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Review Paper

Recurrent Miscarriage

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Abstract

Recurrent miscarriage is defined as the spontaneous loss of two or more successive pregnancies before twenty weeks of gestation. Miscarriages are one of the most familiar complications of human conceptions. Frequency of pregnancy loss in all the clinically recognized pregnancies is approximately 15% in the general population. The risk of recurrent miscarriage is maximum among couples where the maternal age is 35 years or more and paternal age more than 40 years. In this paper, literature on infection, anatomic uterine defects, Hormonal and metabolic disorders, Nutritional factor, Immunological causes, Genetic factors and other risk factors of recurrent miscarriage are reviewed.

Keywords: Recurrent miscarriage, infertility, pregnancy.

Introduction

Reproductive health is a state of complete mental, physical, and social well being which is related to the all stages of reproductive processes[1]. Pregnancy is a complex biological process where after conception a fetus formed as an embryo from a single cell. Pregnancy is a unique immunological challenge where the semi-allergenic fetus survives by escaping maternal immune recognition. Baby will be delivered after the completion of gestational period. The gestation period is typically divided into three trimesters of roughly three months each. Chromosomal instabilities and genetic changes are associated with pregnancy loss. Fetus inherits one half of the chromosomes from the mother and father. A pregnancy loss occurs due to error during the transmission process also during the division of the chromosomes.

Today more and more women decide to delay motherhood because of changes in marriage patterns and now a day's women's at the age of maximum productiveness are more career-orientated. Also there are lots of competition and carrier opportunities, changes in contraception use, social support, and possibly with other factors (e.g. stress, pollutants, and smoking) which are responsible for the increase in miscarriage rate. This trend has been observed in the worldwide and across all groups in the population. The rate of spontaneous miscarraiges increases after the age of 30-35 years as a result of declined potential fertility[2].

Pregnancy loss is a condition with an uncontrolled decrease of reproduction and increasing medical problem similarly in both male and female partners. The existence of some risk factors only in one partner not necessarily connected with infertility of the couple. Couples fertility is reduced when some risk factors are present in both the partners.

Miscarriages are the most common complications of pregnancy. The term miscarriage also known as abortion is used to describe a pregnancy that fails to growth, resulting in demise and removal of embryo or fetus. Approximately 15% of all clinically recognized pregnancies are spontaneously aborted[3]. It is estimated that more pregnancies are lost unpredictably than are in fact carried to term[4]. The exact rate of recurrence is unknown as the miscarriages occurs before the women is aware of her conception. Most of the pregnancy losses are sporadic and non-recurrent, and are frequently caused by chromosome aberrations in the fetus[5].

Recurrent miscarriage was initially defined as the loss of three or more clinically documented conceptions unexpectedly during early gestation. However, the modern definition refers to the spontaneous loss of two or more consecutive pregnancies before twenty weeks of gestation[6]. The World Health Organization (WHO) has defined miscarriage as the loss of a fetus weighing ≤ 500g, which would normally be at 20-22 complete weeks of gestation[1].

Recurrent miscarriage can occur at any stage of pregnancy, it could be early or late pregnancy period. During the first trimester of pregnancy if there is loss of embryo then it is called as early pregnancy loss. If there is loss of fetus after first trimester of pregnancy it is called as late pregnancy loss. A frequency of late pregnancy losses is less as compare to early losses and consist of only 1% of pregnancies[7]. Late pregnancy losses are usually associated with incompetent cervix, premature rupture of membranes, intrauterine growth retardation, preterm labor, or placental abruption. Even if most of the pregnancy losses are random and not repetitive, there is a subset of couples who suffers from the recurrent miscarriage problem.

Causes of pregnancy loss comprises a broad range of both physical factors as well as emotional factors. A couple's unproductiveness may be due to either male factor or female factors, or may be due to both of them. The genetic basis of pregnancy loss is varying and includes chromosomal abnormalities, gene mutations and multifactorial causes.

Recurrent miscarraiges in some couples certifies that some womens are at a risk of having pregnancy loss and there must be specific reaso for this. In general not much work has been carried out to find out the reason for miscarriage. Even after new medical testings and innovative treatments that many couples undergo, the exact reason for pregnancy loss is still unclear.

Etiological factors for Recurrent miscarriage

Recurrent miscarriage has been recognized to various factors concerned with human reproduction. The etiology of recurrent miscarriage is heterogeneous and involves relationship between maternal, paternal and cumulative (placental/fetal) risk factors in pathways related to pregnancy establishment and maintenance.

The recognized etiological factors that might result in recurrent miscarriage fall into two broad categories. First category is alterations in maternal environment in which the fetus grows which includes infection, anatomic, endocrine, genetic and immunological abnormalities. The second category is embryonic defects like chromosomal abnormality which inhibit the development of embryo.

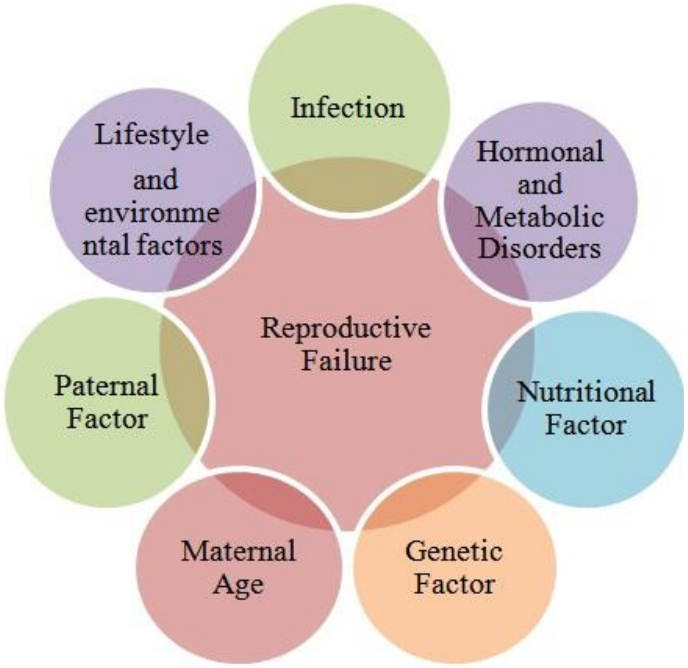

Figure-1
Factors involved in reproductive failure

Alterations in the Maternal Environment

Disorders in various metabolic pathways, hormonal imbalances, nutritional deficiencies, autoimmune disorders, endocrine anomalies, and anatomic defects are the alterations in maternal environment where the fetus grows after implantation. The problems involved are thus classified under the broad categories such as infection, anatomic uterine defects, Hormonal and metabolic disorders, Nutritional factor, Immunological causes.

Infection: TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus and herpes simplex virus) are known to cause sporadic spontaneous pregnancy loss. These infection causing organisms produce toxic metabolic by products. Pregnancy loss due to infectious agents includes direct infection of the uterus, fetus, or placenta, placental insufficiency, chronic endometritis. But there is a limited role for these infections as a main factor for recurrent miscarriage. Further above mentioned types of infections may lead to death of fetus or malformations incompatible with fetal viability[8].

Possible factors that play an important function in the risk of pregnancy loss caused due to infection are either due to: Exposure to infectious organisms like *Toxoplasma gondii*, *Rubella*, *Chlamydia trachomatis* and *Cytomegalo virus* during early gestation period. Abnormal immmunoglobin titre. Chemotherapy or acquired immune deficiency syndrome (AIDS).

It has been reported that bacterial vaginosis in the first trimester of pregnancy has been reported as a causative factor for second-trimester miscarriage or preterm delivery[9]. The role of various infectious agents in recurrent miscarriage is less clear. The most evident risk condition for recurrent miscarriage is exposure to microbes which are responsible to cause infection to placenta. Hence it is recommended to screen all the pregnant women's for infection also to increase the awareness of possibilities of infection born pregnancy loss.

Anatomic uterine defects: The common cause of obstetric complication during pregnancy is anatomical defects of the reproductive system. The most common uterine abnormality found in women with pregnancy loss includes septate, bicornuate uterus. Uterine abnormalities could result in impaired vascularization of pregnancy and limited space for the growing fetus due to distortion of the uterine cavity. As the pregnancy grows to term, a fetus needs more space but the irregular shaped uterus may not be able to enlarge or the weak cervix may start to open up and results in pregnancy loss[10]. Effective treatment for anatomic uterine defects includes corrective surgery on uterus or cervical surgery for making the cervix capable for holding the fetus.

The incidence of malformations related to uterine defects appears to be on higher side in women with late miscarriage compared to women with early miscarriage. But this

comparison further linked to cervical weakness which is related to uterine malformations[9].

Hormonal and metabolic disorders: Endocrine disorders play a major role in approximately 8% to 12% of recurrent pregnancy loss (RPL)[11]. A range of endocrinological events that appears in pregnancy maintenance will finally helps in the successful pregnancy with proper growth and development of endometrium of the fetus.

Progesterone plays important role in early pregnancy phase as it creates a suitable environment for the embryo during implantation period by triggering morphological and physiological changes in the endometrium. Luteal phase deficiency (LPD) was originally thought to derive from inadequate production of progesterone by the corpus luteum and subsequent inadequate endometrial maturation to allow proper placentation. In addition, thyroid gland dysfunction, Diabetes mellitus, polycystic ovary syndrome have also been associated with the risk of frequent pregnancy loss[11].

Pregnant women with untreated excess hyperthyroidism are at risk of having pregnancy loss, fetal heart failure, preterm delivery, fetal growth retardation.

Patients suffering from Diabetes mellitus are at a highest risk of spontaneous abortion, preterm labor and hypertensive disorders. Congenital anomalies are directly related to glycaemic control in the first trimester. At high concentration glucose is teratogenic in nature.

According to the Royal College of Obstetricians and Gynecologists (RCOG) Green-top Guideline No. 17, a risk of first trimester miscarriage and fetal malformations in higher in women's with diabetes mellitus as a result of high level of glycosylated hemoglobin A1c (HbA1c) [9,12].

Luteinizing hormone (LH) hyper secretion which is a frequent feature of polycystic ovarian syndrome (PCOS) has been reported as a causative factor for recurrent miscarriage [9].

Nutritional factor: Eating a healthy and different diet may be a key part of maintaining good health. However, there are certain vitamins and food groups that have a greater impact on reproductive health. Increased intake of iron and multivitamins are healthier for women's. The lack of vitamin A is a reason of increased infant death. Deficiency in folate concentration results in elevation of homocysteine level in blood. The maternal homocysteine level is linked with increased rate of miscarriage and the pregnancy complications such as placental abruption, preeclampsia, decreased birth weight and duration of gestation[8]. Also fetal growth retardation is caused by folate deficiency.

Immunological causes: Immune system of pregnant women recognizes the paternal gene products and antigens which are displayed by conceptus as a foreign material and shows an immune response against the foreign material. Fate of the semiallogenic fetus is reliant on inhibition of the immune response of pregnant women against the foreign material and pregnancy loss may be a result of this suppression failure.

Autoimmune and alloimmune factors are the immune factors associated with recurrent miscarriage. These factors are involved in the synthesis of anti-phospholipid antibodies, anti nuclear antibodies and anti thyroid antibodies.

Anti-phospholipid antibodies affects the blood clotting mechanism and forms blood clots in the placenta which results in the obstruction of blood supply to the fetus. It also responsible for the slow growth of fetus or the fetus will die due to inappropriate blood supply. Maternal blood can be checked for anticardiolipin antibodies or lupus anticoagulant. In cases with high levels a treatment with aspirin or heparin will help to make the blood thinner. About 10-15% miscarriages results due to the problems with the antibody levels. Antinuclear antibodies are auto-antibodies to the DNA which lead to inflammation in the placenta[13].

Alloimmune traits, such as abnormal maternal immune response to antigens of placental or fetal tissues, have been implicated in otherwise unexplained recurrent pregnancy loss. One such response is human leukocyte antigen (HLA) sharing, which impairs the mother's ability to block antibodies. However, studies to date have proved no association between recurrent pregnancy loss and HLA.

Embryonal defects

In most healthy pregnancies, implantation usually occurs after 8-10 days of fertilization. Delay in implantation enhances the percentage of early embryo loss. Chromosomal abnormalities in the conceptus are distinctive factor of spontaneous abortions. Chromosomal abnormalities were responsible in about 50% of first trimester miscarriages, 5% of late pregnancy losses and 0.5% of live births[14]. Cytogenetically abnormal conceptus are usually aneuploidy caused due to meiotic non-disjunction, or polyploidy caused due to abnormalities occurred during fertilization.

Genetic factors: Most women with a history of recurrent abortion receive care from a gynecologist, who may have detected gynecological causes and excluded most serious maternal disorders[15]. Chromosomal rearrangements may not only be lethal to the developing embryo or fetus, but may also cause significant congenital anomalies and mental retardation in an infant, if the pregnancy continues to term. The risk of carrier status is calculated based on the maternal age at second miscarriage, a history of previous miscarriages in self or in a brother or sister of either partner or in the parents of either partner[16].

In couples with bad obstetric history (BOH) percentages of

chromosomal abnormalities vary from 1 to 25% for individuals or to 50% for couples[17].Trisomy is the most common cytogenetic abnormality followed by polyploidy and monosomy X with the incidence of about 50% to 60% in recurrent miscarriages[14].

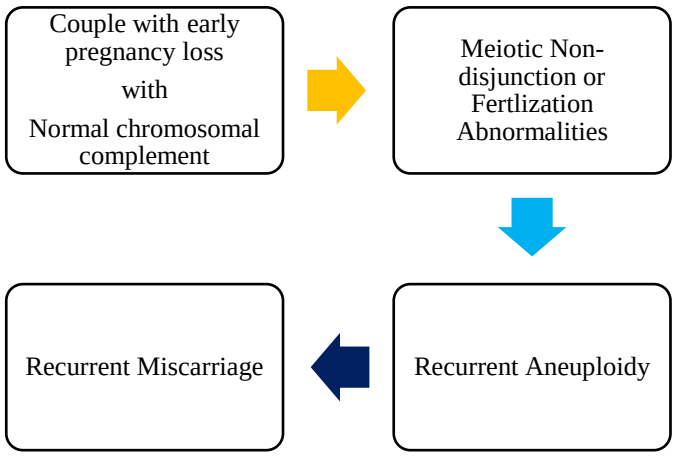

Figure-2
Pathway for repeated pregnancy loss

Balanced reciprocal or Robertsonian translocations are the most common parental chromosomal abnormalities[18]. These translocations may frequently produce an unbalanced gamete which results in the recurrent miscarriage. The frequency of recurrent miscarriage in any one partner of couple with balanced structural chromosomal abnormality is estimated to be about 3-5%.

Other risk factors

Maternal Age: Advanced maternal age is an important factor responsible for recurrent miscarriage. About 10% of clinically recognized conception lost during the pregnancy[19]. Several studies have concluded that the major negative effects are previous pregnancy losses and mother's age 35 years or more than 35 years[19,20,21]. Fetal chromosome abnormalities are the most common cause of recurrent miscarriage associated with continuously increasing age of women postponing childbearing to late 30s and early 40s in many countries. The number of good quality oocyte are less in older mothers as compared to younger mothers, which results in increased chromosomal abnormalities followed by miscarriage[13]. In women's with history of three or more pregnancy losses and no live issue, the risk of miscarriage in future pregnancy is increases to about 50%[14].

Recurrent miscarriages that occur in older age groups (maternal age of ≥35 years and paternal age of >40 years) are likely due to age-related chromosome abnormalities (non-disjunctions), mainly trisomy, rather than to structural translocation[22]. Although high maternal age is also a risk factor in recurrent miscarriage, other causes predominantly drive this disease as the chance of having an early pregnancy loss due to large chromosomal alterations is decreasing with an increasing number of miscarriages in a couple. Heffner 2004 showed correlation between the fertility and miscarriages as a function of maternal age where Heffner found that the frequency of pregnancy loss increases with increasing maternal age and the fertility decreases with increasing maternal age[23].

Paternal Factor: The study of recurrent miscarriage must always be done considering the couple, both male and female and interrelationship between them. Both male and female related causes may be genetic and non-genetic.

Chromosomal anomalies in the zygote are results due to the problems at the time of gametogenesis or during fertilization or during the first cellular divisions of the zygote formation. About 30-40% men in reproductive age group have quantitative or qualitative defects in sperm production[24]. The outcome of male infertility is reflected due to malfunction of spermatogenesis caused by pituitary problems, germ cell aplasia, varicocele and environmental factors, or congenital abnormalities caused due to defective sperm transport or immunological factors or by the production of genetically unbalanced gamete, which leads to loss of pregnancy through miscarriage.

Spontaneous abortion can also occurred due to improper spermatogenesis in male partner. Chromosomal aneuploidy is caused in a sperm when it undergoes meiosis. Increased age in males would be a factor responsible for sperm chromosomal aberrations, such as aneuploidy or DNA strand breaks. Most of the aneuploidy embryos die in-utero and hence chromosomal aneuploidy is the leading cause of failed pregnancy. Increase in paternally inherited genetic mutation in the embryo increases with advanced paternal age as there is continuous replication of male stem cells after puberty[25,26].

A study by Sartorelli et al., 2001 compared men aged 23-39 years with men aged 59-74 years and found a increased incidence rate of sperm chromosome abnormalities in older male[27]. Slotter et al., 2000 concludes that advanced paternal age is associated with a increased risk of having a child with chromosomal defects[28].

Many other studies have reported a positive correlation between increasing male age and DNA damage. Singh et al. 2003 found the percentage of highly damaged sperm DNA in age group 36–57 years was significantly higher compared to the age group 20–35 years[29]. In another study by Spano et al., 2000 who studied 215 couples and found that the sperm DNA damage doubled from paternal age of 25 to 55 years[30].

Environmental factors: Stress affects a great number of biological systems, including the reproductive system. Cultural, occupational, and many other behavioral differences can modify the stress response which subsequently changes the reproductive function.

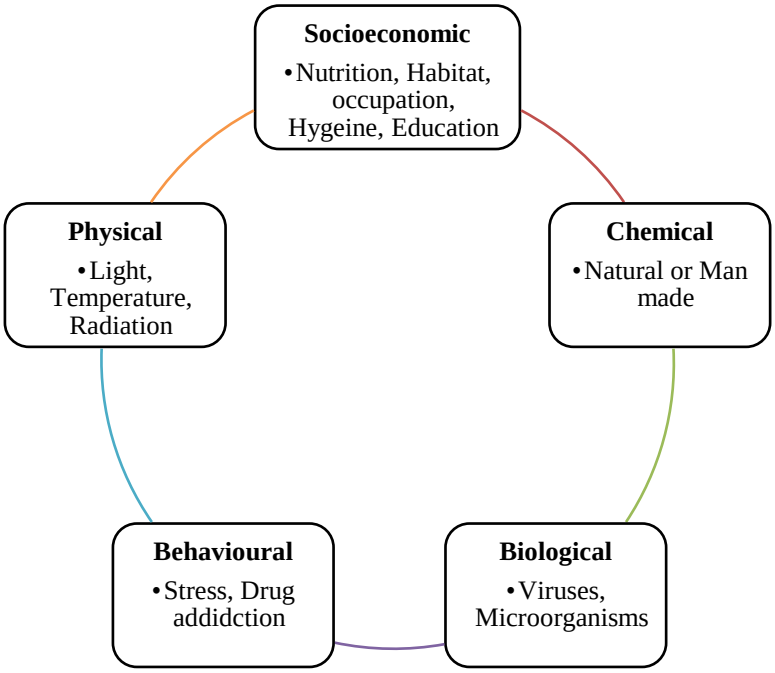

Figure-3
Categories of Environmental factors

Lifestyle and environmental factors is a very sensitive but also complicated issue. Heavy metals (such as lead and mercury), organic solvents, alcohol, and ionizing radiation are confirmed environmental teratogens, and exposure could contribute to pregnancy loss. Caffeine, cigarette smoking, and hyperthermia are suspected teratogens, and the teratogenic impact of pesticides remains unknown. As is everybody, pregnant women are exposed to many exogenous agents, some of which have been associated with the risk of fetal loss.

Unknown Conditions: Sometimes a pregnancy ends unhappily, but it is not technically a miscarriage. Below are the types of situations.

Blighted ovum is a condition where the gestational sac grows without fetal development. The gestational sac will continue to grow and will be noticed only after ultrasound is done. Blighted ovum is caused due to the defect in the fertilization process. During fertilization, instead of creating sac as well as embryo only sac develops.

Ectopic pregnancy is a condition where the implantation of fertilized egg takes place in fallopian tube or into the abdominal cavity. The risk of severe hemorrhage increases in ectopic pregnancy, it could also result in death of pregnant women. When the ectopic pregnancy is discovered, it is necessary to remove the fetus surgically.

Molar pregnancy is a very rare type of pregnancy where an abnormal mass forms inside the uterus after the egg is fertilized. It is a condition where after fertilization, an abnormal mass forms inside the uterus hence the uterus filled with a big cluster. This is caused when an empty egg fertilizes with a sperm or when two sperm fertilizes an egg and both the embryos grows a little as well as an abnormal placenta (called a partial molar). If the embryo grows, it cannot survive for more than three months. Once diagnosed a molar pregnancies it should be removed by D and C.

Stillbirth is also known as intra uterine fetal demise (IUFD). It is a condition when a pregnancy ends after the 20th week. In some cases babies die in uterus or no heartbeat found are diagnosed only after ultrasound is done.

Conclusion

Chromosomal abnormalities are the most common cause of pregnancy loss in couples. Hence chromosomal analysis is an important tool for investigation of couples facing recurrent miscarriage problem which helps in management of such couples. Chromosomal studies provide valuable information for future pregnancy. In addition, the detection of the possible cause of pregnancy loss is usually very comforting for couples, as they usually suffer from depression, anxiety and self-blame for pregnancy loss.

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