REVIEW ARTICLE

RECURRENT MISCARRIAGE AND ASSOCIATED FACTORS

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ABSTRACT

The incidence of recurrent pregnancy loss in women of reproductive age group is 0.5%–3%, And idiopathic causes accounts for 50%–60% of recurrent pregnancy losses. Approximately 30%–50% of conceptions end in spontaneous miscarriage before the completion of first trimester. Miscarriages mostly occur at the time of implantation. The causes of recurrent pregnancy loss are many including parental chromosomal abnormalities, maternal thrombophilias, immunologic causes and endocrine disorders. Recurrent pregnancy loss is an extremely distressing clinical problem for women as well as health professinals. According to current studies the decidualized endometrium act as a biosensor of good quality embyos , if it is faulty ,may lead to implantation of embryos resulting in miscarriage. Other factors implicated in the pathophysiology of miscarriage are Systemic and placental oxidative stress. Vascular endothelial damage, abnormal vascularity of placenta and immunologic reactions have been proposed to play some role in causing recurrent miscarriage. The objective of this review is to discuss the causes of recurrent miscarriage, based on the published research articles.

KEY WORDS: Recurrent pregnancy loss, Immunology, Miscarriage.

INTRODUCTION

The incidence of clinically recognized miscarriage remains around 10-20%.[1]When there are 3 consecutive pregnancy losses before 20 weeks of gestation it is defined as recurrent miscarriage or habitual abortion. In Pakistan the estimated annual miscarriage rate is 29 in 1000 women between the ages of 15-49years and 89,000 women present with miscarriages annually.[2]

It has been estimated that 15% of all ultrasonically diagnosed pregnancies result in miscarriage[3]. In reproductive age group 1–2% women are affected by three or more pregnancy losses and 5% women experience two or more miscarriages.[3] When women with recurrent miscarriage are investigated, the cause of miscarriage unknown in most of the cases.[4]

Table.Maternal Age and Miscarriage Rates

Age in years	Miscarriage rates%
12-19 year	13%
20-24 year	11%
25-29 year	12%
30-34 year	15%
35-39 year	25%
40-44 year	51%
45 year and above	93%

An increase in miscarriage rate is noted with advancing maternal age. Miscarriage rates according to age are shown in table-[1,5] The number and quality of the oocytes become poor as the maternal age advances. Both obese and underweight women have increased risk of recurrent miscarriage.6

Etiologic factors associated with Recurrent miscarriage

Parental and fetal chromosomal defects [7,8],congenital uterine malformations[9], antiphospholipid syndrome[10], thrombophilias,[11] autoimmune disorders, diabetes mellitus ,thyroid disorders and polycystic ovarian syndrome are the factors associated with recurrent miscarriage .[12] To improve future live birth rates in couples with recurrent miscarriage their evaluation is very important.

GENETIC FACTORS

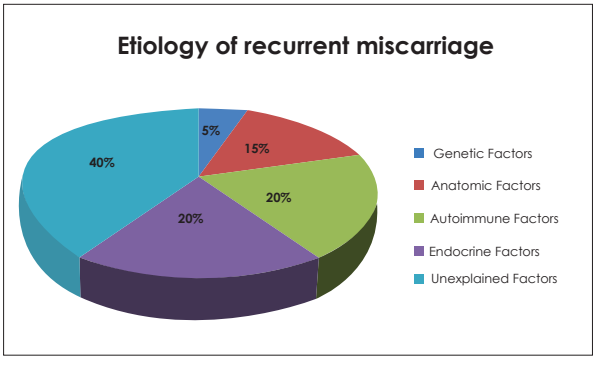

Figure1. The cause of recurrent miscarriage: Genetic factors 2%-5%, Anatomic factors 10%-15%, Autoimmune causes 20%, Endocrine factors for 17%-20% and Unexplained cause (including non APS Thrombophilias) accountsfor 40%-50%.

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Fetal Chromosomal Abnormality :
In elderly women the commonest cause of miscarriage, is chromosomal abnormalities, found in about 70% cases. The incidence reduces to 20% in gestational ages between 13 and 20 weeks. The commonly found defects commonly are trisomy, polyploidy or monosomy.[7]

Parental Chromosomal Abnormalities:
About 2% of recurrent pregnancy losses occur due to Parental chromosomal abnormalities, and most are balanced reciprocal translocations.[13] There is risk of unbalanced translocations in future conceptions in couples with balanced translocations. The risk of unbalanced translocation was only less than 1% in the offsprings. [14] A live birth rates of more than 70% were found in couples with recurrent miscarriage and balanced translocations in future conceptions.[14] Parental karyotype is an expensive investigation and its cost effectiveness has been questioned.[13]

ANATOMICAL DEFECTS
Congenital Uterine Malformations
The incidence of congenital uterine malformations is 6.7% in general population, like septate, bicornuate or arcuate uterus and it is estimated to be 16.7% in women with recurrent miscarriage.[9] Hysteroscopic surgery is recommended to correct uterine malformations.

Cervical Weakness
Cervical weakness is a causative factor in second- trimester miscarriage, can be diagnosed on history, resistance to dilatation by hegars and assessment of cervix by transvaginal ultrasound. Hazards of cervical cerclage are related to surgery and risk of uterine stimulation and preterm labour.[20]

Acquired Uterine Anomaly:
Asherman's syndrome and uterine fibroids are acquired conditions associated with recurrent miscarriage. Large submucous fibroids are associated with lower pregnancy rates and miscarriage.[15]

PROTHROMBOTIC FACTORS
Anti-Phospholipid Syndrome:
Antiphospholipid antibodies (APLs) are IgG, IgM and IgA antibodies which react against negatively charged phospholipids in the cells .They are linked with placental infarction and thrombosis leading to obstetric morbidities[16] .In Antiphospholipid syndrome (APS)there is production of anticardiolipin (ACL) antibodies and lupus anticoagulants and is linked with poor pregnancy outcomes. [17]

The incidence of APS is 15% in first trimester recurrent pregnancy loss, as well as a single second trimester miscarriage.[10,18] Treatment options like Low dose aspirin (LDA), heparin, prednisolone and intravenous immunoglobulin (IVIG) have been implicated but no improvement in pregnancy outcomes seen.There is increased risk of gestational diabetes and preterm delivery. Unfractionated heparin and LDA when used in combination, reduced pregnancy loss by 54%.[19] These treatments are recommended for women with APS and recurrent pregnancy loss.[20]

Thrombophilia
Thrombophilias including factor V Leiden mutation, activated protein C resistance, prothrombin gene G20210A mutation and protein S deficiency have been associated with recurrent pregnancy loss.[11] A complete thrombophilia screen can produce abnormal results in uncomplicated cases in about 20% of women.[21]Thromboprophylaxis by using LDA with or without low molecular weight heparin is recommended to prevent vascular thrombosis and placental infarcts.[22,23]

ENDOCRINOLOGICAL FACTORS
Endocrine diseases like polycystic ovarian syndrome (PCOS), Luteal phase defect (LPD), diabetes mellitus, thyroid disorders, and hyperprolactinemia, account for 17% to 20% of recurrent miscarriage. [24] LPD occurs due to decrease production of progesterone by the corpus luteum needed for conception. At least 40% of women with recurrent miscarriage have PCOS.[25] Hyperinsulinemia found in women with PCOS and insulin resistance may play a role in recurrent miscarriage. Metformin an insulin sensitising drug, decreases the spontaneous miscarriage rate.[26]

There is increased risk of spontaneous miscarriage in women with uncontrolled type 1 diabetes.[27] Untreated hypothyroidism is associated with recurrent miscarriage .2[8] and there is great debate about antithyroid antibodies and recurrent miscarriage in euthyroid women .[29,30] It is likely that women with antithyroid antibodies, become clinically hypothyroid after conception, who received fertility therapy.[31] Pregnancy outcomes may be improved by thyroid hormone replacement in these women.[32]

IMMUNOLOGICAL FACTORS
The fetus is allogeneicically dissimilar and Immunological mechanisms play a roll in the success of pregnancy .High miscarriage rates are associated when antithyroid antibodies are present.[12,33] Women with normal thyroid function tests but anti thyroid antibodies may benefit from treatment with thyroxine. [34]

Obesity:
Obesity is associated with pregnancy-related complications and miscarriage. A meta-analysis in 2008 showed considerably increased miscarriage rates when obese women with a body mass index (BMI) ≥25 kg/m2 are compared to women with a BMI <25 kg/m2 .[35] Obese women with BMI ≥30 kg/m2 showed increased risk of recurrent miscarriage. [36]

Oxidative stress and recurrent pregnancy loss:
This has been implicated that oxidative stress is an important cause of recurrent miscarriage. There is a relation between loss of antioxidant defences and recurrent miscarriage.[37] The level biochemical markers which induce membrane damage like lipid peroxidation products, reach high levels just before miscarriage. [38.] An oxidant/antioxidant imbalance is associated with Miscarriage .[39]

Unexplained Causes
When known and potential causes of recurrent miscarriage are investigated, no definite cause was found in more than 50% of cases. Progesterone supplementation has been found to benefit women with at least 3 losses in decreasing the miscarriage rate.[40] Women with unexplained pregnancy loss also benefit from LDA and its use before and during pregnancy in women with second trimester miscarriages has increased live birth rates.[41,42] Antenatal counselling and psychological support is the most effective therapy for unexplained loss of pregnancy and show future successful pregnancy rates upto.[43]

CONCLUSIONS

The diagnostic tests for recurrent pregnancy loss should include maternal and paternal karyotyping, assessment of uterine anomalies, thyroid function tests, APS, and thrombophilia screening .Some women require evaluation for insulin resistance, ovarian reserve , antithyroid antibodies, and prolactin levels . Treatment should be directed towards treatable causes. Psychological support and antenatal counselling and should be provided to all couples with recurrent miscarriage.

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