SAVREMENI PRISTUP PREVENCIJI GESTACIJSKOG DIJABETESA: MEDIKAMENTOZNA TERAPIJA I DIJETETSKI SUPLEMENTI – PREGLED LITERATURE

PREGLEDNI RAD

REVIEW ARTICLE

CONTEMPORARY APPROACHES TO THE PREVENTION OF GESTATIONAL DIABETES: PHARMACOLOGICAL INTERVENTIONS AND DIETARY SUPPLEMENTS – A NARRATIVE REVIEW

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SAŽETAK

Uvod/Cilj: Gestacijski dijabetes melitus (GDM) predstavlja jednu od najčešćih komplikacija trudnoće i značajan javnozdravstveni problem, sa rastućom učestalošću usled porasta gojaznosti i insulinske rezistencije. Cilj ovog rada bio je da se analizira dostupna literatura o preventivnim strategijama za GDM, uključujući promene životnog stila, suplemente i farmakološke intervencije.

Materijal i metode: Sproveden je pregled literature pretraživanjem baza MEDLINE, Scopus i PubMed za period od 2000. do 2025. godine. Uključene su recenzirane studije koje su ispitivale preventivne mere za GDM, dok su isključene studije koje su se bavile isključivo terapijom već dijagnostikovanog GDM, kao i animalne studije, radovi nedostupni in extenso, kao i radovi koji nisu na engleskom jeziku. Selekciju su nezavisno sprovela dva autora, a u spornim slučajevima postignut je konsenzus svih autora.

Rezultati: Povišen indeks telesne mase pre trudnoće i tokom trudnoće predstavlja najvažniji modifikabilni faktor rizika za razvoj GDM. Najefikasnija preventivna strategija uključuje održavanje normalne telesne mase, pravilnu ishranu i redovnu fizičku aktivnost, pri čemu fizička aktivnost pokazuje najizraženiji efekat. Od suplemenata, mio-inozitol pokazuje potencijal u smanjenju incidencije GDM i poboljšanju glikoregulacije, dok su rezultati za vitamin D, probiotike i omega-3 masne kiseline nekonzistentni. Metformin može smanjiti rizik od GDM kod visokorizičnih trudnica, naročito kod žena sa sindromom policističnih jajnika, ali rezultati studija ostaju kontradiktorni, uz otvorena pitanja o dugoročnim efektima na potomstvo.

Zaključak: Promene životnog stila i higijensko-dijetetski režim ostaju osnova prevencije GDM. Medikamentozna terapija i dijetetski suplementi mogu imati izvesnu ulogu u visokorizičnim grupama, mada nema dovoljno dokaza za njihovu rutinsku primenu. Potrebna su dalja istraživanja radi definisanja optimalnih preventivnih pristupa.

Ključne reči: gestacijski dijabetes melitus, prevencija, mio-inozitol, metformin, dijetetski suplement

ABSTRACT

Introduction/Objective: Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications and an important public health concern, with increasing prevalence driven by rising obesity and insulin resistance. This study aimed to review current evidence on preventive strategies for GDM, including lifestyle interventions, supplementation, and pharmacological approaches.

Material and methods: A literature review was conducted using MEDLINE, Scopus, and PubMed databases for the period from 2000 to 2025. Peer-reviewed studies addressing GDM prevention were included, while studies focused exclusively on treatment of established GDM, animal studies, articles not available in full text, and those not published in English were excluded. Study selection was performed independently by two authors, and in cases of discrepancy, consensus was reached among all authors.

Results: Elevated pre-pregnancy and gestational body mass index is the most important modifiable risk factor for GDM. Lifestyle interventions, including maintenance of normal body weight, a balanced diet, and regular physical activity, represent the most effective preventive strategy, with physical activity showing the greatest impact. Among supplements, myo-inositol shows potential to reduce GDM incidence and improve glycemic control, whereas evidence for vitamin D, probiotics, and omega-3 fatty acids remains inconsistent. Metformin may reduce GDM risk in high-risk populations, particularly in women with polycystic ovary syndrome, but findings are heterogeneous, and concerns remain regarding long-term offspring outcomes.

Conclusion: Lifestyle modification and dietary regimen remain the cornerstone of GDM prevention. Pharmacological therapy and dietary supplements may have a potential role in high-risk groups; however, there is insufficient evidence to support their routine use. Further large-scale studies are needed to establish optimal prevention strategies.

Keywords: gestational diabetes mellitus, prevention, myo-inositol, metformin, dietary supplement

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UVOD

Gestacijski dijabetes melitus (GDM) predstavlja jednu od najčešćih komplikacija trudnoće i sve veći globalni javnozdravstveni problem, kao i značajno finansijsko opterećenje za zdravstveni sistem. Prijavljena prevalencija GDM-a značajno varira među populacijama zbog etničkih razlika i neujednačenih kriterijuma skrininga, krećući se od približno 1% do skoro jedne trećine svih trudnoća. Prema podacima Međunarodne dijabetološke federacije (IDF), približno jedno od šest živorođene dece potiče iz trudnoće komplikovane hiperglikemijom, pri čemu se većina slučajeva pripisuje GDM-u, a ne prethodno postojećem dijabetesu [1]. Uz globalni porast učestalosti gojaznosti, insluinske rezistencije i dijabetesa melitusa tipa 2, prevalencija GDM-a značajno je porasla u različitim populacijama. Sa porastom prosečne starosti trudnica, sve više žena ulaze u trudnoću sa povećanim metaboličkim rizikom [2].

Međunarodna federacija za ginekologiju i akušerstvo (FIGO) naglasila je da hiperglikemija u trudnoći – bilo da je prvi put dijagnostikovana tokom gestacije ili predstavlja prethodno nedijagnostikovan dijabetes – nosi značajne kratkoročne i dugoročne posledice kako za majku, tako i za potomstvo [3]. Pored neposrednih akušerskih i neonatalnih rizika, GDM se sve više prepoznaje kao pokazatelj budućih kardiometaboličkih oboljenja kod žena i njihove dece, što dodatno naglašava njegov značaj rane intervencije i prevencije [1,3].

Prevencija GDM-a treba započeti pre začeća i nastaviti tokom cele trudnoće [1]. Prekoncepcijsko savetovanje usmereno na optimizaciju telesne mase, zdravu ishranu i fizičku aktivnost od ključnog je značaja, naročito u visokorizičnoj populaciji.

Određene genetske mutacije povezane su sa razvojem GDM-a, posebno one koje utiču na metabolizam glukoze i sekreciju insulina. Međutim, GDM se generalno smatra multifaktorijalnom bolešću. Jedan od najvažnijih faktora rizika jeste indeks telesne mase (BMI) pre trudnoće veći od 30 kg/m^2, značajan porast telesne mase tokom rane odrasle dobi ili između trudnoća, kao i gojaznost u ranoj trudnoći, budući da povišene koncentracije slobodnih masnih kiselina smanjuju periferno preuzimanje glukoze i doprinose insulinskoj rezistenciji [3–5]. Ostali značajni faktori rizika uključuju pozitivnu porodičnu anamnezu za dijabetes melitus, sedentarni način života, GDM i fetalnu makrozomiju u prethodnim trudnoćama, kardiovaskularna oboljenja, hipertenziju i hiperlipidemiju [5]. Sindrom policističnih jajnika (PCOS), najčešći endokrini poremećaj kod žena, nije povezan samo sa infertilitetom već i sa povećanim rizikom od metaboličkih poremećaja povezanih sa trudnoćom, uključujući i GDM [6].

Starost majke smatra se važnim faktorom, iako sama po sebi nije direktan faktor rizika. Globalni trend

INTRODUCTION

Gestational diabetes mellitus (GDM) represents one of the most common complications of pregnancy and constitutes a growing global public health concern and significant financial burden to the healthcare system. The reported prevalence of GDM varies widely across populations due to ethnic differences and inconsistent screening criteria, ranging from about one percent to nearly one-third of pregnancies. According to the International Diabetes Federation, roughly one in six live births is associated with hyperglycemia in pregnancy, with the majority of cases attributable to GDM rather than overt diabetes [1]. Closely paralleling the worldwide increase in obesity, impaired glucose tolerance, and type 2 diabetes mellitus, the prevalence of GDM has risen substantially across diverse populations. With an increasing maternal age in pregnancy, more and more women are entering pregnancy at higher metabolic risk [2].

The International Federation of Gynecology and Obstetrics (FIGO) has emphasized that hyperglycemia in pregnancy–whether first recognized during gestation or representing previously undiagnosed diabetes–carries significant short- and long-term consequences for both mother and offspring [3]. Beyond immediate obstetric and neonatal risks, GDM is increasingly recognized as a marker of future cardiometabolic disease in women and their children, reinforcing its importance as a target for early intervention and prevention [1,3].

Prevention of GDM should begin before conception and continue throughout pregnancy [1]. Preconception counseling aimed at weight optimization, healthy nutrition, and physical activity is critical, especially in high-risk populations.

Certain genetic mutations have been associated with the development of GDM, particularly those involving glucose metabolism and insulin secretion. However, GDM is generally considered a multifactorial disease. One of the most important risk factors is prepregnancy BMI > 30 mg/m^2, significant weight gain in early adulthood or between pregnancies, and obesity in early pregnancy, as elevated free fatty acids reduce peripheral glucose uptake and contribute to insulin resistance [3–5]. Other notable risk factors include positive family history of diabetes mellitus, sedentary lifestyle, previous GDM, fetal macrosomia in prior pregnancies, cardiovascular disease, hypertension, and hyperlipidemia [5]. Polycystic ovary syndrome (PCOS), the most common endocrine disorder in women, is not only associated with infertility but also increases the risk of pregnancy-related metabolic disorders, including GDM [6].

odlaganja rađanja doveo je do porasta broja trudnoća u kasnijoj i veoma kasnoj reproduktivnoj dobi, tokom koje dolazi do fizioloških metaboličkih promena. Sa starenjem dolazi do povećanja udela masnog tkiva i smanjenja mišićne mase, što menja metabolizam glukoze. Pored toga, starenje je povezano sa progresivnom rezistencijom insulinskih receptora, poremećajima iskorišćavanja glukoze, hepatičnom insulinskom rezistencijom, smanjenom produkcijom insulina i povećanim hepatičnim klirensom insulina, što zajedno doprinosi poremećaju homeostaze glukoze [2].

GDM se češće javlja kod žena koje pripadaju određenim etničkim grupama, uključujući Hispanoamerikanke, pripadnice starosedelačkih naroda Amerike, Aljaske i Havaja, kao i žene južnoazijskog, istočnoazijskog i pacifičkog porekla [4].

Komplikacije GDM-a kod majke uključuju povećan rizik od preeklampsije, prevremenog porođaja, carskog reza, infekcija i porođajne traume. Žene sa GDM-om takođe imaju značajno veći rizik – procenjuje se 7 do 10 puta veći – za razvoj predijabetesa ili dijabetesa melitusa tipa 2 kasnije u životu [7]. Ostale komplikacije kod majke mogu uključivati polihidramnion, rekurentne infekcije urinarnog trakta i povećan rizik od spontanog pobačaja. Tokom puerperijuma mogu se javiti infekcije, postpartalna hemoragija, tromboembolijski događaji i poteškoće u uspostavljanju laktacije [1].

Fetalne i neonatalne komplikacije prvenstveno uključuju makrozomiju, distociju ramena, neonatalnu hipoglikemiju, sindrom respiratornog distresa, policitemiju, hiperbilirubinemiju, intrauterinu smrt ploda i neonatalni mortalitet. Dugoročne posledice po potomstvo uključuju povećan rizik od gojaznosti, dijabetesa melitusa tipa 2, kardiovaskularnih bolesti i poremećaja iz spektra autizma [1,3].

MATERIJAL I METODE

Autori su izvršili pregled dostupne literature koja se odnosi na prevenciju GDM-a. Sprovedena je sveobuhvatna pretraga baza podataka MEDLINE, Scopus i PubMed za period od 2000. do 2025. godine, korišćenjem kombinacije ključnih reči kao što su: „gestacijski dijabetes melitus“, „prevencija GDM-a“, „izmene u načinu života“, „ishrana“, „fizička aktivnost“, „metformin“, „mio-inozitol“, „dijetetski suplement“ i „vitamin D“.

U pregled su uključeni recenzirani naučni radovi koji su obrađivali preventivne strategije za GDM, uključujući intervencije u načinu života i farmakološke intervencije. Isključene su studije koje su se isključivo bavile lečenjem već dijagnostikovanog GDM-a, istraživanja na životinjama i radovi bez dostupnog teksta u celini. Dodatni relevantni radovi identifikovani su ručnim pregledom referenci odabranih publikacija.

Maternal age is considered an important contributing factor, although not a direct risk factor per se. The global trend of delayed childbearing has led to an increasing number of pregnancies occurring at advanced and very advanced maternal age, during which physiological metabolic changes occur. With aging, body composition shifts toward increased adiposity and reduced muscle mass, altering glucose metabolism. Additionally, aging is associated with progressive insulin receptor resistance, abnormalities in glucose disposal, hepatic insulin resistance, reduced insulin production, and increased hepatic insulin clearance, all contributing to impaired glucose homeostasis [2].

GDM occurs more frequently among women belonging to certain ethnic groups, including Hispanic Americans, Native Americans, Alaska Natives, and Native Hawaiians; as well as those of South or East Asian and Pacific Islander origin [4].

Maternal complications of GDM include an increased risk of preeclampsia, preterm birth, cesarean delivery, infections, and birth trauma. Women with GDM also have a significantly higher risk–estimated to be 7 to 10 times greater–of developing prediabetes or type 2 diabetes mellitus later in life [7]. Other maternal complications may include polyhydramnios, recurrent urinary tract infections, and an increased risk of miscarriage. During the puerperium, women may experience infections, postpartum hemorrhage, thromboembolic events, and difficulties in establishing lactation [1].

Fetal and neonatal complications primarily include macrosomia, shoulder dystocia, neonatal hypoglycemia, respiratory distress syndrome, polycythemia, hyperbilirubinemia, stillbirth, and neonatal death. Long-term consequences for offspring include an increased risk of obesity, type 2 diabetes mellitus, cardiovascular disease, and autism spectrum disorder [1,3].

MATERIALS AND METHODS

The authors reviewed the available literature on the prevention of GDM. A comprehensive search of MEDLINE, Scopus, and PubMed databases was conducted for the period from 2000 to 2025, using a combination of keywords such as “gestational diabetes mellitus”, “GDM prevention”, “lifestyle intervention”, “diet”, “physical activity”, “metformin”, “myo-inositol”, “dietary supplement” and “vitamin D”.

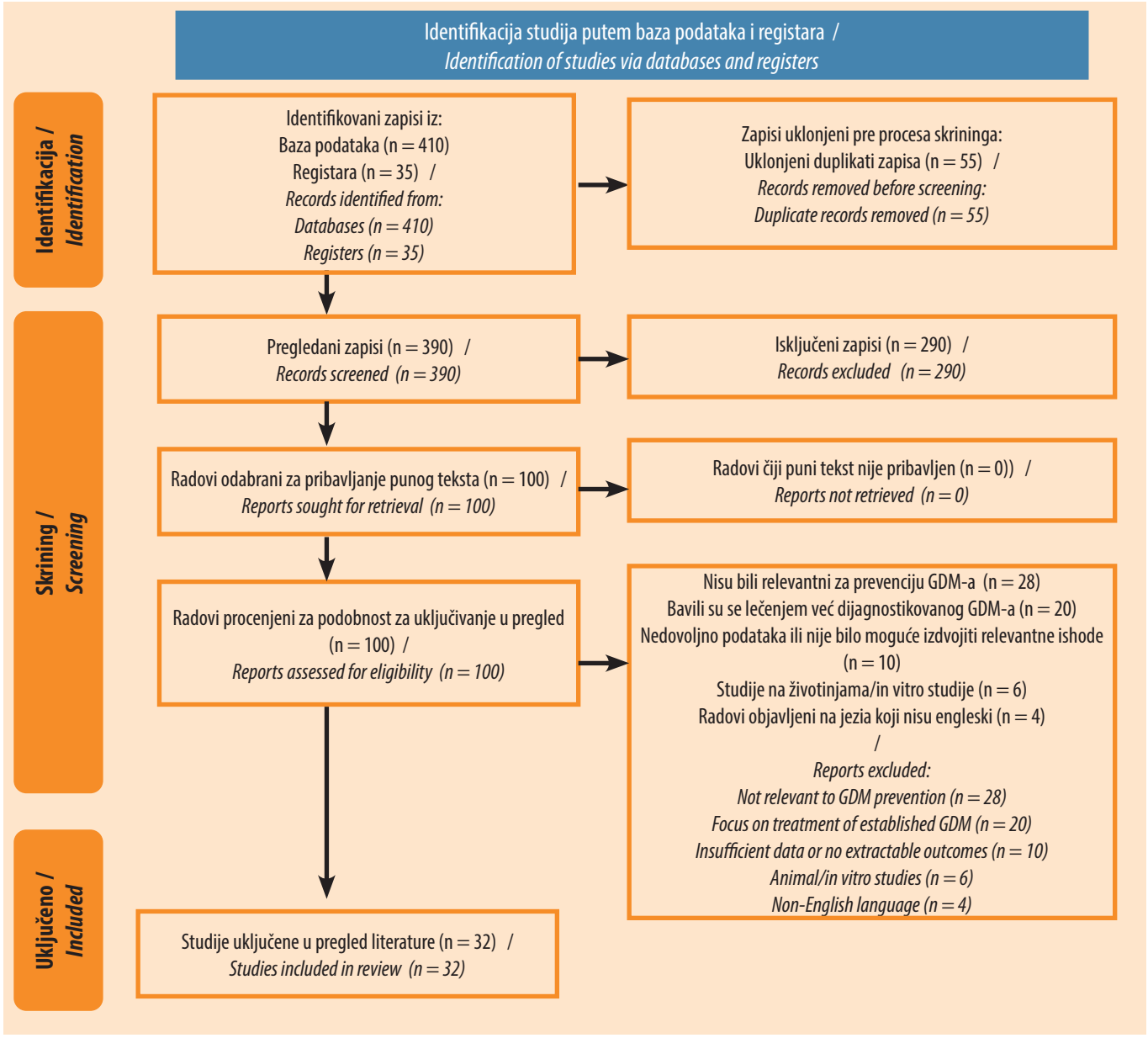
Peer-reviewed articles addressing preventive strategies for GDM, including lifestyle and pharmacological interventions, were included. Studies focusing exclusively on the treatment of already diagnosed GDM, animal studies, and articles without full-text availability were excluded. Additional relevant articles were identified through manual screening of the reference lists of selected papers.

Pretragu literature i selekciju studija nezavisno su sprovela dva autora. Sva neslaganja rešavana su diskusijom, a po potrebi i konsultacijom sa trećim autorom. Odabrane studije su potom analizirane, a ključni nalazi zajednički diskutovani od strane svih autora kako bi se obezbedilo sveobuhvatno i uravnoteženo tumačenje dostupnih dokaza. Primenom ovakvog pristupa nastojalo se da se minimizira potencijalna selekciona pristrasnost.

Rezultati pretrage literature organizovani su u tematske celine, sa fokusom na različite strategije prevencije GDM-a, uključujući modifikacije životnog stila, farmakološke intervencije i suplementaciju. Ukupno su u narativni pregled uključene 32 studije (Slika 1).

The literature search and study selection were conducted independently by two authors. Any disagreements were resolved through discussion and, when necessary, consultation with a third author. The selected studies were then analyzed, and the key findings were discussed collectively by all authors to ensure a comprehensive and balanced interpretation of the available evidence. By applying this approach, we aimed to minimize potential selection bias.

The results of the literature search were organized into thematic sections, focusing on different preventive strategies for GDM, including lifestyle modifications, pharmacological interventions, and supplementation. In total, 32 studies were included in the narrative review (Figure 1).



Slika 1. Prikaz rezultata analize literature prema metodologiji primenjenoj u izradi rada

Figure 1. Summary of the literature analysis using the method illustrated in the preparation of the paper

REZULTATI

Kao što je prethodno navedeno, povišen indeks telesne mase (BMI) pre trudnoće i tokom trudnoće predstavlja značajan i modifikabilan faktor rizika za razvoj ovog oblika dijabetesa. Shodno tome, primarni cilj prevencije GDM-a jeste održavanje normalnog BMI pre začeća, između trudnoća i tokom trudnoće. Kod žena sa povećanim rizikom dodatne mere mogu obuhvatati promene životnog stila, uključujući odgovarajuću ishranu i fizičku aktivnost, kao i primenu određenih suplemenata, poput probiotika, vitamina D i mio-inozitola, pa čak i farmakološke terapijske opcije, kao što je metformin. Opšti cilj svih ovih mera jeste poboljšanje insulinske senzitivnosti i smanjenje telesne mase kada je to neophodno.

DIJETETSKE I FIZIČKE INTERVENCIJE

Nutritivna terapija preporučuje se od trenutka postavljanja dijagnoze GDM-a, bez obzira na to da li će kasnije biti potrebna farmakološka terapija. Prema smernicama FIGO-a, ona podrazumeva plan ishrane sa kontrolisanim unosom ugljenih hidrata koji obezbeđuje adekvatnu nutritivnu podršku, odgovarajući porast telesne mase, normoglikemiju i odsustvo ketoze. Iako umeren kalorijski deficit može biti poželjan radi kontrole telesne mase, on mora biti pažljivo praćen kako bi se sprečila ketoza. Generalno se idealnim smatra dnevni unos između 1.500 i 2.800 kcal. Fizička aktivnost doprinosi kako prevenciji GDM-a, tako i poboljšanju glikemijske kontrole i insulinske senzitivnosti kod žena sa već razvijenim oboljenjem. Aerobni trening umerenog intenziteta najčešće je dovoljan. Intenzivniji trening i redovna fizička aktivnost tokom postpartalnog perioda mogu smanjiti rizik od progresije bolesti i kasnijeg razvoja dijabetesa melitusa tipa 2 [1].

Meta-analiza sprovedena za Američko udruženje za dijabetes (ADA) i Evropsko udruženje za proučavanje dijabetesa (EASD) pokazala je da su sve navedene intervencije efikasne i da ih treba uključiti u standardnu kliničku praksu. Međutim, fizička aktivnost je pokazala najizraženiju korist, naročito kada se sprovodi u grupama ili u zdravstvenim ustanovama, dok je odgovarajući režim ishrane bio efikasan bez obzira na način sprovođenja [8]. Kod trudnica sa visokim rizikom za razvoj GDM-a, same dijetetske mere pokazale su samo ograničenu efikasnost ukoliko nisu bile kombinovane sa fizičkom aktivnošću, što dodatno naglašava značaj vežbanja u prevenciji [9]. Druga istraživanja ukazala su na slične rezultate, prema kojima je fizička aktivnost kao samostalna preventivna mera najefikasnija kod žena koje nisu gojazne, dok se kod gojaznih žena najbolji rezultati postižu kombinacijom vežbanja i dijetetskih intervencija, naročito kod onih bez prethodnih poremećaja glikoregulacije, kao što je insulinska rezistencija povezana sa PCOS-om [10] .

RESULTS

As previously mentioned, a high pre-pregnancy and gestational BMI represent a significant and modifiable risk factor for the development of this type of diabetes. Accordingly, the primary focus of GDM prevention is maintaining a normal BMI before conception, between pregnancies, and during pregnancy. In women at increased risk, additional measures may include lifestyle modifications such as an appropriate diet and physical activity, as well as certain supplements, including probiotics, vitamin D, and myo-inositol, and even pharmacological interventions such as metformin. Overall, the goal is to improve insulin sensitivity and, when necessary, promote weight reduction.

DIETARY AND EXERCISE INTERVENTIONS

Nutritional therapy is recommended from the time of GDM diagnosis, regardless of whether pharmacological treatment is ultimately required. According to FIGO guidelines, this involves a carbohydrate-controlled meal plan that ensures adequate nutrition, appropriate weight gain, normoglycemia, and the absence of ketosis. While modest caloric restriction may be desirable for weight management, it must be carefully monitored to prevent ketonemia. A daily caloric intake of 1.500 to 2.800 kcal is generally considered ideal. Physical activity contributes to both the prevention of GDM and improved glycemic control and insulin sensitivity in women with established disease. Moderate-intensity aerobic exercise is usually sufficient. Enhanced training and regular physical activity during the postpartum period can reduce the risk of disease progression and the subsequent development of type 2 diabetes mellitus [1].

A meta-analysis conducted for the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) demonstrated that all the previously mentioned interventions are effective and should be implemented in standard clinical practice. However, physical activity showed the most pronounced benefits, particularly when performed in group settings or within healthcare facilities, while an appropriate dietary regimen was effective regardless of the mode of implementation [8]. Among pregnant women at high risk of GDM, dietary measures alone were only marginally effective unless combined with physical activity, highlighting the superior importance of exercise in prevention [9]. Another study reported similar findings, indicating that physical activity alone is most effective as a preventive measure in non-obese women, whereas in obese women, the best outcomes are achieved when exercise is combined with dietary interventions, particularly in those without underlying glycoregulatory disturbances such as insulin resistance associated with PCOS [10].

Studija Movve i saradnika takođe je pokazala da je antenatalno vežbanje pod nadzorom trenera imalo najveći preventivni efekat, dok je metformin pokazao samo umeren učinak, čime je dodatno potvrđena superiorna efikasnost fizičke aktivnosti kao preventivne strategije [11] .

INTERVENCIJE DIJETETSKIM SUPLEMENTIMA

VITAMIN D

Koncentracije vitamina D u serumu trudnica sa GDM-om dosledno su bile značajno niže u poređenju sa normoglikemijskim trudnoćama. Deficit vitamina D je prepoznat kao faktor koji doprinosi nepovoljnim reproduktivnim ishodima, uključujući spontani pobačaj, s obzirom na njegovu ključnu ulogu u implantaciji embriona i imunološkoj modulaciji. Pored toga, hipovitaminoza D povezuje se sa povećanim rizikom od GDM-a, preeklampsije i prevremenog porođaja [12,13]. Niske koncentracije vitamina D takođe su uključene u patofiziologiju sindroma policističnih jajnika (PCOS), što dodatno potvrđuje njegovu ulogu u metaboličkoj disregulaciji [14]. Postoji više potencijalnih mehanizama kojima vitamin D može doprineti razvoju GDM-a, uključujući regulaciju sekrecije insulina i ekspresiju insulinskih receptora, modulaciju aktivnosti mitohondrijalnog respiratornog lanca, uticaj na transkripciju gena za insulin, održavanje homeostaze kalcijuma, kao i efekte na diferencijaciju i sazrevanje adipocita [13].

Dokazi koji povezuju nivo vitamina D kod majke sa pojavom GDM-a i dalje su neusaglašeni. Xia i saradnici pokazali su da je deficit vitamina D u prvom trimestru povezan sa povećanim rizikom za razvoj GDM-a, dok Luo i saradnici nisu pronašli linearnu povezanost između koncentracije 25-hidroksivitamina D (25OHD) u ranoj trudnoći i pojave GDM-a [15,16]. Nasuprot tome, više koncentracije 25OHD u 15 ± 1 nedelji gestacije povezivane su sa zaštitnim efektom, iako potencijalna interakcija sa polom fetusa unosi dodatnu nesigurnost u tumačenje rezultata [17]. Takođe je pokazano da su niske koncentracije 25OHD kod majke povezane sa povećanim rizikom od GDM-a, pri čemu na ovu povezanost mogu uticati rasa i etnička pripadnost [18]. Pregled Cochrane sistematskih pregleda ukazuje da je suplementacija vitaminom D povezana sa poboljšanjem metabolizma glukoze, uključujući smanjenje vrednosti glukoze našte, hemoglobina A1c (HbA1c) i koncentracije insulina [19].

Ipak, i dalje nije moguće uzaključiti da li je vitamin D direktno uključen u patogenezu GDM-a i koji su tačni mehanizmi njegovog delovanja [15,16]. Trenutni dokazi su kontradiktorni, a zaključci kontroverzni zbog uticaja brojnih remetilačkig faktora [20]. Zbog toga su potrebne dodatne, dobro dizajnirane multicentrične randomizovane kontrolisane studije kako bi se preciznije definisala uloga vitamina D u prevenciji GDM-a.

The study by Movva et al. also demonstrated that supervised antenatal exercise had the greatest impact on prevention, whereas metformin showed only a modest effect, highlighting the superior efficacy of physical activity as a preventive approach [11].

DIETARY SUPPLEMENT INTERVENTIONS

VITAMIN D

Serum vitamin D levels in pregnant women with GDM have been consistently reported to be significantly lower compared to those observed in normoglycemic pregnancies. Vitamin D deficiency is widely recognized as a contributing factor to adverse reproductive outcomes, including miscarriage, given its essential role in embryonic implantation and immune modulation. Moreover, hypovitaminosis D has been associated with an increased risk of GDM, preeclampsia, and preterm birth [12,13]. Low vitamin D levels have also been implicated in the pathophysiology of polycystic ovary syndrome (PCOS), further supporting the role of vitamin D in metabolic dysregulation [14]. Several potential mechanisms have been proposed to explain vitamin D's contribution to GDM development, including regulation of insulin secretion and insulin receptor expression, modulation of mitochondrial respiratory chain activity, influence on insulin gene transcription, maintenance of calcium homeostasis, and effects on adipocyte differentiation and maturation [13].

Evidence linking maternal vitamin D status to GDM remains inconclusive. Xia et al. reported that first-trimester vitamin D deficiency is associated with increased GDM risk, whereas Luo et al. found no linear association between early pregnancy 25-hydroxyvitamin D (25OHD) levels and GDM [15,16]. Conversely, higher 25OHD concentrations at 15 ± 1 weeks' gestation have been suggested to confer a protective effect, although potential interactions with fetal sex introduce additional uncertainty [17]. Moreover, low maternal 25OHD levels have been associated with increased GDM risk, with evidence suggesting that this relationship may be modified by race and ethnicity [18]. An overview of Cochrane reviews suggests that vitamin D supplementation is associated with improved glucose homeostasis, including reductions in fasting glucose, hemoglobin A1c (HbA1c), and insulin levels [19].

Whether vitamin D is directly involved in the pathogenesis of GDM, and the underlying mechanisms, remain unclear [15,16]. Current evidence is inconsistent, and conclusions remain controversial due to numerous confounding factors [20]. Further well-designed, multicenter randomized controlled trials are required to clarify the role of vitamin D in GDM prevention.

MIO-INOZITOL

Pored konvencionalnog farmakološkog pristupa u lečenju i prevenciji GDM-a ispitivani su i određeni dijeteski suplementi. Među njima, posebnu pažnju privukao je inozitol – prirodno jedinjenje koje postoji u devet stereoizomernih oblika – pri čemu je mio-inozitol najviše proučavan i najčešće korišćen oblik [21,22]. U početku se smatrao vitaminom, ali je danas poznato da se u ljudskom organizmu sintetiše endogeno, ali u ograničenim količinama. Veruje se da deluje kao senzibilizator insulinskih receptora tako što podstiče translokaciju transportera glukoze tipa 4 (GLUT4) na ćelijsku membranu, čime poboljšava preuzimanje glukoze što predstavlja osnovu za njegovu primenu u lečenju GDM-a [21]. Pored toga, mio-inozitol učestvuje u oksidativnom i neoksidativnom metabolizmu glukoze, smanjuje apsorpciju glukoze u dvanaestopalačnom crevu i podstiče sintezu glikogena [23]. Njegova terapijska efikasnost već je potvrđena kod sindroma policističnih jajnika (PCOS), još jednog stanja koje karakteriše insulinska rezistencija [24,25]. Suplementacija mio-inozitolom generalno se smatra bezbednom, pri čemu su neželjeni efekti retki i uglavnom ograničeni na blage gastrointestinalne tegobe [26,27]. Pored terapijske primene, mio-inozitol je proučavan i u prevenciji GDM-a, naročito kod žena sa pozitivnom porodičnom anamnezom za dijabetes melitus tipa 2.

Prospektivna randomizovana placebo-kontrolisana studija sprovedena 2013. godine pokazala je da suplementacija mio-inozitolom tokom prvog trimestra značajno smanjuje incidenciju GDM-a i fetalne makrozomije u poređenju sa placebom [21]. Više studija takođe je pokazalo koristi u regulaciji glikemije i prevenciji GDM-a, iako aktuelne kliničke smernice i dalje naglašavaju promene životnog stila i insulinsku terapiju kao osnovne intervencije [28]. Meta-analiza koju su sproveli Wai i saradnici pokazala je da dnevna suplementacija sa 4 g mio-inozitola značajno smanjuje incidenciju GDM-a, snižava koncentracije glukoze u krvi i umanjuje potrebu za insulinskom terapijom tokom trudnoće. Takođe je povezana sa ređom pojavom prevremenog porođaja, nižim percentilima porođajne mase i manjom incidencijom neonatalne hipoglikemije [20]. Meta-analiza koja je obuhvatila sedam randomizovanih kontrolisanih studija pokazala je da profilaktička primena inozitola značajno smanjuje pojavu GDM-a i poboljšava vrednosti glikemije, uključujući glukozu natašte i rezultate OGTT-a nakon jednog i dva sata. Prevremeni porođaj i hipertenzija povezana sa trudnoćom takođe su bili ređi, dok učestalost carskog reza, distocije ramena, neonatalne hipoglikemije i makrozomije nije bila značajno promenjena. Dodatno, četiri randomizovane kontrolisane studije koje su procenji-

MYO-INOSITOL

In addition to conventional pharmacological treatments, certain dietary supplements have been explored for the management and prevention of GDM. Among these, inositol–a naturally occurring compound with nine stereoisomers–has attracted particular interest, with myo-inositol being the most extensively studied and widely used [21,22]. Initially considered a vitamin, myo-inositol is now known to be synthesized endogenously in humans in limited amounts. It is believed to act as an insulin sensitizer, enhancing glucose transporter type 4 (GLUT4) translocation to the cell membrane, thereby improving glucose uptake and making its use in GDM management logical [21]. Additionally, myo-inositol participates in both oxidative and non-oxidative glucose metabolism, reduces duodenal glucose absorption, and promotes glycogen synthesis [23]. Its therapeutic efficacy has already been established in polycystic ovary syndrome (PCOS), another condition characterized by insulin resistance [24,25]. Myo-inositol supplementation is generally considered safe, with rare adverse effects limited to mild gastrointestinal disturbances [26,27]. Beyond treatment, it has also been studied for GDM prevention, particularly in women with a positive family history of type 2 diabetes mellitus.

A prospective, randomized, placebo-controlled study conducted in 2013 showed that first-trimester myo-inositol supplementation significantly reduced the incidence of GDM and fetal macrosomia compared to placebo [21]. Multiple studies have similarly demonstrated benefits in glycemic regulation and prevention of GDM, although current clinical guidelines continue to emphasize lifestyle modifications and insulin therapy as the primary interventions [28]. A meta-analysis by Wai et al. reported that daily supplementation with 4 g of myo-inositol significantly reduced the incidence of GDM, lowered blood glucose levels, and decreased the need for insulin therapy during pregnancy. It was also associated with a reduced rate of preterm delivery, lower birth weight percentiles, and a decreased incidence of neonatal hypoglycemia [20]. A meta-analysis of seven randomized controlled trials found that prophylactic inositol supplementation significantly reduced the incidence of GDM and improved glucose values, including fasting and 1- and 2-hour OGTT readings. Preterm births and pregnancy-related hypertension were also less frequent, although rates of cesarean delivery, shoulder dystocia, neonatal hypoglycemia, and macrosomia were not significantly affected. Furthermore, four randomized controlled trials evaluating inositol as a therapeutic option in established GDM demonstrated improved insulin resistance and a lower risk of neonatal hypoglycemia [29].

vale inozitol kao terapijsku opciju kod već postojećeg GDM-a pokazale su poboljšanje insulinske rezistencije i manji rizik od neonatalne hipoglikemije [29].

Međutim, pojedine studije, poput onih koje su sproveli Moini i saradnici, naglašavaju da je većina istraživanja sprovedena u Italiji i navode da profilaktička primena mio-inozitola nije smanjila akušerske ili neonatalne komplikacije kao što su carski rez, distocija ramena, vrednosti telesna težine ploda na rođenju, fetalna makrozomija ili neonatalna hipoglikemija [23]. Slične rezultate pokazala je i studija sprovedena u Irskoj, u kojoj nije zabeleženo smanjenje incidencije GDM-a. Posmatrano u celini, dokazi i dalje nisu dovoljno ubedljivi da bi se rutinska primena mio-inozitola tokom trudnoće preporučila sa sigurnošću [30]. Mio-inozitol na osnovu postojećih studija ima povoljniji bezbednosni profil od metformina, koji je često povezan sa gastrointestinalnim neželjenim efektima, a u retkim slučajevima i sa laktacidozom. Kao prirodno prisutan molekul uključen u brojne fiziološke procese, mio-inozitol se razlikuje od metformina, čiji su efekti pre svega farmakološki. Iako su raspoloživi dokazi još uvek ograničeni, trenutni podaci ukazuju da se mio-inozitol generalno dobro podnosi, dok bezbednost metformina tokom trudnoće i dalje ostaje predmet rasprave [31].

OSTALI SUPLEMENTI

Disbioza crevne mikrobiote ima značajnu ulogu u razvoju GDM-a, dok suplementacija probioticima može poboljšati metabolizam glukoze i inflamatorni status. Ipak, njen efekat na prevenciju GDM-a ostaje nedosledan, verovatno zbog razlika u sojevima probiotika, protokolima primene i individualnim odgovorima pacijentkinja.

Omega-3 masne kiseline, kao važni učesnici lipidnog metabolizma sa antiinflamatornim i insulin-senzitizujućim svojstvima, takođe su istraživane zbog potencijalne uloge u prevenciji GDM-a. Međutim, trenutni dokazi ne potvrđuju doslednu korist njihove suplementacije u poboljšanju glikemijske kontrole niti u prevenciji GDM-a, iako su zabeležena skromna poboljšanja lipidnog profila i pojedinih ishoda trudnoće [32].

Pregledni rad koji je obuhvatio 11 Cochrane sistematskih pregleda, 71 kliničko ispitivanje i 23 154 žene ukazuje da određene farmakološke i nutritivne intervencije mogu imati potencijalnu korist u prevenciji GDM-a, ali da snaga i kvalitet dokaza značajno variraju [19]. Dostupni podaci pokazuju da većina nutritivnih suplemenata ima ograničen ili neizvestan efekat u prevenciji GDM-a. Dokazi visokog kvaliteta ukazuju da suplementacija omega-3 masnim kiselinama tokom trudnoće ne smanjuje rizik od GDM-a. Nasuprot tome, dokazi veoma niskog kvaliteta ukazuju na moguću korist probiotika, naročito kada se kombinuju sa dijetetskim intervencija.

However, some studies, such as those by Moini et al., emphasize that most research has been conducted in Italy and report that prophylactic myo-inositol did not reduce obstetric or neonatal complications such as cesarean delivery, shoulder dystocia, birth weight, fetal macrosomia, or neonatal hypoglycemia [23]. An Irish study reported similar findings, showing no reduction in GDM incidence. Taken together, the evidence remains inconclusive regarding the routine use of myo-inositol supplementation in pregnancy [30]. Myo-inositol appears to have a more favorable safety profile than metformin, which is frequently associated with gastrointestinal adverse effects and, in rare cases, lactic acidosis. As a naturally occurring molecule involved in multiple physiological processes, myo-inositol differs from metformin, whose effects are primarily pharmacological. Although available evidence remains limited, current data suggest that myo-inositol is generally well tolerated, whereas the safety of metformin use during pregnancy continues to be a subject of debate [31].

OTHER SUPPLEMENTS

Gut microbiota dysbiosis plays an important role in the development of GDM, while probiotic supplementation may improve glucose metabolism and inflammatory status; however, its effect on GDM prevention remains inconsistent, likely due to differences in probiotic strains, treatment protocols, and individual responses.

Omega-3 fatty acids, as important components of lipid metabolism with anti-inflammatory and insulin-sensitizing properties, have been investigated for their potential role in GDM. However, current evidence does not support a consistent benefit of their supplementation in improving glycemic control or preventing GDM, although modest improvements in lipid profile and certain pregnancy outcomes have been reported [32].

Narrative review that included 11 Cochrane Reviews – 71 trials and 23,154 women suggests that several pharmacological and nutritional interventions may confer a potential benefit in the prevention of GDM, although the strength and quality of evidence remain variable [19]. Current evidence suggests that most nutritional supplements have limited or uncertain effects on the prevention of GDM. High-quality evidence indicates that omega-3 fatty acid supplementation during pregnancy does not reduce the risk of GDM. In contrast, very low-quality evidence suggests a potential benefit of probiotics, particularly when combined with dietary interventions, possibly through modulation of the gut microbiome and reduction of inflammation;

jama, verovatno putem modulacije crevne mikrobiote i smanjenja inflamacije, ali ovi nalazi ostaju neubedljivi. Slično tome, kombinovane strategije suplementacije, kao što su vitamin D sa kalcijumom ili drugim mineralima, kao i intervencije koje uključuju heparin, aspirin, imunizaciju leukocitima ili imunoglobuline, se nisu pokazale efikasnim. Sveukupno, ovo istraživanje ukazuje da, uprkos obećavajućim rezultatima pojedinih intervencija, ukupna baza dokaza ostaje ograničena zbog heterogenosti studija i metodoloških ograničenja. Zbog toga se trenutno nijedna dodatna terapija ne može sa sigurnošću preporučiti za rutinsku prevenciju GDM-a, što naglašava potrebu za daljim velikim, dobro dizajniranim randomizovanim kontrolisanim studijama [19].

FARMAKOLOŠKE INTERVENCIJE

METFORMIN

U određenim slučajevima, oralni hipoglikemijski lekovi, kao što su metformin i gliburid, mogu se koristiti u lečenju i prevenciji GDM-a [33]. Metformin, sintetski derivat bigvanida, ostvaruje više efekata, uključujući inhibiciju hepatičke glukoneogeneze, smanjenje intestinalne apsorpcije glukoze i povećanje perifernog preuzimanja glukoze. Pored regulacije glikemije, metformin utiče i na metabolizam lipida, funkciju mitohondrija i očuvanje krvnih sudova. Kod žena sa GDM-om opisane su promene na placenti, uključujući nezrelost horionskih resica, infarkte placente, horangiozu i povećan broj sincicijalnih čvorova. Ove promene su, međutim, ređe kod žena lečenih metforminom nego kod onih koje su lečene isključivo dijetetskim merama. Ipak, uticaj metformina na placentnu mitohondrijalnu aktivnost izazvao je zabrinutost zbog mogućih rizika po zdravlje ploda, što ukazuje na potrebu za pažljivim praćenjem tokom terapije [34] .

Metformin prolazi placentarnu barijeru, što izaziva zabrinutost zbog potencijalne izloženosti fetusa i sa time povezanih rizika [5,35]. Pojedine studije ukazuju da koncentracije metformina u fetalnoj krvi mogu biti jednake ili čak veće od koncentracija u majčinoj krvi, što dodatno naglašava potrebu za oprezom tokom trudnoće [1]. Zbog toga se, u poređenju sa insulinom, oralni hipoglikemici generalno smatraju manje bezbednim kao terapija prvog izbora, a njihova primena u trudnoći i dalje ostaje predmet kontroverzi [5,35].

Kod pacijentkinja kod kojih je OGTT-om potvrđena insulinska rezistencija, razmatrana je primena niskih doza metformina (približno 250 mg dva puta dnevno) tokom prvog trimestra trudnoće. Ovakav pristup smatra se relativno bezbednim, imajući u vidu da embrionalna faza traje do osme nedelje gestacije, tokom koje majčina i fetalna cirkulacija još nisu u potpunosti povezane. Studija takođe ukazuje da, osim mogućeg po-

however, these findings remain inconclusive. Similarly, combined supplementation strategies, such as vitamin D with calcium or other minerals, as well as interventions including heparin, aspirin, leukocyte immunization, or immunoglobulins, lack sufficient evidence to support their effectiveness. Taken together, these findings highlight that, despite promising signals for certain interventions, the overall evidence base is limited by heterogeneity and methodological constraints. Consequently, no adjunctive therapy can currently be recommended with certainty for routine prevention of GDM, underscoring the need for further large-scale, well-designed randomized controlled trials [19].

PHARMACEUTICAL INTERVENTION

METFORMIN

In certain cases, oral hypoglycemic agents, such as metformin and glyburide, may be used to manage and prevent GDM [33]. Metformin, a synthetic biguanide, exerts multiple effects, including the inhibition of hepatic gluconeogenesis, reduction of intestinal glucose absorption, and enhancement of peripheral glucose uptake. Beyond glycemic regulation, metformin also influences lipid metabolism, mitochondrial function, and vascular health. Placental changes in women with GDM–such as villous immaturity, infarction, chorangiosis, and increased syncytial knots–have been reported, but these alterations appear to be less frequent in women treated with metformin compared to those managed with diet alone. However, metformin's effect on placental mitochondrial activity has raised concerns regarding potential fetal risks, highlighting the need for careful monitoring during therapy [34].

Metformin crosses the placental barrier, raising concerns about potential fetal exposure and associated risks [5,35]. Some studies suggest that fetal blood concentrations of metformin may be equal to or even higher than maternal levels, further underscoring the need for caution during pregnancy [1]. Consequently, compared to insulin, they are generally considered less safe as first-line pharmacological therapy, and their use during pregnancy remains somewhat controversial [5,35].

In patients with confirmed insulin resistance on OGTT, low-dose metformin (approximately 250 mg twice daily) during the first trimester has been considered. This approach is considered relatively safe, given that the embryonic phase extends through the eighth week of gestation, when maternal and fetal circulation are not yet fully connected. The study also suggests that, apart from a potential increased risk of small for gestational age (SGA), other perinatal risks associated

većanog rizika za novorođenče male telesne mase za gestacijsku dob (SGA), drugi perinatalni rizici povezani sa primenom metformina u trudnoći nisu značajni [36]. Međutim, pojedine studije ne preporučuju primenu ovog leka kod trudnica sa hroničnom hipertenzijom, nefropatijama ili sumnjom na zastoj u rastu fetusa [37].

Dobro je poznato da je sindrom policističnih jajnika (PCOS) jedna od najčešćih reproduktivnih endokrinopatija i da je često povezan sa insulinskom rezistencijom, zbog čega predstavlja značajan faktor rizika za razvoj GDM-a. Studija objavljena 2008. godine pokazala je da je incidencija GDM-a bila gotovo devet puta manja kod žena sa PCOS-om koje su nastavile upotrebu metformina tokom trudnoće u poređenju sa ženama koje ovaj lek nisu koristile. Ovaj nalaz naglašava značajnu i klinički važnu ulogu metformina u prevenciji GDM-a [38].

Druga studija, koja je analizirala različite preventivne pristupe i njihove kombinacije, pokazala je da je metformin najefikasniji u prevenciji GDM-a kod žena sa PCOS-om ili povišenim vrednostima glukoze natašte, odnosno kod osoba sa povećanim rizikom za insulinsku rezistenciju, uključujući i žene starije životne dobi. Ova studija takođe naglašava da je najefikasnija strategija započinjanje terapije metforminom pre začeća ili tokom prvog trimestra trudnoće, kada predstavlja jedinu preventivnu meru za GDM [10]. Sa druge strane, kod gojaznih žena metformin nije značajno uticao na smanjenje BMI. Ovi rezultati su u skladu sa ranijim istraživanjima koja ukazuju da primena metformina tokom trudnoće, naročito ukoliko se nastavi tokom cele gestacije uz fizičku aktivnost, može doprineti smanjenju BMI [39].

Na kraju, studija Gluecka i saradnika pokazala je da metformin, u kombinaciji sa odgovarajućim načinom života i dijetetskim režimom, doprinosi kako primarnoj tako i sekundarnoj prevenciji GDM-a kod žena sa PCOS-om [40].

Nedavna meta-analiza koja je obuhvatila kohortne studije i randomizovana kontrolisana ispitivanja pokazala je da profilaktička primena metformina značajno smanjuje rizik od razvoja GDM-a kod visokorizičnih populacija. Ovaj efekat bio je posebno izražen kod žena azijskog porekla, pacijentkinja sa PCOS-om i onih koje su primale više doze metformina [41].

Studija PregMet2 predstavljala je randomizovano, placebo-kontrolisano, dvostruko slepo multicentrično istraživanje sprovedeno u skandinavskim zemljama među trudnicama sa PCOS-om. U studiji je poređen metformin sa placebom tokom cele trudnoće. Rezultati nisu pokazali statistički značajnu razliku u incidenciji GDM-a između dve grupe [42].

Na osnovu trenutno dostupnih istraživanja, metformin se može smatrati bezbednim za primenu tokom trudnoće, ali broj studija koje pružaju konačne dokaze

with metformin use in pregnancy are not significant [36]. However, other studies do not recommend the use of this drug in pregnant women with chronic hypertension, nephropathies, or suspected fetal growth restriction [37].

It is well established that one of the most common reproductive endocrinopathies is PCOS, which is frequently associated with insulin resistance and consequently represents a significant risk factor for GDM. A study published in 2008 indicated that the incidence of GDM was nearly nine times lower in women with PCOS who continued metformin therapy during pregnancy compared to those who did not. This finding highlights the strong and clinically important role of metformin in GDM prevention [38].

Another study, which considered several different preventive approaches and their combinations, demonstrated that metformin is most effective in preventing GDM in women with PCOS or in those with elevated fasting glucose levels, i.e., in individuals at increased risk of insulin resistance, such as those of advanced maternal age, among other factors. This study also emphasizes that the most effective strategy is to initiate metformin treatment before conception or during the first trimester, when it represents the sole preventive approach for GDM [10]. On the other hand, in obese women, metformin use didn't significantly affect BMI reduction. These findings align with previous research, suggesting that antenatal metformin administration, particularly when continued throughout pregnancy in combination with physical activity, may contribute to BMI reduction [39].

Finally, the study by Glueck et al. demonstrated that metformin, combined with a lifestyle and dietary regimen, contributed to both primary and secondary prevention of GDM in women with PCOS [40].

A recent meta-analysis including cohort studies and randomized controlled trials found that prophylactic metformin use significantly reduces the risk of GDM in high-risk populations. This effect was particularly evident among Asian women, patients with PCOS, and those receiving higher doses of metformin [41].

The PregMet2 study was a randomized, placebo-controlled, double-blind multicenter trial conducted in Scandinavian countries among pregnant women with PCOS, comparing metformin with placebo throughout pregnancy. The results showed no significant difference in the incidence of GDM between the two groups [42].

Based on current studies, metformin can be considered safe for use during pregnancy; however, the number of studies providing definitive evidence remains limited. There is a particular need for research

i dalje je ograničen. Posebno su potrebna istraživanja koja procenjuju dugoročne posledice primene metformina, kako po majku, tako i po dete [43].

Istraživanja ukazuju da potencijalni neželjeni efekti metformina na fetus predstavljaju usporen fetalni rast, manju telesu težinu ploda na rođenju i različite metaboličke poremećaje tokom detinjstva i kasnijeg života, uključujući gojaznost. Nasuprot tome, druge studije nisu potvrdile ove nalaze, pa čak navode i manju učestalost spontanih pobačaja kod žena lečenih metforminom [34].

Zbog fetalne hiperglikemije i hiperinsulinemije, najčešća komplikacija GDM-a jeste novorođenče veliko za gestacijsku dob (LGA), što može dovesti do komplikacija poput makrozomije, distocije ramena i neonatalne hipoglikemije [7]. Međutim, Farladansky-Gershnabel i saradnici navode da je kod trudnoća komplikovanih GDM-om primena metformina bila povezana sa većom učestalošću novorođenčadi male telesne mase za gestacijsku dob (SGA) u poređenju sa trudnoćama lečenim insulinom. Smatra se da je ovaj efekat posledica prolaska metformina kroz placentarnu barijeru i njegovog direktnog uticaja na fetalne ćelije, pri čemu dolazi do smanjenja mitohondrijalne aktivnosti i ograničavanja dostupnosti nutrijenata ćelijama, što može nepovoljno uticati na rast i diferencijaciju placentnih i fetalnih tkiva [44]. Sa druge strane, pojedine studije pokazale su da kod gojaznih trudnica sa adekvatnom glikoregulacijom primena metformina ne smanjuje rizik od novorođenčadi malih za gestacionu dob [45].

Poznato je da metformin nije teratogen i da njegova primena tokom trudnoće ne povećava rizik od kongenitalnih anomalija. Međutim, postoje dokazi koji ukazuju da intrauterina izloženost metforminu može imati dugoročne metaboličke posledice po potomstvo [33].

Dugoročne posledice opisane su i kod dece rođene od majki koje su tokom trudnoće koristile metformin. U uzrastu od 18 meseci ova deca bila su viša i teža u odnosu na decu čije su majke lečene insulinom. Tokom druge godine života imala su veću debljinu kožnih nabora (subskapularno i u regiji bicepsa) i veći obim nadlaktice, iako se ukupni procenat telesne masti i rezultati bioimpedance i DXA merenja nisu razlikovali između grupa. Procene motornog, socijalnog i jezičkog razvoja takođe nisu pokazale značajne razlike. Do devete godine života kod dece izložene metforminu intrauterino zabeleženi su veći obim struka, veći odnos obima struka i telesne visine, viši BMI i veća debljina kožnog nabora u predelu tricepsa. Ipak, druge studije nisu potvrdile ove nalaze, navodeći da nisu utvrđene značajne dugoročne razlike između ispitivanih grupa [45].

Studija sprovedena u skandinavskim zemljama pokazala je da primena metformina tokom trudnoće ne dovodi do značajnih razlika u metabolizmu ili gojaznosti

evaluating the long-term effects of metformin use on both the mother and the child [43].

Studies indicate that potential adverse effects of metformin on the fetus may include restricted fetal growth, lower birth weight, and various metabolic disturbances in childhood and later life, including obesity. Conversely, other studies have not confirmed these findings and even report a reduced incidence of spontaneous miscarriage in women treated with metformin [34].

Due to fetal hyperglycemia and hyperinsulinemia, the most common complication of GDM is large for gestational age (LGA), which can subsequently lead to macrosomia, shoulder dystocia, and neonatal hypoglycemia [7]. However, Farladansky-Gershnabel et al. reported that in pregnancies complicated by GDM, the use of metformin was associated with a higher frequency of SGA neonates than in insulin-treated pregnancies. This effect is thought to result from metformin crossing the placental barrier and acting directly on fetal cells, reducing mitochondrial activity and thereby limiting cellular nutrient availability, which may impair the growth and differentiation of both placental and fetal tissues [44]. On the contrary, other studies have shown that in obese, normoglycemic pregnant women, metformin administration does not reduce the risk of LGA [45].

Metformin is not teratogenic, and its use during pregnancy does not increase the risk of congenital anomalies. However, evidence suggests that in utero exposure may have long-term metabolic effects on the offspring [33].

Long-term complications have also been described in children born to mothers treated with metformin during pregnancy. At 18 months of age, these children were found to be taller and heavier compared to those whose mothers received insulin therapy. In the second year of life, they exhibited increased skinfold thickness (subscapular and biceps) and larger mid-upper arm circumference, although overall body fat percentage, bioimpedance measures, and dual-energy X-ray absorptiometry (DXA) results did not differ between the groups. Moreover, assessments of motor, social, and language development showed no significant differences. By age 9, children exposed to metformin in utero had higher waist circumference, waist-to-height ratio, BMI, and triceps skinfold thickness. Nevertheless, other studies have not confirmed these findings, reporting no significant long-term differences between groups [45].

A study conducted in Scandinavian countries indicates that metformin use during pregnancy does not result in significant differences in metabolism or

sti kod dece do uzrasta od 7 –9 godina. Ipak, primećeno je da su deca izložena metforminu intrauterino bila krupnija, sa većim obimom struka, većom telesnom masom i većim odnosom telesne mase i visine [46] . Najduže praćenje dece izložene metforminu intrauterino sprovedeno je u norveškim PedMet studijama. Najznačajniji nalazi ukazali su na povećan BMI, veći odnos obima struka i telesne visine i veću prevalenciju gojaznosti kod dece uzrasta 5–10 godina čije su majke sa PCOS-om koristile metformin tokom trudnoće. U grupi dece izloženih metforminu uočene su više koncentracije 11-deoksikortizola kod dečaka u poređenju sa grupom izloženom placebu. Autori su zaključili da se potencijalni uticaj metformina na steroidogenezu ne može isključiti [47,48]. Dosadašnje meta-analize ukazuju na nižu porođajnu masu praćenu ubrzanim postnatalnim rastom i povećanom količinom masnog tkiva kod dece izložene metforminu do desete godine života. Dugoročni kardiometabolički efekti ove izloženosti ostaju neutvrđeni [49,50]. Takođe postoje podaci koji ukazuju na mogući uticaj paternalne izloženosti metforminu. Nacionalna danska kohortna studija pokazala je da je primena metformina kod očeva u periodu oko začeća bila povezana sa povećanim rizikom od genitalnih anomalija kod muške dece i smanjenim udelom muške novorođenčadi u poređenju sa onim koji su bili na terapiji insulinom [46].

Studija koja je pratila decu do dve godine starosti pokazala je da su deca izložena metforminu intrauterino imala veći udeo potkožnog masnog tkiva u odnosu na intraabdominalno masno tkivo, dok je neurološki razvoj bio komparabilan sa decom čije su majke tokom trudnoće lečene insulinom [33].

DISKUSIJA

Prevencija gestacijskog dijabetesa melitusa (GDM) i dalje predstavlja složenu oblast koja se i dalje razvija, što odražava multifaktorijalnu prirodu bolesti i heterogenost dostupnih preventivnih intervencija. Među farmakološkim strategijama, metformin je privukao veliku pažnju zbog jednostavnosti primene i mogućnosti da poveća osetljivost inulinskih receptora. . Rezultati brojnih studija ukazuju da metformin može biti efikasan u smanjenju incidencije GDM-a, posebno kod visokorizičnih populacija, kao što su žene sa sindromom policističnih jajnika (PCOS), povišenim vrednostima glukoze natašte ili izraženom insulinskom rezistencijom [10,38,41]. Njegov potencijalni efekat najizraženiji je kada se primenjuje pre začeća ili u ranoj trudnoći, što podržava koncept da rana metabolička modulacija može uticati na kasnije gestacijske ishode [10].

Uprkos ovim ohrabrujućim rezultatima, ukupna efikasnost metformina u prevenciji GDM-a ostaje neu-

obesity in children aged 7–9 years. However, it was observed that children exposed to metformin in utero tended to be larger, with greater waist circumference, higher body weight, and a higher weight-to-height ratio [46]. The longest follow-up of children exposed to metformin in utero was performed in the Norwegian randomized placebo-controlled PedMet studies. The main findings showed increased BMI, waist-to-height ratio, and a higher prevalence of obesity among children aged 5–10 years born to mothers with PCOS who received metformin during pregnancy. In a subgroup of offspring exposed to metformin in utero, steroid hormone profiles suggested higher 11-deoxycortisol concentrations in boys than in those exposed to placebo. The authors concluded that the potential effect of metformin on steroidogenesis cannot be excluded [47,48]. To date, meta-analyses suggest lower birthweight followed by accelerated postnatal growth and increased adiposity in children exposed to metformin up to 10 years of age. The long-term cardiometabolic effects of such exposure remain unclear [49,50]. Emerging data also implicate paternal exposure: a nationwide Danish cohort study found that periconceptional metformin use in fathers was associated with an increased risk of genital anomalies in male offspring and a reduced male birth proportion, compared with insulin exposure [46].

A follow-up study, monitoring children up to 2 years of age, found that those exposed to metformin in utero had greater subcutaneous fat than intra-abdominal fat, while neurological development was comparable to that of children whose mothers were treated with insulin [33].

DISCUSSION

The prevention of GDM remains a complex and evolving subject, reflecting the multifactorial nature of the disease and the heterogeneity of available interventions. Among pharmacological strategies, metformin has attracted considerable attention due to its insulin-sensitizing properties and ease of administration. Evidence from multiple studies suggests that metformin may be effective in reducing the incidence of GDM, particularly in high-risk populations such as women with PCOS, elevated fasting glucose levels, or features of insulin resistance [10,38,41]. Its potential benefit appears most pronounced when initiated preconceptionally or in early pregnancy, supporting the concept that early metabolic modulation may influence subsequent gestational outcomes [10].

Despite these promising findings, the overall efficacy of metformin in GDM prevention remains inconsistent across studies. While some trials demonstrate

sklađena među različitim studijama. Dok neka istraživanja pokazuju značajno smanjenje incidencije GDM-a, druga, poput studije PregMet2, nisu uspela da potvrde ove povoljne efekte [38,41,42]. Ove razlike verovatno proizlaze iz razlika u dizajnu studija, karakteristikama ispitanica, vremenu započinjanja terapije i primenjenim dozama. Pored toga, čini se da metformin nema značajan uticaj na smanjenje BMI kod gojaznih trudnica, što ukazuje da su njegovi metabolički efekti izraženiji kod žena sa insulinskom rezistencijom nego kod onih kod kojih je gojaznost dominantni problem [39].

Dodatni aspket kompleksnosti odnosi se na bezbednosni profil metformina tokom trudnoće. Iako dostupni podaci ukazuju da metformin nije teratogen i da se generalno smatra bezbednim, zabrinutost i dalje postoji zbog činjenice da lek lako prolazi kroz placentu i može dostići koncentracije u krvi fetusa jednake ili čak veće nego kod majke [1,33,35,43]. Noviji podaci ukazuju na moguće dugoročne posledice po potomstvo, uključujući manju porođajnu masu praćenu ubrzanim postnatalnim rastom i povećanim rizikom od gojaznosti tokom detinjstva [45,46]. Dugoročna praćenja, uključujući PedMet studije, pokazala su veći BMI i veći odnos obima struka i telesne visine kod dece izložene metforminu intrauterino, što otvara pitanje mogućih promena u metaboličkom programiranju [46]. Takođe su opisane suptilne endokrine promene, uključujući moguće efekte na steroidogenezu, iako njihov klinički značaj još nije razjašnjen. Jedno od glavnih ograničenja postojećih dokaza jeste nedostatak dovoljno velikih multicentričnih randomizovanih kontrolisanih studija sa dugoročnim praćenjem, posebno kada su u pitanju kardiometabolički ishodi kod potomstva.

Postoji i niz dodatnih nerešenih pitanja koja komplikuju primenu metformina tokom trudnoće. Gastrointestinalni neželjeni efekti, uključujući mučninu i povraćanje, mogu ograničiti njegovu upotrebu, naročito kod trudnica sa hiperemezom u trudnoći [31]. Pored toga, poluvreme eliminacije metformina iznosi približno 4–6 sati, ali njegovi farmakodinamski efekti mogu trajati i duže zbog akumulacije u tkivima [33]. To otvara potencijalna pitanja tokom intrapartalnog perioda, kada je trudnicama često ograničen unos hrane i pića *per os*. Iako sam metformin retko izaziva hipoglikemiju, njegovo produženo dejstvo u odsustvu kalorijskog unosa teoretski može doprineti nestabilnim vrednostima glikemije. Ove činjenice ukazuju na potrebu za jasno definisanim kliničkim protokolima za peripartalno vođenje terapije.

Paralelno sa metforminom, inozitoli, naročito mio-inozitol, pojavili su se kao obećavajući nefarmakološki agensi zahvaljujući svojoj ulozi u putevima insulinske signalizacije [21,23,24]. Više studija i meta-analiza

significant reductions in GDM incidence, others–such as the PregMet2 study–fail to confirm these benefits [38,41,42]. These discrepancies likely reflect differences in study design, patient populations, initiation timing, and dosing regimens. Furthermore, metformin does not appear to significantly influence BMI reduction in obese pregnant women, suggesting that its metabolic effects may be more pronounced in insulin-resistant rather than solely obese phenotypes [39].

An additional layer of complexity relates to the safety profile of metformin, particularly in the context of pregnancy. Although current data suggest that metformin is not teratogenic and is generally considered safe, concerns remain regarding fetal exposure, as the drug readily crosses the placenta and may reach fetal concentrations comparable to or exceeding maternal levels [1,33,35,43]. Emerging evidence points to potential long-term effects on offspring, including lower birth weight, accelerated postnatal growth, and an increased risk of childhood adiposity [45,46]. Findings from long-term follow-up studies, such as the PedMet trials, indicate higher BMI and waist-to-height ratios in metformin-exposed children, raising concerns about possible alterations in metabolic programming [46]. Additionally, subtle endocrine changes, including potential effects on steroidogenesis, have been suggested, although their clinical significance remains unclear. A major limitation of the current body of evidence is the lack of adequately powered, multicenter randomized controlled trials with long-term follow-up, particularly regarding offspring cardiometabolic outcomes.

However, several unresolved questions further complicate the use of metformin in pregnancy. Gastrointestinal side effects, including nausea and vomiting, may limit its use, particularly in patients with hyperemesis gravidarum, where symptom overlap may reduce tolerability and adherence [31]. Moreover, metformin has an elimination half-life of approximately 4–6 hours, but its pharmacodynamic effects may persist longer due to tissue accumulation [33]. This raises potential concerns in the intrapartum period, when women are often fasting; although metformin alone rarely causes hypoglycemia, its continued effect in the absence of caloric intake may theoretically contribute to glycemic instability. These considerations highlight the need for clear clinical protocols regarding peripartum management.

In parallel with metformin, inositols–particularly myo-inositol–have emerged as promising non-pharmacological agents due to their role in insulin signaling pathways [21,23,24]. Several studies and meta-analyses report improved glycemic control and reduced incidence of GDM, especially with early initia-

pokazalo je poboljšanje glikemijske kontrole i smanjenje incidencije GDM-a, naročito kada se primena započne rano [20,21,28,29]. Međutim, većina ovih istraživanja sprovedena je u Italiji, što otvara pitanje geografskih i metodoloških pristrasnosti, kao i ograničene mogućnosti generalizacije rezultata na širu populaciju [23]. Nasuprot ranijim istraživanjima na manjim uzorcima, rezultati novijih multicentričnih randomizovanih studija ukazuju da dnevna suplementacija sa 4 g mio-inozitola kod trudnica sa PCOS-om ne dovodi do značajnog smanjenja incidencije GDM-a, preeklampsije niti prevremenog porođaja [51]. Ovi rezultati, u skladu sa Cochrane sistematskim pregledom iz 2023. godine, ukazuju da trenutno nema dovoljno dokaza za rutinsku primenu mio-inozitola u primarnoj prevenciji komplikacija trudnoće u ovoj populaciji [51,52]. Dodatni problem u tumačenju dostupnih dokaza predstavlja heterogenost doza, formulacija i dizajna studija. Iako mio-inozitol pokazuje povoljan bezbednosni profil, još uvek nedostaju velike multicentrične studije visokog kvaliteta [26–28,33].

Istraživani su i drugi dodatni pristupi, uključujući probiotike, suplementaciju vitaminom D, pa čak i antikoagulantnu terapiju niskomolekularnim heparinom [19]. Iako pojedina istraživanja ukazuju na skromna poboljšanja insulinske senzitivnosti i inflamatornih markera, finalni dokazi nisu dovoljni da podrže njihovu rutinsku primenu u prevenciji GDM-a [8,28]. Ove intervencije mogu imati određenu ulogu kod pojedinih podgrupa pacijentkinja, ali njihov klinički značaj i isplativost zahtevaju dodatna istraživanja.

Na kraju, najdosledniji i najsnažniji dokazi i dalje podržavaju modifikaciju životnog stila kao osnovu prevencije GDM-a. Održavanje normalnog BMI pre trudnoće, adekvatno povećanje telesne mase tokom trudnoće, redovna fizička aktivnost i uravnotežena ishrana pokazali su najveću efikasnost u različitim populacijama, istovremeno predstavljajući najbezbednije i najdostupnije preventivne mere [8–11]. Farmakološki i suplementacioni pristupi, uključujući metformin i inozitol, mogu predstavljati dodatne opcije kod pažljivo odabranih visokorizičnih pacijentkinja, ali ne mogu zameniti fundamentalni značaj zdravih životnih navika.

ZAKLJUČAK

Tokom trudnoće, modifikacija životnog stila ostaje kamen temeljac prevencije GDM-a, pri čemu individualizovana medicinska nutritivna terapija i strukturisana fizička aktivnost predstavljaju intervencije prvog izbora.

Rana identifikacija odgovarajućim strategijama poput skrininga je od suštinskog značaja za smanjenje neželjenih ishoda i omogućavanje pravovremenog početka lečenja. Kada mere korekcije životnog stila ne

tion [20,21,28,29]. However, most of these studies have been conducted in Italian populations, raising concerns about potential geographical and methodological bias, as well as limited generalizability to broader populations [23]. Contrary to earlier studies conducted on smaller cohorts, results from recent multicenter randomized trials indicate that daily supplementation with 4 g of myo-inositol in pregnant individuals with PCOS does not lead to a significant reduction in the incidence of GDM, pre-eclampsia, or preterm birth [51]. These findings, consistent with the 2023 Cochrane systematic review, suggest that there is currently insufficient evidence to support the routine use of myo-inositol for the primary prevention of gestational complications in this specific population [51,52]. Additionally, heterogeneity in dosing regimens, formulations, and study designs further complicates the interpretation of the available evidence. While myo-inositol appears to have a favorable safety profile, robust, large-scale, multicenter trials remain lacking [26–28,33].

Other adjunctive approaches, including probiotics, vitamin D supplementation, and even anticoagulant therapies such as low-molecular-weight heparin, have also been investigated [19]. While some studies suggest modest improvements in insulin sensitivity and inflammatory markers, the overall evidence remains insufficient to support their routine use in GDM prevention [8,28]. These interventions may have a role in selected patient subgroups, but their clinical significance and cost-effectiveness require further clarification.

Ultimately, the most consistent and robust evidence supports lifestyle modification as the cornerstone of GDM prevention. Maintenance of a normal pre-pregnancy BMI, appropriate gestational weight gain, regular physical activity, and a balanced diet have demonstrated the greatest efficacy across diverse populations and represents the safest and most accessible interventions [8–11]. Pharmacological and supplemental approaches, including metformin and inositol, may serve as adjuncts in carefully selected high-risk individuals but cannot replace the fundamental importance of lifestyle measures.

CONCLUSION

During pregnancy, lifestyle modification remains the cornerstone of prevention, with individualized medical nutrition therapy and structured physical activity forming first-line interventions.

Early identification through appropriate screening strategies is essential to reduce adverse outcomes and to allow timely initiation of treatment. When lifestyle measures fail to achieve glycemic targets, pharmaco-

dovode do adekvatne kontrole glikemije, neophodna je farmakološka terapija. Insulin ostaje standard lečenja zbog svoje efikasnosti i činjenice da ne prolazi kroz placentu. Međutim, metformin se sve češće koristi u odabranim slučajevima, iako dileme u vezi sa dugoročnim ishodima kod potomstva ostaju nerešene. FIGO naglašava značaj individualnog pristupa terapiji, uzimajući u obzir glikemijsku kontrolu, karakteristike majke, dostupnost resursa i želje pacijentkinje. Važno je naglasiti da prevenciju GDM-a treba posmatrati kao sastavni deo dugoročne prevencije hroničnih bolesti, sa implikacijama za zdravlje majke i deteta koje se odnose i na period daleko izvan trudnoće. Postpartalno praćenje, savetovanje o zdravim životnim navikama i redovno praćenje metaboličkog statusa od ključnog su značaja za smanjenje rizika od razvoja dijabetesa tipa 2 i prekid transgeneracijskog ciklusa kardiometaboličkih bolesti [1].

Iako je metformin široko prihvaćen u kliničkoj praksi kao lek koji poboljšava insulinsku senzitivnost, inozitol, a naročito mio-inozitol, poslednjih godina privlači pažnju kao potencijalna preventivna i terapijska opcija u GDM-u zbog svoje uloge u putevima insulinske signalizacije. Ipak, dostupni podaci ostaju heterogeni, a direktne komparativne studije koje procenjuju njihovu efikasnost, optimalnu dozu, vreme započinjanja terapije i dugoročne ishode po majku i potomstvo i dalje su ograničene. Zbog toga još uvek ne postoje jasne preporuke zasnovane na dokazima koje bi precizno definisale njihove relativne prednosti i potencijalna ograničenja [1,53].

SKRAĆENICE

GDM – Gestacijski dijabetes melitus
BMI – Indeks telesne mase
FIGO – Međunarodna federacija za ginekologiju i akušerstvo
PCOS – Sindrom policističnih ovarijuma
OGTT – Oralni test opterećenja glukozom
GLUT4 – Transporter glukoze tip 4
ADA – Američko udruženje za dijabetes
EASD – Evropsko udruženje za proučavanje dijabetesa
HbA1c – Glikozilirani hemoglobin (hemoglobin A1c)
25OHD – 25-hidroksivitamin D
LGA – Novorođenče veliko za gestacijsku dob
SGA – Novorođenče malo za gestacijsku dob
DXA – Dvoenergetska rendgenska apsorpciometrija (Dual-Energy X-ray Absorptiometry)

Sukob interesa: Nije prijavljen.

logical therapy becomes necessary. Insulin remains the standard treatment due to its efficacy and inability to cross the placenta. However, metformin is increasingly used in selected cases, although questions remain regarding long-term offspring outcomes. FIGO highlights the importance of individualized treatment decisions that balance glycemic control, maternal characteristics, resource availability, and patient preferences. Importantly, GDM prevention should be viewed as an integral component of long-term chronic disease prevention, with implications for maternal and offspring health that extend well beyond pregnancy. Postpartum follow-up, lifestyle counseling, and ongoing metabolic surveillance are essential to reduce progression to type 2 diabetes and to interrupt the intergenerational cycle of cardiometabolic disease [1].

While metformin is widely used in clinical practice as an insulin-sensitizing agent, inositol–particularly myo-inositol–has recently gained attention as a promising preventive and therapeutic option for GDM due to its role in insulin signaling pathways. Nevertheless, available data remain heterogeneous, and direct comparative studies evaluating their efficacy, optimal dosing, timing of administration, and long-term maternal and offspring outcomes are limited. Consequently, clear evidence-based recommendations on their relative benefits and potential limitations remain lacking [1,53].

ABBREVIATIONS

GDM – Gestational Diabetes Mellitus
BMI – Body Mass Index
FIGO – International Federation of Gynecology and Obstetrics
PCOS – Polycystic Ovary Syndrome
OGTT – Oral Glucose Tolerance Test
GLUT4 – Glucose Transporter Type 4
ADA – American Diabetes Association
EASD – European Association for the Study of Diabetes
HbA1c – Hemoglobin A1c
25OHD – 25-hydroxyvitamin D
LGA – Large for Gestational Age
SGA – Small for Gestational Age
DXA – Dual-Energy X-ray Absorptiometry

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