REVIEW ARTICLE

Recurrent Pregnancy Loss: A Tragic Reproductive Failure

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ABSTRACT

Three or more consecutive pregnancy losses are considered as recurrent pregnancy loss (RPL). About 1% of all pregnant women face this distressing problem and o.5% to 5% of spontaneous abortions are recurrent. Genetic, environmental, anatomic, hormonal, infectious and immunological factors are associated with RPL. Sometimes several factors might simultaneously be responsible for RPL. So diagnostic work up is to be extended. Life style changes, hormonal supplementation, anticoagulant and immunotherapy and surgical correction of certain uterine anatomic defects might help the couple to be parent. Genetic problem can be overcome by pre-implantation genetic diagnosis (PGD) and transferring good healthy embryos.

Key Words: Recurrent Pregnancy Loss (RPL), Pre Implantation Genetic Diagnosis (PGD)

Introduction

Recurrent pregnancy loss is (RPL) defined as three or more consecutive losses of pregnancy and this distressing problem affects approximately 1% of all women. Infertility and spontaneous abortion or miscarriage are two forms of reproductive failure. Infertility affects about 10% to 15% of couples. On the other hand the risk of abortion has been confirmed is about 15% to 20%. About 0.5% to 5% of spontaneous abortions are recurrent miscarriage[1,2]. There is some debate about the definition of RPL. Some feel that two rather than three losses are sufficient to define RPL. So in every day practice evaluation is usually initiated after the loss of two pregnancies specially if they have preceded by infertility treatment.

Aetiology of Recurrent pregnancy Loss

Genetic factors

Chromosomal abnormalities of the embryo are the most common cause of sporadic miscarriage. More than half of early losses occur as the result of chromosomal abnormalities[3-6]. Most abnormalities arise from errors in meiosis and advancing maternal age is associated with an increased risk of autosomal trisomy[7,8]. It occurs as a result of sporadic mutation and not inherited from the parents. This mutation and rate of aneuploidy increases with maternal age and may be as high as 50% to 80% for women who are older than 40 years[5,6]. In a few cases abnormality may be inherited and is responsible for about 2% to 4% of RPL. Although most frequent abnormality is balanced translocation (3% to 5%), microdeletion, Robertsonian translocations and structural chromosomal abnormality have also been detected. It can be of maternal and paternal origin.

Toxins and Environmental Factors

Heavy alcohol consumption has been reported to be associated with an increased risk of miscarriage [7,9], though other studies have not shown the same. Smoking has also been associated with RPL, which is positively related to the number of cigarette[3,4]. Caffeine and cocaine also have been linked to pregnancy loss[10]. Stress has also been shown to be associated with higher pregnancy loss rate[11]. Body weight both high and low are associated with adverse pregnancy outcome. The risk of pregnancy loss is high in women with certain chronic maternal diseases e.g. liver, renal and autoimmune diseases. Some medications such as nonsteroidal anti-inflammatory drugs and aspirin are linked to pregnancy loss[12]. Certain environmental effects like radiation and environmental toxin can also influence the outcome of pregnancy[13].

Uterine defects

Anatomic defects can be identified in about 3% to 5% of women with RPL[14,15]. Uterine cavity can be distorted by congenital and acquired defects. Some of these defects are associated with pregnancy loss, but others are not. Septate uterus is a frequent cause of loss where as arcuate uterus is associated with normal progression of a pregnancy. In septate uterus the embryo supposedly implants over the septum which is poorly vascularized leads to arrested development and early pregnancy failure. Both less nutrients due to reduced blood supply and reduced space available for the growing embryo is responsible for high loss rate.

Other abnormalities such as unicornuate or bicornuate uterus cause late second trimester loss and premature labour due to reduced volume of the uterine cavity[16]. Diethyle stilboestral (DES) exposure is associated with uterine and cervical hypoplasia causes second trimester pregnancy loss.

The most common acquired anomaly of the uterus is fibroids particularly beneath the endometrium. According to location fibroids are classified as submucus, intramural and subserous. Submucus fibroid located beneath the muscle layer, which deforms the cavity and endometrium covering them is usually thin and inadequate for normal implantation and responsible for RPL. Intramural fibroid when distort the cavity causes pregnancy loss. So, location, size, and number of the fibroids make a difference in this case. Larger and multiple fibroids are usually associated with adverse pregnancy outcome.

Benign hyperplasia of endometrium called endometrial polyp acts as foreign body within the endometrial cavity induce chronic inflammatory changes that makes endometrium unfavourable for pregnancy. Fibroid which protrudes into the cavity causes same as endometrial polyp. Intrauterine synachea may develop as a result of surgical procedure like curettage or severe endometrities interfere with normal implantation process and can be responsible for pregnancy loss[7].

Infections

The role of viral and bacterial infections in the pathogenesis of recurrent abortion is controversial. Maternal infections with TORCH, mycoplasma, Listeria can cause sporadic pregnancy loss but evidences that these organisms are associated with RPL are lacking.

Endocrine dysfunction

Hormonal problems can disrupt the implantation process and the development of early embryo[17]. Abnormal folliculogenesis due to effect of different hormonal abnormality leads to development of inadequate corpus luteum and luteal phase defect causing early abortions. Poorly controlled or uncontrolled diabetes mellitus do have an increased incidence of early pregnancy loss[18] but there is no evidence that well controlled diabetes mellitus is associated with increased risk of early pregnancy loss[19,20]. Similarly severe thyroid dysfunction is often cited as aetiological factor for recurrent pregnancy loss[21,22] but no direct evidence exists. It has been reported that the presence of thyroid autoantibodies is associated with an increased risk of miscarriage[23, 24].

Luteal phase defect

It is a common finding in patients of recurrent pregnancy loss. Inappropriate corpus luteal function causes decreased release of progesterone and inadequate endometrial preparation. Progesterone plays an important role during implantation and pregnancy. Progesterone is required to induce secretory changes that prepare the endometrium for the arriving embryo. Besides progesterone also has an immunomodulatory effect. It stimulates the production of progesterone induced blocking factor that suppresses natural killer cell activity and increases the Th-2 response. This suppressive effect favours implantation and the progress of early development[25]. Hyperprolactinemia has often been diagnosed among women with recurrent pregnancy loss. In these cases the luteal phase is shortened. Prolactin may interfere the normal activity of the developing placenta and therefore could affect the progress of pregnancy.

Hypersecretion of LH

There is now good evidence that polycystic ovarian syndrome (PCOS) is associated with both subfertility and early pregnancy loss[26-28]. The link between PCOS and early pregnancy loss would appear to be hypersecretion of luteinizing hormone (LH). The mechanism by which LH exerts an adverse effect is not clear. But it has been postulated that raised follicular phase LH may cause premature resumption of meiosis, has lead to

the concept of the production of physiologically aged oocyts[13,29]. LH may cause endometrial defect leading to suboptimal implantation and poor reproductive outcome. LH causes increased secretion of androgen from the ovary. Elevated androgen levels are associated with early pregnancy loss[30,31]. Hypersecretion of LH may therefore act both directly on the oocyte or on the endometrium or both and indirectly through increasing secretion of androgen.

Immunological causes

Autoimmune causes

It has been suggested that a necessary prerequisite for successful pregnancy involves maternal recognition of the embryo leading to protective immune response. The implanting embryo inherits its antigens from both mother and the father. The paternal antigens are identified as foreign by maternal immune system. In order to prevent the rejection of the pregnancy this immune response needs to be modulated. It has been proposed that in otherwise unexplained pregnancy loss dysregulation of the immune system could be responsible for the factor. Many cytokines that modify the immune response are produced during pregnancy. Some of then favor pregnancy like Th2,[11,3, 11,4, 11,5, 10-11, 11-13] and other are toxic to it like Th1, TNF alpha, TNF beta, gamma interferon, 11-2. A shift to Th1 dominance increases the risk for pregnancy loss. Th1 cytokines may directly damage the placenta and possibly activate immune cells that induce reaction[7,23]. Natural killer cells can be found in large numbers in the uterus. They are thought to alter the humoral response to pregnancy and induce the Th1 dominance that would lead to pregnancy loss[8].

Autoimmune disease

The association between raised circulating antiphospholipid antibodies (APAs) and recurrent pregnancy loss is now well established. The knowledge that some women with systemic lupus erythematosus have a poor reproductive outcome led to the discovery that the presence of circulating APAs is a marker for the poor outcome of pregnancy[32]. APAs are immunoglobulin that bind strongly to negatively charged membrane phospholipids. The most common antibodies are anticardiolipin antibodies and lupus anticoagulant though other types of APA exist. The primary antiphospholipid syndrome in which raised circulating APAs are found in association with recurrent pregnancy loss, arterial and venous thrombosis and thrombocytopenia in the absence of overt autoimmune disease is now well – documentated[33-35].

Haematological causes

Intensive angiogenesis,coagulation and fibrinolysis accompany implantation. Coagulation and fibrinolysis are simultaneously ongoing process in the body. A healthy balance is disrupted during pregnancy. Occlusion of the placental vessels may results, which could lead to spontaneous abortion.

Diagnosis

Several factors might simultaneously be responsible for the recurrent reproductive failure. So diagnostic work-up has to extended. Detailed history about previous pregnancy losses may yield important clues. The etiology differs in the first and second trimester. Thorough physical examination can reveal important factors. Height, weight need to be measured, signs of hyperandrogenism should be looked for and breast should be checked for the presence of galactorrhoea. The pelvic examination can identify congenital and acquired genital tract lesions like vaginal septum, duplicated cervix, uterine abnormality and adnexal masses.

Investigations

Imaging studies

Imaging studies play an important role in diagnostic work up. A transvaginal ultraso nography is usually the primary investigative tool for pelvic pathologies. It can evaluate size and position of the uterus, fibroids and adenomyoma of the uterus, duplicate cervix, uterine septum, unicrnuate and bicornuate uterus, endometrial polyps and scarring of the endometrium. Saline infusion into the cavity can improves the diagnostic accuracy of the ultrasound by creating a filling defect by polyps and fibroids in the uterus and lack of distension helps to diagnose the scarring due to Asherman's syndrome.

X-ray like hysterosalpingography (HSG) also can identify the filing defects, scarring and septum. Cervical canal length and competency can be identified by HSG. Funneling of cervical canal indicates cervical incompetency which causes 2nd trimester abortions.

Hysteroscopy offers a more precise evaluation of the cavity. During the procedure intracavitary structures can be directly visualized. Though hysteroscopy alone cannot differentiate between a septate and a bicornuate uterus. Laparoscopy is required to complete the evaluation. Laparoscopy allows to assess the outer surface of the uterus and other pelvic structures. Magnetic resonance imaging (MRI) is an accurate non-invasive technique for evaluation of uterine anomalies but expense limited its use. Intravenous pylography is recommended if congenital anomaly of uterus is diagnosed as congenital anomaly of the uterus is associated with urinary tract abnormality.

Laboratory Testing

Laboratory investigations like hormonal, hematologic, genetic and immunologic testing are required to identify the specific causes.

Hormones

Hormonal testing is used to evaluate ovarian function and to screen endocrinological abnormalities that might influence follicu logenesis, corpus luteum function, implantation and preservation of pregnancy. Ovarian reserve test is done by measuring D3 FSH and E2. Along with these LH, prolactin and thyroid hormone should be tested. If prolactin level is raised MRI of pituitary gland is require to rule out pituitary lesions. Serum progesterone on D21 gives clue about corpus luteum defect.

Blood sugar two hours postparandial is to be done. If raised or there is family history of diabetes mellitus OGTT is to be done.

The diagnosis of antiphospholipid syndrome requires antibody testing on two separate occasions at least 6 weeks apart. IgG or IgM anticardiolipin antibodies need to be present in medium or high titer and the test for lupus anticoagulant needs to be positive.

Though immunological factors are responsible for repeated abortions, routine use of immunological testing (eg natural killer cells, interleukins, TNF alpha) is not recommended unless the patient participates in a clinical study[36, 24].

Finally a karyotype of both partner should be done to exclude any chromosomal defects in either partner. Karyotype of product of conception also can give clue of chromosomal defect of that pregnancy but which will not give any benefit to subsequent pregnancy management.

Treatment

Life style changes

Life style changes might have some role in the management of recurrent pregnancy loss. Weight should be as close to the normal range as possible. Dieting and exercise may be an appropriate recommendation for PCOS patients. Smoking and other harmful habit should be given up. Caffine intake should be reduced as much as possible. Pregnant women need to avoid occupational exposure (radiation) and exposure to environmental toxins (teratogen medications).

Medical treatment

Hormonal treatment

Diabetes, hypothyroidism and hyperprolactinaemia should be treated by insulin, thyroxin and bromocriptine. Bromocriptine should be admini stered after dinner to avoid gastrointestinal upset and hypotension. Cabergolin is another drug for the management of hyperprolactinaemia, which requires less frequent doses.

For inadequate luteal phase ovulation induction is an option to produce multiple follicles and more progesterone. Ovulation induction also has an impact on endometrial development. Another option is to supplement progesterone to support the luteal phase.

Vaginal or intramuscular preparations are used and started in the luteal phase when pregnancy follows. Progesterone is continued up to 12 weeks of gestation. A meta-analysis evaluating progesterone supplementation for the prevention of miscarriage failed to find a significant benefit. When the analysis was limited to those studies involving women with recurrent loss, however, there was a significant reduction in the loss rate[37].

Metformin have been widely used for the management of women with PCOS. When continued during pregnancy it has been associated with a lower rate of spontaneous abortions.

Anticoagulants

Antiphospholipid syndrome is a cause for recurrent abortion. It causes thrombosis of placental vasculature leads to reduced placental circulation. Aspirin is used to prevent thrombocyte aggregation and thromboxane release. Though aspirin alone has not been shown to improve outcome among women with early recurrent pregnancy loss[38]. For women with antophospholipid antibodies but no previous history of thrombosis, prophylactic heparin use is recommended. Usual dose is 5000 IU unfractionated heparin twice a day or 30-40 mg low molecular weight heparin daily in combination with 81 mg aspirin a day. Patients with a history of thrombosis need to be anticoagulated. Women with hyperhomocysteinemia require vitamin B and folic acid supplementation. The patients with hyperhomocystineinemia and history of thrombosis should be anticoagulated. Those with inherited thrombophilias and recurrent loss require prophylactic-dose heparin during pregnancy [27, 39, 40].

Immunotherapy

The role of immunotherapy is controversial. Active immunization with third party or paternal leukocytes and passive immunization using intravenous gammaglobulins (IvIG) have been evaluated. The infusion of lymphocytes is supposed to induce blocking antibodies that would hide the pregnancy from the maternal immune system. IvIG is supposed to shift the cytokine production to induce favorable humoral immune response during pregnancy. Meta-analysis of the trials failed to find a significant benefit with immunotherapy[41]. Only one randomized controlled trial of immunotherapy has shown benefit following treatment[42]. More recent randomized trials have failed to confirm these findings[43, 44].

Surgery

Some anatomic defects require surgical correction. But it is very important to know the exact anomaly. Endoscope procedures are most commonly used to correct the defect. Intrauterine pathologies eg septum, fibroids, polyps can be removed during hysteroscopy. Septum should be excised with scissors or laser. Better homeostasis is achieved with the latter procedures, though thermal injury might lead to scar formation. Reproductive outcome significantly improves after hysteroscopic resection of septum (76% after surgery vs. 20% before surgery)[45]. Polyps are removed by forceps or by gentle curettage and sub mucous fibroids are usually respected during hysteroscopy. Intramural and sub serous fibroids are removed via abdominal approach. The laparoscopic approach gained popularity more recently. Bicornuate uterus is usually associated with problem during the third trimester. So in much selected cases with recurrent 2nd or third trimester abortion bicornuate uterus is to be corrected.

Genetic screening

Preimplantation genetic diagnosis (PGD) allows genetic screening of the embryos before transferring during IVF. Several research groups have assessed whether PGD is beneficial for women with recurrent pregnancy loss, as a great proportion of losses are due to chromosomal anomalies. A small hole is made on the zona pellucida in the cleavage stage embryo to remove 1 or 2 blastomeres for genetic analysis. Flurescent in situ hybridization (FISH) is used to detect numeric and structural chromosomal anomalies and polymerase chain reaction (PCR) is used to detect monogenic disorders. A significant reduction in the loss rate among women over the age of 35 was reported by one group[46]. But others failed to observe a benefit with IVF-PGD among women with recurrent spontaneous abortion[47]. So PGD may not be appropriate for all women with recurrent pregnancy loss, but there may be subgroups for whom its use is justified. Further studies need to identify these subgroups. Donor gametes can be considered for couples with a known genetic defects.

Conclusion

Recurrent pregnancy loss is a tragic situation for a couple, which has got tremendous psychological burden. Though in certain cases cause can be identified, in about 50% cases the exact aetiology remains unknown even after a thorough work-up. Patients with known causes should be treated accordingly. Couples for whom the exact cause is not identified require emotional support and

should be counseled about their chances of normal pregnancy without specific treatment. Some therapies are widely used without any scientific support. Patients usually are agreed to do anything to improve their chances. But we should be very careful not to offer such empirical treatments without sufficient scientific evidence supporting their use rather those are expensive and may be dangerous.

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