

Current Update on Recurrent Pregnancy Loss

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ABSTRACT

Recurrent pregnancy loss is an intense personal calamity to the couples and an arduous clinical challenge to the Obstetricians.

When to evaluate and what constitutes a complete evaluation is still a state of flux. It is justifiable to investigate a couple for cause of pregnancy loss particularly if the female's age is more than 35 years or has history of difficult conception. Women with two pregnancy losses have identifiable losses just as frequently as the one with three losses[1].

While Royal College of Obstetricians and Gynaecologists (RCOG, 2011) has defined Recurrent pregnancy loss (RPL) as the loss of three or more consecutive pregnancies[2], American Society of Reproductive Medicine (ASRM,2012) and European Society for Human Reproduction and Embryology (ESHRE,2017) has recently given definition of RPL as two or more clinical and consecutive pregnancy losses with either ultrasound or histopathological documentation, with exclusion of ectopic and molar pregnancies[3,4]. Thus we should start evaluating the couple after two losses.

Keywords: Pregnancy loss, Obstetricians, Gynaecologists, Thrombophilia.

INTRODUCTION

Recurrent Pregnancy Loss (RPL) constitutes for 1-5% of infertile couple and 12-15% of all pregnancies. True incidence of RPL cannot be estimated as most of the losses occur either before they have been clinically recognized or sometimes even before the first missed period. Out of the total pregnancies 70% female fail to report as 50% tend to undergo spontaneous miscarriage before first cycle and 20% are clinically unrecognized. Only 30% are recognized either by clinically, radiological (appearance of intrauterine gestational sac), histopathological or biochemical evaluation (viable levels of b-HCG) [1,2].

Off late, all the existing guidelines have been updated based on evidence. American College Of Obstetricians and Gynaecologists (ACOG) guidelines have been substituted by guidelines released by American Society of Reproductive Medicine (ASRM, 2012). Royal College of Obstetricians and Gynaecologists (RCOG) guidelines for RPL which were first released in 1998 have been updated from time to time with most recent update in 2012[3]. The most recent are the guidelines by European Society of Human Reproduction and Embryology (ESHRE)[2]. They

were first published in 2006, but later updated and finally replaced by new guidelines in November, 2017. The updated guidelines have even changed the definition of RPL to “two or more pregnancy losses” in place of “three or more pregnancy losses”[4].

On-going through these guidelines, it is found that a series of experience, consensus and evidence based investigations and management protocols have been described considering RPL as a single entity. Thus these guidelines leave the treating obstetricians in management dilemma while dealing such cases. It should be understood that they should tailor the diagnostic investigations according to patient and follow management protocols accordingly, thus should stress on “patient-specific approach”.

HOW SHOULD EVALUATION START?

A dedicated RPL clinic in a well-organized manner with specialist, adequate staff and necessary equipment should be there, for evaluation of infertile, sub fertile and women with RPL[4]. An extensive history taking should never be undermined in cases of RPL. Previous obstetric history, history of any preterm birth, bleeding tendencies,

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hypertension of early onset, whether the pregnancy was documented by radiological or histo-pathological studies should be taken into account. There are a few key counselling points which must be discussed. The couple with RPL should be dealt together with a sympathetic approach. They should be told that even extensive investigation may not find a cause in 50% cases. Most of the cases due to repeated chromosomal abnormalities are usually sporadic in nature and the best prognosis exists for the cases which are unexplained. The importance of follow up for pre-pregnancy follow up and treatment must be stressed upon in particular.

Thus repeated counselling, support and provision of psychological care is an integral part of RPL management and care.

RISK FACTORS AND MANAGEMENT

Subfertile women or women with age more than 35 years have more occurrences of spontaneous pregnancy losses. It has been seen that age of mother and number of preceding pregnancy losses are two independent risk factors for next loss[1,5]. Advancing age of the mother has been seen to be linked to reduction of both quality and quantity of the remaining oocytes. According to a large prospective register linkage study, age-related risk of miscarriage in recognized pregnancies has been seen to be: 13% in 12-19 years, 11% in 20-24 years, 12% in 25-29 years, 15% in 30-34 years, 25% in 35-39 years, 51% in 40-44 years, 93% in ≥ 45 years[6].

Similarly, advanced paternal age has also been identified as a risk factor for pregnancy loss[6]. The female with more than or equal to 35 years of age and the male more than or equal to 40 years of age have maximum risk of pregnancy loss[1,7].

Other maternal factors like obesity, smoking, cocaine use, alcohol intake (3-5 drinks per week), increased coffee consumption also can have a negative impact affect in dose dependent manner[8]. Infact obese women have greater efficacy to achieve pregnancy but have greater tendency of recurrent pregnancy loss. These lifestyle factors play a very important role and need to be modified during preconception counselling. Cessation of smoking and achieving normal weight is recommended by all major guidelines (ESHRE and RCOG)[2,4]. Although there is no direct or indirect evidence of stress in women leading to RPL but is a definite concern. "Tender Loving Care" approach helps in dealing with it appropriately.

Though chromosomal abnormalities in foetus have been cited as the most common reason responsible for 40-50% of first trimester pregnancy losses, but likelihood of loss due to foetal aneuploidy is reduced with successive pregnancy losses[6]. Cytogenetic analysis can only do on products of conception for explanatory purposes[4].

With the report of aneuploidy in the products of conception, there are more chances of successful outcome in successive pregnancy, as aneuploidies are unlikely to get repeated.

Genetic counselling plays a key part for these couples. Paternal cytogenetic analysis and karyotyping can be done after risk assessment of individual couple but is not routinely recommended[4]. It can be suggested according to the genetic history, in presence of history of previous birth of a child with congenital abnormalities, in presence of history of offspring with unbalanced chromosome abnormalities in the family or detection of a translocation in the product of conception.

Upon identification of structural genetic abnormality in parents, options of confirmatory tests like Chorionic Villus sampling or Amniocentesis must be offered to the couple. However there is insufficient evidence suggesting "in vitro fertilization with Preimplantation Genetic Diagnosis" in improving the rate of successful pregnancy outcome in couples with RPL[9].

Thrombophilia

Inherited Thrombophilia: Screening for inherited thrombophilia can only be done for research purposes and not routinely or in women with additional risk factors for thrombophilia (family members with hereditary thrombophilia, or previous VTE) {ESHRE (LEVEL C); ASRM}[3,4,10].

Low risk thrombophilia (factor V Leiden heterozygous, Prothrombin G20210A heterozygous, Protein C or Protein S deficiency): They are just managed with antepartum surveillance without the need of anticoagulants or Prophylactic low molecular weight heparin (LMWH) or Unfractionated Heparin (UFH). Postpartum anticoagulation is needed in cases with simultaneous risk factors like obesity, prolonged immobilization or first degree relative with history of thrombotic episode in first degree relative or history of Venous thromboembolism in self[11].

High risk thrombophilia (Antithrombin deficiency, double heterozygous for Prothrombin gene mutation G20210A and Factor V Leiden mutation homozygous or Prothrombin G20210A mutation homozygous): These cases need to be given prophylactic antepartum anticoagulation therapy along with postpartum anticoagulation therapy with LMWH/UFH for 6 weeks[11].

Thrombophilia with two or more episodes of venous thromboembolism should receive therapeutic dose of LMWH or UFH along with postpartum therapeutic dose heparin therapy for 6 weeks (who were not on long term anticoagulation therapy) and for lifelong (who were on long term anticoagulation therapy)[11].

Acquired thrombophilia: Antiphospholipid Antibody Syndrome is the most common acquired thrombophilia

prevalent in 5-20% of females with recurrent pregnancy loss.

History of RPL or early onset preeclampsia or unexplained pregnancy loss after ten weeks period of gestation along with positive lupus anticoagulant antibodies (LAC), anticardiolipin antibodies (ACL) and anti-beta2 glycoprotein antibodies of medium to high titre on two separate occasions 12 weeks apart suggests the diagnosis of antiphospholipid antibody syndrome (APLA).

It is treated by conjoint therapy of low-dose aspirin (75 mg/day) and unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). This combination has well proven evidence that it decreases the risk of early pregnancy loss in this subcategory of women.

Immunological factors

Antinuclear antibodies (ANA) testing can be done only for explanatory purposes. But HLA determination, measurement of anti-HY antibodies, cytokine testing or cytokine polymorphisms, NK cell testing and anti-HLA antibodies testing is not recommended (ESHRE, 2017)[4].

Anatomical defects

Anatomical defects can be due to congenital mullerian abnormalities or Acquired abnormality like intrauterine synechiae, fibroids or polyps.

Ultrasonography is a safe, readily available, non-invasive and economical modality but has high false positive rates. Transvaginal, three-dimensional ultrasound by skilled and experienced hands is a more precise than two-dimensional ultrasound and is equivalent to MRI for assessing uterine abnormalities. Sonohysterography is another non-invasive and cost-effective modality with almost 95% accuracy in picking up Mullerian anomalies or acquired intrauterine abnormality (like submucosal fibroid, synechiae or polyp) and can be done if MRI is not available. MRI with its ability to image complex uterovaginal anatomy has high sensitivity and specificity.

Women with recurrent pregnancy loss have 3.2% to 6.9% chances of having a major mullerian abnormality[12]. Congenital anomaly most frequently coupled with RPL is the septate uterus. Other abnormalities like Didelphys, unicornuate and bicornuate uterus have more association with preterm labour than early pregnancy losses[3].

Congenital abnormalities

Septate, bicornuate and arcuate uterus has been seen to be related with 44.3%, 36% and 25.7% loss of pregnancy (ASRM 2012). Though no randomized control trials are there but few studies have shown beneficial effect of hysteroscopic septum resection (improving Live Birth Rate and reducing pregnancy loss rates) Hysteroscopic

resection of septum in septate uterus have shown significant fall in abortion rate by 70% leading to successful pregnancy outcome. Metroplasty and uterine reconstruction has not been recommended for Didelphic uterus, bicornuate uterus and unicornuate uterus (ESHRE, 2017)[4].

Acquired abnormalities

Based on observational studies, in Asherman syndrome/ intrauterine synechiae, hysteroscopic removal of synechiae in women with RPL can be done with care to prevent recurrence. For intramural fibroids not distorting the cavity and endometrial polyp less than 1cm, surgical treatment is not recommended. Infact women with fibroids not distorting the uterine cavity can achieve high live birth rates without intervention. According to Saravelos et al. resection of fibromyomas distorting the uterine cavity can eliminate the mid-trimester losses and double the live birth rate in subsequent pregnancies[13]. For submucosal fibroids and endometrial polyps more than 1cm, there is no conclusive evidence that surgical treatment reduces risk of pregnancy loss. In absence of randomised control trials, level C evidence suggests that for significant uterine cavity defects, surgical treatment for correction can be opted for (ASRM, ESHRE)[3,4].

Cervical incompetence is a well-known cause of mid-trimester pregnancy loss. Cervical cerclage/stitch is applied in cases of cervical incompetence in pregnancy. The cerclage is clearly recommended in patients with history of one or more second trimester loss due to painless expulsion. This history indicated cervical cerclage is applied electively at 12-14 weeks gestation. Those having uncertain history of second trimester loss or preterm labour are followed up with monitoring of serial cervical length and those with short cervix (25 mm) on transvaginal ultrasonography between 14-24 weeks should be offered emergency cervical cerclage. On the contrary, rescue cerclage is done in symptomatic women with demonstrable bulging membranes during second trimester, either sonographically or clinically.

ACOG recommends a repeat transvaginal sonography (after 20 weeks) upon identification of short cervix (<25 mm) before 16-20 weeks gestation as cervix is indistinguishable from the lower uterine segment.

Frequent and regular examinations must be done in women (especially in those with pelvic pressure, backache, or increased mucoid discharge) to catch rapid changes in cervix. Based on suspicious history, early or first trimester cerclage is not recommended. There is no evidence to support first-trimester cerclage, even with transabdominal procedures[3,4,14].

Endocrine dysfunction

Any clinical or subclinical endocrine dysfunction calls for investigation and treatment. The symptoms

suggestive of endocrine dysfunction are irregular cycles, galactorrhoea, on and off headaches and vision disturbances. Uncontrolled diabetes mellitus, obesity, Luteinising hormone hypersecretion, luteal phase insufficiency and metabolic syndrome are important contributory factors for RPL.

In all cases of thyroid dysfunction it is very important to attain euthyroid status before conception for optimum pregnancy outcome. According to the latest evidence, the upper limit of TSH is being taken as 2.5 mIU/L. So the aim of baseline TSH level to be achieved is 2.5 mIU/L. There is no recommendation for screening of anti TPO antibody in euthyroid RPL cases. ESHRE recommends Thyroid screening (TSH & TPO antibodies) in all women with RPL[4]. There is an ongoing randomized controlled trial, TABLET (thyroid antibodies and levothyroxine) trial which was a multicentre, double blind, placebo-controlled randomized trial to assess the role of treatment in euthyroid cases of RPL with positive anti TPO (thyroid peroxidase antibodies). It is being done as the results of small trials are inconclusive that levothyroxine treatment in euthyroid women can reduce adverse pregnancy outcomes. The results of this trial are awaited[15,16].

The prevalence of Polycystic Ovary Syndrome among women with RPL can be upto 40%; however, polycystic ovarian morphology (PCOM) cannot predict pregnancy loss amidst ovulatory women with spontaneous conception but having RPL.

There is an important role of Insulin resistance in recurrent pregnancy loss[17,18]. Evidence has shown that Insulin resistance has been seen to be related to increased susceptibility and association with RPL. These women with insulin resistance are advised lifestyle changes or medical treatment to improve their insulin sensitivity before seeking infertility treatment to increase the chances of successful pregnancy. ESHRE however does not recommend assessment of Polycystic Ovarian Syndrome, fasting insulin and fasting glucose in women with RPL to improve next pregnancy prognosis.

Metformin use for improving insulin resistance though recommended for infertility patients, but there are no well conducted trials on the use of metformin to decrease the chance of recurrent pregnancy loss[19].

Hyperprolactinemia can lead to RPL by affecting the hypothalamic-pituitary-ovarian axis thereby impacting folliculogenesis and oocyte maturation, and/or a short luteal phase. Dopamine agonists are indicated for improving raised prolactin levels in symptomatic patients. This can improve the pregnancy outcomes in patient with RPL.

Luteal phase insufficiency is described as a condition of insufficient progesterone levels needed for secretory endometrium allowing for normal implantation and growth of embryo. The assessment of a possible association between luteal phase insufficiency and RPL is

hampered by the diagnostic criteria for luteal phase insufficiency. Luteal phase insufficiency testing is not recommended in women with RPL[4].

Unexplained rpl

Half of the cases of recurrent pregnancy loss remain unexplained. In these cases, there may be a contributory role of immunological causes like presence of cytotoxic antibody, absence of maternal blocking antibodies, disturbances in Natural Killer (NK) function and role of inflammatory mediators in and around pregnancy.

According to recent randomized control trial and Systematic review, paternal cell immunisation, third-party donor leucocytes, and intravenous immunoglobulin do not improve the live birth rate in women with previous unexplained RPL[20,21]. Role of intralipid therapy, granulocyte colony stimulating factor (G-CSF), endometrial scratching and multivitamin supplementation has insufficient evidence to be recommended. Lymphocyte immunization therapy should not be used as they may be associated with life-threatening consequences without significant positive effects. Intravenous immunoglobulin (Ivlg) and glucocorticoids are not recommended. Heparin or low dose aspirin has not shown improvement in live birth rate (ESHRE, 2017).

Chronic endometritis

This being defined as the infiltration of plasma cells with a range of pathogenic organism. The prevalence is dependent upon the detection of inflammation either by biopsied sample or by immuno-histochemistry with antibodies to CD 138[4,22,23].

Though there are studies antibiotics tend to improve the live birth rates. [24]Further research is required including randomized and prospective studies to further prove it and role of screening for endometritis[4].

Infections

Ureaplasma, Mycoplasma, hominis, Chlamydia, Listeria monocytogenes, Toxoplasma, Rubella, Cytomegalovirus and Herpes Virus (TORCH) has been identified in vaginal/cervical secretions/serum of women with sporadic Pregnancy loss. There is no evidence of role of any infection in recurrent pregnancy loss. So routine screening for infection not recommended in females with RPL (ESHRE, 2017, ASRM,2012)[3,4].

Role of progesterone

Progesterone is indispensable for the establishment and continuation of a normal pregnancy. Thus, luteal phase insufficiency has been suggested as a causative factor in RPL. In a study conducted by Stephenson et al. in 2017 vaginal progesterone tend to improve

endometrial milieu as was assessed by cyclin-D levels. [25]As per the European guidelines there is insufficient evidence to recommend the use of progesterone to improve live birth rate in women with RPL and luteal phase insufficiency[3]. However, the Cochrane analysis pooled the results from four small trials and concluded that there was significant lower miscarriage rate in women with RPL receiving progesterone treatment, compared to placebo. Vaginal progesterone during early pregnancy has no beneficial effect in women with unexplained RPL. However, oral dydrogesterone initiated after foetal heart action confirmation may be effective. Benefit from supplementation may be appreciated more if progesterone is started from the luteal phase, rather than after a positive pregnancy test. There is definite evidence-based role of progesterone supplementation up to 12 weeks in women conceiving with Artificial Reproductive Technique.

In PROMISE TRIAL (Progesterone in Recurrent Miscarriage) 2016, first trimester progesterone therapy did not have clinically significant benefits in pregnant women with history of unexplained recurrent miscarriages.

However as per the results of this trial, progesterone supplementation at a dose of 400mg twice daily appeared to be safe for mother and foetus and can be clearly given if indicated, as in Assisted conception treatment[20]. The limitation of this study was that they have not taken into account, the effectiveness of progesterone supplementation during luteal phase of the cycle. As per the evidence-based recommendations by latest European and American guidelines and recent high quality trials, there is no role of progesterone supplementation to improve pregnancy outcome in unexplained recurrent pregnancy loss[3,4,5,20,25].

CONCLUSION

Routine Investigations after two consecutive miscarriages include basic blood tests like Hemogram, HBA1C, Thyroid Stimulating Hormone, Prolactin (in presence of symptoms), transvaginal ultrasonography (USG-TVS), (3D) preferably or Sonohysterography and Antiphospholipid antibody test- [Lupus Anticoagulant (LAC), Anticardiolipin Lipid (ACL) and Anti-beta-2Glycoprotein antibody 12 weeks apart]. Tender loving care along with a systematic approach with good counselling should be given to all. Specific cause-related treatment should be given. Treatment of possible causes like surgical treatment for uterine septum, sub-mucous fibroid and severe intrauterine adhesions, cervical cerclage for cervical incompetence, thyroxin supplementation for subclinical or over hypothyroidism, Low dose aspirin and heparin for Antiphospholipid syndrome and dopamine agonist for hyperprolactinemia should be given. In spite of thorough evaluation, in more than 50% of the women with RPL, etiology remains

unexplained. In these unexplained cases, prognosis remains good, and tender loving care approach appears to play an important role. Empirical treatment is to be avoided. The aim of the management is to identify the etiology and treat it. Different guidelines available differ in the approach leaving the treating clinicians in dilemma. There might be a single or multiples etiologies for RPL in single woman. So the approach needs to be individualized and tailored according to the patient.

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