated. Two approaches have been defined - integrated test and sequential screening.

In ***integrated test***, first trimester combined screening is followed by second trimester quadruple marker screening and combined results are given after completion of process in second trimester and pregnant women who fall into high-risk group, undergo invasive diagnostic testing by amniocentesis. Integrated testing has highest detection rate and lowest false positive rates. However, there is a longer wait time (3-4weeks) between initiation and completion of screening.

In sequential screening, all patients undergo first trimester combined testing and on the basis of screening results, they are assigned three risk categories; low, intermediate and high risk. High risk cases receive genetic counselling and are offered invasive testing by chorionic villous sampling (CVS). Women at low risk have no further testing. Women at intermediate risk are offered continued screening in the second trimester with quadruple test and if the combined risk after first and second trimester testing is high, the patients are offered amniocentesis. Theoretically, sequential screening would

maintain a higher detection rate while reducing the number of patients undergoing second trimester screening tests.

4. Non-invasive prenatal screening (NIPS)

Non invasive prenatal screening (NIPS) is an advanced screening test with high sensitivity and specificity for fetal chromosomal aneuploidy using cell free DNA from maternal serum. Maternal plasma has approximately 5% to 20% of cell free DNA that comes predominantly from placental apoptosis which is fetal in origin.

Testing can be performed starting as early as 9 weeks and until delivery. Overall sensitivity and specificity reported for trisomy 21 is 99.3% and 99.8% respectively for a false positive rate of <1%. Recently with the advancement in the NGS technique few other applications including other aneuploidies and some microdeletions/duplications can also be detected but at a low accuracy depending upon the disorder to be tested.[4]

Main limiting factor to its widespread use as a screening method is its cost as well as chance of inability of getting a report if the fetal fraction is low. At present, SMFM (Society for maternal fetal medicine) has recommended NIPS as the most appropriate screening test for high-risk patients including maternal age 35 years or older at delivery, previous pregnancy affected with trisomy, positive screening results for aneuploidy, including first trimester, sequential, integrated, or quadruple screen. The advantages and disadvantages of NIPT need to be weighed in deciding its utility as a screening test.[5]

NIPS is not a diagnostic test and confirmatory invasive testing is required in the presence of any abnormal screening results. In presence of fetal structural anomaly, decision for fetal karyotyping and or microarray testing should not be deferred by a normal NIPS result.

First Trimester Screening Protocol

With the advances in imaging techniques and availability of better resolution ultrasound machine and a shift in screening for aneuploidy to the first trimester, early screening and detection of congenital anomalies and heart defects at 11-13^{+6} weeks has become possible.

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) provides detailed guidelines for performing first-trimester ultrasound scans, typically conducted between 11 and 14 weeks of gestation. These scans serve multiple critical objectives: confirming pregnancy viability, accurately dating the pregnancy, determining the number of fetuses, assessing chorionicity and amnionicity in multiple pregnancies, and evaluating early fetal anatomy for potential anomalies.[6]

A systematic anatomical survey is conducted to assess fetal structures, including the head and brain, which are examined for integrity and early detection of anomalies. The face is evaluated, focussing on structures like the nasal bone, while the neck is assessed for nuchal translucency (NT) thickness. Abdominal structures are examined to identify defects in the abdominal wall or internal organs, and limb presence and movement are confirmed to ensure normal development.

The uterus is evaluated for structural abnormalities, such as fibroids or anomalies in shape, which may affect pregnancy outcomes. The ovaries and adnexa are also assessed for the presence of masses or other abnormalities. High-resolution ultrasound equipment is utilized, with both trans-abdominal and transvaginal approaches employed as needed to optimize visualization of fetal and maternal structures.

11-13^{+6} weeks scan for early anomaly assessment

Detailed structural assessment by ultrasound has a potential for detection of fetal abnormalities in the first trimester. However the reported efficacy for anomaly detection has considerable variation ranging from as low as 12.5% to high detection rate of 83.7%. This variance is mainly attributed to different population studied, different level of expertise and anatomical check list used. Detection may also be dependent on the natural history of the disorder, the time of onset, the systems involved and the severity of the disease.[7]

Anomalies in the first trimester can be classified into:

a) Always detectable - Anencephaly, body stalk anomaly, alobar holoprosencephaly

b) Potentially detectable - Congenital diaphragmatic hernia, Cardiac defects, neural tube defects

c) Not detectable - Microcephaly, Hydrocephalu, echogenic lung lesions, Agenesis of corpus callosum

Although second trimester scan remains the gold standard to rule out anomalies, early detection of anomalies can be achieved by meticulous scanning in the first trimester with a structured protocol.[8]

Table 1: Summary of Anomalies detectable in the first trimester and their further evaluation

Alobar holoprosencephaly	Associated with aneuploidy	Lethal	Requires testing for recurrence risk
Acrania	Not associated with aneuploidy	Lethal	No testing
Encephalocoele	Usually single gene	When possibly syndromic, prognosis is poor	Requires testing for recurrence risk
Iniencephaly	Not associated with aneuploidy	Lethal	No testing
Omphalocoele	Associated with aneuploidy	Treatable	Requires testing for recurrence risk
Gastroschisis	Not associated with aneuploidy	Treatable	No testing
Megacystis	Associated with aneuploidy	Requires testing for recurrence risk	
Limb body wall complex	Not associated with aneuploidy	Lethal	No testing
Limb defects	Not associated with aneuploidy	No testing	

11 -13+6 weeks Scan for cardiac assessment

With the shift in screening for aneuploidy to the first trimester, early screening and detection of congenital heart defects at 11-13+6 weeks by early fetal ECHO has become possible. However assessment of fetal heart at so early gestation requires high level of expertise and equipment. According to a recent meta-analysis in 2022, structured anatomical assessment protocol must be followed to enhance detection of cardiac defects in the first trimester which should include routine use of 4 chamber and outflow tract view and the use of colour doppler (Figure 2a,b)[9]

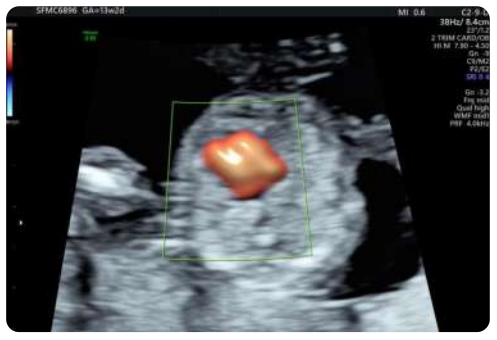


Figure 2a

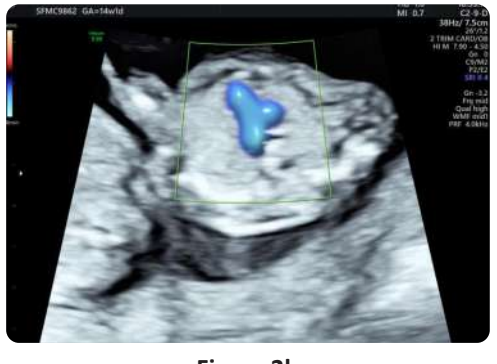


Figure 2b

Detection rate varies according to the type of cardiac anomalies (>60% for ectopia cordis, hypoplastic left and right heart syndrome, Tricuspid atresia, Atrioventricular septa defects, Truncus arteriosus Heterotaxy, Single ventricle and Doublet outlet right ventricle to 25-60 % for pulmonary atresia, Fallots Tetralogy, transposition of great arteries, Ebstein anomaly and Coarctation of Aorta). Poor detection of less than 25% is found in Ventricular or atrial septal defect, pulmonary artery stenosis and Rhabdomyoma.[9]

Pooled detection rate of cardiac defects in the first trimester has been reported to be between 17% to 29% in different studies before 2013.[10] In the recent meta-analysis of 2022 there is an improvement in proportion of cardiac cases diagnosed in the first trimester to 63% in low risk fetuses and 79% in high risk pregnancies.[9]

Detection of major congenital heart defects at 11-13 weeks scan can be improved by their association with first trimester soft markers which are easily detectable, like increased nuchal translucency, absent or reversed a wave in ductus venosus or a tricuspid regurgitation. Increased nuchal translucency > 95thcentile predicts 37-44% of major cardiac defects. NT > 99th centile is associated with more than 20 times increased risk of major heart defects. In chromosomally normal fetus, increased NT combined with absent or reverse a wave in ductus venosus is associated with three-fold increase likelihood of major cardiac defects. Tricuspid regurgitation is a frequent finding in 1/3rd of euploid fetuses with heart defects.

11 -13+6 weeks Scan for screening for Spina Bifida

Diagnosis of open spinal defect in the second trimester by typical intracranial findings due to Chiari Type II malformation and scalloping of frontal bones is well known. Obliteration of intracranial translucency during the 11-13^{+6} weeks scan as a marker for open neural tube defect was first reported by Chaoui et al in 2008. An abnormal posterior cranial fossa in NT scan can help predict open spina bifida using Intracranial translucency (IT). Presence of intracranial translucency between 11-13^{+6} weeks can confidently exclude open spina bifida (Figure 3) [11]

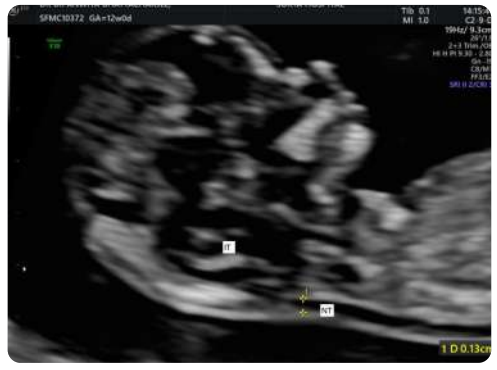


Figure 3

The open spina bifida is associated with dislocation of the brainstem and compression of the fourth ventricle and cisterna magna in the confined space between the occipital bone and the sphenoid bone. Obliteration of Intracranial Translucency (IT) in the first trimester suggests open neural tube defect. [12]

Other first trimester markers for open neural tube defect which have been suggested are the 4 versus 3-line view, brain stem (BS)-to-brain stem-occipital bone (BSOB) distance ratio (BS/BSOB) greater than 1, the position relationship between the maxillo-occipital (MO) line and the midbrain-BS junction (midbrain-BS junction below or nearly on the MO line), the crash sign and the BPD or BPD/AC below the fifth percentile.[13]

Increased NT in euploid fetus: a marker for structural defects

Even if conventional karyotyping is normal, increased NT is predictive of adverse pregnancy outcome, because it is associated with several fetal malformations, congenital heart defects, genetic syndromes, intrauterine death and miscarriages.

Prevalence of fetal anomalies increases exponentially once Nuchal Translucency is >3.5 mm or > 99 centile for gestational age (Figure 4). These chromosomally normal fetuses with an enlarged NT still require meticulous evaluation by a detailed ultrasound examination and echocardio-graphy.[14] Long term outcomes of fetuses with increased NT, euploid fetus and normal anomaly scan in the second trimester have not found any increased neonatal or long term adverse outcome or neurodevelopmental delay.[15]

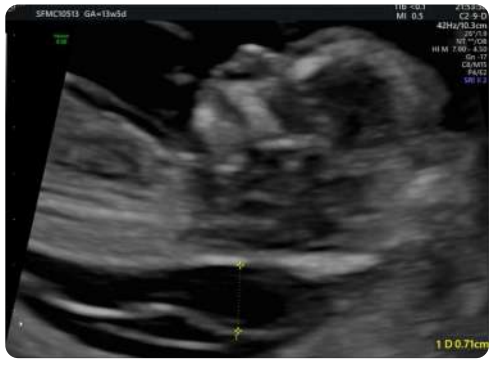


Figure 4

Structural anomalies and Syndromes whose prevalence is substantially higher in fetuses with increased NT are:

- Cardiac defects
- Congenital Diaphragmatic Hernia
- Omphalocele
- Body Stalk anomaly
- Skeletal Dysplasia(Achondrogenesis, Achondroplasia, Camptomelic dysplasia, Thanatophoric dysplasia)
- Magacystis
- Fetal Akinesia deformation syndrome (FADS)
- Asphyxiating thoracic dystrophy
- Joubert syndrome
- Noonan syndrome
- Smith Lemili Opitz syndrome, Jarco Levin Syndrome, Roberts syndrome, Fryns syndrome

Mid Trimester Anomaly Screening Protocols (TIFFA Scan/Anomaly scan)

Universal ultrasound screening for fetal structural abnormalities is generally recommended at 18-22 weeks of gestational age for various conditions like anencephaly, open spina bifida, cleft lip, diaphragmatic hernia, gastroschisis, exomphalos, serious cardiac defects, bilateral renal agenesis and lethal skeletal dysplasia.

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) provides a standardized protocol for performing the routine mid-trimester anomaly scan, typically conducted between 18 and 22 weeks of gestation. This scan aims to systematically evaluate fetal anatomy, identify structural anomalies, and assess overall fetal well-being.[2]

The examination begins with a comprehensive evaluation of the fetal anatomy. The **head and brain** are assessed for skull shape and integrity, cerebral ventricles, midline falx, cavum septi pellucidi, cerebellum, and cisterna magna. The **face** is analyzed for the orbits, lenses, and the presence of cleft lip. The **spine** is examined in sagittal and transverse planes to detect neural tube defects or vertebral abnormalities. Thoracic structures are reviewed for lung symmetry and appearance, along with the positioning of the heart. A detailed **cardiac evaluation** includes the four-chamber view and, when feasible, assessment of the outflow tracts to identify congenital heart defects.

The **abdomen** is scanned to visualize the stomach, bladder, kidneys, umbilical cord insertion, and abdominal wall for any defects, such as gastroschisis or omphalocele. Limb anatomy is reviewed to ensure the presence and appropriate growth of all long bones, and biometric measurements, including biparietal diameter, head circumference, abdominal circumference, and femur length, are obtained to estimate fetal growth and gestational age.

Additional assessments include evaluating **amniotic fluid volume** for abnormalities like oligohydramnios or polyhydramnios, and the placenta is analyzed for location, morphology, and relationship to the cervix, identifying conditions like **placenta** previa. Cervical length measurement is recommended, particularly in cases at risk for preterm labor. The **uterus and adnexa** are also inspected for any structural abnormalities or masses.

High-resolution ultrasound equipment is essential, with optimized settings for to each fetal region for clear imaging. A systematic, stepwise approach is critical, ensuring all anatomical structures are assessed thoroughly. Documentation of findings with representative images is mandatory, especially for abnormal findings. Counselling is provided to explain findings, and a detailed report is generated, including recommendations for follow-up investigations when necessary. Adherence to these protocols ensures the highest standard of care and enables early detection of anomalies.[2]

Genetic sonogram: Approximately one third of foetuses affected with trisomy 21, have a major or minor structural variation identifiable on USG. Chromosomal defects associated with certain second trimester sonographic features (also known as soft markers), including biometric parameters (e.g., short length of femur and humerus, pyelectasis, increased nuchal fold, ventriculomegaly, hypoplastic or absent nasal bone, early fetal growth restriction and morphologic signs (e.g, choroid plexus cysts, echogenic bowel, echogenic intracardiac focus). These “soft markers” are physical characteristics which are not themselves abnormalities or defects but occur more commonly in foetuses affected with DS.

The detection of any of the above markers during a routine sonogram warrants careful anatomical survey aimed at identifying additional markers because the finding of multiple markers indicates high risk for chromosomal anomaly. The soft markers that significantly increase the likelihood of trisomy 21 are thickened nuchal fold, borderline ventriculomegaly, absent or hypoplastic nasal bone, echogenic bowel, aberrant right subclavian artery. However, relying only on USG to identify Down syndrome is not recommended.[16]

The list of soft markers and their likelihood ratios are given below[16]

Marker	Positive LR	Negative LR	Pooled LR for isolated marker
Intracardiac echogenic focus	5.83	0.8	0.95
Mild ventriculomegaly	27.52	0.94	3.81
Increased nuchal fold	23.3	0.8	3.79
Echogenic bowel	11.44	0.9	1.65
Mild hydronephrosis	7.63	0.92	1.08
Short humerus	4.81	0.74	0.78
Short femur	3.72	0.8	0.61
Aberrant right subclavian artery	21.48	0.71	3.94
Absent or hypoplastic nasal bone	23.27	0.46	6.58

Major Fetal Structural Anomalies

Detecting major fetal structural anomalies in the second trimester scan helps to identify abnormalities associated with severe morbidity or that are incompatible with life, so that couple can make an informed choice about termination of pregnancy within constraints of law. Its also detects abnormalities which require early neonatal intervention or which may benefit from in-utero fetal therapeutic interventions.

Congenital Cardiac defects

Cardiac anomalies constitute the most common congenital anomalies in neonates. The vast majority of congenital cardiac anomalies are diagnosed in pregnancies that are not at high risk of congenital heart defects. Hence ultrasound remains the best screening modality for the antenatal diagnosis of congenital cardiac anomalies.

Nearly half of the cardiac anomalies are lethal or require complex surgeries. Complex cardiac defects like large atriventricular septal defects, valvular atresias / severe valvular stenosis, hypoplastic left or right ventricle, cardiomyopathies usually have a worse prognosis either due to the anomaly itself or its association with other structural anomalies and/or chromosomal aneuploidies or metabolic disorders. Relatively non-lethal with good post surgical results include isolated septal defects, isolated transposition of great vessels, fallots tetralogy with good size pulmonary artery and milder varieties of coarctation of aorta. These cases need detailed evaluation and counselling for further prognostication by a team of obstetrician, perinatologist, neonatologist, geneticist and a pediatric cardiologist. Further antenatal monitoring is necessary by an expert fetal medicine / fetal cardiac specialized centre for worsening of cardiac function, signs of heart failure or development of hydrops and deciding the timing/ mode of delivery at a centre with good neonatal intensive care unit for initial assessment and stabilisation.

Functional anomalies like arrhythmias, whether bradyarrhythmias or tachyarrhythmias are usually due to cardiac structural anomalies like tumors, maternal SLE and other autoimmune diseases, maternal medications, and disorders like long QT syndrome.

Structural Cardiac abnormalities[17] commonly associated with genetic causes include

1. Atrioventricular canal defect (Endocardial cushion defect)
2. Conotruncal abnormalities
3. Heterotaxy syndromes
4. Cardiac rhabdomyomas
5. Aberrant right subclavian artery

In most cases, there is a wide range of cardiac phenotypes that can be associated with genetic conditions. In some cases, there is a direct phenotype-genotype correlation, for example, the presence of cardiac rhabdomyomas with tuberous sclerosis (Figure 5).

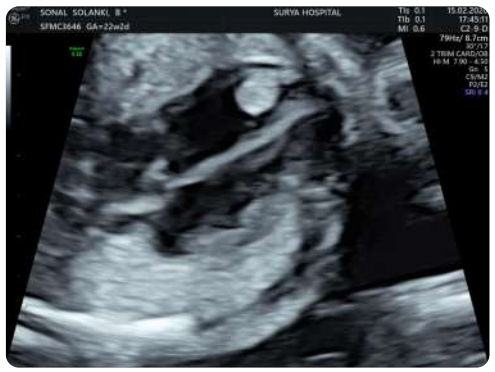
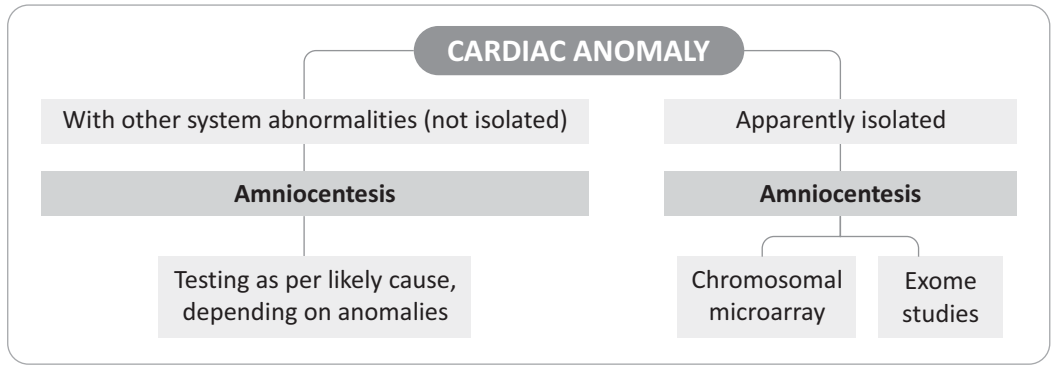


Figure 5

Endocardial cushion defects and overriding great vessels are usually features of aneuploidy. Conotruncal anomalies are usually due to aneuploidies and Di George syndrome, both of which can be diagnosed using chromosomal microarray. Features such as radial ray defects with cardiac abnormalities point towards Holt Oram syndrome, which is due to a single gene defect, requiring exome studies.



When a cardiac anomaly is diagnosed on ultrasound, a careful search should be made to diagnose other abnormalities that may give clues to the diagnosis, or even direct the tests to be performed in order to arrive at the diagnosis. A detailed history, which includes history of consanguinity, any affected siblings, family history of cardiac and other abnormalities in family members, sudden cardiac deaths, unexplained deaths, etc. should be sought.

CNS abnormalities

Central nervous system abnormalities also are wide-ranging, from mild ventriculomegaly, posterior fossa abnormalities, spinal abnormalities, and cortical abnormalities to holoprosencephaly. Most abnormalities of the brain are genetic in origin. Spinal abnormalities like open neural tube defects are usually multifactorial. As with all anomalies, a careful search should be performed to diagnose other associated abnormalities, which will help to determine the path to arrive at the diagnosis.

The most prevalent types of neural tube defects are anencephaly, encephalocele and spina bifida. Large open neural tube defects (Figure 6) especially the ones at upper vertebral levels (cervical and thoracic) usually have a poor prognosis with devastating morbidity and multiple disabilities due to the associated brainstem herniation, neural involvement and other spinal defects like short spine, kyphoscoliosis etc. These are usually detected at the time of anomaly scan or earlier and are often terminated due to high postnatal morbidity. Smaller lesions like a meningocele without cord tethering may be detected later in pregnancy or after birth due to the small size and lack of classical signs of tentorial herniation and have a better prognosis with surgery.

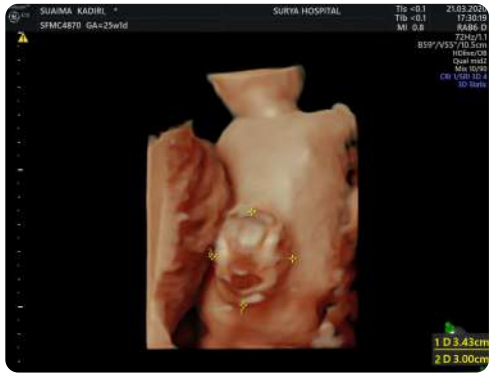


Figure 6

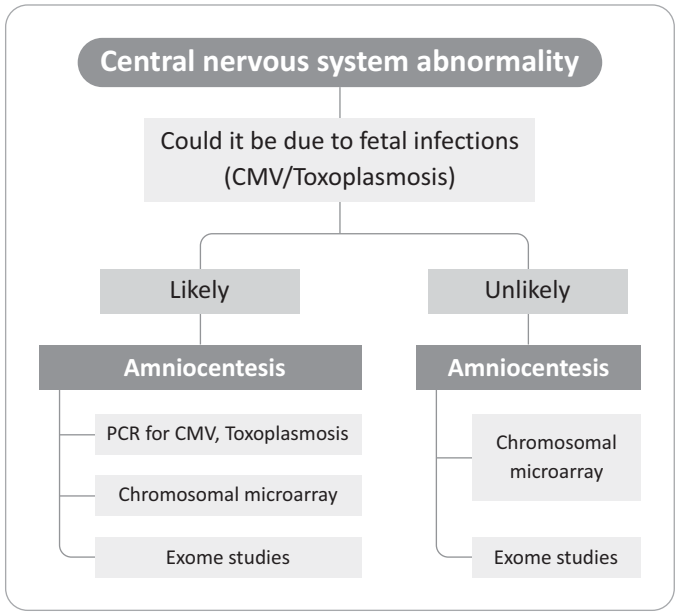
Central nervous system abnormalities that can be diagnosed on ultrasonography include

1. **Ventriculomegaly**
2. **Disorders of ventral induction**
   a. Alobar holoprosencephaly
   b. Semilobar holoprosencephaly
   c. Lobar holoprosencephaly
3. **Disorders of dorsal induction**
   a. Anencephaly
   b. Encephalocele
   c. Open spina bifida
4. **Cerebral abnormalities**
   a. Lissencephaly
   b. Porencephaly
   c. Megalencephaly
   d. Schizencephaly
   e. Agenesis of corpus callosum
5. **Posterior fossa abnormalities**
   a. Dandy walker malformation
   b. Inferior vermian hypoplasia
   c. Joubert syndrome
   d. Rhombencephalosynapsis

Certain cerebral abnormalities like malformations of cortical development may not be evident at the time of the mid-trimester anomaly scan, but they may be diagnosed at subsequent growth scans.

Amniocentesis is indicated in the presence of CNS abnormalities to rule out fetal infections using PCR. This is important as many abnormalities including cerebral calcifications and destructive lesions may be due to fetal infection by cytomegalovirus (CMV) and Toxoplasmosis. Microarray and exome studies are performed to diagnose the genetic causes, if any.

A genetic diagnosis, if established is useful to rule out the same disorder in the first trimester itself in subsequent pregnancies. If the pathogenic gene or microdeletion/ duplication syndrome is diagnosed, Chorionic villus sampling can be offered in the next pregnancy to determine if the fetus will be affected.



Fetal genitourinary anomalies

Renal abnormalities are among the more commonly diagnosed anomalies on antenatal ultrasound. Renal pyelectasis is one of the soft markers for aneuploidy. Bilateral renal agenesis is universally lethal due to subsequent oligohydramnios and ensuing pulmonary hypoplasia. All urinary tract dilatation (Figure 7) require 3-4 weekly antenatal monitoring for worsening, oligohydramnios, cortical thickness and echogenicity and fetal maturity so as to decide time of delivery balancing the risk of prematurity versus worsening renal function.

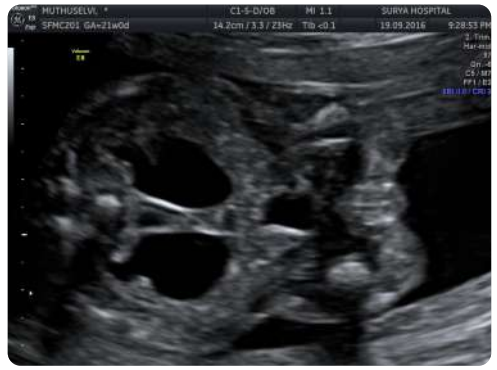


Figure 7

Renal abnormalities can be due to[18]

1. **Defects in renal ascent or migration - ectopic kidneys**
2. **Renal parenchymal abnormalities**
   a. Cystic kidneys
   b. Echogenic kidneys
3. **Pelvicalyceal abnormalities**
   a. Pelviureteric junction obstruction
   b. Vesicoureteric reflux
   c. Urethrovesical junction abnormalities like ureterocoele
   d. Bladder outflow obstruction
      I. Posterior urethral valve
      ii. Urethral atresia

Since fetal urine majorly contributes to the amniotic fluid volume, abnormalities leading to loss of renal function cause severe oligohydramnios. Persistent severe oligohydramnios is a cause of Potter sequence - pulmonary hypoplasia, facial dysmorphism and limb abnormalities.

Horseshoe kidneys are associated with aneuploidy. In the presence of other organ system abnormalities, karyotypic abnormalities should be suspected.

Multicystic dysplastic kidneys and echogenic kidneys are associated with gene mutations. There are multiple genes responsible for renal parenchymal and cystic changes. Beckwith-Wiedemann syndrome and Meckel-Gruber syndrome are associated with enlarged and echogenic kidneys. In addition, isolated renal anomalies are seen in

a. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
b. Autosomal Recessive Polycystic Kidney Disease (ARPKD)
c. Multicystic dysplastic kidneys - numerous single gene mutations

A detailed ultrasound to look for associated abnormalities should be performed. Macrosomia, liver enlargement and omphalocoele with renal abnormalities suggest Beckwith-Wiedemann syndrome. Cardiac rhabdomyomas & renal involvement are seen in Tuberous sclerosis. Polydactyly, occipital encephalocoele and echogenic kidneys are seen in Meckel-Gruber syndrome. Echogenic kidneys, hepatic calcifications and central nervous system abnormalities may be seen in fetal infections.

In addition, a detailed history of consanguinity, family history of oligohydramnios, renal failure, renal transplantation, need for dialysis at a young age etc. should be sought.

A genetic diagnosis is important in renal disorders as many of these abnormalities are diagnosed in the late second or in the third trimesters. Amniocentesis can be challenging in the case of severe oligohydramnios. If a genetic pathogenic variant is identified, prenatal testing can be offered in the first trimester by CVS in subsequent pregnancies.

Skeletal system

Skeletal dysplasia constitute a diverse spectrum of skeletal abnormalities with different presentations on antenatal ultrasound. They can be lethal or non-lethal. There may be multiple genotypes associated with a single abnormal phenotype.[19]

Skeletal dysplasia may present as

1. Shortened bones
2. Poor bone mineralization
3. Bowed bones
4. Fractured bones
5. Skull abnormality
6. Small thorax
7. Polydactyly

The most important aspect in the diagnosis of skeletal dysplasia is in the prediction of lethality of the condition. The major factors associated with lethality include

1. Early onset of severe bone shortening
2. Narrowing of the thorax/bell-shaped thorax
3. Polyhydramnios (due to reduced swallowing ability and breathing movements as a result of narrow thorax)
4. Severe bone hypomineralization

A general rule of thumb for skeletal dysplasia is, the earlier it is diagnosed, the more lethal the dysplasia. Achondroplasia is the most common skeletal dysplasia which is compatible with life, but it is rarely evident before the third trimester. In addition, when the diagnosis of short bones is made, fetal growth restriction (FGR) should be ruled out. The early ultrasound (dating scan), Doppler ultrasound for uterine and fetal blood supply, and serial scans help to rule out FGR as a cause for short bones.

The genetic test of choice for skeletal dysplasia is exome studies

Potentially detectable in

First Trimester (Lethal)	Second trimester (Lethal/morbidity-causing)	Third trimester (Non-lethal)
For example-	**For example-**	**For example-**
• Thanatophoric dysplasia • Camptomelic dysplasia • Hypophosphatasia	• Short rib-polydactyly syndromes • Osteogenesis imperfecta types II, III, IV • Chondrodysplasia punctata	• Achondroplasia

Fetal gastrointestinal anomalies

Intestinal atresia is a common cause of neonatal obstruction, secondary to mesenteric vascular accidents during intrauterine life. The most common type is esophageal atresia, followed by atresia in the jejunoileal region and in the duodenum. Duodenal atresia can be diagnosed by the Double-bubble sign of the stomach and the proximal duodenum, connected by the pylorus across the midline (Figure 8). Polyhydramnios is usually seen due to bowel obstruction. It is usually seen in the late second trimester.

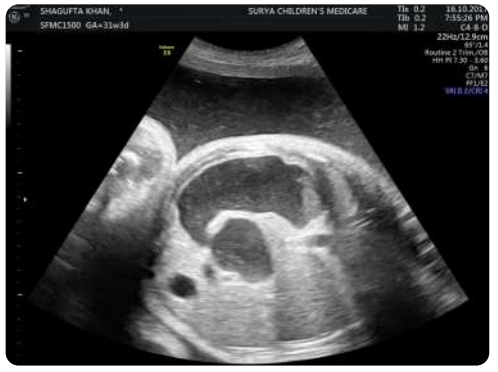


Figure 8

Anorectal atresia (ARA) is a major congenital malformation and it is frequently associated with other anomalies. An association between vertebral, anal, cardiovascular, tracheoesophageal, renal & limb malformations has been recognized and termed the VACTERL syndrome. Anorectal anomalies are also found frequently in association with sacral agenesis and lower limb hypoplasia as part of the caudal regression syndrome.

Higher the obstruction earlier is the time of presentation in antenatal period by visualization of polyhydramnios and dilated bowel loops proximal to the obstruction. Prenatal diagnosis of bowel obstruction and referral to tertiary centre with early neonatal surgical correction reduces morbidity due to aspiration pneumonia or further abdominal distention with respiratory embarrassment if undiagnosed.

Congenital lung malformations

Fetal thoracic masses include Congenital Pulmonary Adenomatoid Malformation (CPAM) (Figure 9) and broncho-pulmonary sequestration (BPS). Both of these fetal lung masses when associated with hydrops are nearly 100% fatal. Congenital Pulmonary Airway Malformation Volume Ratio (CVR) helps determine the risk of development of hydrops and is an important parameter which is to be considered when counselling such patients. CVR is the volume of the CPAM mass normalized for gestational age. A CVR of <= 1.6 at presentation suggests that the risk of hydrops developing is low in the absence of a dominant large cyst. A CVR > 1.6 or a CPAM with a dominant large cyst increases risk of developing hydrops. The natural history of this lung lesion may be progression/ regression or remains stable antenatally and hence require monitoring prenatally. In the postnatal period, early thoracoscopic surgery (between 4 and 6 months) is indicated if neonate is symptomatic, with few pre and post-operative complications, limited chest deformation during growth and limited impact on pulmonary growth and low parental anxiety.

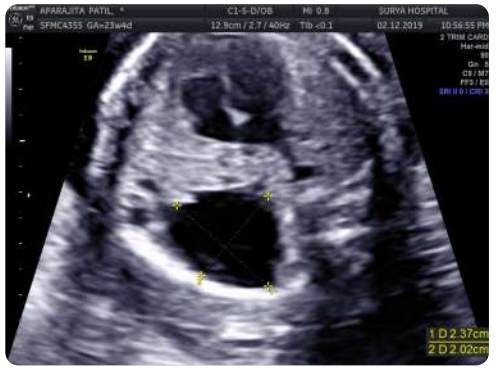


Figure 9

Diaphragmatic hernia can be seen on the left side, with the stomach, small intestine and sometimes, loops of the large intestine in the thorax, displacing the heart to the right. A right-sided hernia consists of the liver pushing the heart to the left. Depending on the size of the hernia, it may be diagnosed at any stage of pregnancy, with larger hernias being diagnosed earlier. The prognosis is generally poorer when diagnosed in the first or the early second trimesters.

Congenital diaphragmatic hernia is a malformation with important implications due to high mortality and high association with aneuploidies . If diagnosed before 26 weeks gestation with associated liver herniation and a low lung to head circumference ratio (LHR <1) they have a relatively poor prognosis with conventional therapy after birth. LHR is the ratio of opposite normal lung area to the head circumference at that gestation. The mainstay of management includes meticulous initial evaluation of LHR and extent of liver herniation, chromosomal analysis, antenatal monitoring of the fetus for signs of worsening, cardiac dysfunction and development of hydrops under expert feto-maternal unit care, delivery near term at a tertiary care centre with NICU set-up, standard protocols for management of neonate at birth including initial intubation, stabilisation and treatment of pulmonary hypertension and then surgical management.

Anterior abdominal wall defects

Anterior abdominal wall defects, including gastroschisis, omphalocoele and limb body wall complex, are common fetal anomalies. While omphalocele is associated with a high risk of antenatal mortality due to its association with other congenital anomalies and chromosomal aneuploidies, an isolated omphalocele carries a good post-surgical prognosis in the neonatal perio. On the other hand gastroschisis is not associated with other major anomalies or chromosomal aneuploidies but these neonates may have a complex postnatal period depending upon the extent of organ involvement. Limb body wall complex and Pentology of Cantrell are universally lethal during antenatal life and are mostly terminated. Antenatal detection of these anterior abdominal wall defects enables detailed prenatal planning, amniocentesis for chromosomal aneuploidy in omphalocele, antenatal monitoring for intestinal obstruction and appropriate intrauterine transfer, delivery in a tertiary referral centre with prompt access to paediatric surgery and early surgical intervention.

Conclusion

With the advances in imaging techniques and availability of better resolution ultrasound machines, it is becoming possible to detect major structural defects in first trimester. Although second trimester scan remains the gold standard to rule out anomalies, early detection of anomalies can be achieved by meticulous scanning in the first trimester. There is a shift in screening for aneuploidy to the first trimester where early detection of genetic disorders at 11-13+6 weeks allows early decisions and/ or reassurance. Strict standardized technique and extensive training and auditing is of utmost importance for the same. Genetic sonogram along with quadruple screen continues to have its place where opportunity for first trimester screen was missed.

Prenatal pediatric surgical consultation may have a significant impact on the perinatal management of the fetus with a surgically correctable congenital anomaly. This allows the affected families with valuable insight into the need for delivery in an appropriate setting, by the safest mode of delivery, at the gestational age appropriate to minimize effects of the anomaly and surgical management of the anomaly.

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Figure 1: USG image of Normal Nuchal Translucency measurement

Figure 2a: Early fetal ECHO 4 chamber view on color Doppler.

Figure 2b : Early fetal ECHO outflow tracts on color Doppler (tick sign)

Figure 3 : Intracranial translucency at NT scan

Figure 4: USG image of Increased Nuchal Translucency

Figure 5: Cardiac Rhabdomyoma

Figure 6: Open Neural tube defect

Figure 7: Pelviureteric junction obstruction

Figure 8: Duodenal atresia

Figure 9: Congenital pulmonary airway obstruction

4 Rational management of birth defects - preventing despair

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Birth defects are encountered in 3-5 % of all live births and account for significant morbidity and mortality in the perinatal period. Timely Prenatal Diagnosis and rational management of birth defects can help in improving the overall perinatal health scenario to a large extent. In contemporary medicine the role of antenatal ultrasound in detecting congenital anomalies cannot be over- stated. Based on the developmental time line of the fetus *in utero*, the prenatal diagnosis of fetal anomalies may vary in terms of period of gestation.[1] The diagnosis of a birth defect in any fetus is a cause of great disappointment in the couple and family that is expecting the child. Managing birth defects and preventing despair is a challenging but vital process for families, healthcare professionals, and communities. Birth defects, which can range from minor physical abnormalities to life-threatening conditions, require a combination of medical care, emotional support, and awareness to help families cope.

The previous chapter deals with timely prenatal diagnosis of congenital anomalies and we will focus on managing the pregnancy in a rational manner after such a diagnosis is established

Modifying pregnancy care after diagnosis of any fetal anomaly

Once any fetal anomaly has been diagnosed, the awareness of this condition leads to tremendous anxiety in the parents and the family. The first and foremost task of the care givers is to ensure that the family receive adequate information regarding their situation in a coherent and non biased manner. The important issues during work up of any fetal anomaly include the exclusion of other associated anomalies, genetic associations and the availability of multidisciplinary collaboration for postnatal care as shown in Fig 1.

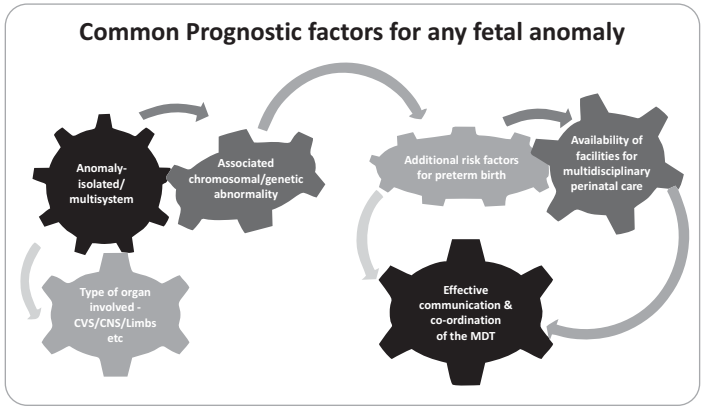

Figure 1: Prognostic factors for fetal anomalies

Once the prognosis is established, the couple will either decide to discontinue the pregnancy or plan to follow up antenatally with the fetal medicine unit and opt for postnatal treatment of the anomaly.

- The modification of pregnancy care plan in cases where the parents opt to terminate the pregnancy is primarily directed towards the mother's safety and also includes consideration to the fetal perinatal pathology and genetic tests (eg chromosomal microarray) done to elucidate the etiology of the condition and seek methods of preventing recurrence. Families may benefit from genetic counseling to understand the likelihood of birth defects based on family history or previous pregnancies, and to make sense of a diagnosis.
- When the couple opt to continue the pregnancy despite the fetal anomaly an dplan for postnatal treatment, a functional "multidisciplinary care team"(MDCT) should be instituted including the Obstetrician, Fetal medicine specialist, Neonatologist, Clinical geneticist and a relevant paediatric sub specialist (eg. Ped Cardiologist, Ped Neurologist or Ped Surgeon etc)[3]
- Effective communication between members of this MDCT is imperative to help achieve the final common goal of a good perinatal outcome. Ensuring that families have access to clear, accurate information about the birth defect and available treatments can empower them to make decisions that align with their values and desires for their child's future.

Role of *in utero* intervention in fetal anomalies

In utero interventions for fetal anomalies aim to address or correct abnormalities detected during pregnancy, providing opportunities to improve fetal health outcomes. Following diagnosis of a potentially treatable condition, the patient needs to be referred to a Fetal medicine centre with sufficient expertise in diagnosis and all therapeutic options. The decision to intervene by invasive fetal therapy is on of great responsibility & the fundamental principles of medical ethics should be carefully weighed before such decisions are taken. The following criteria were proposed by Harrison et al in 1982[4] to justify *in utero* intervention in any fetal anomaly :

1. Accurate diagnosis and staging possible, with exclusion of associated anomalies
2. Natural history of the disease is documented, and prognosis established.
3. Currently no effective postnatal therapy.
4. *In utero* surgery proven feasible in animal models, reversing deleterious effects of the condition.
5. Interventions performed in specialised multidisciplinary fetal treatment centres within strict protocols and approval of the local Ethics Committee with informed consent of the mother or parents.

Some of the common indications for invasive fetal therapy are as follows:

Fetal blood/HSCT transfusion : Although not typically a "birth defect", fetal anemia can be lethal to the fetus and *in utero* transfusion is a life saving therapeutic procedure.[5] Intra-uterine fetal blood transfusions can correct fetal anemia in cases of alloimmunization,

anemia from viral infections, or anemia resulting from genetic disorders such as alpha thalassemia or pyruvate kinase deficiency. *In utero* hematopoietic stem cell transplantation (IUHSCT) is novel fetal therapy[6] with exceptional promise for improving the postnatal outcomes of multiple fetal genetic diseases.

Shunt placement : In cases of bilateral pleural effusions, shunts have been used to drain the excess fluid in relieve the pressure on the lungs. The clinical course of fetal hydrothorax ranges from spontaneous regression to a progressive course with the development of fetal hydrops, polyhydramnios and extreme preterm birth or fetal demise *in utero*. Prenatal management options include repetitive thoracocentesis, thoracoamniotic shunting,[7] Pleurodhesis with OK-432 or premature delivery. The aim of shunting is to improve the fetal hemodynamics by decompressing the heart and lungs to counteract the development of hydrops and pulmonary hypoplasia. Similar shunts have also been tried for lower urinary tract obstruction in the fetus with limited success but in cases like Hydrocephalu, these procedures are no longer recommended.

Fetoscopic laser therapy : Used for conditions like twin-to-twin transfusion syndrome, where laser surgery is performed to correct abnormal blood flow between twins. Twin-to-twin-transfusion syndrome (TTTS) is a very important cause of handicap and death in monochorionic twins. TTTS resuts from unbalanced A-V anastomoses between the two fetal circulations leading to an unbalanced blood and fluid transfer. If left untreated, this condition can progress and has a very poor survival rate. Fetoscopic laser has been shown to be the best first line treatment, which aims to "dichorionise" the MC placenta thus arresting the inter-twin transfusion. Fetoscopic laser coagulation of chorionic plate anastomoses is safe and effective. There is level I evidence that it is the best treatment modality, in particular when the placental surface is lined along the vascular equator.[9]

Fetal surgery: Open fetal surgery by Hysterotomy and primary repair have been used for conditions such as spina bifida, congenital diaphragmatic hernia, and fetal tumors. The myelomeningocele study(MOMS trial) phenomenally changed the paradigm for management of open neural tube defects by establishing primary in utero repair as very effective. The surgical technique described in the MOMS is an open surgery consisting in laparotomy, uterine exteriorization, large hysterotomy, exposing the fetus's back for defect closure, and subsequent uterine wall closure with a technique is similar to that used in the postnatal period: identification and separation of the neural placode from the surrounding epithelium, dura mater closure, myofascial closure, and skin closure.[9] Subsequently further research has allowed equally effective results from a fetoscopic repair technique that obviously carries more safety for the mother.[10]

Gene therapy (experimental): Research is ongoing into fetal gene therapy for conditions like cystic fibrosis or certain metabolic disorders. Novel *in utero* treatments are under active investigation for these and many other genetic diseases using hematopoietic stem cells, enzyme replacement therapy, antisense oligonucleotides, cellular pathway inhibitors, nanoparticles, adeno-associated virus vector (AAV), and many other biotechnologies.[10]

The most important ethical aspect of fetal surgery is that these highly specialized procedures should be offered only by teams, and individuals that are familiar with and experienced in management of the pathology involved & the execution of these procedures.

Conclusion

Preventing despair in the face of birth defects involves a combination of medical care, emotional support, and community involvement. It's important to approach the situation with hope, a focus on the child's potential, and a willingness to seek out resources that can help families cope.[3] By offering understanding, practical assistance, and compassion, society can help families navigate the complex journey of raising a child with a birth defect and minimize feelings of isolation and despair.

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5 “Environment” paradigm - is that increasing the risk of birth defects?

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The environment surrounds us always. We live and breathe it!

The Fetus lives in the uterus, surrounded by Liqour Amnii and gets nutrition by the maternal blood via the placenta.

The question, which we ponder here, is - Can the environment affect the fetus *in utero* and cause birth defects? When it comes to fetal exposures, any exposure that occurs by way of the mother typically is considered “environmental.” An agent that can cause a birth defect is known as a teratogen.

A relatively small proportion of birth defects can be attributed, to specific environmental causes such as maternal disease (e.g., rubella) or use of pharmaceuticals (e.g., valproic acid, an anticonvulsant and mood stabilizer).[1]

The intrauterine environment of the developing embryo/fetus is determined by maternal factors such as health/disease status, lifestyle, medication, exposure to environmental teratogens, as well as the maternal genotype. To make the equation more complex certain genetic characteristics of the embryo/fetus also predispose it to developmental abnormalities.[2] Thus, both genetic and environmental factors contribute to the highly complex etiology of structural birth defects, as all the fetus exposed to environmental or chemical pollution are not developing malformations or any abnormality, genetic factor predisposes certain fetus making them susceptible. In other words, a person can inherit a gene that increases sensitivity to an environmental trigger eg: Neural tube defects, oral clefts and congenital heart defects, by disrupting highly regulated embryonic developmental processes. These are known as multifactorial birth defects.

Lets look at the commonly known teratogen and known substances which we caution the pregnant patient against-

General substances

Alcohol - Alcohol passes very quickly through the placenta to the fetus, and the unborn baby feels a drink almost as fast as a pregnant woman. In Fetal alcohol syndrome (FAS) The children are born with a small head and body, retarded physical growth, mental retardation, shorter and lighter in weight than normal, heart defects, and poor coordination. But what is a safe intake of alcohol that a woman can have - A glass of wine? every day or once a month ?? The safe minimal dose of alcohol in pregnancy is not yet known. It is accepted at present, that with 100 proof alcohol, two ounces per day increases the risk of FAS: one ounce of alcohol probably increases the risk: and under one ounce has not been demonstrated as to its potential risk. One thing to remember with FAS is that the damage is not reversible.

Tobacco - The placenta acts as the fetus’ lungs and if nicotine is passed through, it speeds up the fetal heart and interrupts the baby’s respiratory movements. Smoking reduces the amount of oxygen available to the fetus, which could slow tissue growth, cause congenital abnormality and stillbirth.

Caffeine & Tea - Tests done with animals have indicated that caffeine can cause deformities in skeletal and bone development. Women who are pregnant are advised to limit the amount of caffeine generally to one cup a day.

Drugs

Tranquilizers - With barbiturates, the baby may have tremors, restlessness, and irritability and amphetamines may cause birth defects. Thalidomide was also used as a tranquilizer. It caused deformities of the arms and legs in the children of virtually every mother who took the tranquilizer during her first trimester.

Antibiotics

Tetracycline should not be used during pregnancy. It has been found it can effect the growth of the baby’s bones during the time when it is taken. Also it may cause yellow mottling and staining of the baby’s first teeth.

Streptomycin should not be taken since it can cause deafness in the baby.

Infectious diseases -

Rubella (German Measles) - The virus can cause deafness, heart defects, mental retardation, cataracts, glaucoma, damage to the central nervous system, stillbirth, and miscarriage.

Syphilis - The baby can be born with congenital syphilis - heart defects, joint deformity, blindness, deafness, sores, and mental retardation may appear later on in life.

Radiation -

There is no safe threshold for radiation wherein there is no harm or damage. Radiation in high doses can partially destroy the genetic material that acts as a blueprint for normal cell development. Exposure of the fetus to very high levels of x-rays can lead to serious abnormalities like small heads (microcephaly) with associated retardation, bone defects in the skull, spinal and eye defects, cleft palate, and severe limb deformities.

Metals

Lead, mercury, nickel and manganese have been associated with poor reproductive outcome. Women exposed to lead include those in paint industry or artist and painters. Lead readily crosses the placenta, and has been found to have teratogenic effects as well as is known to affect the hormonal environment needed to maintain the pregnancy. There is a documented relationship between childhood lead exposure and the emergence of aggressive behavior and early juvenile delinquency and subsequent adult criminality in later life.[3]

Mercury (Hg) is a dangerous heavy metal element that can accumulate in plants and animals and change into methylmercury (MeHg). Being more susceptible to MeHg than adults, embryos and young children can suffer long-lasting neurodevelopmental abnormalities from exposure to MeHg during prenatal nutrition (4). Mercury exposure has been identified in dental assistants preparing amalgams. This has been linked to spontaneous abortion as well as reduced fertility.

Organic Solvents

Women working in clothing, textile, paint and plastic industries and health care professionals are exposed to organic solvents. Khattak S et al in a prospective study demonstrated that women exposed occupationally to organic solvents had a 13-fold risk of major malformations as well increased risk for miscarriages in previous pregnancies while working with organic solvents.[5]

Plastics

Ragusa et al. presented the first study addressing the issue of MPs in the human placenta in 2021. Six human placentas in all were analyzed in this investigation. Twelve MP particles altogether, measuring between 5 and 10 µm in size, were found in four of these placentas, with polypropylene being the most often recognized type.[6]

Air Pollution

It has been associated with congenital birth defects, as well as with low birth weight and intrauterine growth restriction. Jedrychowski et al surveyed pregnant women in Poland exposed to fine particulate matter (PM 25) and assessed its effect on birth outcomes. They showed an association with low birth weight and reduced head circumference in children born to above group of women.[7] Air pollution has also been associated with congenital cardiovascular birth defects. The Developmental Origins of Health and Disease idea contends that the early exposure of a fetus have a profound effect on its programming. Early life aging indicators like telomere length and mitochondrial DNA content are connected to prenatal air pollution exposure (8). Many studies have reported that air pollution exposure may result in fetal thrombosis, an accumulation of arsenic in maternal and cord blood, preterm delivery, low birth weight, congenital heart defects and other impacts[9]

Stress

Maternal stress has been found to be associated with birth defects, low birth weight, preterm delivery and early onset preeclampsia. A recent population-based case control study found a positive association between maternal stress [two months before and after conception] and cleft lip, cleft palate and transposition of great vessels[10]

Advice to women when planning a pregnancy for prevention of birth defects

There are many steps a woman can take to lower her chances of having a child with a birth defect, including staying healthy before deciding to become pregnant. That's because a woman often does not know she is pregnant in the first few weeks, which can be crucial for the health and development of the baby. Lack of sufficient folic acid in the diet, for example, is one environmental factor now being remedied with supplements and food fortification, and folic acid is started as a preconception vitamin.

Among other environmental exposures with some incriminating evidence are other nutrient imbalances, maternal smoking and alcohol use, pesticides, tap water disinfection by-products, plastics and plastics components, solvents, metals, and numerous air pollutants.

So some points to be advised are -

- Stop smoking
- Eat a healthy diet
- Maintain a healthy weight: Women who are overweight may experience medical problems such as high blood pressure and diabetes, and women who are underweight may have babies with low birthweight.
- Medical management of preexisting conditions: Take control of any current or preexisting medical problems, such as diabetes or high blood pressure.
- Folic acid: Taking 400 micrograms of folic acid each day can help lower the risk of neural tube defects, or birth defects of the brain and spinal cord.
- Avoid exposure to alcohol and drugs during pregnancy.
- Avoid exposure to harmful substances: These include lead, pesticides, and radiation (i.e., x-rays), which may harm the developing fetus.
- Lower your risk for infection. Pregnant women should avoid eating undercooked meat and raw eggs and avoid all contact and exposure to cat feces and cat litter, which may contain a parasite, toxoplasma gondii, that causes toxoplasmosis. Other sources of infection include insects that have been in contact with cat feces.

In Conclusion,

The full range of substances to which the embryo and fetus may be vulnerable is not yet known. We possibly know, and have only touched the tip of the iceberg of what could happen; there is still much, much more to discover. It is wise to weigh the risks versus the benefits of taking any foreign substance during pregnancy, especially in the first eight weeks when the embryo is forming. The belief that the placenta acted as a barrier and filters out all harmful substances for the baby is not correct.

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