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Metabolic Syndrome in the Etiopathogenesis of Recurrent Pregnancy Loss: A Systematic Review

Nabieva Ranokhon Muzaffar qizi[1], Ataxodjaeva Fotima Abduraimovna[2]

[1] Tashkent State Medical University, Tashkent, Uzbekistan

[2] Department of Obstetrics and Gynecology, Tashkent State Medical University, Tashkent, Uzbekistan

E-mail (1): ranoxon.abdazova@gmail.com

E-mail (2): fatimaataxodjayeva@gmail.com; p.atakhodjaeva@tashmeduni.uz

ORCID (1): 0009-0007-1040-9087; ORCID (2): 0009-0007-4304-1506

Abstract. Recurrent pregnancy loss (RPL) often remains unexplained even after routine evaluation, which makes potentially modifiable risk factors especially important. Metabolic syndrome (MetS) has gained attention in this context because it combines central obesity, insulin resistance or dysglycemia, hypertension, and atherogenic dyslipidemia into a single adverse reproductive phenotype. This systematic review summarizes current evidence on the role of MetS in the etiopathogenesis of RPL. The available literature suggests that women with RPL more often demonstrate metabolic abnormalities, higher body mass index, oxidative stress, and immune-inflammatory imbalance. Among the most consistent findings are increased malondialdehyde (MDA), reflecting enhanced lipid peroxidation, and a shift toward a pro-inflammatory cytokine profile, commonly characterized by higher interleukin-6 (IL-6), lower or relatively insufficient interleukin-10 (IL-10), and an increased IL-6/IL-10 ratio. Taken together, these data support the idea that MetS creates a biologically unfavorable background for implantation, placentation, and early fetal development. Despite heterogeneity across studies, metabolic assessment before conception appears clinically relevant in women with RPL.

Keywords: recurrent pregnancy loss; recurrent miscarriage; metabolic syndrome; insulin resistance; oxidative stress; malondialdehyde; IL-6; IL-10; obesity.

Relevance

Recurrent pregnancy loss (RPL) remains one of the most difficult problems in reproductive medicine because a substantial proportion of cases still have no clearly established cause after standard evaluation. Major modern guidelines generally define RPL as the loss of two or more pregnancies, whereas older definitions often used three losses [5,28]. RPL affects approximately 1-2% of couples and continues to impose a major medical, psychological, and social burden [5,28].

In parallel, metabolic syndrome (MetS) is no longer viewed only as a cardiometabolic construct. It is increasingly recognized as a systemic disorder with reproductive relevance, characterized by central obesity, dysglycemia or insulin resistance, elevated blood pressure, hypertriglyceridemia, and low high-density lipoprotein cholesterol [1-3,7,13]. The diagnostic concept of MetS has evolved from the World Health Organization and EGIR definitions, which emphasized insulin resistance, to ATP III, IDF, and later harmonized criteria that use combinations of key metabolic abnormalities [1-3,7,13].

The biological plausibility linking MetS and RPL is strong. Adipose tissue is now recognized as an active endocrine and inflammatory organ rather than a passive fat depot [15]. Pregnancy itself requires tightly coordinated immunologic shifts: relative pro-inflammatory predominance during implantation, relative anti-inflammatory balance during fetal growth, and renewed inflammation before labor [24]. Within this framework, insulin resistance, dyslipidemia, endothelial dysfunction, oxidative stress, and cytokine imbalance may disrupt implantation, early placentation, and maternal-fetal immune tolerance [8,10,14,16,19,24,32-34].

Research objective: To summarize current evidence on the role of metabolic syndrome in the etiopathogenesis of recurrent pregnancy loss, with particular emphasis on oxidative stress and inflammatory-cytokine mechanisms.

Materials and methods.

A structured literature search was performed for English-language publications indexed in PubMed and complemented by searches of major publisher platforms and Google Scholar up to March 2026. Search terms included combinations of 'recurrent pregnancy loss', 'recurrent miscarriage', 'metabolic syndrome', 'insulin resistance', 'obesity', 'oxidative stress', 'malondialdehyde', 'IL-6', 'IL-10', 'cytokines', 'implantation', and 'placentation'. Clinical guidelines, systematic reviews, meta-analyses, observational studies, and mechanistic studies relevant to women of reproductive age were prioritized. Reference lists of key publications were also screened manually.

Studies were included if they addressed at least one of the following: the relationship between MetS or its components and RPL; oxidative stress biomarkers in RPL; inflammatory cytokine patterns in RPL; or metabolic-inflammatory mechanisms with potential relevance to reproductive loss. Case reports, duplicate publications, and studies without clear relevance to RPL or metabolic dysfunction were excluded.

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This manuscript was designed as a qualitative systematic review. Because of substantial heterogeneity across studies in RPL definitions, MetS criteria, clinical phenotypes, gestational timing, laboratory methods, and biomarker platforms, no formal meta-analysis was undertaken in the present paper.

Results.

Current evidence suggests that women with RPL frequently carry a measurable metabolic burden even when they do not have a classic endocrine diagnosis. In a study of women with unexplained RPL, MetS was identified in 24.4% of participants, while 82.6% had at least one MetS component; moreover, a greater number of metabolic abnormalities was associated with a higher miscarriage burden [18]. In a separate systematic review and meta-analysis, women with RPL had a significantly higher maternal body mass index than controls, with a pooled mean difference of 0.7 kg/m2, supporting the concept that adverse metabolic phenotype is overrepresented in this population [11]. These findings do not by themselves prove causality, but they support the view that MetS-related traits cluster in women with recurrent reproductive failure [11,18].

From a mechanistic perspective, MetS may contribute to RPL through several converging pathways. Central obesity and insulin resistance promote adipocyte hypertrophy, altered adipokine secretion, endothelial dysfunction, dyslipidemia, and chronic low-grade inflammation [15]. These abnormalities are biologically relevant to implantation and placentation because early trophoblast invasion, decidual remodeling, vascular adaptation, and maternal immune tolerance are highly sensitive to oxidative and inflammatory stress [15,24,32-34].

One of the most reproducible links between MetS and RPL is oxidative stress. Although no universally standardized oxidative stress biomarker panel exists, malondialdehyde (MDA) remains one of the most frequently used markers of lipid peroxidation in reproductive research [23]. Multiple studies summarized in recent reviews have shown that women with RPL have elevated MDA levels in plasma and placental tissue [35]. In Saudi cohorts, plasma MDA reached 7.87 +/- 0.96 nmol/mL in recurrent miscarriage patients versus 5.73 +/- 0.76 nmol/mL in healthy pregnant women and 5.03 +/- 0.70 nmol/mL in non-pregnant controls; placental MDA was also significantly higher in the miscarriage group [4]. Another study showed higher plasma MDA in recurrent miscarriage (5.95 +/- 0.91) than in healthy pregnancy (5.12 +/- 0.81), together with marked increases in whole-blood and placental lipid peroxidation [17]. Other reports documented elevated MDA and increased MDA/vitamin E ratios in women with recurrent losses, supporting sustained oxidative burden [6,12]. Taken together, these findings indicate that lipid peroxidation is a plausible contributor to trophoblast-endometrial dysfunction and defective placentation in RPL [4,6,12,17,23,35].

The same oxidative signature is also observed in metabolic disorders relevant to reproductive-age women. In obese women, MDA was substantially higher when MetS was present than when obesity occurred without MetS (8.57 +/- 5.5 vs 4.6 +/- 3.2 nmol/mL; p = 0.008), suggesting that metabolic clustering amplifies oxidative damage beyond adiposity alone [22]. In another study, obese women had higher serum MDA than eutrophic controls (2.52 +/- 0.31 vs 2.13 +/- 0.26 umol/L) [27]. Likewise, women with polycystic ovary syndrome showed higher MDA than controls (3.12 +/- 0.66 vs 2.41 +/- 0.56 nmol/mL), reinforcing the concept that metabolically adverse reproductive phenotypes share an oxidative background [29]. Thus, when MetS coexists with RPL, oxidative injury may intensify rather than simply accumulate [22,27,29].

Inflammatory and immunoregulatory mechanisms provide a second major bridge between MetS and RPL. Successful pregnancy depends less on absolute concentrations of single cytokines than on the dynamic balance between pro-inflammatory and anti-inflammatory signals [24,33,34]. In mid-gestation pregnancies among women with prior RPL, circulating IL-6 was significantly higher and IL-10 significantly lower than in women without such history; the IL-6/IL-10 ratio was also markedly increased, indicating a systemic pro-inflammatory shift [21]. In a related study, women with RPL demonstrated reduced Treg-cell proportions and elevated IL-6/TGF-beta and IL-6/IL-10 ratios, again pointing toward impaired immunologic tolerance [20]. However, cytokine data are not entirely uniform: in first-trimester missed miscarriage, one study found no statistically significant differences in serum IL-6, TNF-alpha, or IL-10 between cases and controls, underscoring that cytokine patterns vary by clinical phenotype, gestational age, and biological compartment [24]. Even so, the dominant trend in the RPL literature supports a relative shift toward pro-inflammatory signaling and weakened regulatory buffering [9,20,21,24,33].

Metabolic syndrome itself also shows heterogeneous but clinically relevant cytokine alterations. In young patients with MetS, IL-6 and IL-10 were increased while IL-2 was decreased, suggesting simultaneous inflammatory activation and dysregulated T-cell control [31]. In middle-aged women, higher IL-6 concentrations were associated with hypertriglyceridemia and insulin resistance, while TNF-alpha correlated with abdominal obesity, indicating that inflammatory markers may map more strongly to individual MetS components than to the syndrome as a single entity [26]. Conversely, a postmenopausal cohort showed lower TNF-alpha and a higher IL-10/TNF-alpha ratio in MetS, which may reflect compensatory anti-inflammatory responses rather than genuine protection [30]. These discrepancies are important because they imply that the cytokine signature of MetS is context-dependent, but they do not negate the central conclusion that MetS alters immune-metabolic homeostasis in ways that may become reproductively unfavorable in susceptible women [26,30,31].

Debate

The available literature supports a coherent model in which MetS contributes to RPL through interrelated metabolic, oxidative, vascular, and immunologic pathways. Direct clinical evidence shows that MetS and its components are common among women with unexplained RPL, while indirect evidence demonstrates that obesity, insulin resistance, and dyslipidemia are each linked to oxidative stress and inflammatory activation [11,18,22,26,27,29]. In biological terms, MetS appears to lower the threshold for reproductive failure by creating a hostile peri-implantation environment characterized by adipose dysfunction, reactive oxygen species excess, endothelial injury, and disturbed immune tolerance.

Oxidative stress deserves particular emphasis because it is one of the few mechanisms repeatedly demonstrated across both RPL and MetS-related phenotypes. MDA has practical advantages because it is measurable in blood and, in some studies, in placental tissue; it is also suitable for dynamic follow-up across preconception and pregnancy-related intervals. At the same time, MDA is not a perfect biomarker, and analytical variability remains a recognized limitation [23]. Therefore, its use is best interpreted as part of a broader pathophysiologic framework rather than as a standalone diagnostic test. Even with this limitation, the repeated elevation of MDA in RPL, obesity, polycystic ovary syndrome, and MetS strongly supports the hypothesis that redox imbalance is a core shared pathway [4,6,17,22,23,27,29,35].

The inflammatory evidence is persuasive but more heterogeneous. Some studies consistently show elevated IL-6, reduced IL-10, and increased IL-6/IL-10 ratios in women with RPL, whereas others fail to detect significant differences in early gestation or in specific miscarriage phenotypes [20,21,24]. This inconsistency likely reflects genuine biological diversity rather than simple methodological weakness. Cytokines fluctuate by trimester, tissue compartment, concurrent disorders such as thrombophilia or polycystic ovary syndrome, and the degree of metabolic burden. For this reason, the most informative interpretation may lie not in isolated cytokine values, but in the balance between pro-inflammatory and anti-inflammatory networks [20,21,24,33,34].

Clinically, these findings support inclusion of metabolic assessment in women with RPL, especially when the standard etiologic work-up is unrevealing. Screening for abdominal obesity, blood pressure elevation, dysglycemia, hypertriglyceridemia, low high-density lipoprotein cholesterol, and markers of insulin resistance may help identify patients whose reproductive risk is being amplified by a treatable metabolic background. Still, the present evidence base is not yet sufficient to claim that correction of MetS will uniformly prevent RPL. The major gaps remain the lack of unified MetS and RPL definitions across studies, the scarcity of prospective reproductive-age cohorts, and the limited number of intervention trials designed around reproductive rather than cardiovascular outcomes [5,11,18,35].

Conclusion

Metabolic syndrome appears to play a meaningful role in the etiopathogenesis of recurrent pregnancy loss. The association is biologically plausible and is supported by converging evidence from clinical, biochemical, and immunologic studies. Insulin resistance, visceral adiposity, endothelial dysfunction, oxidative stress, and cytokine imbalance may together impair implantation, placentation, and the maintenance of early pregnancy. Among the candidate mediators, MDA and the IL-6/IL-10 axis are especially informative, although both remain influenced by methodological and phenotypic heterogeneity. In practical terms, MetS should be considered a relevant preconception and reproductive risk phenotype in women with RPL. Future longitudinal and interventional studies are needed to determine whether systematic metabolic correction before conception can improve live birth outcomes.

References

1. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
2. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet Med. 2006;23(5):469-80.
3. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-53.
4. Al-Sheikh YA, Ghneim HK, Alharbi AF, Alshebly MM, Aljaser FS, Aboul-Soud MAM. Molecular and biochemical investigations of key antioxidant/oxidant molecules in Saudi patients with recurrent miscarriage. Exp Ther Med. 2019;18(6):4450-60.
5. Atik RB, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open. 2023;2023(1):hoad002.
6. Baban RS. Oxidative stress in recurrent pregnancy loss women. Saudi Med J. 2010;31(7):759-63.
7. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med. 1999;16(5):442-3.
8. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006;441(7090):235-8.

9. Calleja-Agius J, Brincat MP. Recurrent miscarriages: what is the role of cytokines? Gynecol Endocrinol. 2008;24(12):663-8.
10. Cheng SB, Sharma S. Interleukin-10: a pleiotropic regulator in pregnancy. Am J Reprod Immunol. 2015;73(6):487-500.
11. Eapen A, Hayes ET, McQueen DB, Beestrum M, Eyck PT, Boots C. Mean differences in maternal body mass index and recurrent pregnancy loss: a systematic review and meta-analysis of observational studies. Fertil Steril. 2021;116(5):1341-8.
12. El-Far M, El-Sayed IH, El-Motwally AE, Abou Hashem I, Bakry N. Tumor necrosis factor-alpha and oxidant status are essential participating factors in unexplained recurrent spontaneous abortions. Clin Chem Lab Med. 2007;45(7):879-83.
13. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
14. Fantini MC, Becker C, Monteleone G, Pallone F, Galle PR, Neurath MF. TGF-beta induces a regulatory phenotype in CD4+CD25- T cells through Foxp3 induction and down-regulation of Smad7. J Immunol. 2004;172(9):5149-53.
15. Fernandez-Sanchez A, Madrigal-Santillan E, Bautista M, Esquivel-Soto J, Morales-Gonzalez A, Esquivel-Chirino C, et al. Inflammation, oxidative stress, and obesity. Int J Mol Sci. 2011;12(5):3117-32.
16. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther. 2006;8 Suppl 2:S3.
17. Ghneim HK, Alshebly MM. Biochemical markers of oxidative stress in Saudi women with recurrent miscarriage. J Korean Med Sci. 2016;31(1):98-105.
18. Hilali NG, Sak S, Incebiyik A, Uyanikoglu H, Sak ME, Incebiyik H, et al. Recurrent pregnancy loss and metabolic syndrome. Ginekol Pol. 2020;91(6):320-3.
19. Hirano T. IL-6 in inflammation, autoimmunity and cancer. Int Immunol. 2021;33(3):127-48.
20. Jameel S, Bhuwalka R, Begum M, Bonu R, Jahan P. Circulating levels of cytokines (IL-6, IL-10 and TGF-beta) and CD4+CD25+FOXP3+Treg cell population in recurrent pregnancy loss. Reprod Biol. 2024;24(1):100842.
21. Jameel S, Bhuwalka R, Jahan P. Association of circulating IL-6 and IL-10 levels during mid-gestation with recurrent pregnancy loss history and severity: a South Indian study. Explor Immunol. 2025;5:1003209.
22. Karahan Yilmaz SK, Eskici G, Mertoglu C, Ayaz A. Adipokines, inflammation, oxidative stress: critical components in obese women with metabolic syndrome. Prog Nutr. 2021;23(1):e2021009.
23. Khoubnasabjafari M, Ansarin K, Jouyban A. Reliability of malondialdehyde as a biomarker of oxidative stress in psychological disorders. Bioimpacts. 2015;5(3):123-7.
24. Kwiatek M, Geca T, Kwasniewska A. Pro- and anti-inflammatory cytokines in the first trimester-comparison of missed miscarriage and normal pregnancy. Int J Environ Res Public Health. 2021;18(16):8538.
25. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425-33.
26. Mruczyk K, Cisek-Wozniak A, Molska M, Skoczek-Rubinska A. The role of inflammatory markers in linking metabolic syndrome to cognitive decline in middle-aged women: a focus on TNF-alpha and IL-6. Metabolites. 2025;15(3):186.
27. Noronha NY, Pinhel MAS, Nicoletti CF, Quinhoneiro DCG, Pinhanelli VC, Oliveira BAP, et al. Green tea supplementation improves oxidative stress biomarkers and modulates IL-6 circulating levels in obese women. Nutr Hosp. 2019;36(3):583-8.
28. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103-11.
29. Rahsepar M, Mahjoub S, Esmaeilzadeh S, Kanafchian M, Ghasemi M. Evaluation of vitamin D status and its correlation with oxidative stress markers in women with polycystic ovary syndrome. Int J Reprod Biomed. 2017;15(6):345-50.
30. Sinatora RV, Chagas EFB, Mattera FOP, Mellem LJ, Santos ARO, Pereira LP, et al. Relationship of inflammatory markers and metabolic syndrome in postmenopausal women. Metabolites. 2022;12(1):73.
31. Sumerkina VA, Telesheva LF, Golovneva ES. Association of the cytokine profile and metabolic syndrome components in young patients. Russian Journal of Immunology. 2022;25(4):535-40.
32. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10):a016295.
33. Vilotic A, Nacka-Aleksic M, Pirkovic A, Bojic-Trbojevic Z, Dekanski D, Krivokuca MJ. IL-6 and IL-8: an overview of their roles in healthy and pathological pregnancies. Int J Mol Sci. 2022;23(23):14574.
34. Yang X, Tian Y, Zheng L, Luu T, Kwak-Kim J. The update immune-regulatory role of pro- and anti-inflammatory cytokines in recurrent pregnancy losses. Int J Mol Sci. 2023;24(1):132.
35. Zejnullahu VA, Zejnullahu VA, Kosumi E. The role of oxidative stress in patients with recurrent pregnancy loss: a review. Reprod Health. 2021;18(1):207.