Comprehensive Molecular Diagnostics and Advanced Gene Expression Analysis

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Lecture 49 : Reproductive genetics and genetic counselling

Hello everyone. Namaskar and welcome back to module 10 of comprehensive molecular diagnostics and advanced gene expression analysis course. Today our topic is reproductive genetics, genetic counseling and patient educational aspects. So, we will be covering the lecture under these following headings. We will be discussing actually the aspect of reproductive genetics mainly deals with infertility. So, what are the causes of infertility, what are the various genetic factors because it is a genetic related course.

We will be focusing on the genetic factors that will help us to understand how genetic diagnosis can help in understanding the infertility. And then in the later half of the later part of this lecture series we will be discussing on genetic counseling, what is the purpose indication, what are the various who are the very best beneficiaries, what are the phases, how where can we apply the genetic counseling, what are the role of primary care provider and various patient education aspects alright. So, we will start with reproductive genetics and the very first thing that we should know what is infertility. Now, infertility the term is often has been converted to sub fertility right.

So, it actually defines the failure to conceive failure of a couple to conceive after one year of unprotected regular sexual intercourse alright. Now this sub fertility can be primary or secondary mind it whenever couple has been diagnosed with any irreversible condition where they cannot conceive in any way then we can use the term infertility right. Wherever when we are exploring a delay we do not know the cause there is a chance. So, we use the term sub fertility right. So, primary infertility or primary sub fertility actually means the couples who did not have any previous pregnancies and now they are being explored and they are having difficulty in conceiving for the first time.

So, this is primary sub fertility or primary infertility alright. Now what is secondary? So, this infertility may be primary and secondary as I told you sub fertility. So, secondary infertility or sub fertility is referred to a situation where a couple who actually have delivered birth previously, but now they are finding it difficult to conceive or carry out pregnancy to term alright. So, this is the basic concept of fertility and infertility and

sub fertility. Now let us explore the various causes what are the various reasons.

So, there are multitude of reasons alright. So, to start with there are ovulatory disorders multiple disorders related to ovulatory cycle for example, polycystic ovulation syndrome it hampers ovulation one of the primary causes of infertility the main causes of infertility in the females. In males there can be multiple reasons why that relates I mean that results in fertility quality of sperm, as a sperm here there are many diseases many factors will be discussing also. Infertility again not only related to ovulation problem in fallopian tube blockage or damage any anatomical blockage or any damage between infection or any other mucus thick mucus secretion problem will lead to improper implantation of the egg not only implantation receive of the sperm going of the migration of the sperm into the cavity it will be problematic right. So, this is very important cause of infertility.

There can be multiple uterine issues anatomical issues related to the uterus multiple diseases like endometriosis that actually results in infertility. Next age very important the fertility in females decreases with age. So, one more than 35 to 40 the chance of conceiving decreases right compared to when the mother is below 30 years of age. So, very important age is inversely related with fertility. Again endocrine disorders for example, see this whole ovulation is a inter complex interplay intricate interplay of multiple hormones and again there may be problem in pituitary problem in gonadal hormone or even problem in thyroid stimulating hormone they can abruptly hamper the fertility and they may lead to sub fertility in many cases.

Again sexually transmitted infections STIs sexualized with diseases STDs as you say it again they will lead to an unfavorable environment and they may lead to infertility very important. So, both the partner should be checked for sexually transmitted infection and in some cases diseases like gonorrhea may affect the organs gonadal organs in such a way that may cause irreversible damage and the couple may find it difficult to conceive all right. The lifestyle factors unhealthy food habit obesity excessive smoking excessive use of alcohol all these things again one of the very common cause of infertility the improper act of doing. So, all these factors have been found to have a leading cause contributor in infertility. Again stress and mental health very important with excessive stress and improper mental health scenario will definitely lead to problems in fertility.

So, it is very important when someone is a couple is planning it is very important for them to be stress free and they should have a boosted mental health. And lastly our point of interest among all these factors in this course are genetic factors there are multiple genetic factors they can be broadly classified they can be pinpointed to males and females they can be pinpointed up to the genetic level. So, we should know every factor and pay or focus special importance on genetic factors for this course. So, this will be our point of discussion in this course forward. So, what are the genetic factors that are

driving infertility? Now in this slide I will be sharing with you few general happenings a few general events that may lead to infertility.

Number one deletion what do you mean by deletion a piece of chromosome is missing all right. So, chromosome deletion very important cause of infertility. Inversion all right chromosomal inversion where the piece of chromosome is upside down very important very important in male infertility chromosomal inversion again. So, deletion inversion mutation you already know wherever there is a change in gene sequences that may lead to multiple diseases right from hereditary disorder inherited disorders that will lead to either direct problems or they may lead to a scenario that will lead to multiple infection and that can indirectly lead to infertility. Next aneuploidy all right aneuploidy you already know where there are too few or too many chromosomes a specific set of chromosomes there are multiple specific aneuploidies for which genetic testing was being done we already read about all of them again one of the major leading causes of infertility.

Next translocation right. So, these chromosomal translocation is a phenomena where one part of the chromosome gets detached and gets attached to another part of the chromosome all right. So, that can also lead to infertility. So, deletion inversion mutation aneuploidy and translocation these are the various chromosomal abnormalities or direct genetic factors that will lead to infertility in some way or another all right. So, these infertility cause of infertility genetic causes of infertility are many right.

So, for our better understanding of streamline discussion we will be discussing them with respect to females and with respect to males. So, let us first start with genetic factors that are arriving that responsible for female sub fertility. Number one hereditary in I mean genetic disorders right. So, you have been listening to this term you have been learning this term cystic fibrosis cystic fibrosis trans membrane region. So, this is the gene CFTR gene which whose mutation leads to disease known as cystic fibrosis right and we are discussing it with respect to women minded cystic fibrosis can happen in both males and females either sex it is not a sex specific disease.

So, this cystic fibrosis leads to poor nutrition resulting in thicker cervical mucus right the mucosal clearance is absolutely destroyed. So, it leads to lung problems and it leads to wherever there is a phenomena of mucus clearing mucus becomes thicker. So, there are repeated chest infection and there are multiple mucus clearance issues in the ovary and ovulation issues right. So, these are inherited disorders for example, sickle cell anemia where there is a mutation in the beta hemoglobin B gene right it will be gene. So, they do not directly cause infertility, but a patient of sickle cell anemia all right may present with infertility because there is a risk of infection.

Sickle cell anemia patients are plagued with multitude of disorders and that can lead to infertility all right. So, there have been incidences where a patient has presented with infertility on exploration he or she have been found to have a hemoglobin disorder ok. Next Kalman syndrome right very important another genetic disorder rare genetic disorder main mutation. So, there are multiple varieties of Kalman syndrome there can be autosomal there can be X-linked the main variety is the X-linked variety. So, these are the various genes which have been there all approximately 20 genes there are 20 genes that can be problematic in Kalman syndrome all right and these cause infertility why because of the bodies inability to produce pituitary or hypothalamic hormone.

So, when there is no pituitary or hypothalamic hormone releasing hormone that will not lead to synthesis or secretion of FSH or LAS that is follicle stimuli stimulating hormone or luteinizing hormone and which in turn will not produce estrogen and progesterone which are the main hormones that help in ovulation. So, very important Kalman syndrome one of the very important cause of genetic cause of infertility in females. Next primary ciliary dyskinesia all right DNA I 1 and DNA H 5 these are the genes which are mutated. So, what happen actually it is a cilia you you might be knowing what a cilia is these are micro organs which run in a streamlined motion and that helps in propulsion of many things in tubal structures it can be a foreign organism, it can be fluid, it can be mucus multiple things. So, when this cilia is dysfunctional due to a mutated gene again that will lead to infertility all right.

So, abnormal cilia in fallopian tubes will actually destroy the phenomena of migration of the exam gametes all right. So, very important rare genetic disorder identified stamped to be a cause of female infertility primary ciliary dyskinesia and just like cystic fibrosis it also leads to chronic RTI that is respiratory tract infection. Next Turner syndrome so, mind it we in this class we are learning about all these genetic abnormalities you already know what tests to use to these genetic for abnormalities. If you know the gene you can now design the primers you can now design the probes you can now use multiple processes to detect these mutation detect these abnormalities right that some will that already have been discussed. So, let us now apply expand our knowledge you already know what we need to do next with what we need to do that is the thing we are learning.

So, Turner syndrome again X 0 is a chromosomal disorder where a female is born with only one X chromosome right one X chromosome is missing right and that leads to ovarian dysfunction premature ovarian failure early ovarian failure and that leads to infertility very important. Fragile X syndrome all right FMR 1 gene fragile X messenger gene. So, fragile X syndrome again a rare genetic disorder that can affect the women fertility all right. So, mind it FMR 1 gene associated with ovarian dysfunction. So, question might come there might be multitude of these diseases named.

So, which one does not lead to infertility right the names are similar all these names are similar if you are if you are not from medical background right and we can also give the question match the following type right. So, very important knowing the name of the diseases and knowing the name of the genes. Next primary ovarian insufficiency also known as early menopause we know we have got a I mean as per the normal physiology this is a definite age of menarche when the menstrual cycle starts in a female and there is a definite age of menopause after which the physiological menstruation stops and then the fertility span ends. However, in multiple diseases so and that usually happens at the around at 40 to 45 years right it varies from patient to I mean case to case. However, when the ovary stops functioning before there is a 40 it is definitely a case of primary ovarian insufficiency and all these factors I mean fragile X syndrome, terminal syndrome they all lead to ovarian failure they all lead to primary ovarian insufficiency abbreviated as P O I, but there are multiple other known disorders you can look up and read discussing all of them again the super speciality gynecology that is based on this.

So, it is beyond the scope of this lecture to discuss all the genetic reasons of infertility female infertility, but I encourage you those who are interested enough you can look up what are the genetic mutations in primary ovarian insufficiency you will definitely find this what else right. Next chromosomal translocation. So, chromosomal translocation are one of the most or rather leading cause of recurrent miscarriages alright. So, if a woman has got history of multiple miscarriages one should definitely investigate the possibility of chromosomal translocation right. BRCA gene mutation BRCA genes are I mean associated with breast cancer right.

So, you see they do not directly lead to infertility. However, breast and ovarian cancer association is very well known now and most of the patients with BRCA mutation they do present with infertility upon investigation and upon research they have been it has been found that main leads due to decreased ovarian reserve and all these patients of BRCA mutation do end up in earlier menopause. So, that is the main problem why this leads to female infertility and I mean there are the list goes on and on. So, there are two diseases that I would like to mention here that is endometriosis and polycystic ovarian syndrome. They are multifactorial disorders they are not strictly a chromosomal or genetic disorder, but research is on and there are definite genetic components that have been found to be the contributor in development of all these diseases.

So, definitely if we are discussing genetic factor may be not now there will be a genetic marker that can detect endometriosis and polycystic ovarian syndrome or PCOD polycystic ovarian disorder all right. So, these are factors that affect female infertility. Now let us discuss the factors that are governing that driving male infertility. So, behind it we are continuing with reproductive genetics we have covered female infertility. So, let us move on with male infertility very important gonadal aneuploidies

right.

So, Kleinfelter syndrome. So, men with Kleinfelter syndrome what do they have they have an extra X chromosome. So, 47 XXY all right 47 XXY instead of XY. So, this chromosomal abnormality can lead to problems in that may lead to infertility. So, what are the problems underdeveloped testes all right underdeveloped gonads will definitely to infertility there will be impaired sperm production there will be low male hormone level that is testosterone levels all right very important. Y chromosome microdeletion very very very important Y chromosome microdeletion is a leading cause of male infertility right there are more journals on male infertility compared to female infertility.

The genetic reasons are more common in males the other lifestyle little reason and all other anatomical reasons are mainly leading to female infertility. As I told you there are genetic factors that are there in females, but genetic factors infertility mainly concerns the male couple right male partner. So, deletion in specific regions of Y chromosome can affect sperm production and they are associated with male infertility. The AZF region there is a region in Y chromosome that is the azospermia factor that is very important any change any alteration in that region will lead to infertility right. Azospermia means phenomena where there is lack of sperm in the semen all right and that will definitely lead to infertility mind it the major leading cause of female I mean infertility is often the subpar sperm quality right.

Next again our familiar name has again returned CFTR gene that is cystic fibrosis. So, now, you can understand why we were paying so much attention to cystic fibrosis why do western countries pay so much attention to cystic fibrosis because it leads to infertility one of the basic physiology of life right. So, how does it I mean alter the fertility or how does it hamper the fertility males its leads to problem in the vas difference mainly congenital bilateral absence of vas difference all right this is the very I mean pathognomine finding that is related to cystic fibrosis and this leads to obstructive azospermia absence of sperm in the ejaculate. So, congenital absence of vas difference vas difference is anatomical tubes and organ through which the sperm it is a part of the genital tract of males through which the sperm from the source is delivered to the ejaculate. However, congenital absence of vas difference will lead to azospermia and infertility and specially if it is bilateral it will lead to infertility.

Next androgen receptor ER gene mutation. So, we read in Kleinfelter syndrome there is less production of male hormones due to underdeveloped testes what if the male hormone is produced normally, but they cannot act the receptor is problematic right. So, mutation in the androgen receptor gene can result in androgen insensitivity syndrome very very very important again a leading cause of male infertility right. So, this what happens the body does not regularly respond to male sex hormones right and this

impacts the normal sperm development sex hormones testosterone is very essential for sperm development is the fundamental part of reproductive system physiology right. However, it is hampered in case of androgen receptor mutation. So, study ER gene mutation detection finding we can detect male infertility in that way.

Cartilage here hypolatia again a very important is a rare genetic disorder that can lead to multiple problems short stature, hair abnormality, immune system problem and in some cases it also affects male fertility all right. So, when I mean you know when I mean the infertility is unknown when you are searching for unknown reasons of infertility often the rarest of the rare diagnosis comes to mind and should be explored right. Therefore, we are learning all the genetic factors that are contributing so that we can design I mean we often we are well equipped with the knowledge. So, that we can prove into the diagnostics of infertility using molecular using molecular diagnostics. So, again cartilage here hypoplasia same way it deals with I mean hampers with the sperm production and leads to infertility.

Again myotonic dystrophy it is a genetic disorder that have multiple again multisystemic disorders all right including the muscles and endocrine system specifically it leads to testicular atrophy and sperm abnormalities all right. Next we are not done yet we are dealing with chromosomal abnormalities other than Kleinfelter syndrome. So, these chromosomal abnormalities may be structural or numerical abnormalities chromosome right other than the sex chromosome. So, other than Kleinfelter 47XXY there can be 47XYY right there can be multiple such variants right even if we leave apart X chromosome other chromosomal abnormality can lead to infertility male infertility right that have not been discussed earlier. Next Prader-Willi syndrome right these are the I mean imprinting disorders right genetic imprinting.

So, Prader-Willi syndrome again can experience hypogonadism that is underdeveloped testis. So, we are exploring reasons why the sperm is absent or why the sperm is not properly formed and then we enlist a list of reasons what can lead to and then we explore the genetic markers that we need to look into right. And in cases whether a multitude of genetic markers for example, these diseases that I am mentioning there are multiple research groups that have found multiple mutation leading to these diseases not in case of Prader-Willi, Prader-Willi you already know what is the problem, but anyway detection of that is also easy, but what it leads to it leads to hormonal imbalances underdeveloped testis and ultimately infertility. Again lastly luteinizing hormone receptor. So, LHR gene mutation all right that can also affect the response of leading cells in the testis all right.

So, luteinizing hormone is not only present in females it is present in both males and females right and luteinizing hormone leads to impaired testosterone production and

sperm development. Therefore, in this class we have explored what is infertility, what are the various causes of infertility and among the multiple causes we have delineated the most important genetic factors that are causing infertility both in males and females. So, in the next part we will be discussing what are the implication with these knowledge how we can prepare a couple for genetic counselling. So, we know at this point we know what are the genetic what is genetic testing, what are the problems that may lead to genetic disorders. So, the next part will be much easier for you to understand how genetic counselling is done you will find these concept much overlapping with genetic testing the concepts are interchangeable the one how we prepare a patient for testing is basically counselling.

So, the indication beneficiaries phases we will find it easier to understand, but that is a topic of our next class. So, these are my references for this series and I thank you for your patient hearing. Thank you.