

PRECISION PRECONCEPTION HEALTH: INTEGRATING METABOLIC, INFLAMMATORY AND NUTRIGENOMIC BIOMARKERS FOR EARLY REPRODUCTIVE AND INTERGENERATIONAL RISK STRATIFICATION

ION MEREUȚĂ^{a,b,*}, VLADIMIR CARAUȘ^a and IURIE CARAUȘ^c

^a Moldova State University, 60 Alexei Mateevici Street, MD-2009, Chisinau, Republic of Moldova.

^b Corresponding Member of the Academy of Sciences of Moldova

^c IMSP Institute of Mother and Child, 93 Burebista Street, MD-2062, Chisinau, Republic of Moldova.

* Corresponding author: Ion Mereuță, e-mail: ion.mereuta@usmf.md

Received July 23, 2026

The preconception period is a distinct biological stage during which the health of both women and men may influence fertility, the course of pregnancy and, through mechanisms that remain incompletely elucidated, offspring health. The interplay among metabolic and nutritional status, chronic low-grade inflammation, oxidative stress, behavioural factors and environmental exposures supports extending the scope of preconception care beyond conventional preparation for pregnancy. In this integrative narrative review, we critically examine the integration of established clinical and biochemical parameters with inflammatory biomarkers, metabolomics and nutrigenomic information for early reproductive risk stratification.

Based on the literature reviewed, we propose the Preconception Precision Prevention Window (PPPW) as a conceptual framework. The model involves a stepwise assessment, progressing from the identification of risk factors and characterisation of the metabolic and reproductive phenotype to selected molecular investigations, individualised intervention and reassessment. Within this approach, precision derives from selecting information that can meaningfully alter preventive or clinical management rather than from increasing the number of tests. Clinical implementation of this paradigm requires methodological standardisation, prospective validation and evidence of added value beyond established assessment.

Keywords: preconception health; precision prevention; infertility; metabolomics; nutrigenomics.

INTRODUCTION

Infertility is an important public health problem; the World Health Organization (WHO) estimates that approximately one in six people experience infertility during their lifetime [1]. The 2025 WHO global guideline on the prevention, diagnosis and treatment of infertility emphasises addressing modifiable risk factors while ensuring access to specialist assessment and treatment [2]. This guidance supports a gradual shift from an exclusively reactive approach towards identifying risk before reproductive dysfunction becomes clinically manifest.

The preconception period offers an important opportunity for such a preventive approach. Diet, weight and metabolic status, physical activity, smoking, alcohol consumption, micronutrient status, chronic diseases and occupational or environmental exposures may influence reproductive health before

conception [2,3]. The Developmental Origins of Health and Disease (DOHaD) concept extends this perspective by suggesting that the periconceptual biological environment may have consequences for subsequent development [4,5].

An important conceptual development is the systematic inclusion of men in preconception assessment. Recent evidence supports considering the couple as the unit of preventive assessment, with evaluation of the metabolic, nutritional, behavioural and reproductive health of both partners [6,7].

The aim of this review is to critically examine the integration of clinical, metabolic, inflammatory and nutritional parameters with metabolomic and nutrigenomic technologies, and to propose a stepwise model for characterising the preconception biological phenotype and stratifying individual risk.

REVIEW METHODOLOGY

This article was designed as an integrative narrative review rather than a systematic review. Thematic searches were performed in PubMed/MEDLINE, and relevant WHO documents and professional recommendations were consulted, with the literature updated through September 2026. Priority was given to guidelines, systematic reviews, meta-analyses and evidence syntheses published between 2021 and 2026, while earlier seminal sources were retained for core preconception and DOHaD concepts. The analysis focused on evidence-supported modifiable factors, the incremental value of omics technologies and the distinction between biomarkers with clinical utility and those that remain exploratory.

THE PRECONCEPTION PERIOD AS A WINDOW FOR PREVENTION

Contemporary preconception care includes the identification of chronic diseases, behavioural and nutritional factors, relevant medications, toxic exposures and modifiable reproductive risks ^{2,8}. However, a 2026 meta-analysis of preconception lifestyle interventions in women found no significant overall differences in clinical pregnancy or live-birth rates [9]. Improvements in metabolic health and an increased probability of conception should therefore not be regarded as automatically equivalent outcomes.

Clinical assessment remains the foundation of this approach: evaluation of female infertility should be systematic and efficient in its use of resources [10], while standardised semen analysis remains central to male assessment [11,12]. Precision medicine should not replace these tools; rather, when justified, it should help characterise the biological heterogeneity that exists within the same clinical categories.

METABOLIC AND NUTRITIONAL PHENOTYPE

Metabolism and reproduction are closely interconnected. Diet and metabolic status are relevant preconception determinants of reproductive health in both women and men [13–15]. Available data support biologically plausible associations, including those involving Mediterranean dietary patterns; however, study

heterogeneity does not permit the definition of a universally applicable “fertility diet” [13–15].

Before molecular personalisation of nutrition is considered, overall diet quality, correction of documented deficiencies and optimisation of metabolic health should be ensured.

Weight status illustrates the need for such nuance. An unfavourable preconception body mass index (BMI) is associated with reduced female fecundity [16]. In a meta-analysis of preconception weight-loss interventions, the probability of pregnancy increased, whereas the live-birth rate did not change significantly [17]. In men, excess adiposity is associated with impairment of several semen parameters [18]. The preventive goal should therefore remain optimisation of the metabolic phenotype and reduction of associated risks, rather than promising restoration of fertility through weight loss alone.

INFLAMMATION AND OXIDATIVE STRESS

Physiological inflammation participates in ovulation, implantation and tissue remodelling, whereas chronic low-grade inflammation may impair folliculogenesis, oocyte quality and hormonal signalling [19]. In men, redox balance is equally important: reactive oxygen species serve physiological functions, but excessive levels may damage membranes and mitochondria, impair motility and compromise sperm DNA integrity [20].

These relationships do not justify the routine use of broad panels of “oxidative stress” biomarkers or systematic antioxidant supplementation. The Cochrane review of antioxidants for male subfertility rated the certainty of evidence for several clinical outcomes as low or very low [21]. In the proposed model, inflammatory and redox markers have a contextual role rather than serving as stand-alone fertility tests.

METABOLOMICS: FROM CONVENTIONAL BIOCHEMISTRY TO MOLECULAR PHENOTYPING

Metabolomics enables the simultaneous analysis of a large number of metabolites and provides a dynamic representation of the biochemical phenotype [22]. In conditions associated with female infertility, alterations have

been reported in amino acid, lipid, glucose and energy metabolism [22,23].

A 2026 systematic review of follicular-fluid metabolomics identified recurrent changes in glucose, lactate, fatty acids, lipids and amino acids across different infertility contexts [24]. These signals are promising, but heterogeneity in analytical platforms, pre-analytical conditions and study populations currently prevents the definition of a universally applicable clinical profile.

The same gap between biomarker discovery and clinical application is evident in reproductive multi-omics. Integration of transcriptomics, epigenomics, proteomics and metabolomics may reveal biological patterns that cannot be captured by an isolated marker, yet standardisation, external validation, cost and integration into clinical practice remain major limitations [25]. Candidate multi-omic biomarkers have also been identified in male infertility [26,27], but most remain at the research stage. Metabolomics should therefore be regarded as a tool for molecular phenotyping and biomarker discovery, with potential for future stratification, rather than as a substitute for standard assessment.

NUTRIGENOMICS AND PERSONALISED NUTRITION

Metabolic responses to diet vary among individuals, including as a function of genetic characteristics and metabolic phenotype. Nutrigenomics and nutrigenetics seek to characterise interactions between genetic variation and dietary response [28], while gene–nutrient mechanisms relevant to metabolism and oxidative stress have been proposed in male infertility [29]. The biological plausibility of these mechanisms should not be conflated with the clinical validation of commercial nutrigenetic tests.

The existence of a biochemical relationship between a micronutrient and reproduction does not in itself demonstrate benefit from supplementation. A recent umbrella review concluded that the available evidence is insufficient to recommend nutritional supplements for improving outcomes in female infertility, primarily because the certainty of evidence is low or very low [30]. In our view, personalisation of nutrition should follow a logical sequence: clinical phenotype → metabolic

and nutritional status → documented deficiencies → dietary intervention → genetic or omic information only when it provides demonstrable added value.

PATERNAL HEALTH AND THE INTERGENERATIONAL DIMENSION

An important shift in the preconception paradigm is the recognition of the father's role in shaping the biological environment before conception. A 2026 review published in *The Lancet* showed that paternal preconception health remains insufficiently integrated into research, practice and policy despite its relevance to reproductive and family health [6].

Experimental and epidemiological studies suggest that paternal obesity, diet, smoking, age and other exposures may be associated with changes in DNA methylation, non-coding RNAs or sperm chromatin [31–33]. However, a 2025 systematic review including [28] observational human studies found a high or very high risk of bias in most studies and limited overlap among the reported epigenetic signatures [31].

Current evidence on paternal epigenetics does not support individualised risk prediction. The clinically robust conclusion is more straightforward: preconception health should be addressed in both partners. Similar caution is required when interpreting environmental exposures: some chemicals with endocrine-disrupting properties are associated with altered fecundity, but exposure assessment and control of confounding remain challenging [34].

FROM AN ISOLATED BIOMARKER TO INTEGRATED STRATIFICATION

Reproductive biology cannot be reduced to a single biomarker. We therefore propose a hierarchical stratification in which clinical, metabolic and reproductive assessment forms the foundation, while inflammatory biomarkers and omics technologies are added selectively, in proportion to individual risk and to the likelihood that the result will alter preventive or clinical management.

Table 1

Levels of preconception risk stratification

Level	Assessment	Examples	Current status
I	Clinical and behavioural	age, history, BMI/waist, BP, diet, smoking, alcohol, physical activity, exposures	Established
II	Metabolic and biochemical	glucose/HbA1c when indicated, lipids, liver/renal function, complete blood count, selected micronutrients	Established / indication-dependent
III	Reproductive and endocrine	ovarian/endocrine assessment, semen analysis, specific investigations	Established
IV	Inflammatory/redox	selected markers in defined clinical contexts	Adjunctive
V	Metabolomic	amino acid, lipid and energy-metabolism profiles	Emerging
VI	Nutrigenomic	gene–nutrient interactions; molecular response to diet	Emerging
VII	Multi-omic	integration of genomics, epigenomics, transcriptomics, proteomics and metabolomics	Research-stage

Note. BMI – body mass index; BP – blood pressure; HbA1c – glycated haemoglobin. The status category reflects the current level of clinical integration of each assessment domain.

Progression to higher levels is not mandatory. The complexity of assessment should be proportionate to individual risk and to the clinical utility of the information obtained.

THE PPPW CONCEPTUAL FRAMEWORK PROPOSED BY THE AUTHORS

Based on the convergence of the evidence reviewed, we propose the Preconception Precision Prevention Window (PPPW). PPPW is neither a

diagnostic test nor a validated clinical protocol; rather, it is a conceptual framework proposed by the authors to organise preconception assessment in a stepwise manner and to select investigations according to individual risk.

Within this architecture, precision is not defined by the number of tests performed. It results from adapting the level of investigation to the individual biological phenotype and to the probability that the information obtained will lead to a justified preventive or clinical action.

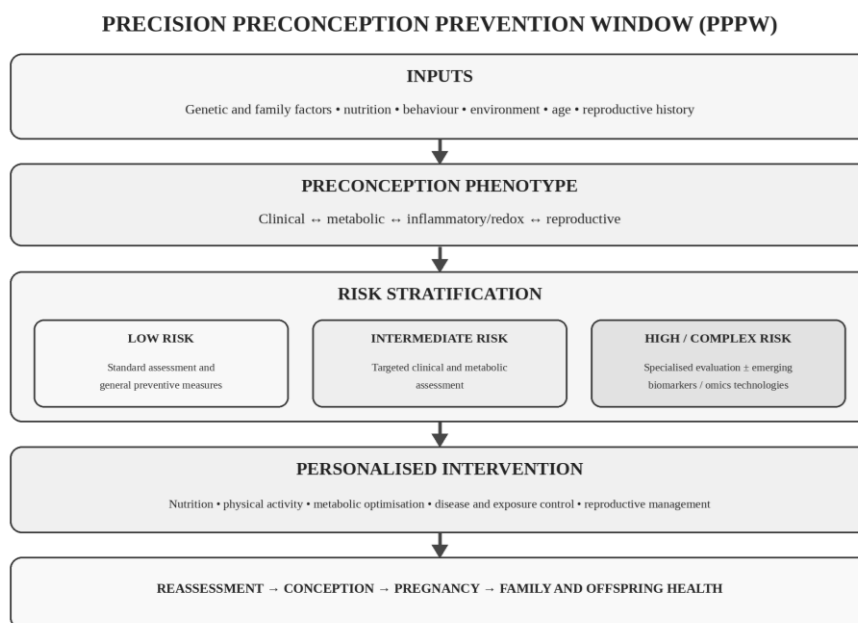


Fig. 1 – Conceptual model of the Preconception Precision Prevention Window (PPPW). Source: developed by the authors.

Note. PPPW – Preconception Precision Prevention Window. Progression to advanced investigations is not mandatory; the level of assessment is adapted to individual risk and to the clinical utility of the information obtained.

LIMITATIONS AND RESEARCH PRIORITIES

Implementation of this paradigm requires standardisation of pre-analytical and analytical procedures, because metabolomics and multi-omic analyses are sensitive to the analytical platform, diet, medication, sampling time and specimen processing [22–25]. A biomarker identified in one cohort becomes clinically relevant only after its reproducibility, external validity and added value over existing tools have been demonstrated.

Extensive biological profiling may generate findings of uncertain individual significance and may lead to over-investigation and unjustified medicalisation. In addition, genomic and multi-omic profiling in reproductive medicine raises issues related to consent, confidentiality, secondary use of genomic information and transparency of analytical models [25]. Research priorities should therefore focus on identifying signatures that are reproducible, interpretable and useful for clinical decision-making rather than simply increasing the number of measured markers.

CONCLUSIONS

The preconception period represents an important opportunity for preventive medicine and should be approached from the perspective of both partners. Current evidence supports assessment of modifiable metabolic, nutritional, behavioural and reproductive factors. Chronic low-grade inflammation and oxidative stress are biologically relevant mechanisms; however, the corresponding biomarkers should not be used as stand-alone reproductive tests in the absence of adequate validation.

Metabolomics, nutrigenomics and multi-omics enable more refined characterisation of biological heterogeneity, but at present their value is better established for research, molecular phenotyping and biomarker discovery than for routine preconception screening.

We propose the PPPW framework, structured as follows: risk factors → clinical and metabolic phenotype → reproductive assessment → additional evaluation proportionate to risk → individualised intervention → reassessment. The model is intended to avoid both underassessment of modifiable risks and excessive use of technologies that do not change medical decision-making.

The future of precision preconception health will depend not on an unlimited expansion of testing, but on identifying information that is relevant to the individual being assessed and to the clinical context. Integration of reproductive medicine, physiology, biochemistry, nutrition and molecular biology may transform the preconception period into an active phase of prevention. Prospective validation of the model and demonstration of its impact on reproductive and family outcomes remain essential before large-scale implementation.

Editorial declarations

Authors' contributions. I.M., V.C. and I.C. contributed to the conception of the review, selection and critical appraisal of the literature, interpretation of the evidence, drafting and critical revision of the manuscript. All authors approved the final version and accept responsibility for the content of the article.

Conflicts of interest. The authors declare no conflicts of interest relevant to this article.

Funding. No specific external funding was received for the preparation of this review.

Ethics approval and informed consent. Not applicable. This article is a review of the literature and does not report new research involving human participants or animals, nor does it include individual patient data.

Data availability. No new datasets were generated; all information analysed is derived from the published sources cited in the manuscript.

Declaration on the use of artificial intelligence tools. Artificial intelligence-based tools were used solely for editorial and language assistance during manuscript preparation. They were not used as sources of scientific evidence and do not meet authorship criteria. The authors critically reviewed the content, sources and wording and take full responsibility for the final version.

REFERENCES

1. World Health Organization. Infertility prevalence estimates, 1990–2021. Geneva: World Health Organization; 2023.
2. World Health Organization. Guideline for the prevention, diagnosis and treatment of infertility. Geneva: World Health Organization; 2025.
3. Stephenson J, Heslehurst N, Hall J *et al.* Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet*. 2018;391(10132):1830–1841. doi:10.1016/S0140-6736(18)30311-8.
4. Fleming TP, Watkins AJ, Velazquez MA *et al.* Origins of lifetime health around the time of conception: causes and consequences. *Lancet*. 2018;391(10132):1842–1852. doi:10.1016/S0140-6736(18)30312-X.
5. Velazquez MA, Fleming TP, Watkins AJ. Periconceptional environment and the developmental origins of disease. *J Endocrinol*. 2019;242(1):T33–T49. doi:10.1530/JOE-18-0676.

6. Huang JY *et al.* More equitable preconception health: paternal life course opportunities for better pregnancy, child, and family outcomes. *Lancet*. 2026;407(10537):1459–1470. doi:10.1016/S0140-6736(26)00148-0.
7. Doe PF, Nimo FA, Odoom E *et al.* Couple-based preconception care as a gender-responsive strategy for improving health and well-being: a systematic review. *Reprod Health*. 2026 Jun 19. doi:10.1186/s12978-026-02385-y.
8. Suto M, Inaoka K, Suzuki D *et al.* Behavior changes to promote preconception health: a systematic review. *BMC Womens Health*. 2025;25:23. doi:10.1186/s12905-024-03544-8.
9. Torkel S, Mantzioris E, Villani A, *et al.* Preconception lifestyle interventions for women—a systematic review and meta-analysis of intervention characteristics and behaviour change techniques. *Hum Reprod Update*. 2026;32(1):105–127. doi:10.1093/humupd/dmaf021.
10. Practice Committee of the American Society for Reproductive Medicine. Fertility evaluation of infertile women: a committee opinion. *Fertil Steril*. 2021;116(5):1255–1265. doi:10.1016/j.fertnstert.2021.08.038.
11. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 6th ed. Geneva: World Health Organization; 2021.
12. Brannigan RE, Hermanson L, Kaczmarek J, Kim SK, Kirkby E, Tanrikut C. Updates to Male Infertility: AUA/ASRM Guideline (2024). *J Urol*. 2024;212(6):789–799. doi:10.1097/JU.0000000000004180.
13. Alesi S, Habibi N, Silva TR *et al.* Assessing the influence of preconception diet on female fertility: a systematic scoping review of observational studies. *Hum Reprod Update*. 2023;29(6):811–828. doi:10.1093/humupd/dmad018.
14. Tully CA, Alesi S, McPherson NO *et al.* Assessing the influence of preconception diet on male fertility: a systematic scoping review. *Hum Reprod Update*. 2024;30(3):243–261. doi:10.1093/humupd/dmad035.
15. Maitin-Shepard M, Werner EF, Feig LA *et al.* Food, nutrition, and fertility: from soil to fork. *Am J Clin Nutr*. 2024;119(2):578–589. doi:10.1016/j.ajcnut.2023.12.005.
16. Zhou J, Zhang Y, Teng Y *et al.* Association between preconception body mass index and fertility in adult female: a systematic review and meta-analysis. *Obes Rev*. 2024;25(10):e13804. doi:10.1111/obr.13804.
17. Caldwell AE, Gorczyca AM, Bradford AP *et al.* Effectiveness of preconception weight loss interventions on fertility in women: a systematic review and meta-analysis. *Fertil Steril*. 2024;122(2):326–340. doi:10.1016/j.fertnstert.2024.02.038.
18. Santi D, Lotti F, Sparano C *et al.* Does an increase in adipose tissue “weight” affect male fertility? A systematic review and meta-analysis based on semen analysis performed using the WHO 2010 criteria. *Andrology*. 2024;12(1):123–136. doi:10.1111/andr.13460.
19. Ameho S, Klutstein M. The effect of chronic inflammation on female fertility. *Reproduction*. 2025;169(4):e240197. doi:10.1530/REP-24-0197.
20. Potiris A, Moustakli E, Trismpioti E *et al.* From inflammation to infertility: how oxidative stress and infections disrupt male reproductive health. *Metabolites*. 2025;15(4):267. doi:10.3390/metabo15040267.
21. de Ligny W, Smits RM, Mackenzie-Proctor R *et al.* Antioxidants for male subfertility. *Cochrane Database Syst Rev*. 2022;5(5):CD007411. doi:10.1002/14651858.CD007411.pub5.
22. Kobayashi H, Imanaka S. Recent progress in metabolomics for analyzing common infertility conditions that affect ovarian function. *Reprod Med Biol*. 2024;23(1):e12609. doi:10.1002/rmb2.12609.
23. Zhang Y, He C, He Y, Zhu Z. Follicular fluid metabolomics: tool for predicting IVF outcomes of different infertility causes. *Reprod Sci*. 2025;32(4):921–934. doi:10.1007/s43032-024-01664-y.
24. D’Arco Correa L, Souza Peruzzato F, Rauh Muller YM. Metabolomic alterations in follicular fluid across female infertility conditions in IVF: a systematic review. *J Assist Reprod Genet*. 2026 Jun 4. doi:10.1007/s10815-026-03925-y.
25. Liu X, Bin C, Gao Q *et al.* Multi-omics biomarkers in female fertility: from oocyte quality to endometrial receptivity and clinical translation. *Biomark Res*. 2026;14:46. doi:10.1186/s40364-026-00914-2.
26. Podgrajsek R, Hodzic A, Stimpfel M, Kunej T, Peterlin B. Insight into the complexity of male infertility: a multi-omics review. *Syst Biol Reprod Med*. 2024;70(1):73–90. doi:10.1080/19396368.2024.2317804.
27. Zakaria A, Diawara I, Bouziyane A, Louanjli N. Exploring human sperm metabolism and male infertility: a systematic review of genomics, proteomics, metabolomics, and imaging techniques. *Int J Mol Sci*. 2025;26(15):7544. doi:10.3390/ijms26157544.
28. Singar S, Nagpal R, Arjmandi BH, Akhavan NS. Personalized nutrition: tailoring dietary recommendations through genetic insights. *Nutrients*. 2024;16(16):2673. doi:10.3390/nu16162673.
29. Nkansah EO, Xu B, Lan Y, Zafar MI. Positioning nutrigenomics and nutrigenetics within the framework of male infertility exploration. *Reprod Toxicol*. 2025;137:109043. doi:10.1016/j.reprotox.2025.109043.
30. Pandey C, Maunder A, Liu J *et al.* The role of nutrient supplements in female infertility: an umbrella review and hierarchical evidence synthesis. *Nutrients*. 2025;17(1):57. doi:10.3390/nu17010057.
31. Sum KK, Burton MA, Garcia-Maurino Alcazar C, Teh AL, Godfrey KM, Huang JY. Strength of evidence for paternal influence on offspring epigenome in observational human studies: a systematic review and risk-of-bias appraisal for non-randomized exposures. *Epigenetics*. 2025;20(1):2594322. doi:10.1080/15592294.2025.2594322.
32. Wu X, Zhang W, Chen H, Weng J. Multifaceted paternal exposures before conception and their epigenetic impact on offspring. *J Assist Reprod Genet*. 2024;41(11):2931–2951. doi:10.1007/s10815-024-03243-1.
33. Wu D, Zhang K, Guan K *et al.* Future in the past: paternal reprogramming of offspring phenotype and the epigenetic mechanisms. *Arch Toxicol*. 2024;98(6):1685–1703. doi:10.1007/s00204-024-03713-6.
34. Ashley-Martin J, Hammond J, Velez MP. Assessing preconception exposure to environmental chemicals and fecundity: strategies, challenges, and research priorities. *Reprod Toxicol*. 2024;125:108578. doi:10.1016/j.reprotox.2024.108578.