Course Name :An Overview on Maternal Health Antenatal, Intranatal and Postnatal Care

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Week:08

Lecture:01

Teratology, Teratogens and fetotoxic agents

Good morning students. Welcome you all to today's session for the NPTEL online certified course on the topic and overview on maternal health, the antenatal, intranatal and postnatal care. I am Dr. Barnali Ghosh, an obstetrician and gynecologist working at B.C.Roy Medical College and Medical Research Center, IIT, Kharagpur. Today it is a very important topic for discussion that is teratogenicity. The fetotoxic agents and the teratogens which prove detrimental to the fetus if taken during the period of pregnancy.

The concepts to be covered in today's class are the different teratogens, the stages of fetal development and the most teratogenic period among the whole duration of pregnancy, the categorization of the drugs as per FDA and the teratogenic effect of various drugs on the fetus. Keywords for today's lecture, teratogen, FDA category of drugs and the various anomalies or syndromes that are present in the fetus due to certain drug exposure during the period of pregnancy like Ebstein's anomaly, fetal hydantoin syndrome, fetal valproate syndrome and fetal alcohol syndrome. So, coming to the discussion proper, starting with the definition of a teratogen. So, it is any agent which can be any medication or a drug or a chemical, right, any disease of the mother occurring during the period of pregnancy.

Most importantly, you know the various viral disease like rubella which is a very known teratogenic effect. It has, it is detrimental to the fetus. It causes different teratogenic effects on the fetus if there is rubella infection in the initial stages of pregnancy or it can be certain environmental agents in the form of radiation, in the form of heat, right. So, any agent that is able to interfere with the fetal development and leads to permanent birth defects is called a teratogen. And the response or the effect can vary from having no effect at all on the fetus to any type of lethal response in the form of any malformation, growth restriction or intrauterine growth restriction, right.

Any type of functional disorder like cognitive impairment or neurodevelopmental delay and even death, right. So, this can be the result from teratogen exposure during the period of pregnancy. Coming to the placenta, placental membrane is a semi-permeable membrane and

most drugs which are mainly lipophilic can cross the placenta by simple passive diffusion, right, except large organic ions which have a high molecular weight like heparin and insulin. These does not cross the placenta because of their large molecular weight. So, what are the factors that influence the effect of a teratogen? Firstly coming to the physio-chemical properties of the drug.

Number one is the lipid solubility. If the drug is lipid soluble, then it can easily pass through the placenta by simple passive diffusion. Next is molecular size. I have already discussed that large molecular weight drugs or teratogens cannot pass, right. If it is more than 1000 Dalton, it will not pass the placenta, right.

It will not pass the placenta as in case of heparin or insulin. Protein binding, more amount of drug if it is protein bound, then it cannot cross the placenta. If free from of the drug is present, if there is more amount of free from, then it will be easily crossing the placenta. Next is the concentration of the free drug. If it is high, if the concentration is high, that means it will easily pass through the placenta, right.

Through diffusion or through facilitated diffusion, any procedure but the concentration gradient will aid in the passage of the drug. And lastly the degree of ionization and the tissue pH, right. So say the tissue pH of the placental cells, it is ionic, right. So more positive charge inside the cell. So if the drug free form is also positively charged, then there will be certain hindrance in entry into the cells.

So degree of ionization and tissue pH will determine the easy passage of the drugs into the cells. So that was regarding the properties of the teratogen. Now coming to the stage of fetal development or the period of gestation at which the exposure has taken place. So there are various stages of fetal development right from the time of fertilization up to delivery and the most teratogenic period is the period of organogenesis when the different organs of the fetus are being formed and any exposure to teratogen during this period of organogenesis can cause the maximum detrimental effect. It is the most teratogenic period for the fetus.

And then next is duration of exposure. For how many duration, for how many days or how many months there is this exposure. Any exposure to radiation for how long the exposure is taking place is important. Lastly the utero placental blood flow. More the utero placental blood flow, more the exposure of the teratogen to the placental tissues and more chance of effect on the fetus.

Also the placental surface area, right. If it is more, then more passage through the placenta. Placental thickness. If the placental thickness is less, then there is more chance of passage of drug to the fetus. So in a nutshell as the pregnancy progresses, the placental thickness decreases, the placental surface area increases.

So transfer of drug increases, transfer of drug increases in later stages of pregnancy, in late pregnancy, right. So these were the influencing factors. Now coming to the discussion about the stages of fetal development. It starts with the pre embryonic period, right. So what is the pre embryonic period? It is the period from the day of fertilization up to 2 weeks or 17 days.

Now if you calculate from LMP, you have to add another 14 days. So from the LMP it is day 0 to day 31, which is the pre embryonic period. And what happens in this pre embryonic period? There is only mitosis, only increase in cell number, right. So the cells are in cleavage stage, right. Next is the embryonic period, which is the period of organogenesis.Very important, this is the vital period. And this extends from, you know, this is up to 2 weeks, 0 to 2 weeks from fertilization. And this is from 3 to 8 weeks after fertilization, that is 17 to 56 days after fertilization, which when calculated from LMP will come day 31 to day 71. And this is the most teratogenic period, most teratogenic period, right. So any exposure, I will come to one by one what happens in which period the fetus is will determine the effect of the fetus by the teratogenic drug.

And lastly, so this is the embryonic period and third is the fetal period, which is starting from 9 weeks after fertilization up to the delivery. And this period is actually the period of growth. Mitosis has already taken place and there is only growth and neurodevelopment, right, neural brain development occurring throughout the period of pregnancy. So this is after day 71 up to delivery. So coming to one by one, pre embryonic period, that is the first 2 weeks from fertilization and this period I have told that it is the cleavage stage where the cells are in mitosis, it is increase in number of cells and if there is any teratogenic exposure during this period, it will follow the all or none law.

What does that mean? All or none law, that means that if there is any teratogenic exposure, right, it will either have no effect, it will either have no effect or it will cause fetal death, right, that is fetal loss. So all or none law, either the fetus is lost because it is, you know, just a bundle of cell and any insult to any one of the cell can cause the total loss of the fetus, right, or if there is, you know, somehow the dose of the teratogenic exposure is less or the duration is less and there is not so much of effect on the cells, then there will be no effect on the fetus and the fetus will continue to grow as it would be growing in an case of normal pregnancy. So that is all or none law for the pre embryonic period. Now coming to the period of, you know, embryonic period also called as the period of organogenesis, which is three to eight weeks post fertilization. Here exposure if occurs to harmful drugs during this period of organogenesis, then there will be major birth defect and gross malformation.

So this is called as the most teratogenic period for the fetus. So this period is very vital. Any drug exposure, unwanted drug exposure should not happen during this period. And thirdly is the

period of growth and maturation, neural development, brain development, which starts from nine weeks onwards up till delivery, which is also called as the fetal period and any exposure to drugs during this period will not induce major malformation because the organ development or organ structure formation has already been taken place, right? But it can produce minor morphologic abnormalities in the form of growth retardation or IUGR or functional defect in the form of cognitive impairment or neurodevelopmental delay. So that was regarding the period of fetal development and the time of teratogenic exposure.

However, to note that CNS is sensitive to toxic effects throughout pregnancy. So throughout pregnancy, any teratogen when exposed, it can cause, you know, effect on the brain, on the nervous system, on the central nervous system, that is the brain and the spinal cord leading to cognitive impairment, leading to neurodevelopmental delay, right? So, CNS will be growing all throughout the pregnancy and thus it can be, you know, it can happen that it can, you know, any teratogen will affect the CNS even in the later stages of pregnancy. So, that was the fetal period, right? So, fetal, we have discussed the stages of fetal development, we have discussed the definition of teratogen and the various factors that influence the effect of the teratogen on the fetus. Now, coming to radiation exposure in pregnancy, we know that in pregnancy radiation exposure should not happen and the maximum permissible x-ray that can, you know, that can safely be given in pregnancy is 5 rad. And in chest x-ray exposure is only 0.05 rad. So, it is less, very less. So, that means, chest x-ray can be done in a pregnant woman if necessary. What is safe in pregnancy? USG is safe, only MRI, plain MRI is also safe, dental x-ray little bit, very small amount of x-ray exposure is permissible. X-ray in case of emergency when we do for, you know, x-ray of head and neck or any limb like, you know, hands or legs following a trauma or any chest x-ray can be done in pregnancy. But to note that gadolinium MRI, that is contrast MRI or CT scan should not be done, cannot be done, you know, in pregnancy.It is contraindicated in pregnancy. You know, if the exposure, if there is more radiation and for a longer duration of time then most common anomaly, you know, most common anomaly due to radiation exposure in pregnancy is microcephaly, right. So, that was related to the radiation exposure which we have discussed that chest x-ray can be, you know, done if required in a pregnant woman. Now, coming to the period of pregnancy and effect of radiation. So, period of pregnancy number 1 is for the first 2 weeks safe is up to or less than 5 rad, you know, 1 rad is 0.1 gyri. So, less than 5 rad is safe for the first 2 weeks of pregnancy. Up to 16 weeks less than 5 rad is safe. Say if exposure occurs and it is more than 5 rad then what will happen? It can lead to congenital malformation and we have just now read which is the most common that is microcephaly. It can lead to IUGR. It can lead to neurological impairment and sometimes radiation.

So, radiation exposure can lead to certain cancers in the fetus like leukemia. So, these are all happening when the radiation exposure is more than the permissible limit and if the pregnancy is more than 16 weeks that means, that the period of organogenesis has already, you know, occurred. So, in that case up till 50 rad is safe, right. So, that was regarding the radiation

exposure in pregnancy. Now, coming to the classification the FDA classification of drugs, right, the different drugs and it has been different, you know, categorized into 4 to 5 groups.

So, what is category A? Category A means that, you know, it is safe in pregnancy, safe, the drug can be given in pregnancy. So, animal studies or human studies, you know, both have shown in animal studies it has been shown that there is no effect on the animal offspring and in human study it has also been shown that there is no effect on the human fetus, right. So, it is safe in pregnancy. Category B is, you know, there is no evidence of risk. So, it is, you know, likely to be safe, likely to be safe, say there is, you know, for that drug no human studies is available and in animal studies it has shown to be teratogenic.

Animal studies show risk is present, right. So, in humans there is no evidence or say the in animal studies risk is present and in human studies if done there is no risk. So, it is likely to be safe and it can be given in pregnancy. What is category C? Where the risk cannot be ruled out, there may be some risk. So, in human studies it shows, you know, in animal studies it is, you know, it is evident, it is quite sure that risk is present, risk is present in animals.

In humans there may be no study. So, from the animal study you can deduce that yes it has a, you know, possibility of risk also on the human fetus. So, risk cannot be ruled out and, you know, it should be given meticulously only when required and if required the benefit should outweigh the risk, right, only then it should be given. And what is category D? Category D meaning that there is positive evidence of human fetal risk and it should own, you know, only in life saving conditions. In life saving conditions where the benefits literally outweigh the risk, in those cases only these drugs can be used in a pregnant woman.

So, that was A, B, C and D. And last category is the category X which is contraindicated. Now, these drugs under the category X are contraindicated in pregnant women or women who are planning to conceive because there is a definite risk, there is a definite risk on the fetus, right. So, there is a definite risk and it cannot be used in pregnancy if there is any exposure of such drug during the period of pregnancy then the fetus is in jeopardy, is at risk and you need to, you know, look for the various anomalies or malformations in the fetus by USG. So, that was regarding the different FDA categorization of the drugs. Now, what well known teratogens? Some of them are we know they are well known and they should not be used they come under the category X of the FDA classification.

They are isotretinoin, isoretinoid. So, this is a, you know, medicine for the skin acne or you know given by the dermatologist and it should not be, should not be given during the period of pregnancy. So, before prescribing the dermatologist should always confirm that she is not pregnant. Next is ACE inhibitors or ARB, angiotensin receptor blocker, angiotensin converting enzyme inhibitor these are all antihypertensives, losartan. So, these cannot be used in

pregnancy. Valproic acid, anti-epileptic drug cannot be used in pregnancy.

Lithium, mood stabilizing drug used in manic depressive psychosis cannot be used in pregnancy. Thalidomide used previously now it has been banned, but it is causing you know detrimental effect on the fetus cannot be used in pregnancy. Methotrexate given in case of ectopic pregnancy or you know in different anti-cancer medication anti-folate. So, it cannot be used in pregnancy. Mifepristone, misoprostol these are all teratogenic drugs which should be avoided strictly during pregnancy.

Statins, right? Then there are many, right? So, hormones, androgens, androgens, then your Danazol. Now, if these drugs are given always prescribe an additional contraceptive pills or contraceptive device to the female so that during this medication the female does not get pregnant. So, that was the list of the teratogens, right? Now, coming to one by one. First is the drugs that lead to limb defects in the fetus.

There are three, you know thalidomide. These are all well known teratogens. There are many I have picked up only a few which we use repeatedly, you know for day to day practice and if the patient becomes pregnant you should be cautious and you should change, either change the drug, stop the drug or if already exposure has taken place, you know you need to sometimes counsel for termination of pregnancy. So, thalidomide is one such drug which is not used now, but it is very teratogenic and it causes limb defect, right? So, it is proved teratogenic drug when used in pregnant women and the syndrome called as phocomelia where there is proximal limb defects, right? So, we will see one picture of this. This is the phocomelia.

See these are the proximal limb defects. No hands, feet, no proximally the limbs are smaller. They are defective and also associated with facial defect. You can see you know some skull changes in the shape of the skull, in the shape of the eyes there can have some changes. So, that is due to thalidomide leading to Focomylia in the fetus.

Next is warfarin. Warfarin also causes limb defect. It actually is a cartilage defect, right? So, warfarin when given to mother say if there is a history of APLA, if there is a history of autoimmune, any type of autoimmune platelet disorder or thrombocytopenia where you need to give warfarin to the mother, you know if she wants to become pregnant then you have to stop warfarin and change to heparin which is you know which is safe in pregnancy. So, what warfarin does if there is any exposure of warfarin during the period of organogenesis there will be you know warfarin fetal warfarin syndrome. What is that? That is this is called as Di Sala syndrome. What happens there? There is hypoplasia, see that picture. Hypoplasia of the nasal bridge, that means the depressed nasal bridge, then stippled epiphysis of femur, humerus and calcaneum.

Choanal atresia, atresia of the choana leading to you know bleeding from the nose, right? And cartilage defect that is called as chondrodysplasia punctata and in 50 percent cases they are associated with CNS malformation. So, warfarin in the first trimester is contraindicated and if required you need to change to heparin. You need to change to heparin. In the second trimester warfarin again can be started, but in the third trimester again heparin is shifted. Why? Because warfarin if there is any overdose or you know say any type of complication, bleeding complication in the mother due to this warfarin administration it does not have an antidote, but heparin have an antidote which is protamine sulphate.

So, that I was you know discussing. So, if there is coagulation disorder in the mother and she has become pregnant. So, she was taking warfarin. Now she has become pregnant. Now warfarin is contraindicated in pregnancy because it crosses placenta, but heparin, heparin is polar, it is large molecular weight molecule and so it does not cross the placenta. So, you shift from warfarin to heparin, right? Why warfarin first trimester I have told that there is possibility of teratogenicity that is the Di Sala syndrome and in second and third trimester there is risk of bleeding.

Sometimes in second trimester we can give warfarin, but in third trimester again we change back to heparin. Why? Because heparin has an antidote in the form of protamine sulphate and if there is any possibility or any case of surplus administration of heparin, then you can reverse the picture by protamine sulphate injection. So, that was the drugs leading to limb defects and lastly is the amniotic band syndrome, right? This is due to severe oligohydramnios, right? So, severe oligohydramnios and there will be leading to distal limb defects. Now, mostly due to ACE inhibitors or ARB. So, angiotensin converting enzyme inhibitors, Losartan, Telmesartan these cannot be given in pregnancy or angiotensin receptor blocker, they will cause oligohydramnios which will cause you know severe oligohydramnios, snow liquor so the limbs are folded and there can happen that there is limb defects associated with pulmonary hypoplasia which is called as Potter's syndrome, right? So, that was regarding the drugs that led to limb defects.

Now, we will be discussing the drugs which are associated with cardiac defect. Number one is lithium. Lithium is a drug which is used in manic depressive psychosis, right? So, it is a mood stabilizing drug. So, if the mother is taking lithium, then also she should discontinue the lithium immediately after you know she has started planning her pregnancy.

Why? Because it leads to some cardiac defects. What happens? So, this is the tricuspid valve. Tricuspid valve having the anterior leaflet, the posterior and the septal, right? So, this is the posterior and this is the septal leaflet. Now, in case of lithium exposure what occurs there is downward displacement of these two leaflets. The septal leaflet and the posterior leaflet there is downward displacement. So, downward displacement of the posterior and the septal leaflet of the tricuspid valve leading to tricuspid regurgitation also you know enlargement of the you

know right ventricle.

So, it is called as atrialization of right ventricle. This defect, this cardiac defect together is called as Ebstein anomaly. Right? So, that was due to lithium exposure. Here you can see in Epstein anomaly due to lithium exposure, this tricuspid valve leaflet, the anterior and the septal leaflet, they have you know not the anterior, the posterior and the septal leaflet will go downward and that will lead to enlarged right ventricle or atrialization of the right ventricle and tricuspid regurgitation, right? So, tricuspid regurgitation, cardiovascular anomaly mainly valvular heart defect involving the tricuspid valve occurs in Ebstein anomaly which is due to lithium exposure. Another drug is SSRI, selective serotonin reuptake inhibitor of which paroxetine is the most important one which can cause CNS abnormality in the fetus. So, if there is any chance of exposure or you know intake of paroxetine by the mother during pregnancy, then you should go for fetal echo to look for cardiac defects in the fetus.

So, that was regarding the cardiac defects, drugs causing cardiac defects. Now, coming to drugs causing cardiac defect as well as facial dysmorphia, right? So, these both occurring by the drugs they are isotretinoin. What happens? Facial defect in the face there can occur cleft lip, cleft palate, microtia or anotia that means, the opening of the mouth that is small and micrognathia is the tongue is small, right? So, that is the facial defect and it can be associated with cardiac defects, CNS defect or thymic defect. So, that is all know occurring due to isotretinoin and that I have told that it is a dermatological drug and it should not be given in pregnancy by the dermatologist, right? Next is phenytoin.

Phenytoin is actually an anti epileptic drug. So, there is CVS defect, there is associated limb defect, no hypoplasia of the diaphragm, the digits. Now, the digits will be small, the nails the small, you know nails will be small, right? The distal nails and there will be associated facial mid facial defect. I have the picture for you. So, this is you know the fetal hydantoin syndrome which is due to sorry phenytoin which is due to phenytoin. What happens? So, in the face see there is depressed nasal bridge, the nose is depressed or nose is somewhat flat and also the philtrum, the upper lip, the upper lip is very thin and there is no philtrum.

This philtrum is absent of the upper lip. So, absent philtrum and you know small upper lip, thin upper lip, right? You know I have already told the nasal bridge, depressed nasal bridge, flat nose and also in the eyes, eyes see the palpebral fissure is narrow, narrow palpebral fissure and sometimes there is ptosis, right? So, it can there can be ptosis, narrow palpebral fissure, hypertelorism, these are all the facial defect occurring in fetal hydantoin syndrome. So, narrow palpebral fissure, hypertelorism, absent philtrum, then you know thin upper lip and in the limb defects I have told that the distal the digits are small, small digits, small distal nails. So, these come under the fetal hydantoin syndrome and lastly is due to alcohol which is fetal alcohol syndrome. Here also the facial features are seen as in case of fetal hydantoin syndrome. See this

is the short palpebral fissure, the palpebral fissure is short like this it will happen that will be short, right? So, short palpebral fissure and there will be hypertelorism, epicanthic folds, the eyes will be drawn up like this, eyes will be drawn up, right? And nose, nose the nasal bridge is flattened, short nose or depressed nose, flat mid face.

Indistinct philtrum, this is the philtrum, there is no philtrum or absent philtrum and thin upper lip. So, that is also in case of fetal alcohol syndrome. Now alcohol is strictly contraindicated during pregnancy and as such binge drinking is very very dangerous. What is binge drinking? More than 6 drinks per week or for 2 consecutive weeks or if the female or the pregnant mother is taking more than 3 drinks per occasion for 20 such occasions. This is a case of binge drinking which can lead to you know grave conditions of the fetus leading to growth impairment, leading to facial defect as in fetal alcohol syndrome, leading to brain growth that means, IUGR.

There is no growth retardation, right? The head circumference is less than 10th percentile and behavioral impairment in case if it is less than 3 years there will be you know neurodevelopmental delay and if the age is more than 3 years then there will be cognitive impairment. So, all these are associated in case of alcohol exposure in pregnancy and we need to educate the mother to refrain from alcohol during the period of pregnancy. So, next coming to nerve palsy. So, the drugs causing nerve palsy is your misoprostol.

Misoprostol causes Mobius syndrome. What happens in Mobius syndrome? There is 6th and 7th nerve palsy, right? So, 6th and 7th nerve palsy is seen with misoprostol that is in Mobius syndrome. So, in first and second trimester it is contraindicated. Misoprostol is contraindicated, right? But in third trimester it can be given and sometimes misoprostol now it is banned but previously misoprostol was given for induction of labor, right? But in first and second trimester it cannot be given because it is teratogenic and it causes Mobius syndrome in the fetus. Now coming to decreased urine output in the fetus. So, what drugs I have discussed ACE, ACE inhibitors or ARB angiotensin receptor blockers like low certain, tell me certain say these causes decreased urine output and sometimes anuria.

It can cause anuria in the neonate. So, this decreased urine output will lead to oligohydramnios and due to this severe oligohydramnios there will be also associated limb defects because the limbs will be compressed. There is less space for the limbs for the limb movements and that will lead to limb defects, distal limb defects to be more particular and also you know there is no space for the lungs to have some expansion or to have some breathing or to have some movements inside the uterus. So, that will also cause pulmonary hypoplasia. So, these three together, these three triad is known as Potter's syndrome which is seen with your ACE inhibitors or ARB blockers.

So, that was leading to decreased urine output in the fetus. Now the last part of today's class

that is drugs causing facial dysmorphology, right? So, we have already discussed the drugs which causes both facial as well as cardiac defect. So, that will also come here. So, that is isotretinoin, then your phenytoin causing fetal hydantoin syndrome and alcohol. Now mostly the mid facial defect that is depressed, flat mid faces, the nasal bridge is depressed, the nose is flat, there is no philtrum, the upper lip is thin and that has no featureless mid facial defect.

So, that was one. Next is with methotrexate. Methotrexate will also lead to facial dysmorphology and should not be used in pregnancy. Then sometimes it is also seen with glucocorticoids, right? So, if steroids are given to a pregnant mother, it can lead to facial dysmorphology and when it is you know given before 10 weeks of gestational age, then it can lead to cleft lip and cleft palate, right? So, these were associated with glucocorticoid administration in pregnancy. So, when corticosteroids are given see there is cleft palate. So, the palate there is no gap in the palate.

So, this is cleft palate, right? And cleft lip. So, this is cleft lip and also sometimes both may be present cleft lip and cleft palate. So, that is the facial dysmorphology. Also corticosteroids will lead to adrenal fetal adrenal atrophy, right? So, there will be adrenal atrophy and that will lead to growth retardation or intrauterine growth retardation. Also due to adrenal atrophy, there will be no corticosteroid synthesis. Fetal cortisol synthesis will be hampered that will prevent in you know initiation of labour leading to post term or post dated pregnancy.

So, these are all associated with administration of different types of drugs to the mother during pregnancy. So, we should be very very cautious regarding the administration of any medicine, right? To a pregnant mother. So, that was for today's class. The rest part of the teratogenic effect will be dealt with in the next class. Thank you.