

# Recurrent Pregnancy Loss: An update

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## ABSTRACT

Recurrent pregnancy loss (RPL), a very distressing situation for the patient and physician, occurs in 1-5% of women who conceive. The cause of recurrent miscarriage is multifactorial, it may be caused by thrombotic, fibrinolytic, genetic, infectious, chromosomal, anatomic, endocrine, or immune abnormalities, but more than 33% of cases remain unexplained. Thrombophilic and fibrinolytic defects are raising issues regarding the cause of RPL. Fibrinolysis is a novel research avenue in the recurrent miscarriage field. A systematic review to explore the risk factors of recurrent pregnancy loss was done. Articles that contained population based, epidemiological and prospective studies were selected and data concerned with prevalence, possible etiology and future directions of RPL was compiled. The objective of this review is to appraise and explore the latest research in the field of different causes of recurrent miscarriage especially fibrinolysis, a new area of research, which needs to be explored by randomized studies, meta-analysis and systematic reviews. Well designed multicentre research trials with large sample size are necessary to produce strong evidence-based medicine.

**KEY WORDS:** *RPL (Recurrent Pregnancy Loss), Thrombophilia, Fibrinolysis, PAI-1(Plasminogen Activator Inhibitor-1).*

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## INTRODUCTION

Miscarriage is the most common problem of early pregnancy.<sup>11</sup> It can be spontaneous or induced. Spontaneous abortion is defined as pregnancy loss before 20 weeks of gestation without outside interference.<sup>2</sup> The reported prevalence of spontaneous miscarriage in Pakistan is 6.5%<sup>3</sup>, In fact it is higher than this because most of the cases are not reported. Recurrent pregnancy loss (RPL) is defined as repeated pregnancies (consecutive three or more) that ends in spontaneous miscarriage of the fetus before 20 weeks of gestation, affects about 1-5% of women who conceive.<sup>4</sup> However the American society of reproductive medicine defines RPL as two or more consecutive pregnancy losses (documented by ultrasound or histopathological examination) before 20th week of gestation.<sup>5</sup> Pregnancy loss can result from thrombotic, fibrinolytic, genetic, infectious, chromosomal, anatomic, endocrine, or immune abnormalities.<sup>6</sup> In Asia, Researchers are trying to explore the above causes of recurrent pregnancy loss but less consideration is given on the fibrinolytic aspect. Impaired fibrinolysis in patients of recurrent pregnancy loss still needs to be investigated thoroughly and on a large scale to make an association. In this review we have given few important aspects of fibrinolysis in the field of RPL.

## DISCUSSION

### Uterine Anatomical Abnormalities

Anatomic abnormalities of uterus are found nearly in 10% to 15% cases of RPL and are generally considered to cause miscarriage by intervenening the vasculature of the endometrium, causing abnormal and inadequate placentation, includes, congenital uterine anomalies, intrauterine adhesions, and uterine fibroids or polyps. In congenital uterine anomalies, the uterine septum is strongly linked to RPL with approximately 76% risk of spontaneous miscarriage among affected patients.<sup>7</sup> About 2.7% to 16.7% congenital uterine anomalies are present in the general population of fertile women and in 1.8% to 37.6% of patients with recurrent miscarriage (2 or more consecutive losses). Hysteroscopic septum resection increases the live birth rates approximately 85%.<sup>8</sup>

### Harmonal and Metabolic Factors

(PCOS) polycystic ovarian syndrome, luteal phase defects, diabetes mellitus, thyroid disease, and hyperprolactinemia are among the endocrinological disorders in approximately 17% to 20% cases of RPL.<sup>7</sup> Evaluation of endocrine disorders must include measurement of the levels of thyroid-stimulating hormone (TSH). Other testing that can be considered includes insulin resistance, serum prolactin, anti thyroid antibody according to the presentation of the patient.<sup>7</sup>

### Infections

Ureaplasma urealyticum, Mycoplasma hominus, Chlamydia, Lysteria monocytogenes, Toxoplasma gondii, Rubella, Cytomegalovirus, Herpes virus have been identified more frequently in vaginal and cervical cultures and serum from women with sporadic miscarriages.<sup>9</sup> There is no persuasive data that infections cause recurrent pregnancy loss.

### Lifestyle, Environmental Factors

Cigarette smoking has been considered to have an unfavorable effect on trophoblastic function and is related to an increased risk of sporadic pregnancy loss.<sup>8</sup> Obesity has also been shown to be related with an increased risk of RPL.<sup>10</sup> Other factors, for instance, cocaine use<sup>8</sup>, consumption of alcohol (3-5 drinks per week), and caffeine (greater than 3 cups of coffee) have also been associated with risk of miscarriage.<sup>8</sup>

### Chromosomal Abnormalities

Chromosomal abnormalities are the frequent cause of spontaneous miscarriage.<sup>11</sup> In Women of above 35 years of age, risk of miscarriage increases due to increased incidence of trisomic pregnancies.<sup>12</sup> Evidence suggests that 12% of the patients with the history of recurrent miscarriages have chromosomal abnormalities.<sup>13</sup> In a study done in India Chromosomal aberrations were found in 8.57% of patients in which Numerical abnormalities 0.95%, Structural abnormalities 2.87% and polymorphic variants were 4.76%. This shows that cytogenetic analysis can be considered while exploring the cause of recurrent pregnancy loss.<sup>13</sup>

### Thrombophilia

Thrombophilia is a condition of hypercoagulability and has been associated with adverse pregnancy outcomes. Thrombophilia may be acquired or inherited. More than 50% of women suffering from unexplained recurrent pregnancy loss have predisposition to thrombosis.<sup>14</sup> The frequent morphological findings in a tissue of spontaneous miscarriage are intravenous blood clots<sup>15</sup> and increased intervillous space fibrin<sup>15</sup> which indicates hemostasis dysfunction. The normal coagulation pathway is essential for the successful pregnancy. Disorder in coagulation pathway may cause hypercoagulability that may be the basis of placental insufficiency and RPL.<sup>16</sup>

### Inherited Thrombophilia

The inherited group of thrombophilia includes antithrombin deficiency, prothrombin mutation, factor V Leiden (FVL) mutation, protein C and S deficiencies and hyperhomocysteinemia.<sup>16</sup> Thrombophilia further augments the hypercoagulable state of pregnancy resulting in thrombosis of the placental vasculature leading to adverse pregnancy outcomes.<sup>17</sup> Maternal thrombophilia has recently been recognized as a major cause of adverse pregnancy outcome, including recurrent pregnancy loss, still-birth, severe pre-eclampsia, placental abruption, and intrauterine growth restriction.<sup>18</sup>

The most common inherited disorders are deficiencies of antithrombin, protein C, protein S, Activated Protein C Resistance due to factor V Leiden (FVL) mutation, mutation of the prothrombin gene (G20210A), and thermolabile mutation for methylene-tetrahydrofolatereductase. In a study from Malaysia, Thrombophilia was identified in 26% of women with recurrent miscarriage.<sup>19</sup> In another study conducted in India, the risk of pregnancy loss with protein S deficiency was the highest risk observed for any heritable thrombophilia, followed by protein C, factor V Leiden, endothelial protein C receptor, antithrombin III deficiency, and beta448 fibrinogen polymorphism.<sup>20</sup> In another study done in Pakistan, inherited thrombophilia was found with a frequency of 2.3% for protein C deficiency, 1.4% for protein S deficiency, 1.5% for antithrombin deficiency, 14.2% for FVL mutation and 2.0% for homocysteinemia.<sup>21</sup>

### Acquired Thrombophilia

Anti Phospholipids Syndrome is the most common cause of acquired thrombophilias. Pregnancy loss is significantly associated with APS (antiphospholipid antibody syndrome). Recurrent pregnancy loss is one of the essential diagnostic criteria of APS. It is associated with RPL, severe pre-eclampsia, IUGR, and placental abruption. Different studies have shown lupus anticoagulant positivity in RPL ranging from 9 to 17%, while the occurrence of aCL (anti cardiolipin) in RPL ranged from 11 to 42%.<sup>22</sup>

### Fibrinolysis

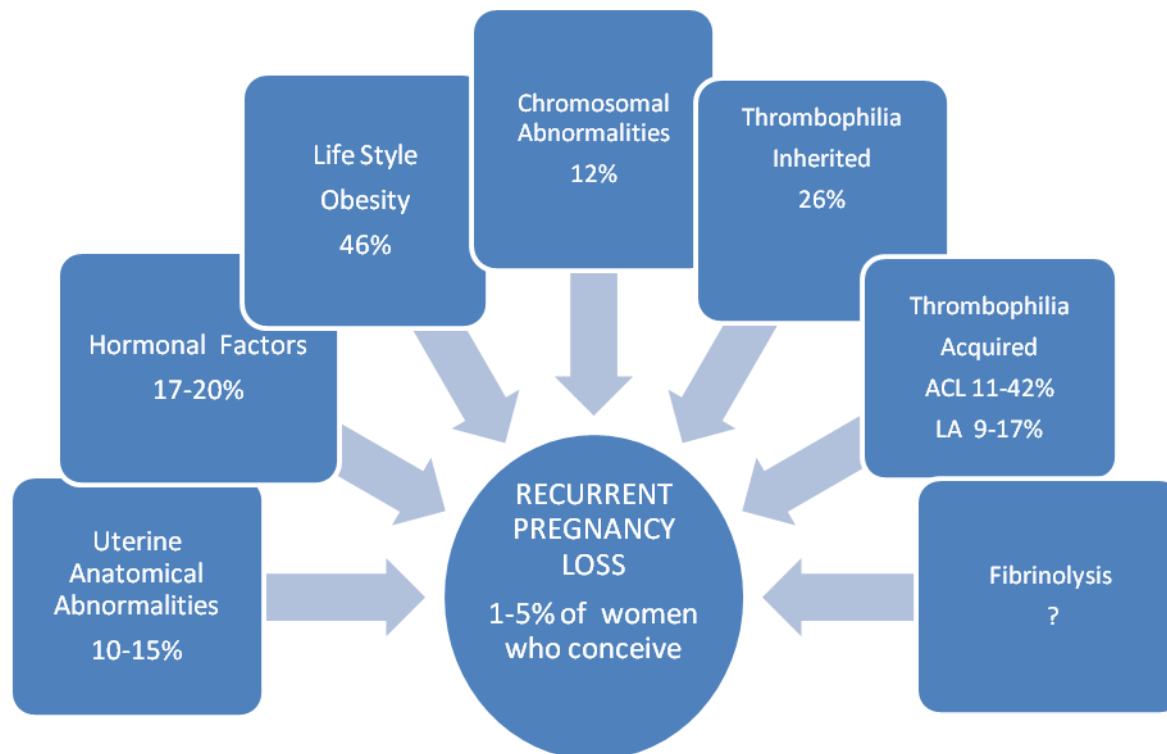
The fibrinolytic enzyme system is implicated in many physiological and pathophysiological processes which include prevention of formation of fibrin clots in the circulatory system, removal of fibrin deposits from blood vessels, activation of metalloproteinases which are capable of degrading extracellular matrices, and cell migration.<sup>23</sup> Plasminogen activator inhibitor-1 (PAI-1) is a linear glycoprotein consists of 379 amino acids, plays a key role in the control of plasmin formation.<sup>24</sup> It is produced by the vascular endothelium and is also present in platelets, considered to be an important regulatory element in fibrinolysis.<sup>25</sup> Plasminogen activator inhibitor-1 (PAI-1) belongs to the family of serine protease inhibitors (SERPINs), inhibits plasminogen activation by tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). Tissue plasminogen activator is generally considered to be responsible for intravascular plasminogen activation while uPA is the main plasminogen activator on migrating cells, and its activity is regulated by the U-PA receptor (u-PAR) present on different cells. PAI-1 therefore inhibits intravascular fibrinolysis as well as cell-associated proteolysis.<sup>26</sup>

At present, the fibrinolytic system is thought to be a clue to new thrombotic pathogenic mechanisms.<sup>27</sup> Females suffering from recurrent pregnancy loss are in a prothombic condition even outside pregnancy.<sup>28</sup> It is reported for the first time in a study that patients with unexplained recurrent pregnancy loss have an impairment of fibrinolysis, as established by a prolonged Clotting time (CLT).<sup>29</sup> The CLT, a

worldwide fibrinolysis assay, is considered to be a better technique for detecting the risk of venous and arterial thrombosis than conventional laboratory testing of fibrinolytic

factors. Plasma hypofibrinolysis due to high plasma levels of plasminogen activator inhibitor-1 (PAI-1) has recently been reported as a basis of venous thrombosis.<sup>30</sup>

**Figure 1. Causes of recurrent pregnancy loss**



## CONCLUSION

Apart from other factors, haemostatic factors also play an important role in implantation and placentation; hence defective maternal haemostatic response might be responsible for recurrent pregnancy loss. Therefore, all patients with unexplained RPL should be screened for haemostatic defects which includes screening for thrombophilia (inherited and acquired), fibrinolytic and platelets defects. Evidence suggests that blood coagulation defects are responsible for 55–62% of recurrent miscarriages. Recently it is reported that patients with unexplained recurrent pregnancy loss have impairment of fibrinolysis. Plasminogen activator inhibitor-1 is the main

inhibitor of fibrinolysis in the blood circulation by inhibiting tissue plasminogen activator (t-PA). Increased activity of plasminogen activator inhibitor -1 has been shown to have a positive association with early pregnancy loss, so recurrent pregnancy loss in the absence of other explanations (e.g., uterine anomalies, chronic maternal disease) may be frequently accompanied by imbalances in the fibrinolytic system. More prospective studies with quality of research are required to establish the causal link between fibrinolytic defects and adverse pregnancy outcome. Further interrogation of the exact pathophysiological mechanisms involved in pregnancy with a good study design and large sample size could be advantageous.

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