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1 Epigenetic Dysregulation in Recurrent Pregnancy Loss: The Pivotal Roles of DNMT and TET Enzymes

2 Short title: DNMT and TET in RPL

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11 Abstract

12 Recurrent pregnancy loss (RPL) defined as two or more consecutive miscarriages poses significant challenges in reproductive medicine
13 due to its multifactorial etiology including genetic immunologic and environmental factors. Emerging evidence highlights the critical
14 role of epigenetic modifications particularly DNA methylation in RPL. This review explores the involvement of DNA methyltransferase
15 (DNMT1 DNMT3A DNMT3B) and ten-eleven translocation (TET1 TET2 TET3) enzymes in regulating embryonic and placental
16 development. Dysregulation of these enzymes disrupts the balance between methylation and demethylation leading to aberrant gene
17 expression and increased miscarriage risk. Studies demonstrate altered DNMT and TET expression in chorionic and decidual tissues of
18 RPL patients correlating with global hypomethylation or hypermethylation of key developmental genes. Genetic polymorphisms in
19 DNMT and TET genes further elevate RPL susceptibility. Diagnostic approaches including RT-qPCR bisulfite sequencing and



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20 methylation microarrays enable precise assessment of epigenetic profiles offering potential biomarkers for early risk prediction.
21 Therapeutically DNMT inhibitors like 5-azacytidine TET activators such as vitamin C and emerging CRISPR-based epigenetic editing
22 present promising avenues for restoring epigenetic balance though challenges like safety and specificity remain.

23 **Key words: Recurrent Pregnancy Loss, Epigenetic, DNMT, TET**

24

25 **Introduction**

26 Recurrent pregnancy loss (RPL) defined as two or more consecutive miscarriages represents a complex and multifactorial issue in
27 obstetrics and gynecology that significantly affects women's physical and psychological well-being. Various causes have been reported
28 including genetic immunologic hormonal and environmental factors; however, in many cases the exact cause remains unidentified [1-
29 4]. A highly relevant and emerging area in understanding the etiology of RPL is the study of epigenetic modifications that regulate gene
30 expression without altering DNA sequences [5]. DNA methylation is a central epigenetic mechanism catalyzed by the DNA
31 methyltransferase (DNMT) enzyme family. These enzymes add methyl groups to cytosine residues in DNA playing a key role in gene
32 regulation and cellular identity. Conversely the ten-eleven translocation (TET) enzyme family serves as active DNA demethylators
33 converting 5-methylcytosine into 5-hydroxymethylcytosine thus facilitating epigenetic reprogramming. A precise balance between
34 DNMT and TET activity is essential in regulating processes critical to embryonic and placental development. Disruption of this balance
35 may lead to epigenetic abnormalities and ultimately cause pregnancy failure.

36 This study reviews the roles of DNMT1, DNMT3A, DNMT3B and TET1, TET2, TET3 genes in RPL. It integrates molecular insights
37 diagnostic methodologies and both clinical and preclinical evidence while presenting novel therapeutic considerations.

38 **1. Scientific Background**



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39 1.1 Epigenetic Regulation in Pregnancy

40 Epigenetics refers to heritable changes in gene expression that do not involve changes to the DNA sequence. Mechanisms include DNA
41 methylation, histone modification and regulation by non-coding RNAs [6]. Among these methylation at CpG sites is a principal process
42 influencing gene activation and cellular fate [7,5]. DNA methylation is especially critical in growing tissues such as the placenta and
43 embryonic cells playing vital roles in healthy fetal development [8]. DNMT enzymes are classified into three major types: DNMT1,
44 DNMT3A and DNMT3B. DNMT1 maintains methylation patterns post-cell division whereas DNMT3A and DNMT3B mediate de novo
45 methylation essential during early development stages [9]. TET enzymes (TET1, TET2, TET3) catalyze the oxidation of 5-
46 methylcytosine to 5-hydroxymethylcytosine reversing DNA methylation and enabling gene expression changes [10].

47 1.2 Role of DNMT1, DNMT3A and DNMT3B in Pregnancy and Miscarriage

48 Extensive studies highlight the pivotal roles of DNMTs in regulating DNA methylation in placental and trophoblastic cells [11].
49 Alterations in expression or function of these enzymes can result in abnormal methylation profiles and impaired expression of critical
50 pregnancy-related genes [12]. DNMT1 is essential for genomic stability and imprinting gene regulation; reduced DNMT1 in placental
51 tissue is associated with early miscarriage [13]. DNMT3A/3B control de novo methylation; dysfunction in these enzymes affects
52 developmental and imprinted gene expression. For example DNMT3B knockout in mice leads to developmental failure and miscarriage
53 [14].

54 1.3 Role of TET Enzymes in Pregnancy and Miscarriage

55 TET enzymes regulate gene expression via demethylation and are active in early embryogenesis particularly in germ cell epigenetic
56 reprogramming [15]. TET1 is expressed in embryonic stem cells and regulates gene expression via demethylation [16]. TET2 functions
57 in adult tissues and blood cells but its role in pregnancy and placental regulation is being explored [10]. TET3 plays a key role in post-



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fertilization genome reprogramming [15]. Reduced expression or activity of these enzymes may disrupt DNA demethylation and critical gene regulation necessary for successful pregnancy.

1.4 Clinical and Laboratory Evidence Linking DNMT and TET to RPL

Studies show altered DNA methylation patterns and expression of DNMT and TET genes in placental tissues of women with RPL [17]. Decreased DNMT1/DNMT3B and increased TET1/TET2 expression were correlated with hypomethylation of developmental regulatory genes [12]. Methylome and transcriptome analyses also reveal disrupted methylation/demethylation pathways in defective placental development linked to RPL.

1.5 Genetic Polymorphisms in DNMT and TET Genes Associated with RPL Risk

Studies on single nucleotide polymorphisms (SNPs) in DNMT and TET genes have uncovered potential genetic predispositions to RPL. SNPs such as rs1569686 in DNMT3B and rs2228611 in DNMT1 are linked to increased miscarriage susceptibility. Regulatory region variations in TET2/3 also affect gene expression and elevate RPL risk [18,19].

1.6 Epigenetic Regulation of Imprinted Genes and Pregnancy Outcomes

Imprinted genes like IGF2 PEG10 and MEST are crucial for placental function and fetal growth. Abnormal methylation due to disrupted DNMT/TET function may lead to RSA [20].

Research confirms that DNMT and TET enzymes maintain methylation balance. Their dysfunction by altered expression or genetic variation may result in epigenetic anomalies and increased miscarriage risk. Further large-scale studies using advanced multi-omics technologies are needed to deepen our understanding.

2. Human Studies on Chorionic and Decidual Tissues in RSA



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76 2.1 Importance of Chorionic and Decidual Tissues in Pregnancy

77 Chorionic villi and decidua are essential placental components supporting fetal development. Chorionic tissue contains trophoblasts
78 involved in implantation and nutrient exchange while decidual tissue hormonally primed endometrium comprises immune cells
79 fibroblasts and epithelial cells [21,22]. Epigenetic changes in these tissues significantly influence implantation placental development
80 and pregnancy maintenance. Hence analyzing methylation patterns and gene expression in these tissues provides insights into RSA [23].

81 2.2 DNA Methylation and Gene Expression in Chorionic Tissue

82 Recent studies examined epigenetic changes in chorionic tissue from RSA patients. Results reported decreased DNMT1/DNMT3B
83 expression linked to global hypomethylation and abnormal regulation of placental development genes. Also they found increased
84 TET1/TET2 expression correlated with reduced 5-methylcytosine and elevated 5-hydroxymethylcytosine indicating methylation-
85 demethylation imbalance [12].

86 2.3 Epigenetic Alterations in Decidual Tissue and Their Effect on RSA

87 Decidual tissue has also been scrutinized for epigenetic dysregulation in RSA. Studies reported decreased DNMT3A/3B expression in
88 RSA patients' decidua linked to abnormal methylation of implantation-related genes. Also they observed reduced TET3 expression
89 suggesting impaired demethylation and disruption of gene expression vital for pregnancy maintenance [24].

90 2.4 Comparative Studies of Chorionic and Decidual Tissues in RSA

91 Some studies compared methylation and gene expression between both tissue types. Reports identified consistent DNMT1
92 downregulation and TET1 upregulation in both tissues with more pronounced changes in chorionic tissue suggesting systematic
93 epigenetic defects in placental structures. Also findings linked methylation alterations in imprinted gene regulatory regions to
94 implantation failure with stronger associations in decidual tissue [25].



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95 2.5. Clinical Implications and Diagnostic Potential

96 Based on the aforementioned findings alterations in DNMT and TET gene expression and DNA methylation patterns in chorionic and
97 decidual tissues may serve as potential biomarkers for early prediction of recurrent pregnancy loss (RPL) risk. Implementing these
98 markers in clinical settings may facilitate preventative measures and targeted therapy [26]. However, several challenges and limitations
99 are noted in human studies: 1-Limited access to early pregnancy tissue samples which are usually available in cases of miscarriage
100 whereas collecting healthy control samples is considerably more difficult. 2-Genetic variability environmental factors and differences
101 in experimental methodologies may contribute to inconsistent findings. 3-Future studies should include simultaneous analysis of
102 multiple epigenetic components and correlate these with clinical factors to build a more holistic understanding.

103 3. Animal Models and Laboratory Studies on DNMT and TET in Recurrent Pregnancy Loss

104 3.1 Importance of Animal Models in Epigenetic Pregnancy Research

105 Human research is inherently constrained by ethical considerations and limited sample access during critical stages of pregnancy. Hence
106 animal models particularly murine provide valuable platforms for exploring molecular and epigenetic mechanisms associated with
107 pregnancy complications including miscarriage [27].

108 3.2 DNMT Knockout and Knockdown Models During Pregnancy

109 Complete DNMT1 knockout in mice results in early embryonic lethality demonstrating the enzyme's essential role in methylation
110 maintenance and embryo survival [28]. Placenta-specific knockout models confirm its involvement in imprint gene methylation and
111 placental development [29]. Dual knockout of DNMT3A and DNMT3B causes early miscarriage and severe developmental
112 abnormalities in mice. Knockdown studies of DNMT3B highlight impaired trophoblast growth and placental dysfunction [9].

113 3.3 Role of TET Enzymes in Animal Models



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114 TET1-deficient mice exhibit abnormal demethylation elevated 5-methylcytosine reduced placental growth and increased miscarriage
115 rates. The enzyme plays a critical role in epigenetic reprogramming post-fertilization. Knockouts of TET2 and TET3 also display
116 placental demethylation defects. TET3 deletion impairs developmental gene demethylation and causes early pregnancy failure [15].

117 3.4 Cell-Based Laboratory Models

118 Trophoblast cell lines from humans and mice have been used to study DNMT and TET functions. DNMT inhibitors like 5-azacytidine
119 reduce DNA methylation and alter gene expression critical for implantation and placental development. TET inhibition causes 5-
120 methylcytosine accumulation and reduces active demethylation in genome regions vital to embryogenesis [30,31]. Impaired DNMT1,
121 DNMT3A and DNMT3B activity leads to widespread epigenetic dysregulation placental insufficiency and miscarriage. TET enzymes
122 are vital for active DNA demethylation and early epigenetic reprogramming; their absence correlates with early fetal loss. These models
123 allow for molecular investigations into RPL and may identify new therapeutic targets for its prevention.

124 4. Molecular Mechanisms of DNMT and TET in Recurrent Pregnancy Loss

125 Understanding how DNMT and TET regulate methylation and demethylation in placental and uterine tissues is key to decoding the
126 epigenetic causes of miscarriage.

127 4.1 DNMT-Mediated DNA Methylation and Gene Expression

128 DNMT1, DNMT3A and DNMT3B catalyze methyl group addition at CpG sites typically silencing gene expression especially in
129 promoter regions. Imprinted genes (e.g. IGF2, PEG10) are essential for fetal and placental growth; their aberrant methylation due to
130 DNMT dysfunction can lead to miscarriage. Aberrant DNA methylation may alter maternal immune gene expression triggering immune
131 rejection of the fetus and resulting in pregnancy loss [32,20].

132 4.2 TET Enzymes in Active DNA Demethylation and Epigenetic Reprogramming



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133 Through active DNA Demethylation TET1–3 convert 5-methylcytosine into 5-hydroxymethylcytosine and other derivatives facilitating
134 methyl group removal and epigenetic reprogramming [33]. Early Reprogramming are critical in early pregnancy with disruptions leading
135 to implantation failure and developmental defects [15]. Through regulation of developmental and placental genes TET enzymes activate
136 genes involved in cellular differentiation and placental structure; reduced activity may silence essential genes and trigger miscarriage.

137 **4.3 DNMT–TET Interplay in Maintaining Epigenetic Balance**

138 In dynamic balance DNMTs and TETs have antagonistic yet complementary roles in maintaining DNA methylation homeostasis.
139 Imbalance can lead to epigenetic disorders and disease. In disrupted equilibrium reduced DNMT or hyperactive TET expression may
140 cause global hypomethylation and vice versa. RPL tissues exhibit such dysregulation [34].

141 **4.4 Signaling Pathways Influenced by DNMT and TET**

142 Epigenetic changes in inflammation-related genes may exacerbate chronic placental inflammation a recognized factor in miscarriage.
143 In placental development pathways genes governing trophoblast differentiation and placental angiogenesis are epigenetically regulated;
144 their misexpression due to methylation errors affects placental function [35].

145 **4.5 Environmental and Stress Effects on DNMT and TET Activity**

146 Environmental stressors, oxidative stress malnutrition and toxin exposure may alter DNMT and TET activity disrupt methylation
147 patterns and increase RPL risk [36].

148 **5. Diagnostic Techniques for Measuring DNMT/TET and DNA Methylation in RPL Patients**

149 Accurate quantification of epigenetic changes specifically DNMT and TET expression and DNA methylation is crucial in identifying
150 high-risk patients for RPL.



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151 5.1 Methods to Measure DNMT and TET Expression

152 RT-qPCR quantifies mRNA expression of DNMT and TET genes with high precision; widely used for comparing chorionic and decidual
153 samples. Western Blot detects protein levels of DNMT and TET offering insight into post-translational changes. Immunohistochemistry
154 (IHC) uses specific antibodies to visualize DNMT/TET spatial distribution and expression intensity in tissues. RNA-Seq allows genome-
155 wide transcriptomic profiling uncovering complex expression changes in DNMT/TET genes [37-40].

156 5.2 DNA Methylation Assessment Techniques

157 Bisulfite Sequencing is the gold standard for mapping methylation sites by converting unmethylated cytosine to uracil. Methylation-
158 Specific PCR (MSP) is sensitive and cost-effective method for detecting methylation in specific gene regions. MeDIP (Methylated DNA
159 Immunoprecipitation) employs anti-5mC antibodies for large-scale methylation profiling. Methylation Microarrays analyze thousands
160 of methylation sites simultaneously; used for broad methylation screening in RPL patients. Bisulfite Cloning and Electrophoresis
161 classical methods to validate methylation status in target genes [41,42].

162 5.3 Detection of 5-Hydroxymethylcytosine (5hmC)

163 Dot Blot Assay is semi-quantitative method using anti-5hmC antibodies to assess global 5hmC levels. IHC for 5hmC visualizes tissue
164 distribution of 5hmC using targeted antibodies. TAB-Seq (TET-Assisted Bisulfite Sequencing) differentiates between 5mC and 5hmC
165 at single-nucleotide resolution [43-45].

166 Combining these methods in chorionic and decidual samples allows identification of epigenetic biomarkers associated with RPL.
167 Integrating

168 6. Therapeutic Strategies Targeting DNMT and TET Pathways in Recurrent Pregnancy Loss



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169 Given the crucial role of DNMT and TET enzymes in the epigenetic regulation of gene expression and their impact on successful
170 pregnancy targeting these pathways represents a promising avenue for therapeutic intervention in recurrent pregnancy loss (RPL).

171 **6.1 DNMT Inhibitors**

172 5-azacytidine and 5-aza-2'-deoxycytidine (Decitabine): These cytosine analogs are well-known DNMT inhibitors that covalently bind
173 to DNMTs blocking their activity and reducing DNA methylation levels. While primarily used in cancer therapy preliminary studies
174 indicate that controlled dosing and timing may help normalize epigenetic patterns related to pregnancy and miscarriage [46]. Limited
175 administration in animal models has shown improvements in methylation profiles and reduced RPL incidence; however extensive
176 clinical trials are needed to confirm efficacy and safety in humans.

177 **6.2 Modulating TET Activity**

178 TET Activation: Vitamin C acts as a cofactor for TET enzymes and has been shown to enhance DNA demethylation by increasing 5-
179 hydroxymethylcytosine levels and promoting epigenetic reprogramming [47]. Such effects may contribute to improved pregnancy
180 outcomes.

181 Micronutrients and Diet: Folate and B-complex vitamins also influence DNA methylation and enzymatic activity of DNMTs and TETs
182 supporting epigenetic balance through nutritional modulation [48].

183 **6.3 Targeted Molecular Therapies**

184 Monoclonal Antibodies and Small Molecules: Advances in biotechnology have enabled the development of specific molecules and
185 antibodies designed to modulate DNMT or TET activity selectively [49].

186 Epigenetic Genome Editing: Technologies such as CRISPR/dCas9 fused to methylation or demethylation enzymes allow precise editing
187 of epigenetic marks. These approaches may become effective therapeutic tools for RPL in the future [50].



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188 6.4 Therapeutic Considerations and Challenges

189 Safety and Side Effects: DNMT inhibitors may produce widespread genomic effects and pose safety concerns during pregnancy
190 requiring comprehensive risk assessment.

191 Target Specificity: Therapeutic strategies must selectively target placental or uterine cells without affecting other tissues.

192 Dosage and Timing: Optimal dosing and timing are critical for the success of epigenetic interventions.

193 Integrative Therapies: Combining epigenetic treatments with hormonal and immunological therapies may yield synergistic benefits.

194 Biomarker Development: Epigenetic biomarkers are needed to monitor therapeutic response and predict treatment outcomes.

195 7. Conclusion

196 Extensive evidence indicates that alterations in DNMT1, DNMT3A, DNMT3B and TET1, TET2, TET3 gene expression and activity
197 are closely associated with RPL. These enzymes maintain epigenetic homeostasis through the methylation and demethylation of DNA
198 processes essential for embryonic development and placental function. Any imbalance in DNMT/TET activity may trigger epigenetic
199 dysregulation leading to impaired fetal growth and recurrent miscarriage. Both molecular and clinical studies show that changes in
200 DNMT and TET levels in pregnancy-related tissues such as the placenta and uterus correlate with increased miscarriage risk.
201 Environmental factors, nutritional status and oxidative stress may also contribute to epigenetic instability. Advanced diagnostic tools
202 for measuring gene expression, DNA methylation levels and 5-hydroxymethylcytosine profiles enable early risk assessment and may
203 inform future preventive and therapeutic approaches. Interventions aimed at restoring DNMT/TET function via pharmacological
204 inhibitors dietary supplementation or genome-editing technologies offer hopeful prospects in the management of RPL.

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211 **Ethical approval**

212 This research was approved by the ethics committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1402.077).

213 **Conflict of interest**

214 The authors declare that there is no conflict of interest regarding the publication of this paper.

215 **Consent for Publication**

216 This manuscript is a narrative review article and does not contain any individual person's data, such as personal details, images, or
217 videos. Therefore, no consent for publication is required.

218 **Data Availability statement**

219 Data availability is not applicable to this article as no new data were created or analyzed in this study.

220

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