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Loss of Pregnancy, Causes and Counseling

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Abstract: Human pregnancy is a beautiful experience that goes through a large number of biological events. From the time of its inception to the final stage of parturition, several mechanisms, genes, hormones, physiological changes and emotional plangencies are involved. Despite the scientific advancement in the area of reproductive biology, we still do not know the number of genes involved in the sustenance of pregnancy, their sequential expression, timing of silencing and their overall regulation. The availability of fine-tuned level of several hormones, the timely progress of the fetal development along with the health of the mother and her emotional well-being tend to guarantee the normal birth of a baby. However, close to about 15% pregnancy loss is estimated globally. This occurrence warrants the search of cases, causes and possible remedial measure. We have included some still other uncharacterized factors that seem to be crucial for the sustenance of pregnancy and for eventual successful parturition. These seemingly innocuous factors include microbiomes, Microplastics, environmental pollutions, professional hazards, stress, nutritional deficiency, rampant food adulteration and use of tobacco and alcohol. In addition, how a pregnant female is treated in her family is equally important for her emotional health. Following the loss of pregnancy, the importance of counseling to affected mother becomes important. Thus, a genetic counselor has an equally important role to play in the society. This review is aimed to collect, collate and summarize possible factors responsible for the loss of pregnancy and subsequent genetic counseling. It is envisaged that this review will be useful for researchers, doctors, nurses and health care professionals enhancing its overall awareness and nuances culminating into a happy, healthy and successful family life.

Keywords: Chromosomal abnormalities, Environmental pollution, Genetic counseling, Hormonal imbalance, Loss of pregnancy, Microplastics, Telomere, Y chromosome.

I. Introduction

Everyone is familiar with the term pregnancy but not of its biology. In order for us to understand this biological phenomenon, we need to study the biological basis, uncover the hormonal roles, assess the chromosomal aberration, chromatin condensation, genome organization, gene expression and gene regulation for their involvement in sustenance of successful pregnancy. Further, we also have to look at the epigenetic modification and involvement of other factors such as Microplastics, rampant environmental pollution, Microbiome, and food adulteration. Emotional quotient is equally important for successful culmination of pregnancy. Normal chromosomes have been implicated with the success of pregnancy and aberrant ones with the loss of pregnancy. One of the most interesting and enigmatic parts of the chromosome is the constant adjustment of telomeric (end) sequences. These sequences are carefully organized, packed and repacked after every cell division. If anything goes wrong, the consequences are far too many and too debilitating for the mother and child. Pregnancy loss, also known as miscarriage, is a heartbreaking experience that affects family individuals and couples. It is estimated that up to 20% of known pregnancies end in miscarriage, with many more going unreported. Unwanted pregnancy loss can cause a lot of suffering and sorrow. There are parallels and divergences among all kinds of losses. All of these could be linked to sadness, anxiety, and worry about being infertile in the future. Pregnancy loss can occur for a number of causes, including chromosomal abnormalities, hormone imbalances, and infection from microbiomes. Further, Microplastics, cosmetics, uterine abnormalities, immunological variables, lifestyle choices, and age of the mother are equally important. By controlling all the risk factors and receiving the right diagnosis and care, pregnancy loss can be prevented in many cases. When a woman loses a pregnancy, she goes through a phase of tremendous grief. Several medical conditions can

result in miscarriages, many of which are beyond a person's control. However, being aware of the risk factors, symptoms, and causes can help one better to comprehend the situation and seek support or treatment. Women who experience infertility are likely to experience despair. Consider how things will work out at the end rather than how everything is ruined right now. At this crucial juncture, their families must provide them with emotional support. Studies have demonstrated the advantages of preconception care by men. This results in better pregnancy outcomes and overall health of the female spouse. Thus, men can improve their spouses' physical and emotional well-being. A nutritious, well-balanced diet combined with exercise is advantageous. We provide a critical appraisal of the reasons for the loss of pregnancy, likely remedial measure and role of counselling to the affected mother.

II. Chromosomal Abnormalities

In all abnormal or suspected pregnancies, immediately after birth, chromosomal analysis of the mother and child may be conducted as a first and basic step to ensure that chromosomes are normal. Chromosomal abnormalities, aberration, structural and numerical variations may lead to the loss of pregnancy. Molar pregnancy and miscarriage are two examples of these difficulties. A molar pregnancy is a rare complication involving unusual growth of trophoblast cells. These cells typically become the organ that feeds to growing foetus. This organ is also called placenta. There are two types of molar pregnancy which include complete molar pregnancy and partial molar pregnancy. Partial molar pregnancy may cause complications such as severe bleeding, high blood pressure, formation of ovarian cysts and hyperthyroidism [1].

III. Molar Pregnancies

As mentioned earlier, molar pregnancy involves unusual growth of trophoblast cells that forms placenta. In a complete molar pregnancy, the placental tissue swells and appears to form fluid-filled cysts but there is no foetus (Fig. 1).

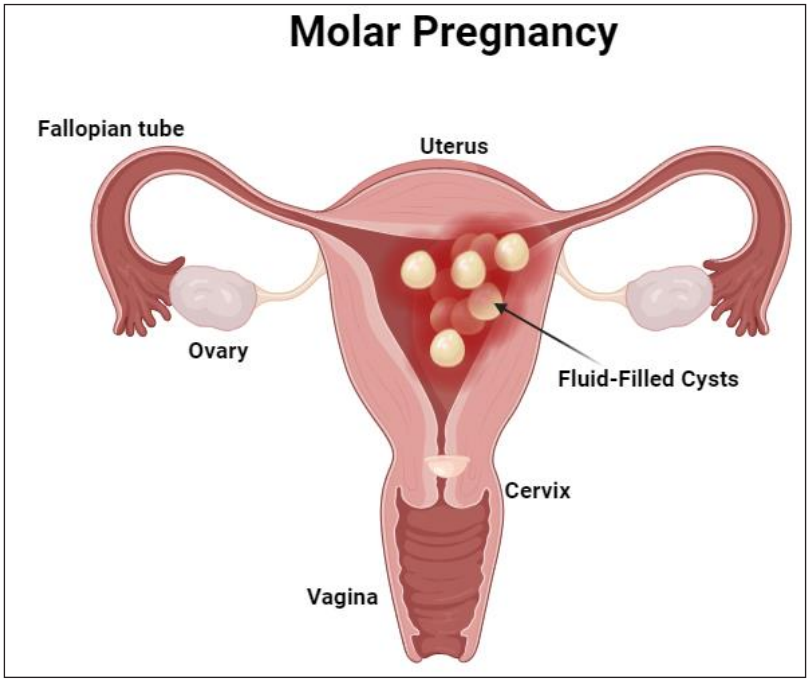

Fig. 1

Fig. 1 shows the osteon of fluid filled cysts inside the uterus. There could be several cysts.

In a partial molar pregnancy, the placenta might have both regular and irregular tissue. There may be a foetus, but that does not survive and miscarried early during the pregnancy. A molar pregnancy can have serious complications, including a rare form of cancer. A molar pregnancy may seem like a regular pregnancy at first. However, most molar pregnancies cause dark brown to bright red vaginal bleeding during the first three months, severe nausea and vomiting, sometimes formation of grape like cysts that pass from the vagina. Pelvic pressure pain is common in all such cases [2]. Because of improved ways of detecting a molar pregnancy, most are diagnosed in the first trimester. If it is not found in the first three months, a uterus may grow quickly and become too large early in the pregnancy. This may lead to high blood pressure and release of protein in the urine (called Preeclampsia). This happens before 20 weeks of pregnancy. Formation of ovarian cysts and overactive thyroid, also known as hyperthyroidism are common in such cases [3].

IV. Causes of Molar Pregnancies

An egg fertilized atypically causes a molar pregnancy. Human cells normally have 23 pairs of chromosomes. In a typical fertilization, one chromosome from each pair comes from the father, the other one from the mother. In a complete molar pregnancy, one or two sperm fertilize an egg. The chromosomes from the mother's egg may be missing or don't work. The father's chromosomes are copied but none from the mother. In a partial or incomplete molar pregnancy, the mother's chromosomes are present, but the father supplies two sets of chromosomes [4]. The embryo then has 69 chromosomes instead of 46. This most often occurs when two sperm fertilize a single egg, resulting in an extra copy of the father's genes. This is a serious chromosomal imbalance. If there is one molar pregnancy, another one is more likely to happen. A repeat molar pregnancy happens on average of 1 out of every 100 people. Further, age of mother older than 43 and younger than 15 enhances the risk factor. Even after removing a molar pregnancy, molar tissue might remain and continue to grow. This is called Persistent Gestational Trophoblastic Neoplasia (GTN). GTN happens more often in complete molar pregnancies than that in partial ones [5].

One sign of persistent GTN is a high level of human chorionic gonadotropin (HCG) — a pregnancy hormone — after the molar pregnancy has been removed. In some cases, the mole that causes the molar pregnancy goes deep into the middle layer of the uterine wall. This causes bleeding from the vagina. Persistent GTN is usually treated with chemotherapy. Another possible treatment is removal of the uterus, known as hysterectomy. Rarely, a cancerous form of GTN known as choriocarcinoma develops and spreads to other organs. Choriocarcinoma is usually treated successfully with chemotherapy. A complete molar pregnancy is more likely to have this complication than a partial molar pregnancy. Thus, molar pregnancy may be a potential cause of loss of pregnancy involving chromosomes [6].

The aetiology and pathology of habitual abortion can be attributed to chromosomal abnormalities in both the parents and the embryo. Chromosome abnormalities, which are believed to occur in 50% or more of cases, are the most common cause of first trimester miscarriage in the absence of underlying medical issues. Both numerical and structural chromosomal anomalies result in the gain or loss of genetic material correlating with the pregnancy loss [7]. If chromosomal abnormalities of the parents are inherited by the embryo, this becomes a significant risk factor of abortion. Chromosomal anomalies are associated with mother's age, developmental rates, and embryo morphology. One of the main reasons of recurrent miscarriages is translocation of the chromosome in either partner. This is because couples with aberrant embryonic karyotypes have a worse prognosis for a subsequent pregnancy than couples with normal chromosome karyotypes [8]. Chromosome analysis is the first line of diagnosis for a couple who report loss of pregnancy as mentioned earlier. A molar pregnancy is an aberrant pregnancy in which the placenta villi proliferate and exhibit hydropic degeneration, while the embryo does not develop or develops improperly. The molar chromosomes in complete hydatidiform moles (Androgenic moles) are exclusively of the paternal origin, and they often have a 46XX karyotype. Molar pregnancy in the subsequent gestation is uncommon; with sporadic partial or total hydatidiform moles of androgenic origin and its likelihood is about 1% [9]. A hydatiform mole (also known as a molar pregnancy) is a gestational trophoblastic disease (GTD), which originates from the placenta and can metastasize. It is unique in that the tumor originates from gestational tissue rather than from maternal tissue. Hydatiform moles (HM) are categorized as complete and partial and are usually considered the non-invasive form of gestational trophoblastic disease. While hydatiform moles are typically deemed benign, they are premalignant and do have the potential to become malignant and invasive. This activity describes the pathophysiology, evaluation, and management of hydatiform moles and highlights the role of the interprofessional team in the management of affected patients.

Foetal demise in utero refers to the loss of a foetus at any stage. It can also result from genetic abnormalities. Foetal death is defined by the National Centre for Health Statistics as any death that occurs before a human conception is fully expelled from the mother, regardless of the length of pregnancy, and that is not an induced termination of pregnancy [10]. In addition, there are several other factors that are equally responsible for the loss of pregnancy (Fig. 2). Besides aberrant chromosomes, the other factor is hormonal imbalance. During the course of pregnancy, the hormonal imbalance becomes cause of concern leading to fatigue, weight loss, anxiety, irritability, and mood swings. These complications result in severe diabetes, premature birth, miscarriage, low birth weight of the child, affecting mother's health and her psyche. The details of hormonal imbalance have been given in the forthcoming pages. Physical activities and exercise are helpful both for men and women. However, women who are pregnant need to remain physically more active. Moderate exercise therefore is not only beneficial for mother but also for growing foetus in the womb. Yet another contributory factor could be abnormal reproductive organs. In such a situation, medical intervention is warranted. Similarly, we all remain under immune surveillance all the time which is also true for a pregnant female. If a female is suffering from immunological disorders, her pregnancy may be at risk or severely affected. This again calls for through check-up and medical intervention by an immunologist. Our lifestyle contributes to our overall well-being. A healthy lifestyle means a healthy and robust physique and pleasant disposition. However, an unhealthy one will severely affect the health making us prone to a large number of diseases. Thus, an unhealthy lifestyle is the mother of all comorbidity. Use of alcohol, tobacco and other such substances affect our mind and body in a big way. Our body and digestive systems have not been designed to process chemicals and carcinogens. All such substances may

be avoided. Notwithstanding these unhealthy habits that we adopt gullibly, we face other enormous challenges routinely in our life. One such challenge is the presence of Microplastics in almost everything in our life including our own body.

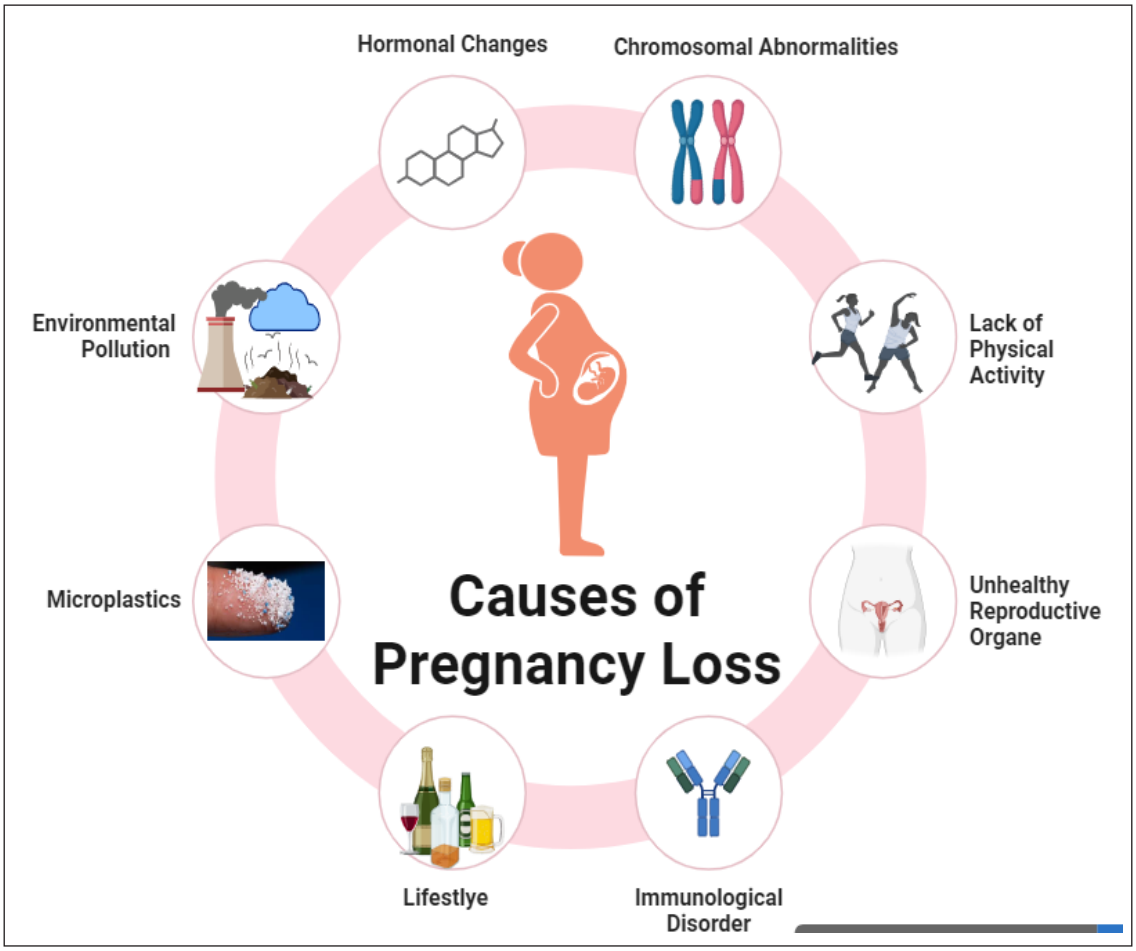

Fig. 2

Fig. 2 shows there are different factors that may lead to the loss of pregnancy individually or collectively.

V. Microplastics and Its Impact on Pregnancy

When bigger plastic goods break down, Microplastics (MP) are formed. Microplastics are ubiquitous in the natural world, occurring in significant amounts in rivers, seas, groundwater, soil and sediment habitats, sewage systems, and even the air we breathe. The majority of plastics now in use are very resistant to biodegradation [11]. They can, however, be broken down into micro and nanoscale plastics by mechanical and photochemical processes. MPs are the most extensively researched plastic particles in relation to female reproductive toxicity in mammals. Majority of studies examining the influence of MPs have been conducted on male reproduction. Oral exposure to Microplastic (MPs) causes these particles to accumulate in uterine tissue and several ovarian compartments, including increasing follicles [12]. The exposed animals' ovaries showed altered follicular dynamics, including a decrease in the number of developing and mature follicles and an increase in atretic and cystic follicles. They also showed decreased weight and cytoskeletal protein expression. Simultaneously, there are discernible modifications in the signalling of reproductive hormones. This was shown by a decrease in the levels of anti-mullerian hormone (AMH) and estradiol (E2) in the bloodstream and an increase in the levels of testosterone, follicle stimulating hormone (FSH), and LH [13].

The mice that were exposed to MP show detectable alterations in the length of the oestrous cycle, a loss in ovarian reserve, a drop in the rates of embryo implantation, and reduced litter sizes. An increasing body of research indicates that MPs build up inside the placenta have an impact on its healthy operation. This is crucial because the placenta perform all foetal-to-mother transactions all the time. First reported in 2020, the placental tissue of rats treated with MPs has since been replicated in several mouse investigations, with noted structural and functional implications [14]. Reduced glycogen-containing cells inside the placental endocrine-functioning junctional zone, smaller placentas, and poorly established feto-placental vasculature have been observed in exposed females [15].

Complications from immune cell imbalances in the uterus and placenta (e.g., decreased uterine natural killer cells, changed macrophage ratio) are probably the cause of the defective remodelling of the uterine spiral arteries. Transcriptome and metabolic investigations of placentas exposed to MP show disruptions in the metabolism of amino acids, glucose, and cholesterol [16]. In a recent study, human placental tissues from pregnancies that had normal or C-section delivery showed MP build-up [17]. This establishes that MP is floating around in the bodies of the foetus and pregnant female.

VI. Environmental Pollution and Fetal Development

It is commonly known that there is a connection between environmental contaminants and poor results for reproductive and developmental health. The consequences of environmental contaminants on developing foetuses during early life and at the maturity are the cause of serious concern. Prolonged exposure to pollutants can have long-term impacts on reproductive health affecting the pregnancy outcomes, lowering the immunity to illnesses, impacting children's mental development, and raising the risk of cancer [18]. Therefore, reduction to pollution exposures during early life is important before conception to avoid harmful effect to foetal development. Research has demonstrated that exposure to pollutants during the first 1,000 days of life may harm a child's development and health, leading to stunted growth besides causing harm to important organs like the brain, lungs, reproductive, and immune systems [19]. Exposure to environmental pollutants during pregnancy and fertilisation may have an effect on one's health in the future. Owing to environmental pollution, the most vulnerable times are during the pregnancy and infancy. Reduced chromosomal integrity, shorter telomere length, higher uterine vascular resistance, decreased foetal growth, preterm birth, and increased gestational diabetes all can be the consequences of the deposition of metal in the placenta. One of the most detrimental impacts of air pollution during pregnancy is placental vascularization [20]. The knowledge about the effects of pollution on human health has expanded significantly in recent years. Many studies have shown that exposure to pollutants during pregnancy is harmful for the development of the mother-foetus. This may even have a significant long-lasting impact on the pregnancy [21]. Environmental pollution includes common chemical pollutants encompassing pesticides and herbicides, volatile organics such as benzene, toluene, and chloroform; heavy metals such as lead, cadmium, mercury, and arsenic; air contaminants such as carbon monoxide, ozone, particulate matter, second-hand smoke and other persistent organic pollutants. This is by no means a complete list. Further, the quality and quantity of these pollutants are inconsistent in and around the environment. Thus, many of us may not be aware of this lurking danger in our vicinity. A foetus's vulnerability to environmental factors will not only affect the growth and development but also leave a lasting impact resulting even in debilitating diseases. Environmental pollution coupled with ignorance on the part of parents could be worst scenario. Thus, we not only have to address this issue but also enhance the overall awareness highlighting the nuances of environmental pollution [22].

VII. Telomere and Loss of Pregnancy

The nucleoprotein caps that shield the ends of uninemic chromosomes are called telomeres. The duplex tandem repeats TTAGGG, which end in a single stranded 30 nucleotides overhang, make up the telomeres of mammals. The specialised proteins known as the sheltering complex are tightly linked to this DNA sequence, that stop uncapped DNA ends from inducing senescence responses and DNA damage [23]. Thus, telomeres are essential for suppressing DNA damage signals and preserving the integrity of the eukaryotic genome. Cell cycle arrest and DNA repair reactions are triggered by critical telomere attrition levels, and they can cause cellular damage in and around themselves [24]. Moreover, it is established that elevated levels of oxidative guanine base adduct production are linked to placental stress [25]. Placental senescence is further exacerbated by a decrease in telomerase activity as human pregnancy goes on. Compared to term pregnancies, the placentas from normal early pregnancies have noticeably higher telomerase activity [26]. It may be noted that placental telomere length (TL) shortens throughout gestational period. The shortest telomeres at term are consistent with decreasing telomerase expression during human pregnancies [27]. Because telomeres were 25% longer in placenta than in cord blood from the same source.The first study comparing TL in placenta tissue with that in other tissues, such as cord blood, concluded that telomere shortening is unlikely to have a significant role in senescence or terminal maturation of the placenta [28]. It has been discovered that term placentas (37-42 weeks) have longer telomeres than other human tissues at birth [29]. Therefore, in healthy term pregnancies, telomere attrition is unlikely to cause labour. On the other hand, early placental ageing has been linked to a number of unfavourable pregnancy outcomes [29]. Pre-eclampsia, intrauterine growth restriction, gestational diabetes, and stillbirth have all been linked to altered placental organization TL [30]. Pregnancy loss is commonly described as a nonviable intrauterine pregnancy up to 20 weeks gestation. It is sometimes referred to as miscarriage or spontaneous abortion as mentioned earlier. The typical pregnancy loss is during the early stages, which happens in the first trimester. Patients and healthcare professionals may get frustrated and confused by the vague symptoms of vaginal bleeding and uterine cramps linked to pregnancy loss in cases of normal, ectopic, and molar pregnancies [31].

VIII. Role of the Human Y Chromosome in Pregnancy

Apart from skewed X chromosome inactivation in females, rampant microdeletions of Y chromosome linked genes equally

contributes to miscarriage and recurrent pregnancy loss (RPL) [32]. Genes involved in testis formation, adult spermatogenesis start and maintenance are found on the human Y chromosome [33]. Due to its abundance of ampliconic and palindromic sequences, the long arm of the Y chromosome (Yq) is prone to intra-chromosomal deletions because it self-recombines during spermatogenesis. Male infertility is caused by copy number variation of the Y chromosomal genes often due to deletions [34]. At least 180 million years ago, autosomes gave rise to the mammalian sex chromosomes. Acquiring the gene that determines the testis was the initial step in the Y chromosome's differentiation, which was then, followed by extensive inversions and a progressive suppression of recombination between the X and Y chromosomes [35].

One of the two sex chromosomes in humans is the Y chromosome (the other is the X chromosome). One of the 23 pairs of human chromosomes in each cell is made up of the sex chromosomes. The Y chromosome makes up to over 2 percent of the entire DNA in cells and spans more than 65 million DNA base pairs. Every human cell typically contains one pair of sex chromosomes [36]. Males have one X and one Y chromosomes, while females have two X chromosomes. Genetic research is currently focused on identifying the genes located on each chromosome. The estimated number of genes varies because of the different methods that are used by researchers to estimate the number of genes on each chromosome. However, it is largely believed that human have 20,000-22,000 genes and each gene has two copies barring a few ones located on the Y chromosomes.

It is estimated that between 70 and 200 genes are located on the Y chromosome and give instructions on how to make proteins [37]. The Y chromosome is unique to males, and as such, the genes on it are typically involved in the development and determination of male sex. The SRY gene, which causes a foetus to develop into a male, determines a person's sex as it encodes DNA binding protein known as testis-determining factor (TDF). The ability for males to father biological children is dependent on other genes located on the Y chromosome. Microdeletions in the Azoospermia Factor (AZF) region of chromosome result in abnormal spermatogenesis and lack of sperm cells. Several genes are found in the pseudo autosomal regions (PAR) of the Y chromosome that include PAR1 and PAR2. PAR1 has a total of 16 genes (PLCXD1, GTPBP6, PPP2R3B, SHOX, CRLF2, CSF2RA, IL3RA, SLC25A6, ASMTL, P2RY8, AKAP17A, ASMT, DHRSX, ZBED1, CD99, XG) whereas PAR2 has only 5 genes (VAMP7, IL9R, HSPRY3, SYBL1, and CXYorf1). Men and women therefore possess two functional copies of these genes. For normal development, these pseudo autosomal genes are required [38-39].

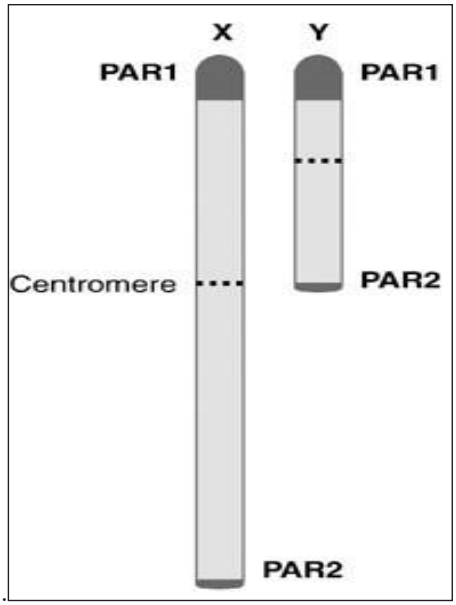

Fig. 3: Diagrammatic Illustration of Human Male Sex Chromosomes Showing Position of the PAR1 and PAR2 Regions

It may be noted that a total of 21 genes are located in the PAR1 and PAR2 of the sex chromosome. However, it is not clear if any or all the genes are involved in the RPL. Thus, more work on this line is warranted to gain an insight into this inauspicious phenomenon of the loss of pregnancy [40]. Lifestyle variables might also contribute in microdeletion of Y chromosome. Higher concentration of nicotine affects the percentage of viable spermatozoa and accelerates DNA fragmentation/ apoptosis. Abnormally high alcohol intake also highly linked to azoospermia [41]. These are a few examples related to unhealthy lifestyle and their consequences.

IX. Hormonal Imbalance

Hormones are essential during pregnancy because they control several bodily processes that promote a healthy and normal growth of the foetus. Hormonal abnormalities, however, have the potential to upset this delicate balance causing miscarriage. Investigating the link between hormone imbalance and miscarriage is crucial. Human chorionic gonadotropin (hCG), progesterone, oestrogen, prolactin, and thyroid hormone are involved in this process. Hormonal imbalances may be caused by an overactive or underactive thyroid. If the uterine lining fails to form normally for implantation and the feeding of a fertilised egg, hormonal abnormalities may result in miscarriage. Increased prolactin levels may interfere with the uterine lining's during the growth.

Table I: Age-Related Risk of Miscarriages

Sr. No.	*Maternal Age (Years)*	*Miscarriage Risk (%)*
1.	12–19	13
2.	20–24	11
3.	25–29	12
4.	30–34	15
5.	35–39	25
6.	40–44	51
7.	≥45	93

Hormones are essential for conception, and age has a big impact on it. An advanced maternal age enhances the chances of miscarriage. Table I shows age wise of miscarriage risk. A woman's egg supply is limited at birth and decreases in both quantity and quality as she ages. Hormonal changes associated with ageing may have an impact on implantation and prenatal development. Substance misuse, smoking, and inadequate diet can all raise the chance of miscarriage [42]. Similarly, we must take into consideration that deprivation of sleep is not only unhealthy but it may affect pregnancy as well. Complete 8 hr sleep has such a wonderful effect on the body and mind that the entire repair is done during this period of time. In the absence of proper sleep, the cycle is disturbed and our circadian rhythm is altered. This is true for all of us including a pregnant female. Thus, women who don't get enough sleep during pregnancy may have higher risks of developing pregnancy complications including Preeclampsia, or high blood pressure.

One steroid hormone that is vital to reproduction is progesterone. The pregnancy hormone progesterone is crucial for the development of the uterine lining and the implantation of the embryo. Pregnancy loss may result if there are any ups and downs. Twenty to sixty percent of women with luteal phase insufficiency state that their habitual abortions are caused by insufficient progesterone secretion. This is released by the corpus luteum during the secretory phase of the menstrual cycle and early pregnancy. Progesterone levels below normal cause the endometrium to become undeveloped and remain unable to support implantation and embryo growth. A disruption in endometrial protein release may indicate endometrial dysfunction brought on by a progesterone shortage [43]. Progesterone is necessary for a successful embryonic implantation because it alters the mucous membrane of the uterus. Progesterone also improves uterine quiescence, inhibits uterine contractions, and controls the mother's immune response to prevent embryo rejection [44]. Headaches, mood swings, and irregular uterine flow can all be symptoms of low progesterone. It could result in miscarriage or spotting during pregnancy. It could potentially indicate an ectopic pregnancy. Hormone therapy or progesterone supplements are two possible treatment options. It is mostly produced in the ovaries each month after an ovulation which is essential to both the maintenance of pregnancy and the menstrual cycle. The menstrual cycle is regulated in part by progesterone. But preparing the uterus for pregnancy is its primary function. Progesterone assists in thickening the uterine lining each month after ovulation, preparing the uterus for implantation of blastocyst. Menstruation starts when progesterone levels fall and there is no fertilised egg [45]. Progesterone aids in maintaining the uterine lining during pregnancy if a fertilised egg implants in the uterine wall. In women who are not pregnant, low progesterone may result in irregular uterine bleeding. Period irregularities or nonexistence may be a sign of insufficient progesterone and malfunctioning ovaries. In the event of pregnancy, the uterus retains progesterone levels until the baby is born. The body will generate more progesterone, which is what causes nausea and breast tenderness, among other pregnant symptoms. A uterus might not be able to bring the pregnancy to term if progesterone levels are too low. Low progesterone during pregnancy might cause miscarriage and spotting. An ectopic pregnancy may be indicated by low progesterone. Foetal death or miscarriage may ensue from this condition [46].

The development of female sexual traits is attributed to the steroid hormone oestrogen, which is connected to the female reproductive organs. The mucous membrane lining the uterus, known as the endometrium, is likewise created and maintained by oestrogens. They raise the weight and size of the endometrium as well as its blood flow, protein content, and enzyme activity. Additionally, oestrogens cause the uterine muscles to grow and contract. These contractions are crucial for the wall's ability to shed dead tissue during menstruation, childbirth, and placenta delivery [47]. During pregnancy, the risk of miscarriage is increased by high levels of oestrogen. Unbalanced hormone levels cause the uterine environment to become unstable, which makes it harder for a pregnant woman to proceed successfully. Miscarriage risk is increased by low oestrogen levels. A woman whose oestrogen levels are below normal may find it difficult to get pregnant. Excessive levels of oestrogen have a detrimental effect on pregnancy, impairing implantation, trophoblast invasion, and endometrial and uterine blood flow receptivity. During the early stages of pregnancy, elevated oestrogen levels can raise the risk of miscarriage because hormonal imbalances can disrupt the stability of the uterine environment. Pregnancy causes a woman's body to create more oestrogen than she does throughout her lifetime. Elevated oestrogen promotes nutrition transfer, enhances blood vessel construction, and aids in the foetus's growth. During the third trimester of pregnancy, the high amount of oestrogen reaches its pinnacle. One may have nausea during the first trimester of pregnancy due to the sudden rise of the oestrogen. It aids in the growth of the milk duct during the second trimester, which causes the breasts to enlarge [48].

Table II: Hormones, Microplastics and Microbiome Involvement During and After Pregnancy

Sr. No.	*Hormones*	*During Pregnancy*	*After Pregnancy*	*Role of Polyester*	*Role of Microbiome*
1.	HUMAN CHORIONIC GONADOTROPHIN (hCG)	Produced by placenta during pregnancy.	Disappear entirely during the third week of postpartum.	Not known yet.	Not known yet.
2.	PROGESTERONE	Progesterone helps establish the placenta. It stimulates growth of blood vessels that supply the womb.	Decrease as soon as the baby and the placenta are delivered. Progesterone inhibits lactation during pregnancy.	It reduces the level of progesterone.	Increase the rate of Gastro-intestinal-tract.
3.	ESTROGEN	Oestrogen helps the uterus grow, maintains its lining, and helps foetal organs develop. Activates and regulates production of other hormones.	Decrease as soon as the baby and the placenta are delivered.	It reduces the level of estrogen.	Increase the rate of Gastro-intestinal-tract.
4.	OXYTOCIN	Oxytocin levels rise at the start of labour, stimulating contractions of uterine muscle.	Surges immediately following birth to compensate for the initial drops in progesterone and estrogen.	Not known yet.	Not known yet.
5.	PROLACTIN	Prolactin is the main hormone needed to produce breast milk. It contributes to enlargement of the mammary glands and prepares them for milk production.	Increases to encourage milk production.	Not known yet.	Not known yet.
6.	RELAXIN	Relaxin inhibits uterus contraction to prevent premature birth.	The level of relaxin in your body drops after birth but remains at a decreased level for several months.	Not known yet.	Not known yet.
7.	MELATONIN	Maintain foetus's circadian rhythms and foetal growth & development. Support the development of the foetus's nervous system and brain etc.	Regulate postpartum sleep-wake cycles.	Not known yet.	Not known yet.

During pregnancy, various hormones play crucial roles in supporting foetal development, preparing the mother's body for childbirth, and maintaining a healthy pregnancy. After pregnancy, various hormones continue to play important roles in the postpartum period, supporting physical recovery, breast feeding, and emotional well-being. Besides involvement of several hormones and their careful regulation for the sustenance of normal pregnancy, microbiome and Microplastics are implicated. Although not much data is available on the involvement of Microplastics and their ill effects on the pregnancy but the microbiomes are present in almost all the part of the human body. This is an area that warrants serious research to rule out the possibility of the involvement of Microplastics and microbiome in normal and risky pregnancies.

X. Immunological Disorder

Lupus, rheumatoid arthritis, and Hashimoto's thyroiditis are among the illnesses that might make the immune system targets the foetus resulting in miscarriage. Immunological illnesses such as thrombophilia, antiphospholipid syndrome, cytokine imbalance, defective natural killer cells, and immunogenic

variables can all play a role in miscarriages. Many reproductive failures during ovulation, fertilisation, implantation, and pregnancy are frequently linked to adverse immunological responses. For instance, women with subclinical ovarian failure, premature ovarian failure, or infertile circumstances have shown autoantibodies against ovarian steroid-producing cells, lymphoplasmacellular infiltrate surrounding steroid-producing cells in the ovary, and elevated concentrations of the complement breakdown product C3a and terminal complement complexes [49]. Today, there is universal acceptance of the autoimmune involvement for recurrent abortions, which frequently occur in the second trimester of pregnancy. This is due to the existence of anti-phospholipid primary syndromes associated with recurrent abortions related to vein thrombosis, coupled with laboratory evidence of anti-phospholipid antibodies that persist in peripheral blood [50].

XI. Future Direction

Repeated abortions, also known as RPL can be caused by a combination of genetic, hormonal, anatomical, immunological, and lifestyle factors. Although the following list seems to be adequate but each sub-topic is full of nuances that one needs to study in details.

- Chromosomal abnormalities may be of several types. However, if in single chromosome, some sequences are deleted or inserted, that may not appear at the chromosome level. Thus, this needs very different level of expertise to address such issue. Chromosomal abnormalities also include copy number of the genes and reshuffling of exon and intron. This is how a new gene is born. However, copy number variation (CNV) may also be uncovered. Nonetheless, chromosomal analysis will still be required. This is because CNV of a gene may not be reflected at the chromosome level.
- Hormonal imbalances (e.g., thyroid disorders, polycystic ovary syndrome) implicate several hormones. It is important to pin point which one (single) or what all (multiple ones) that are related to the loss of pregnancy. This clearly warrants more study by endocrinologist. Better still if these endocrinologist work in a team of clinicians, geneticist, environmentalist, toxicologist, gynecologist and immunologist.
- Uterine anomalies (e.g., septate uterus, fibroids). How often this condition alone is responsible for the loss of pregnancy is worth pursuing either as an individual or as a member of a team to address the issue.
- Immunological factors (e.g., autoimmune disorders, blood clotting disorders). This aspect of work needs an immunologist or Immunogeneticist to ensure if the immune system is normal.
- Infection in any condition to anyone is bad. However, it is worse in case of pregnancy. Infection could be simple listeriosis, toxoplasmosis or due to the presence of heavy metals. The early diagnosis will go a long way to find a remedial measure.
- Advanced maternal age is much too obvious and this can easily be avoided not for the sake of eugenics but for the child health.
- Male factor infertility (e.g., low sperm count, poor sperm quality). About 30 years ago, male infertility used to be about 10%. Now it has reached to about 20%. The overall sperm count has slide down to 15-20 million sperms per ejaculate. Thus, the quality and quantity both have suffered a great deal. This can be ameliorated if diagnosed properly on time.
- Uncontrolled diabetes is much too common in the society world over. There are some very sensitive people who care for their diabetes and ensure that the same stays within the limit. Routine exercise, a disciplined life, nutritious and balanced food are some of the tried and tested mantra of life.
- Thyroid disease is equally common but the same can be treated if diagnosed early.
- Environmental toxins (e.g., lead mercury). Such toxins are generally contributed by the polluted environment. Thus, precaution and timely measure may ameliorate this condition. Further, with concerted efforts, environmental pollution may be arrested or minimized.
- Lifestyle factors (e.g., smoking, excessive alcohol consumption, sleep deprivation). Despite statutory warning on such products, these are still consumed and the result is bad because the effect is irreversible. However, with genetic counseling, disciplined life and deep sense of determination, one can come out of this situation.
- Psychological stress is much too common these days. It could be because of job related or due to social setup or interpersonal relationship. This issue too can be addressed by genetic counseling.
- Vitamin deficiencies (e.g., vitamin D, folate) are all too well known. Timely test of vitamin D and supplementation of the same may ameliorate the situation.
- Human health is the biggest blessing. However, a person may suffer from a single diseases or comorbidity. In both the condition, reproductive potential of a person is affected. In order to keep fit and fine, one must resort of healthy practices and disciplined life coupled with timely intake of nutritious food. Health is not only wealth but more than that and must be taken seriously.
- Certain medical conditions (e.g., antiphospholipid syndrome, lupus) surely need medical intervention. Thus, for the maintenance of reproductive potential, one must have good health.

- Finally, if loss of pregnancy occurs, one should approach a genetic counselor. This will lessen the suffering and pain besides providing much needed solace. The genetic counselor is expected to be knowledgeable professional, aware of the family background of the affected mother and must be a medical expert. He should not only understand the nuances of pregnancy, but also its sustenance and the medical reasons for the loss.

XII. Conclusion

Notwithstanding our enhanced understanding on pregnancy, its loss could still take place. This is because any damage done at the genetic level cannot easily be fixed. It's important to note that in many cases, the cause of repeated abortions may remain unknown even after thorough medical evaluation. If one is experiencing recurrent pregnancy loss, it's essential to consult a healthcare provider or a fertility specialist to determine the underlying cause and take appropriate treatment.

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