Ruolo della nutraceutica nella gestione della donna diabetica in gravidanza

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Nutraceutici, integratori ed alimenti funzionali

CATEGORIA	DEFINIZIONE	ESEMPI
Nutraceutico	Estrazione naturale Azioni salutistiche	Monacoline Policosanoli Berberina
Integratore alimentare	Nutrienti nella dieta Da supplementare	Minerali Vitamine Omega-3
Alimento funzionale	Cibi arricchiti di sostanze naturali salutistiche	Cibi arricchiti in: fibre, fitosteroli, omega-3

Cicero 2012

Nutraceutico: neologismo originato dalle parole nutrizione e farmaceutico . Componente alimentare o principio attivo presente negli alimenti e che ha effetti positivi per il benessere e la salute, ivi inclusi la **prevenzione** e il **trattamento** delle malattie

Stephan De Felice, 1989

NUTRACEUTICO: LA DEFINIZIONE DEL MINISTERO DELLA SALUTE

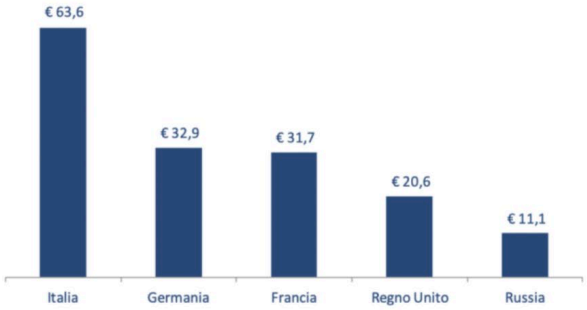
La legislazione italiana inquadra i **nutraceutici** nella categoria degli **integratori alimentari**, che però a differenza dei primi non dovrebbero avere funzione preventiva o curativa ma solo di **"ottimizzazione" delle funzioni fisiologiche**. Inoltre in Italia i nutraceutici possono essere commercializzati dopo una semplice segnalazione agli uffici ministeriali secondo la procedura del **silenzio assenso**.

In mancanza di precise **linee guida ministeriali**, tutto ciò ha portato all'esplosione di un **mercato** di prodotti proposti come **"modulatori fisiologici" di diverse funzioni** che tuttavia contengono spesso sostanze la cui attività non è dimostrata, sottodosate o addirittura inattive. Non solo: la loro **sicurezza a lungo termine** e le loro possibili **interazioni con farmaci** non sono in genere adeguatamente vagliate. Per questo grande importanza è rivestita dalla qualità produttiva.

Ministero della Salute

Il mercato

Graf. 9 - Spesa pro-capite nei maggiori mercati europei (Rsp, €, 2020)

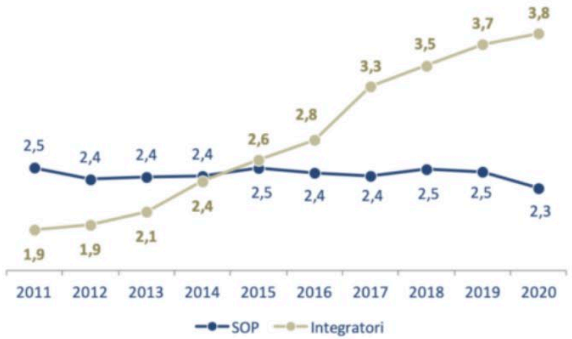


Fonte: Area Studi Mediobanca su fonti diverse

Graf. 3 - Il mercato italiano degli integratori (milioni di euro e variazione percentuale anno su anno)

Fonte: Area Studi Mediobanca su dati Federsalus

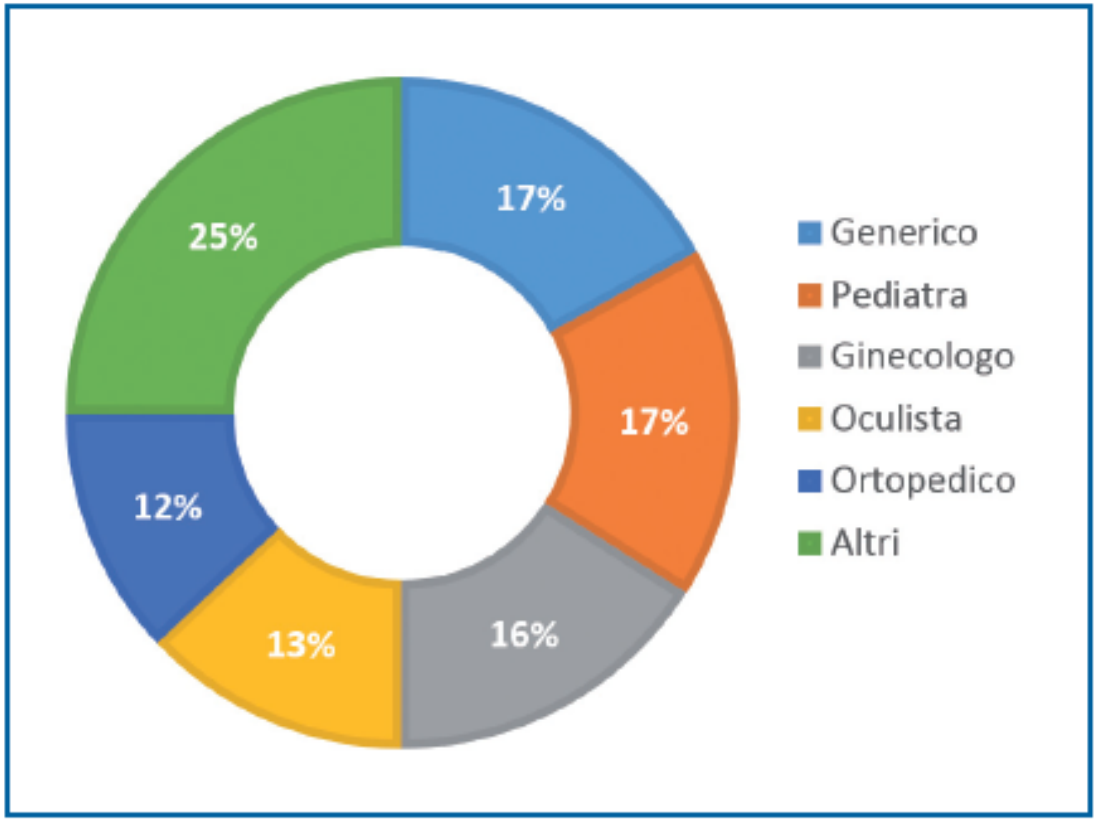
Graf. 4 - Il mercato italiano degli integratori e dei SOP (2011-2020 miliardi di euro)



Fonte: Area Studi Mediobanca su dati Federsalus e Assosalute

I maggiori prescrittori

Figura 10
Integratori: quota per tipologia di medico sul totale dei consigli.
Fonte: QuintilesIMS Medical Audit - Anno Mobile Giugno 2016.



Principali criticità

Mancanza di legislazione

- ✓ **Standardizzazione delle materie prime**
- ✓ **Titolazione dei principi attivi**
- ✓ **Dosaggio e tossicità**
- ✓ **Controllo contaminanti (specie chimici)**
- ✓ **Validazione dell'efficacia mediante trial clinici**

Lead Article

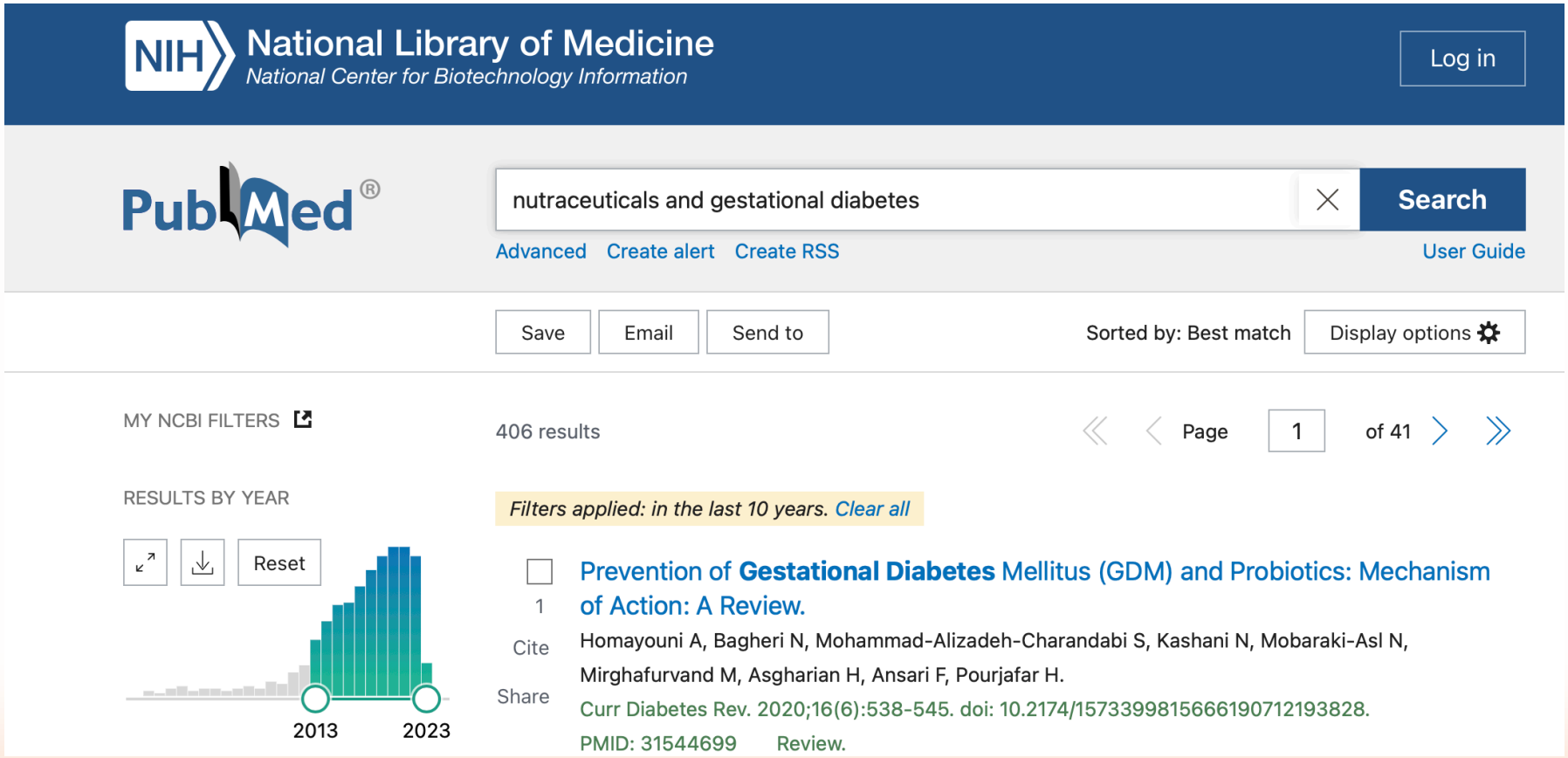
Safety and efficacy of supplements in pregnancy

Benjamin Brown and Ciara Wright

There is substantial evidence on the importance of maternal diet for the health of the fetus. The nutrient status of the fetus is mostly dependent on maternal intake and it has been known for many years that deficiencies in critical nutrients can lead to malformations and poor health outcomes for both the mother and offspring. It is because of this that, often, pregnancy is a time that expectant mothers will focus on their health and nutrient intake.

Supplement use is very common in pregnancy. Studies show that multivitamin use (excluding folic acid alone) ranges **from 78% to 98%** in different cohorts across the United States, Canada, and Australia.

Il supporto scientifico



Review Article

Evaluating Traditional Chinese Medicine and Herbal Products for the Treatment of Gestational Diabetes Mellitus

Studies found **that many pregnant women turn to complementary and alternative medicine for health maintenance or symptom relief**, such as herbal medicine and acupuncture from traditional Chinese medicine.

In China, the most updated research found that on average, 14.8% of women develop GDM, and the risk increases significantly in older (26.7%) and overweight/obese women (30.3%)

Three major herbal medicine/herbal products that were associated with glycemic control in gestational diabetes, including Zuo Gui Wan, red raspberry leaves, and Orthosiphon stamineus.

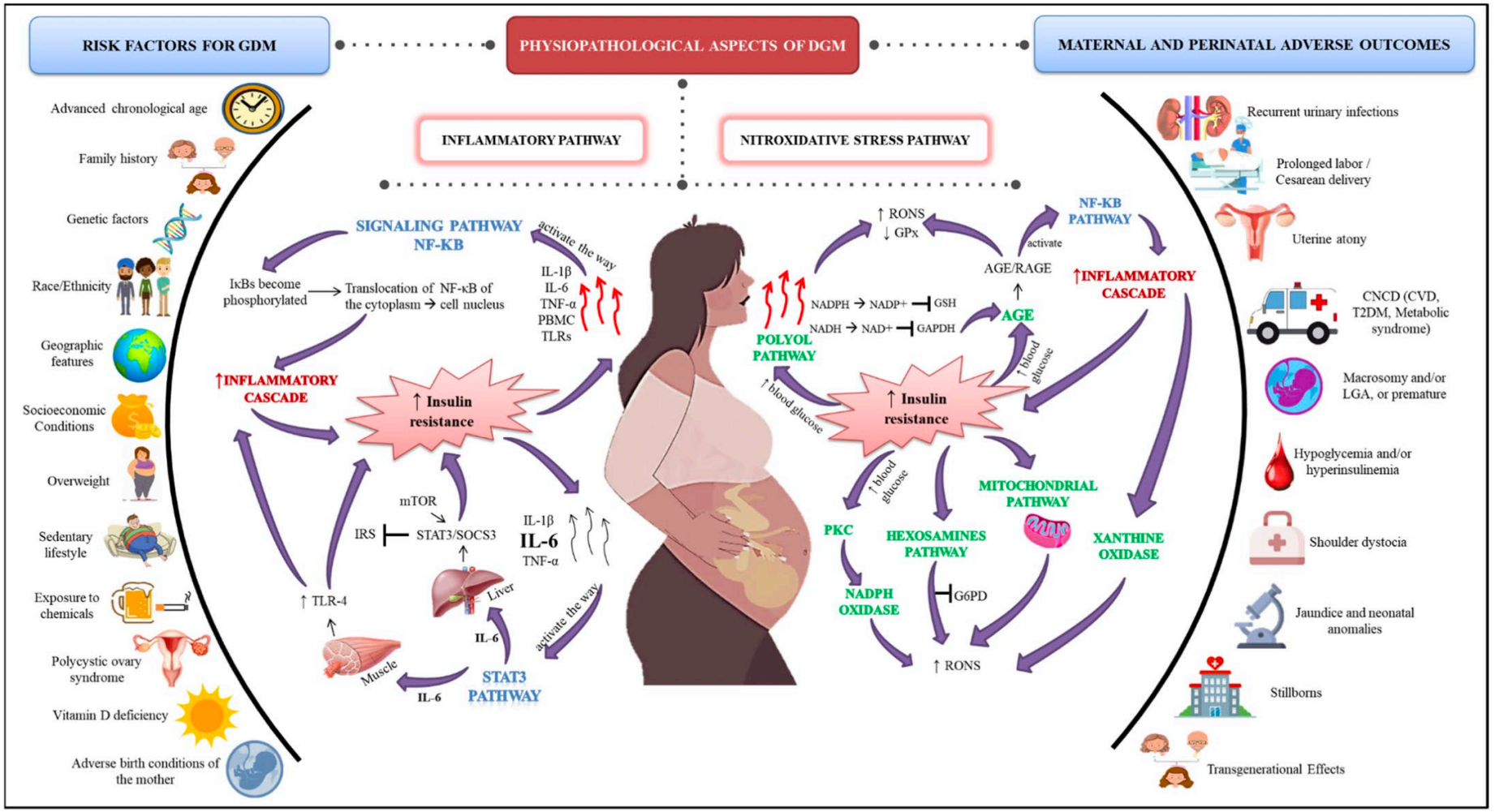
Table 1: The medicinal constituents of Zuo Gui Wan.

Pharmaceutical name	Chinese name (pin yin)	Chinese name (characters)	Common English name
Rehmanniae radix praeparata	Shu Di Huang	熟地黄	Prepared Rehmannia root
Rhizoma dioscoreae oppositae	Shan Yao	山药	Common yam rhizome
Fructus corni officinalis	Shan Zhu Yu	山茱萸	Asiatic cornelian cherry fruit
Cervi cornus colla	Lu Jiao Jiao	鹿角胶	Deer antler glue
Colla carapacis et plastri testudinis	Gui Jia Jiao	龟甲胶	Glue of tortoise shell
Fructus lycii chinensis	Gou Qi Zi	枸杞子	Barbary wolfberry fruit
Semen Cuscutae Chinensis	Tu Si Zi	菟丝子	Dodder seed
Radix Achyranthis Bidentatae	Niu Xi	牛膝	Two-toothed Achyranthes root

Given its dual benefits for both the mother and fetus, Zuo Gui Wan may be a good therapeutic alternative or an augmentation to western medicine for GDM patients.

Journal of Diabetes Research
Volume 2019, Article ID 9182595, 6 pages

Inflammatory and oxidative stress aspects in GDM



Vitamina D

Vitamin D and Metabolic Diseases: Growing Roles of Vitamin D

®-cell in the pancreas that secretes insulin has been shown to contain VDRs as well as the 1 alpha hydroxylase enzyme.

Evidence indicates that vitamin D treatment improves glucose tolerance and insulin resistance

Vitamin D deficiency leads to reduced insulin secretion. Supplementation with vitamin D has been shown to restore insulin secretion in animals

In Type 2 DM patients insufficient vitamin D and calcium appears to hinder glycemic control and that supplementing both nutrients may be necessary to optimize glucose metabolism

Journal of Obesity & Metabolic Syndrome 2018;27:223-232

Association of A1C Levels With Vitamin D Status in U.S. Adults

Data from the National Health and Nutrition Examination Survey

RESEARCH DESIGN AND METHODS — We examined the association between serum 25 hydroxyvitamin D [25(OH)D] and A1C levels in 9,773 adults (age ≥18 years old) participating in the 2003–2006 National Health and Nutrition Examination Survey. Multivariate linear regression analyzed the association after accounting for potential confounders.

RESULTS — Serum 25(OH)D levels were inversely associated with A1C levels in subjects age 35–74 years ($P = 0.0045$) and those who did not report a history of diabetes ($P = 0.0282$).

CONCLUSIONS — These findings support a mechanistic link between serum vitamin D concentrations, glucose homeostasis, and the evolution of diabetes in a large segment of the U.S. adult population. Screening people with elevated A1C levels for vitamin D insufficiency should be considered.

Diabetes Care **33:1236–1238, 2010**

Effects of calcium–vitamin D co-supplementation on glycaemic control, inflammation and oxidative stress in gestational diabetes: a randomised placebo-controlled trial

Table 3 Metabolic profiles, inflammation and biomarkers of oxidative stress at study baseline and after a 6-week intervention in pregnant women with GDM who received either calcium plus vitamin D supplements or placebo

Variable	Placebo group[a] (n=28)			Calcium plus vitamin D group[b] (n=28)			p value[c]
	Week 0	Week 6	Change	Week 0	Week 6	Change	
Calcium (mmol/l)	2.03±0.32[d]	2.00±0.38	−0.03±0.34	2.03±0.44	2.20±0.34	0.17±0.48	0.08
Vitamin D (nmol/l)	49.05±34.30	50.80±35.48	1.75±15.36	43.11±28.17	91.30±54.60*	48.19±46.64	<0.001
FPG (mmol/l)	4.42±0.59	4.68±1.06	0.26±0.92	5.14±0.71	4.25±0.64*	−0.89±0.69	<0.001
Insulin (pmol/l)	88.39±50.13	97.56±64.43	9.17±38.50	77.87±36.51	64.32±28.73	−13.55±35.25	0.02
HOMA-IR	2.93±1.66	3.56±2.69	0.63±2.01	2.93±1.34	2.02±0.89*	−0.91±1.18	0.001
HOMA-B	63.32±39.94	65.29±44.84	1.97±28.51	48.45±26.87	47.68±23.87	−0.77±29.66	0.63
QUICKI	0.33±0.03	0.33±0.05	−0.002±0.02	0.33±0.01	0.35±0.03*	0.02±0.03	0.003
Total cholesterol (mmol/l)	5.11±1.20	5.33±1.47	0.22±0.96	5.10±1.01	5.06±1.20	−0.04±1.01	0.33
Triacylglycerol (mmol/l)	2.09±0.69	2.05±0.68	−0.04±0.63	2.02±0.78	2.14±0.84	0.12±0.58	0.36
LDL-cholesterol (mmol/l)	2.79±0.88	3.05±1.08	0.26±0.74	2.94±0.81	2.71±0.87	−0.23±0.79	0.02
HDL-cholesterol (mmol/l)	1.36±0.44	1.34±0.44	−0.02±0.24	1.22±0.27	1.37±0.33*	0.15±0.25	0.01
Total: HDL-cholesterol ratio	3.93±0.86	4.11±0.80*	0.18±0.37	4.32±1.21	3.83±0.96*	−0.49±1.09	0.003
hs-CRP (ng/ml)	6,451.03±3,924.81	6,244.83±4,192.56	−206.20±4,006.65	7,391.83±4,693.09	7,384.93±3,692.78	−6.90±4006.65	0.83
NO (μmol/l)	54.04±28.65	51.69±28.40	−2.35±28.65	60.39±32.56	66.48±29.41	6.09±34.07	0.32
TAC (mmol/l)	724.71±176.51	789.39±176.47*	64.68±128.19	702.08±190.66	751.34±129.29	49.26±140.80	0.67
GSH (μmol/l)	761.69±383.11	714.42±365.83	−47.27±203.63	570.91±97.73	622.05±127.85	51.14±131.64	0.03
MDA (μmol/l)	2.69±1.42	3.62±1.83*	0.93±2.00	2.99±0.53	3.05±0.72	0.06±0.66	0.03

[a] Received placebos for calcium daily and for vitamin D twice during the study: at study baseline and on day 21 of intervention

[b] Received 1,000 mg calcium carbonate daily plus 50,000 U vitamin D_3 twice during the study: at study baseline and on day 21 of intervention

[c] Obtained from repeated measures ANOVA

[d] All values are mean ± SD. Baseline values of FPG, HOMA-B, QUICKI, GSH and MDA were significantly different between the two groups

*Different from Week 0, $p<0.05$

Diabetologia (2014) 57:1798–1806

Table 2. Randomized clinical trials with alternative therapies for the treatment of GDM.

Source	Type of Study	Population	Sample Size *	Intervention	Main Findings
Karamali et al. (2020) [165]	Randomized clinical trial, double blind	Teerã, Iran	I: 18 C: 18	Selenium supplementation (200 µg/day)	↑ expression of PPAR-γ and GLUT-1, but did not affect the gene expression of LDLR and LP(a) ($p < 0.05$), compared with the control.
Gomez et al. (2020) [166]	Randomized clinical trial, double blind	Buenos Aires, Argentina	I: 15 C: 15	3 tablespoons of extra virgin olive oil daily	The placenta of pregnant women showed regulation on PPARα expression and pro-inflammatory markers (IL-1β and TNF-α), and ↑ the expression of miR-518d ($p < 0.05$), compared with the control.
Gunasegaran et al. (2020) [176]	Randomized clinical trial, double blind	Puducherry, India	I1: 34 I2: 36	I1: Vit D (1000 UI/day) + calcium (1000 mg/day) I2: Vit D (250 UI/day) + calcium (500 mg)	I1↓ the serum levels of glucose, insulin, LDL-c, and total cholesterol and ↑ the levels of HDL-c and total GSH ($p < 0.05$), compared with I2.
Jamilian et al. (2020) [179]	Randomized clinical trial, double blind	Arak, Iran	I: 30 C: 30	2 flaxseed oil (1000 mg) capsules/day, containing 400 mg of α-linolenic acid	Seriously ↓ levels of glucose, insulin, insulin resistance, VLDL-c, total cholesterol, CRP, and MDA, and ↑ sensitivity to insulin, nitrite, and GSH ($p < 0.05$), compared with the control.
Karamali et al. (2018) [172]	Randomized clinical trial, double blind	Teerã, Iran	I: 30 C: 30	Magnesium–zinc–calcium–vitamin D co-supplementation	Co-supplementation: ↓ serum glucose, insulin, HOMA-IR, TG, and VLDL-c, while increasing the QUICKI index ($p < 0.05$) compared with the control.
[illegible] (2019) [178]	[illegible] double blind	Changchun, China	[illegible] C: 270	[illegible] (500 mg)	[illegible] outcomes ($p < 0.05$) compared with the control.
Jamilian et al. 2016 [173]	Randomized clinical trial	Arak, Iran	I: 30 C: 30	1 capsule/day formulated with vit D3 (1000 IU) + evening primrose oil (1000 mg)	Supplementation ↓ serum levels of glucose, insulin, HOMA-IR, QUICKI, VLDL-c, LDL-c, and total cholesterol ($p < 0.05$), compared with the control.
					0.05), compared with the control.

GRUPPO DI STUDIO INTERASSOCIATIVO AMD-SID DIABETE E GRAVIDANZA

POSITION STATEMENT

Integratori vitaminici, inositolo e probiotici nelle donne con iperglicemia in gravidanza.

VITAMINA D: SUMMARY BOX

- Non vi è consenso circa i range di normalità dei livelli di Vitamina D in gravidanza.
- Attualmente non sussistono evidenze tali da poter raccomandare la supplementazione con Vitamina D per la prevenzione e/o il trattamento del GDM.
- Altri fattori, quali il BMI, potrebbero interferire nella valutazione dei livelli di vitamina D.

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CATEGORIE A RISCHIO DI CARENZA DI ACIDO FOLICO

Vengono considerate categorie a rischio di carenza di acido folico le seguenti:

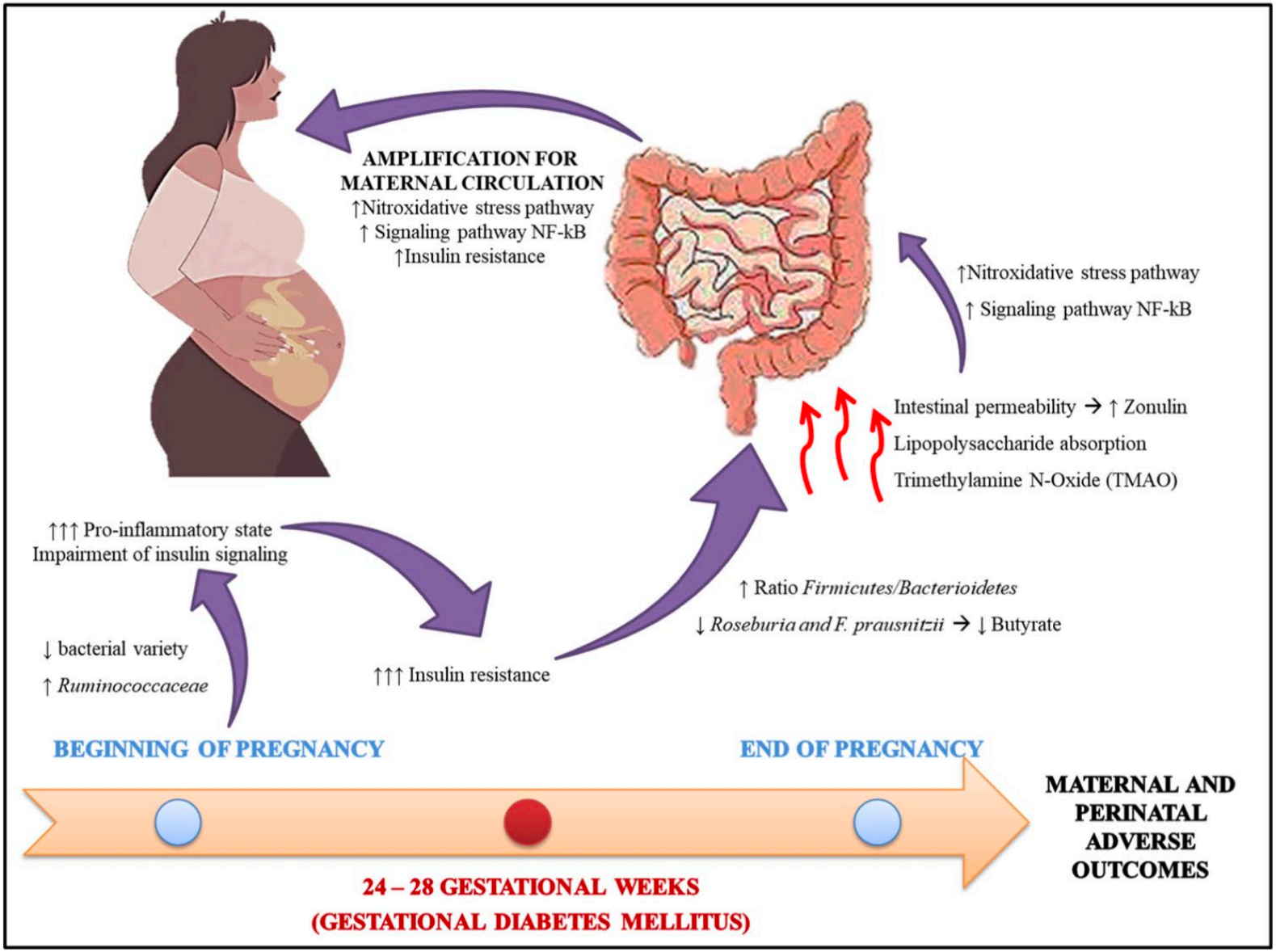
- **Diabete tipo 1 e tipo 2 (31)**
- **Obesità (31)**
- **Polimorfismi dei geni coinvolti nel metabolismo dell'acido folico (31):** alcuni polimorfismi della metilentetraidrofolato reduttasi (MTHFR) sono associati ad una minor concentrazione di folato (32) e a un maggior rischio di NTD (33). In taluni casi sono stati riscontrati autoanticorpi antagonisti diretti contro i recettori dei folati (34).
- **Donne in terapia con farmaci ad attività antifolica**: carbamazepina, valproato, sulfamidici, metotrexate etc (31,35).
- **Donne in terapia con estroprogestinici**: una metanalisi condotta su 27 studi ha mostrato che le donne che assumono terapia orale anticoncezionale potrebbero necessitare di dosi maggiori di acido folico per raggiungere i livelli target (31,36).
- **Sindromi da malassorbimento**: Circa il 5% delle donne in età riproduttiva riporta in anamnesi malattie da malassorbimento quali il Morbo di Crohn in cui è ridotto l'assorbimento dell'acido folico a livello ileale (31,37)
- **Fumo**

ACIDO FOLICO: SUMMARY BOX

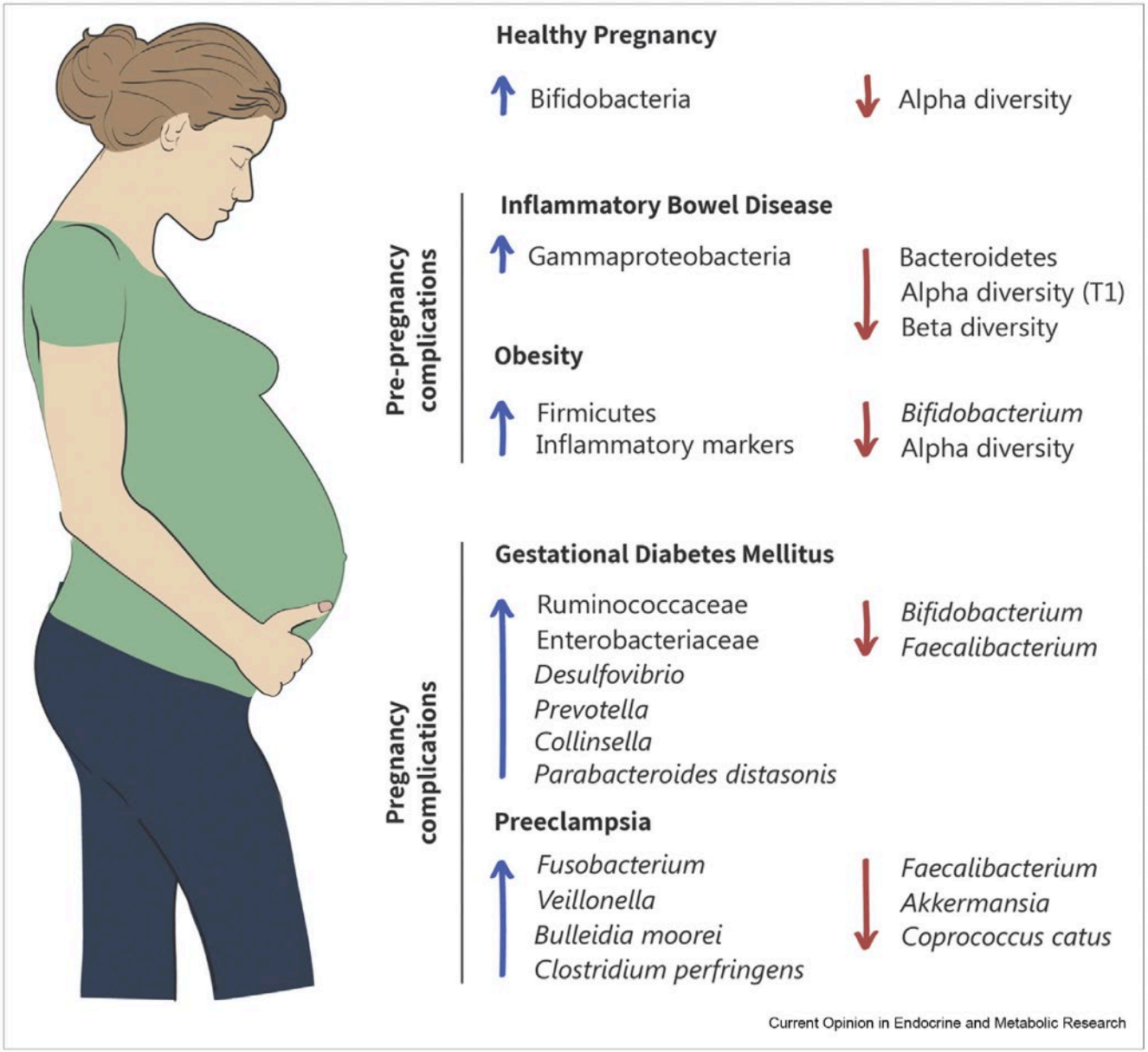
- La supplementazione con acido folico preferibilmente tre mesi prima del concepimento (e comunque almeno un mese prima del concepimento) è raccomandata per tutte le donne.
- Tale supplementazione è sicura e vantaggiosa sia per la madre che per il figlio.
- Le donne ad elevato rischio di NTD, tra le quali le donne affette da diabete, dovrebbero assumere 4-5 mg di acido folico/die.
- Attualmente non sono state identificate correlazioni fra impiego di acido folico e rischio di diabete gestazionale e/o controllo glicemico.

Rischio NTD in paziente diabetica in scarso controllo durante il primo trimestre di gravidanza 10 v> popolazione generale.

interaction between GDM and intestinal microbiota, inflammatory, and oxidative stress processes



Dysbiosis



There is a growing body of evidence regarding the association between gut microbiota and metabolic disorders, including obesity, T2DM, and GDM.

Dysregulation of the gut microbiota, known as dysbiosis, reduces the release of SCFA and other antimicrobial molecules.

These changes can lead to dysregulation in insulin secretion, insulin sensitivity, and appetite regulation.

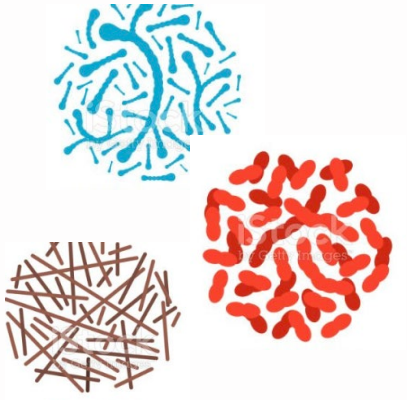
Most critical is the increase in gut wall permeability, allowing endotoxins' systemic entrance, resulting in low-grade inflammation.

Current Opinion in Endocrine and Metabolic Research 2021, **18**:133–138

probiotici

Probiotics

defined by the World Health Organization (WHO) as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”



They are reported to:

- improve microbial balance in the gastrointestinal tract,
- increase the colonic microbial diversity,
- improve intestinal barrier function,
- attenuate inflammation
- regulate insulin production

- probiotic supplementation during pregnancy modulates gut microbiota composition and improves glucose and lipid metabolism

Table 1. Randomized clinical trials with supplementation of probiotics, alone or in combination, for the treatment of gestational diabetes mellitus.

Source Sample	Population	Size *	Supplementation	Dose/Duration	Main Findings
Karamali et al. (2016) [118]	Iran	I: 30 C: 30	*L. acidophilus* + *L. casei* + *B. bifidum*	2×10^9 CFU/ 6 weeks	Supplementation with probiotics ↓FBG, serum insulin, TG, and VLDL-c, and improved insulin resistance indexes.
Hajifaraji et al. (2018) [150]	Iran	I: 27 C: 29	*L. acidophilus LA-5* + *B. BB-12* + *S. thermophilus STY-31* + *L. delbrueckii bulgaricus* + *LBY-27*	$>4 \times 10^9$ CFU/ 8 weeks	Supplementation with probiotics significantly ↓CRP and TNF-α. MDA, GPx and GR in women in the intervention group.
Kijmanawat et al. (2019) [153]	Thailand	I: 28 C: 29	*Bifidobacterium* + *Lactobacillus*	2×10^9 CFU/ 4 weeks	In women with diet-controlled GDM, supplementation with probiotics ↓FBG and insulin resistance compared with the control.
Babadi et al. (2018) [154]	Iran	I: 24 C: 24	*L. casei* + *B. bifidum* + *L. fermentum* + *L. acidophilus*	2×10^9 CFU/ 6 weeks	Probiotic supplementation improved the expression of genes related to insulin; glycemic control; inflammation; lipid profile, and oxidative stress markers, such as ↓MDA and ↑TAC, compared with the control.
Badehnoosh et al. (2018) [155]	Iran	I: 30 C: 30	*L. acidophilus* + *L. casei* + *B. bifidum*	2×10^9 CFU/ 6 weeks	Probiotic supplementation improved FBG, and CRP, ↑TAC, and ↓MDA, without affecting pregnancy outcomes.
Nabhani et al. (2018) [156]	Iran	I: 45 C: 45	*L. acidophilus* + *L. plantarum* + *L. fermentum* + *L. gasseri* + FOS	$1.5–7.0 \times 10^{9–10}$ CFU + 38.5 mg/ 6 weeks	Symbiotics had no effect on FBG and insulin resistance/sensitivity indexes. However, an ↑ in HDL-c and TAC was seen, and a ↓ was seen in blood pressure in the intervention group.
Jamilian et al. (2019) [157]	Iran	I: 29 C: 28	*L. acidophilus* + *B. bifidum* + *L. reuteri* + *L. fermentum* + Vitamin D	8×10^9 CFU/ 6 weeks +50.000 UI every 2 weeks	↓FBG, serum insulin, CRP, and MDA; ↑TAC and GSH; and improved insulin resistance scores.
Karamali et al. (2018) [158]	Iran	I: 30 C: 30	*L. acidophilus* + *L. casei* + *B. bifidum* + Inulin	2×10^9 CFU/ 6 weeks +800 mg	Symbiotic supplementation ↓CRP and MDA; ↑TAC and GSH; and↓ the rates of cesarean section, hyperbilirubinemia and hospitalization in NB, without affecting other pregnancy outcomes.

Table 1. *Cont.*

Source Sample	Population	Size *	Supplementation	Dose/Duration	Main Findings
Ahmadi et al. (2016) [159]	Iran	I: 35 C: 35	*L. acidophilus* + *L. casei* + *B. bifidum* + inulin	2×10^9 CFU/ 6 weeks +800 mg	Symbiotics ↑ insulin metabolism markers, and the insulin sensitivity index as well as ↓VLDL-c and TG.
Jafarnejad et al. (2016) [160]	Iran	I: 41 C: 41	*S. thermophilus* + *B. breve* + *B. longum* + *B. infantis* + *L. acidophilus* + *L. plantarum* + *L. paracasei* + *L. delbrueckii subsp. Bulgaricus*	15×10^9 CFU/ 8 weeks	No differences were observed in FBG, glycated hemoglobin, serum insulin, and insulin resistance indices. However, ↓CRP, IL-6, and TNF-α were observed, without changes in IL-10 and IFN-γ.
Dolatkhah et al. (2015) [161]	Turkey	I: 29 C: 27	*L. acidophilus LA-5* + *B. BB-12* + *Streptococcus thermophilus* + *STY-31* + *L. delbrueckii bulgaricus LBY-27*	$>4 \times 10^9$ CFU/ 8 weeks	↓FBG and insulin resistance index, and less weight gain in those in the intervention group.
Lindsay et al. (2015) [162]	Ireland	I: 74 C: 75	*L. salivarius*	1×10^9 CFU/ 6 weeks	No beneficial effect on glycemic control or pregnancy outcomes. ↓ in total and LDL-c in the supplemented group.

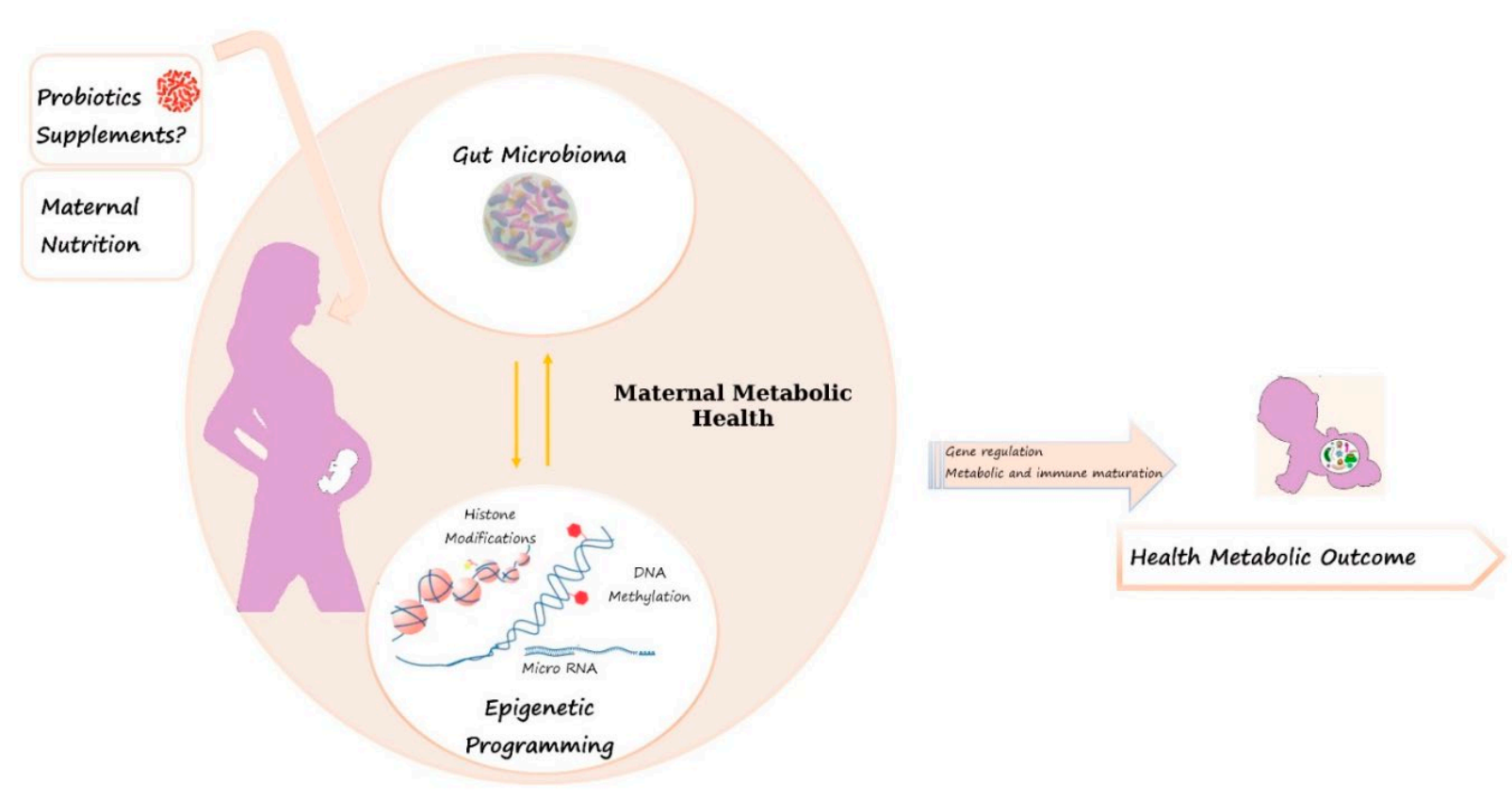

Probiotics Supplements?
Maternal Nutrition
Gut Microbioma
Maternal Metabolic Health
Histone Modifications
DNA Methylation
Micro RNA
Epigenetic Programming
Gene regulation
Metabolic and immune maturation
Health Metabolic Outcome

Table 2. *Cont.*

Source	Type of Study	Population	Sample Size *	Intervention	Main Findings
Jamilian et al., (2018) [167]	Randomized clinical trial, double blind	Arak, Iran	I: 20 C:20	2 capsules/day of fish oil (1000 mg), containing 180 mg EPA + 120 mg DHA	↑ expression of PPAR-γ, IL-1, and TNF-α ($p < 0.05$), compared with the control.
Karamali et al. (2018) [172]	Randomized clinical trial, double blind	Teerã, Iran	I: 30 C: 30	Magnesium–zinc–calcium–vitamin D co-supplementation	Co-supplementation: ↓ serum glucose, insulin, HOMA-IR, TG, and VLDL-c, while increasing the QUICKI index ($p < 0.05$) compared with the control.
Gao et al., 2017 [181]	Randomized clinical trial, double blind	Hebei, China	I: 123 C: 121	Enrichment of margarine with phytosterols (every 10 g of margarine, 2 g of phytosterols, twice a day)	Supplementation ↑ maternal and neonatal outcomes in patients with GDM.
Zhang et al., 2017 [182]	Randomized clinical trial, double blind	Shandong, China	I: 176 C: 150	1 capsule/day of EGCG (500 mg)	Supplementation ↑ maternal diabetes parameters and ↓ risk of neonatal complications ($p < 0.05$), compared with the control.
Yuan et al. 2016 [169]	Randomized clinical trial	Chongqing, China	I: 20 C: 22	Pepper with capsaicin (5 mg/day)	Supplementation ↓ serum concentrations of glucose, insulin, HOMA-IR, OGTT, total cholesterol, TG, and the risk for LGA births and ↑ the serum levels of apolipoprotein B and CGRP ($p < 0.05$), compared with the control.
Jamilian et al. 2016 [173]	Randomized clinical trial	Arak, Iran	I: 30 C: 30	1 capsule/day formulated with vit D3 (1000 IU) + evening primrose oil (1000 mg)	Supplementation ↓ serum levels of glucose, insulin, HOMA-IR, QUICKI, VLDL-c, LDL-c, and total cholesterol ($p < 0.05$), compared with the control.
Sun et al. 2016 [170]	Randomized clinical trial	Shandong, China	I: 64 C: 65	2 *Artemisia* extract tablets/day (200 mg)	Supplementation ↑ insulin sensitivity through upregulation of adiponectin.
Asemi et al. 2015 [180]	Randomized clinical trial, double blind	Kashan, Iran	I: 35 C: 35	1 tablet/day of selenium (200 µg)	Significantly ↓ serum glucose, insulin, HOMA-IR, CRP, MDA, and plasma GSH concentrations ($p < 0.05$), compared with the control.

Table 2. Randomized clinical trials with alternative therapies for the treatment of GDM.

Source	Type of Study	Population	Sample Size *	Intervention	Main Findings
Jamilian et al., (2018) [167]	Randomized clinical trial, double blind	Arak, Iran	I: 20 C:20	2 capsules/day of fish oil (1000 mg), containing 180 mg EPA + 120 mg DHA	↑ expression of PPAR-γ, IL-1, and TNF-α ($p < 0.05$), compared with the control.
Gomez et al. (2020) [166]	Randomized clinical trial, double blind	Buenos Aires, Argentina	I: 15 C: 15	3 tablespoons of extra virgin olive oil daily	The placenta of pregnant women showed regulation on PPARα expression and pro-inflammatory markers (IL-1β and TNF-α), and ↑ the expression of miR-518d ($p < 0.05$), compared with the control.
Gunasegaran et al. (2020) [176]	Randomized clinical trial, double blind	Puducherry, India	I1: 34 I2: 36	I1: Vit D (1000 UI/day) + calcium (1000 mg/day) I2: Vit D (250 UI/day) + calcium (500 mg)	I1↓ the serum levels of glucose, insulin, LDL-c, and total cholesterol and ↑ the levels of HDL-c and total GSH ($p < 0.05$), compared with I2.
Jamilian et al. (2020) [179]	Randomized clinical trial, double blind	Arak, Iran	I: 30 C: 30	2 flaxseed oil (1000 mg) capsules/day, containing 400 mg of α-linolenic acid	Seriously ↓ levels of glucose, insulin, insulin resistance, VLDL-c, total cholesterol, CRP, and MDA, and ↑ sensitivity to insulin, nitrite, and GSH ($p < 0.05$), compared with the control.
Hajimoosayi et al. (2020) [174]	Randomized clinical trial, double blind	Teerã, Iran	I: 37 C: 33	3 ginger tablets/day (1500 mg), with consumption after main meals	↓ serum levels of blood glucose, insulin, and the HOMA-IR index ($p < 0.05$), compared with control.
Yang et al. (2019) [178]	Randomized clinical trial, double blind	Changchun, China	I: 268 C: 270	1 capsule/day of cod liver oil (500 mg)	↓ serum levels of glucose, lipids, CRP, HOMA-IR, and adverse perinatal outcomes ($p < 0.05$) compared with the control.
Ostadmohammadi et al. (2019) [177]	Randomized clinical trial, double blind	Kashan, Iran	I: 27 C: 27	Zinc co-supplementation (zinc gluconate 233 mg/day) + Vit E (400 IU/day)	Supplemented group ↓ the serum levels of HOMA-IR insulin, total cholesterol, LDL-c, and QUICKI ($p < 0.05$), compared with the control group. It positively regulated the gene expression of PPAR-γ and LDLR ($p < 0.05$), compared with the control.

Omega 3

A review of guidance on fish consumption in pregnancy: Is it fit for purpose?

19 national guidelines and 3 international guidelines

The guidelines were largely based on the mercury content of fish with far less consideration being given to the positive beneficial effects nutrients provided by fish.

O-3-PUFA and D.H. are also derived from plats such as leafy greens, seeds and nuts.

Public Health Nutr. 2018 August ; 21(11): 2149–2159.

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2021 Mar; 165(1):8-12.

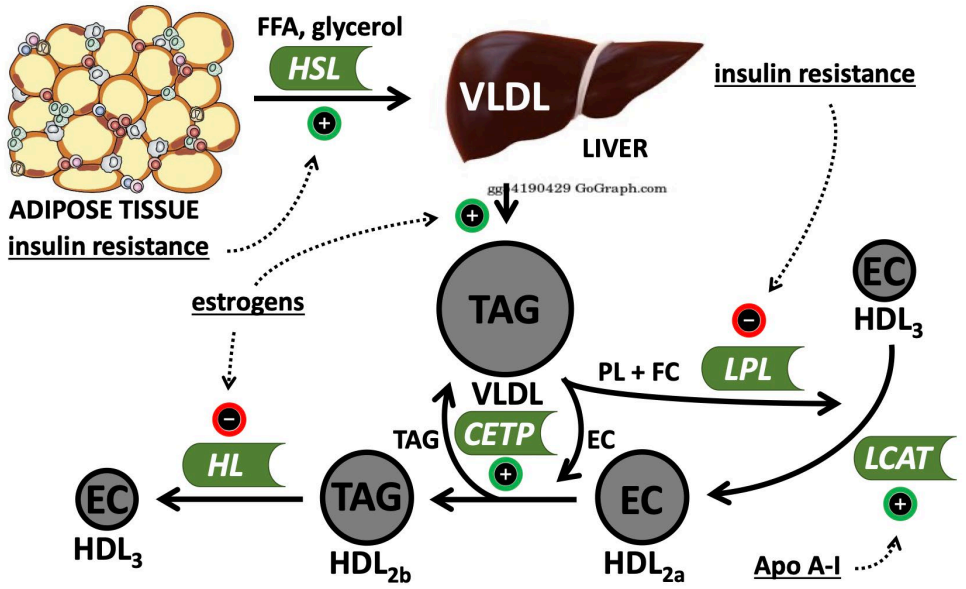
Changes in serum lipid levels during pregnancy in women with gestational diabetes. A narrative review

Lubica Cibickova, Jan Schovanek, David Karasek

Table 1. Changes in lipid particles during pregnancy in GDM (ref.[19]).

Changes in lipid particles during pregnancy in GDM
↑ total cholesterol
↑↑ triglycerides and VLDL particles
↔ LDL cholesterol, ↑ small dense LDL particles
↑ HDL2 particles, ↓ HDL3 particles

VLDL = very-low-density lipoprotein, LDL = low-density lipoprotein, HDL = high-density lipoprotein; ↑ increased, ↑↑ significantly increased, ↔ not influenced, ↓ decreased



A pregnancy with GDM is associated with mixed dyslipidaemia with predominantly elevated TG concentrations with a shift towards small, dense LDL particles as can also be found in other insulin resistance states such as type 2 diabetes mellitus.

Women who develop GDM have significantly increased TG concentrations and decreased HDL concentrations in early pregnancy. Both lean and obese women with higher TG concentrations are at an increased risk for developing GDM (a 1.8-fold increase in risk in the lean group vs. a 2.7-fold increase in the obese group) while lean women with high HDL are protected.

Physiological pregnancy dyslipidaemia differs from the pathological dyslipidaemia seen in GDM also by a parallel increase in HDL-C levels with total cholesterol and the atherogenic index (LDL-C / HDL-C) remains principally unchanged during pregnancy.

Journal of Diabetes and its Complications
Volume 37, Issue 4, April 2023, 108451

Effects of omega-3 supplementation on glucose and lipid metabolism in patients with gestational diabetes: A meta-analysis of randomized controlled trials

Results

Six randomized controlled trials (331 participants) were included in the meta-analysis. The levels of fasting plasma glucose (FPG) (WMD = −0.25 mmol/L; 95 % CI: −0.38, −0.12), fasting insulin (WMD = −17.13 pmol/L; 95 % CI: −27.95, −6.30), and homeostasis model of assessment-insulin resistance (WMD = −0.51; 95 % CI: −0.89, −0.12) were lower in the omega-3 group compared to their levels in the placebo group. The results of the analysis of lipid metabolism showed that triglycerides (WMD = −0.18 mmol/L; 95 % CI: −0.29, −0.08) and very low-density lipoprotein cholesterol (WMD = −0.1 mmol/L; 95 % CI: −0.16, −0.03) decreased in the omega-3 group, while high-density lipoproteins (WMD = 0.06 mmol/L; 95 % CI: 0.02, 0.10) increased. Compared to the placebo group, inflammatory factor serum C-reactive protein (SMD = −0.68 mmol/L; 95 % CI: −0.96, −0.39) decreased in the omega-3 group.

Conclusion

Omega-3 supplementation can decrease the levels of FPG and inflammatory factors, enhance blood lipid metabolism, and reduce insulin resistance in patients with GDM.

inositoli

Effetti del decifit di inositoli

Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes

James J DiNicolantonio , James H O'Keefe

How states of insulin resistance deplete myo-inositol

- Reduced synthesis (reduced biosynthesis via decreased enzyme function).
- Increased breakdown (upregulation in the enzyme that breaks down myo-inositol).
- Decreased penetration into cells (competition with glucose).
- Greater cellular release/reduced cellular uptake (sorbitol competition).
- Greater loss in the urine (glucose competes for myo-inositol reabsorption in the kidneys).

Consequences of myo-inositol deficiency[7]

- Altered Na-K-ATPase activity.
- Diabetic neuropathy, nephropathy and retinopathy.
- Diabetic nephropathy.
- Worsening of insulin resistance.
- Elevated fasting and postprandial glucose and insulin levels.

Review

Myo-Ins supplementation in at-risk pregnant women

Authors	Year of study	Population	Incidence of GDM (%)	
			Study group	Placebo group
Matarrelli et al. [10]	2013	At risk for GDM	6	71
Santamaria et al. [11]	2015	Overweight (BMI between ≥ 25 and < 30 kg/m^2)	11.6	27.4
Facchinetti F et al. [12]	2013	Overweight (BMI of >27 kg/m^2)	19.4	40.0
D'Anna et al. [13]	2015	Obese (BMI of >30kg/m^2)	14	33.6
D'Anna et al. [14]	2013	Family history of diabetes	6	15.3
Farren et al. [8]	2017	Family history of diabetes (combination therapy of myo-Ins and D-Chiro-Ins)	23.3	18.3
D'Anna et al. [15]	2012	PCOS	17.4	54

4,000 mg of myo-Ins plus 400 µg of folic acid per day throughout their pregnancies

Tahir F, Majid Z (September 16, 2019) Inositol Supplementation in the Prevention of Gestational Diabetes Mellitus. Cureus 11(9): e5671. DOI 10.7759/cureus.5671

Inositoli e stress ossidativo e low grade inflammation

Myoinositol Reduces Inflammation and Oxidative Stress in Human Endothelial Cells Exposed In Vivo to Chronic Hyperglycemia

ROS

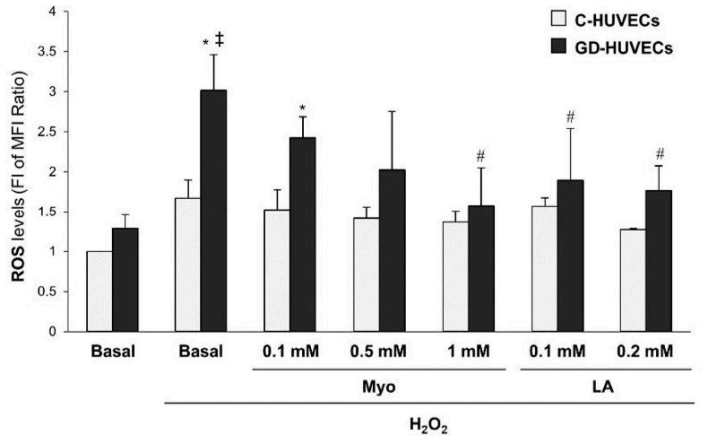
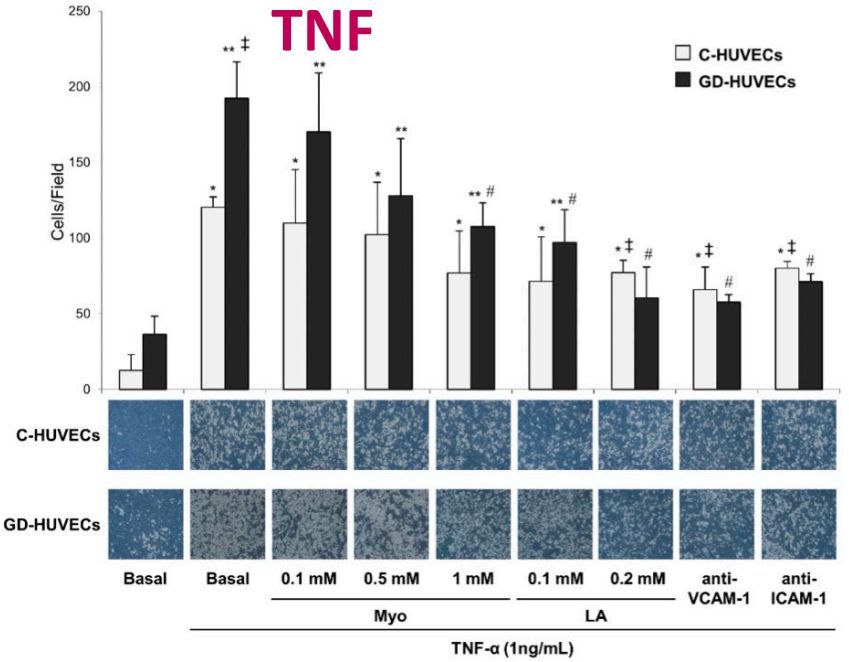


Figure 4. Effect of in vitro treatment with Myo on ROS levels in C- and GD-HUVECs. * $p < 0.005$ vs. Basal GD-HUVECs, ‡ $p < 0.005$ vs. H_2O_2 C-HUVECs, # $p < 0.05$ vs. H_2O_2 GD-HUVECs.

TNF

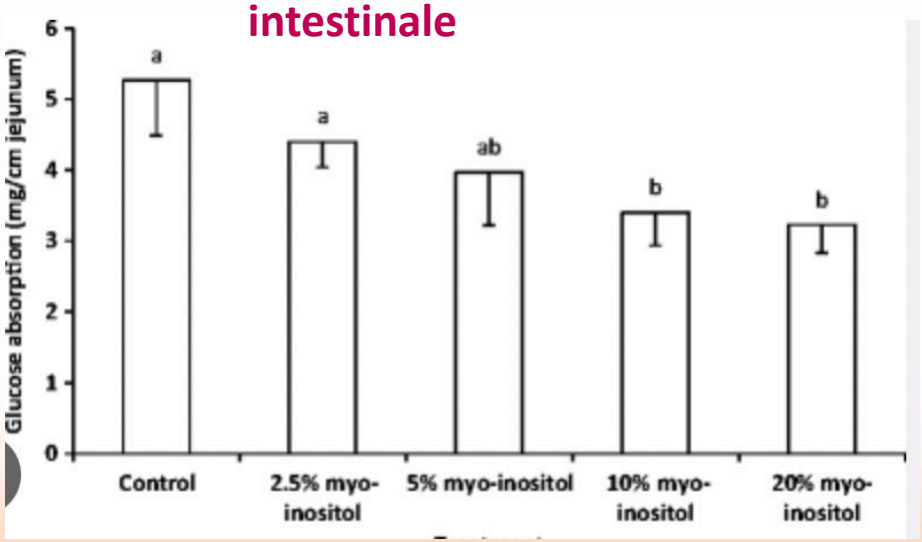


Inositoli e insulino resistenza

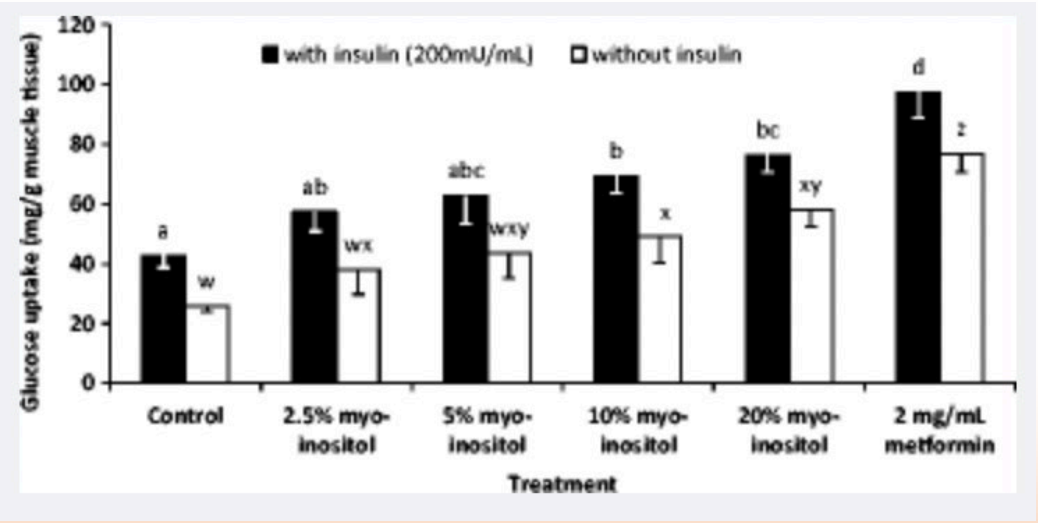
Myo-inositol inhibits intestinal glucose absorption and promotes muscle glucose uptake: a dual approach study

J Physiol Biochem. 2016 Dec;72(4):791-801.

Assorbimento di glucosio intestinale



Uptake di glucosio nel muscolo



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Research Article

The Effectiveness of Myo-Inositol and D-Chiro Inositol Treatment in Type 2 Diabetes

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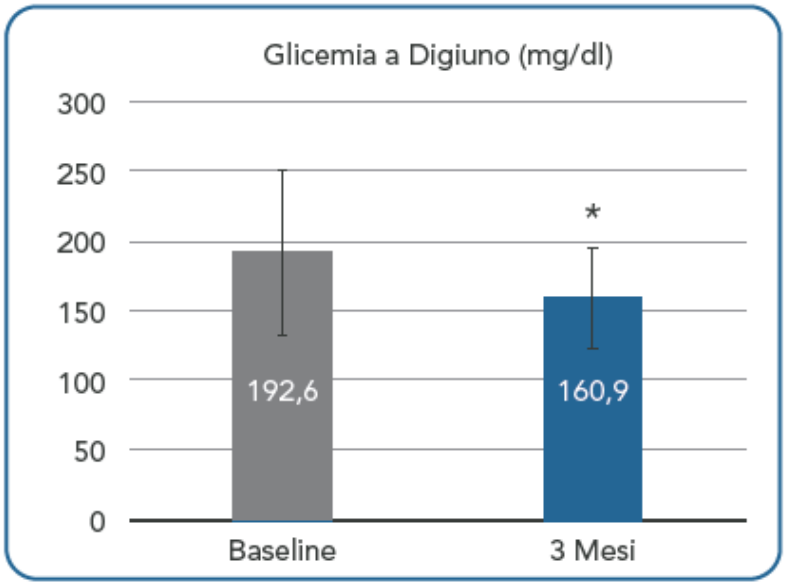
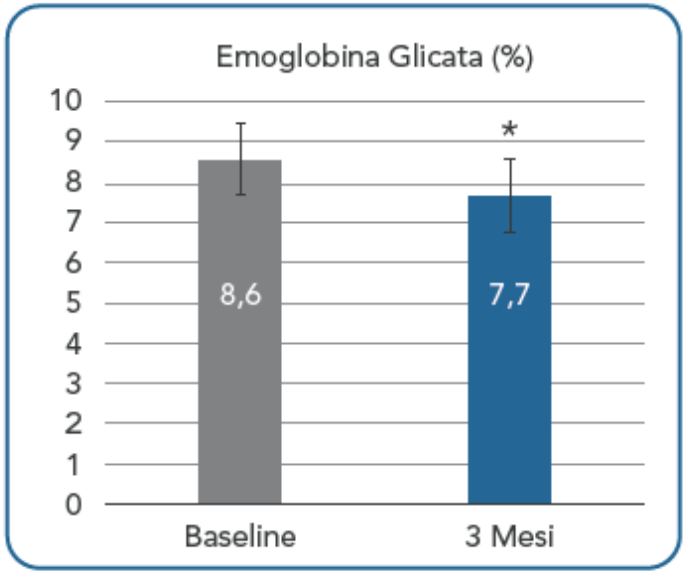
Inositol has been used as a supplement in treating several pathologies such as PCOS, metabolic syndrome, and gestational diabetes. Both myo-inositol and its isomer d-chiro-inositol showed insulin mimetic effects in conditions of insulin resistance. Type 2 diabetes (T2DM) is a condition typically caused by insulin resistance. There is a lack of evidence of inositol use in T2DM. We evaluated the effectiveness and safety of myo-inositol and d-chiro-inositol treatment in T2DM. This was a pilot study involving a consecutive sample of patients with T2DM with suboptimal glycemic control (HbA1c 7.0–10.0%) already treated with glucose-lowering agents. Patients (23.1% males, mean age of 60.8 ± 11.7 years) took for three months a combination of myo-inositol (550 mg) and d-chiro-inositol (13.8 mg) orally twice a day as add-on supplement to their glucose-lowering drugs. Possible occurrence of side effects was investigated. After three months of treatment fasting blood glucose (192.6 ± 60.2 versus 160.9 ± 36.4; $p = 0.02$) and HbA1c levels (8.6 ± 0.9 versus 7.7 ± 0.9; $p = 0.02$) significantly decreased compared to baseline. There was no significant difference in blood pressure, lipid profile, and BMI levels. None of the participants reported side effects. In conclusion, a supplementation with a combination of myo- and d-chiro-inositol is an effective and safe strategy for improving glycemic control in T2DM.

1. Introduction

Inositol is a cyclitol present in animal and plant cells. It can be present in nine distinct stereoisomers, myo-inositol being the most represented. D-chiro-inositol is an inositol isoform derived from myo-inositol through an epimerization process and this reaction is insulin dependent [1]. Both myo- and d-chiro-inositol showed insulin mimetic effects in animal models of insulin resistance [2, 3]. They have been studied in basic research and their potential has been recognized as very promising [4]. A specific physiological myo-/d-chiro-inositol ratio exists in different human tissues [5]. The distinctive ratio depends on the specific biological function these molecules have. Indeed, looking at the molecular pathway of inositols, after insulin links with the cell, inositol-second messengers are produced. While d-chiro-inositol-based second messengers promote glycogen synthesis, second messengers based on myo-inositol regulate glucose intake increasing the activity of glucose transport proteins. Recently, a new supplement formulation conforming to this physiological ratio has been designed [6, 7]. Given inositol pivotal role in regulating many metabolic pathways and hormonal signalling, its use in clinical settings is steeply growing. Inositol has been mainly used as a supplement in treating several pathologies such as PCOS [8], metabolic syndrome [9, 10], and gestational diabetes (GDM) [11]. In the case of GDM, a condition defined as a glucose impairment first detected in pregnancy, a preventive role of inositol for GDM onset was recognized [12–14]. In addition, inositol has been studied as a therapeutic option for the treatment of GDM [15, 16]. The main effect of inositol when used in pregnancy is decreasing the level of insulin resistance. Consequently, a potential role of inositol as a treatment option could be hypothesized for other conditions typically characterized by insulin resistance. The most common disease in which insulin resistance represents a significant factor is type 2 diabetes mellitus (T2DM). It is characterized by a double pathophysiological alteration represented on one side by an increase in insulin resistance, that is, the inability of the action of blood circulating insulin, due to a resistance of the target tissues; on the other side, by



* p= 0,02



20 pazienti con DMT2 trattati per 3 mesi con 550 mg di MI e 13,8 mg di DCI, due volte al giorno

MI E DCI 40:1 RIDUCONO SIGNIFICATIVAMENTE I LIVELLI DI GLICEMIA A DIGIUNO E DI EMOGLOBINA GLICATA

Two studies met the inclusion criteria

142 pregnant women recruited between 2008 and 2011
Caucasian

Intervention
4000 mg myo-inositol plus 400 mcg folic acid per day for eight weeks

Comparison 1. Myo-inositol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Large-for-gestational age	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.58]
2 Weight gain during pregnancy (kg)	1	69	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-3.25, 2.25]
3 Body mass index change (kg/m2)	1	73	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-2.35, -0.65]
4 Additional pharmacological treatment (insulin therapy)	2	157	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.08, 1.73]
5 Fasting OGTT (mmol/L)	2	142	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-0.59, -0.35]
6 1-hour OGTT (mmol/L)	1	73	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.73, -0.07]
7 2-hour OGTT (mmol/L)	1	73	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.46, 0.06]
8 Gestational age at birth (weeks)	1	73	Mean Difference (IV, Fixed, 95% CI)	2.10 [1.27, 2.93]
9 Preterm birth (less than 37 weeks' gestation)	1	84	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.09, 10.56]
10 Birthweight (g)	1	73	Mean Difference (IV, Fixed, 95% CI)	16.0 [-209.72, 241.72]
11 Neonatal hypoglycaemia	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.85]

Review

Inositols, Probiotics, and Gestational Diabetes: Clinical and Epigenetic Aspects

Ester Vitacolonna [1,2,*], Maria Masulli [3], Luisa Palmisano [3], Liborio Stuppia [2,4] and Marica Franzago [1,2]

Table 2. Studies on inositol supplementation to treat gestational diabetes.

Ref.	Study Design	Time to Supplementation	Type of Supplementation	Participants	Main Results
Corrado et al. 2011 [37]	RCT	From GDM diagnosis	n = 24 2000 mg di MI + 200 mcg folic acid twice a day n = 45 400 mcg folic acid	69 women with GDM	Lower HOMA-IR in MI group ($p < 0.001$) Higher adiponectin in MI group ($p = 0.009$)
Di Biase et al. 2017 [38]	RCT	From GDM diagnosis	n = 67 DCI 500 mg twice a day n = 70 placebo	137 women with GDM	Lower post-prandial glucose ($p < 0.005$), insulin dose ($p = 0.026$), and weight gain ($p = 0.015$) in DCI group Lower abdominal circumference in DCI group ($p < 0.001$)
Fraticelli et al. 2018 [2]	RCT	From GDM diagnosis	n = 20 2000 mg MI + 200 mcg folic acid twice a day n = 20 500 mg DCI + 400 mcg folic acid n = 20 1100 mg MI + 27.6 g DCI + 400 mcg folic acid n = 20 400 mcg folic acid	80 Caucasian women with GDM	Lower HOMA-IR ($p < 0.001$) and weight gain ($p < 0.005$) in MI group Lower need of insulin therapy in MI group Lower insulin dose in MI group Lower birth weight in MI, DCI, and MI/DCI groups ($p = 0.032$)
Pintaudi et al. 2018 [3]	Case-control study	From the 30th week of gestation	n = 6 4000 mg/day MI + 400 mcg folic acid n = 6 400 mcg folic acid	12 Caucasian women with GDM	Lower glycemic variability in MI group ($p < 0.001$) No significant differences on neonatal outcomes
Kulshrestha et al. 2021 [40]	RCT	From GDM diagnosis	n = 50 1000 mg MI twice a day n = 50 control group	100 Asian Indian women with singleton pregnancy and GDM	Lower plasma glucose in MI group ($p = 0.008$) Lower need of insulin treatment in MI group (6.1% vs. 22.0%, $p = 0.02$) Lower birth weight in MI group ($p = 0.018$)

Inositoli e NTD

Review

Myo-Inositol as a Key Supporter of Fertility and Physiological Gestation

Table 4. Studies involving myo-inositol as a preventive treatment against NTDs in women with a previous pregnancy affected by NTD despite folate supplementation.

Study	Patients	Protocol	Findings
Cavalli et al. 2008 [63]	3 women with at least one previous pregnancy affected by folate-resistant NTD	Open-label treatment with 500 mg per day from at least two months before and until 60 days after conception	NTD incidence: 0%
Cavalli et al. 2011 [64]	9 women with at least one previous pregnancy affected by folate-resistant NTD	Open-label treatment with 1000 mg per day from at least two months before and until 60 days after conception	NTD incidence: 0%
Greene et al. 2016 [65]	47 randomized and 22 non-randomized women with at least one previous pregnancy affected by NTD	Randomized, double-blind, placebo-controlled treatment with 500 mg twice per day; women who declined randomization decided to take myo-inositol plus folic acid (19 patients), or folic acid only (3 patients)	NTD incidence in randomized patients: 0% in the treatment group versus 5.3% in the control group NTD cases in the non-randomized patients: 0 in the myo-inositol plus folic acid group versus 2 in the folic acid alone group Overall NTD incidence: 0% in the treatment group versus 13.63% in the control group

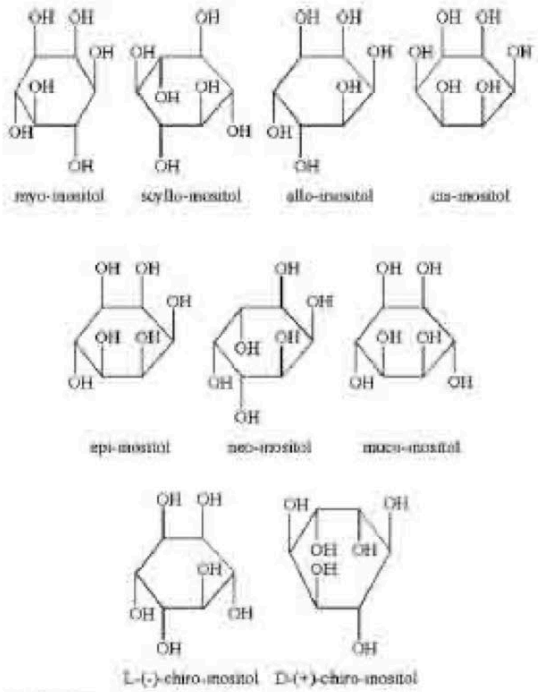


Fig. 1 Inositol stereoisomers

Significant Sources of Myo-Inositol (MI)

Endogenous synthesis: 2-4g MI/day may be produced from glucose in humans.

MI occurs in foods as:

1. Phytic acid (also called myo-inositol hexaphosphate or IP6) is often a component of the insoluble fiber of the bran found in seeds. Significant amounts of IP6 are found in grains, legumes, nuts or certain citrus fruits.

2. Phosphatidyl-myo-inositol is found in plant- and animal-derived foods.

Estimated average MI intake is 900 mg/day

Supplements: MI and IP6

Significant sources of D-*Chiro*-Inositol (DCI)

Foods: buckwheat, soy, lentils, beans, wheat germ

Supplements: DCI (derived from demethylating pinitol found in carob)

Significant sources of D-Pinitol (methylated DCI)

Foods: carob, soy

Supplements: pinitol

Inositol Phosphates IP1 to IP6

IP6 is converted to MI or IP1 to IP5 by intestinal flora and in human metabolism

(MI) Myo-Inositol

Phosphatidylinositols (PI) & Phosphatidylinositol-Phosphates (PIP)

MI to DCI conversion (about 8%) is catalyzed by an epimerase enzyme. Its activity may be reduced in the state of insulin resistance to as low as 1%, for example.

D-*Chiro*-Inositol (DCI)

Approx. 33% of pinitol may be converted to DCI in humans. It is not clear if pinitol can be utilized in human physiology without first being converted to DCI

D-Pinitol (Methylated DCI)

Placental Inositol Reduced in Gestational Diabetes as Glucose Alters Inositol Transporters and IMPA1 Enzyme Expression

Reshma A Pillai,[1,*] Mohammed O Islam,[1,*] Preben Selvam,[1,*] Neha Sharma,[1] Anne HY Chu,[2] Oliver C Watkins,[1] Keith M Godfrey,[3] Rohan M Lewis,[4] and Shiao Y Chan[1,2]

Results: Placental inositol content was 17% lower in GDM compared with non-GDM. Higher maternal mid-gestation glycemia were associated with lower placental inositol. Increasing fasting glycemia was associated with lower protein levels of the *myo*-inositol synthesis enzyme, IMPA1, and the inositol transporters, SLC5A11 and SLC2A13, the expression of which also correlated with placental inositol content. In vitro, higher glucose concentrations reduced *IMPA1* and *SLC5A11* mRNA expression. Increasing fasting glycemia positively associated with customized birthweight percentile as expected in cases with low placental inositol, but this association was attenuated with high placental inositol.

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 2, e875–e890

European Review for Medical and Pharmacological Sciences 2014; 18: 270-274

Myo-inositol, D-chiro-inositol, folic acid and manganese in second trimester of pregnancy: a preliminary investigation

A. MALVASI[1], F. CASCIARO[2], M.M. MINERVINI[2], I. KOSMAS[3], O.A. MYNBAEV[4], E. PACELLA[5], V. MONTI CONDESNITT[6], A. CREANZA[1], G.C. DI RENZO[7], A. TINELLI[8]

Table II. Comparison of clinical characteristics and hematochemical parameters of two groups at time 30 and 60 days. Data are mean ± SD.

Variables	Time = 30			Time = 60		
	Control group (n = 24)	MDFM group (n = 24)	*p**	Control group (n = 24)	MDFM group (n = 24)	*p**
Total Chol	225.79 ± 10.67	209.54 ± 6.6	0.0001	232.66 ± 8.82	185.37 ± 10.8	0.0001
LDL	154.16 ± 12.04	141.95 ± 12.57	0.0013	158.33 ± 11.96	124.83 ± 9.90	0.0001
HDL	71.66 ± 7.22	67.58 ± 10.80	0.0903	74.33 ± 7.68	60.54 ± 10.25	0.0001
TG	170.20 ± 10.32	154.91 ± 7.44	0.0001	175.70 ± 8.85	136.37 ± 7.63	0.0001
Glucose (blood)	82.20 ± 6.16	77.29 ± 4.05	0.0021	82.25 ± 7.15	77.41 ± 4.19	0.0064
Mean pressure (systolic)	121.04 ± 6.91	119.16 ± 6.53	0.033	119.16 ± 6.86	115.83. ± 7.89	0.125
Mean pressure (diastolic)	78.75 ± 8.10	75.20 ± 5.98	0.091	77.5 ± 10.10	75.41 ± 7.50	0.421

*Statistical analysis was obtained with Student's *t*-test between the two group.

European Review for Medical and Pharmacological Sciences 2018; 22: 6567-6572

Effects of myo-inositol on glucose variability in women with gestational diabetes

B. PINTAUDI[1], G. DI VIESTE[2], F. CORRADO[3], G. LUCISANO[4], L. GIUNTA[5], R. D'ANNA[3], A. DI BENEDETTO[5]

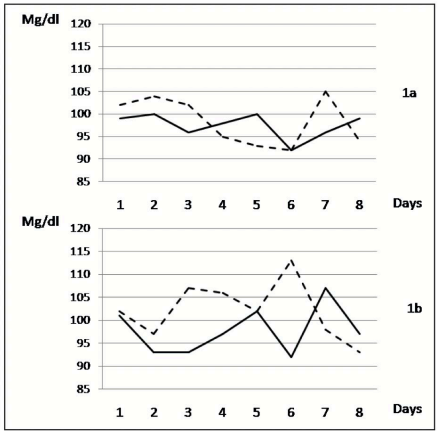


Figure 1. Daily mean glucose values recorded by continuous glucose monitoring system. Figure 1a reports data of the period before the treatment was started. Figure 1b reports data after the beginning of the treatment. Continue lines are women treated with myo-inositol; dotted lines are controls.

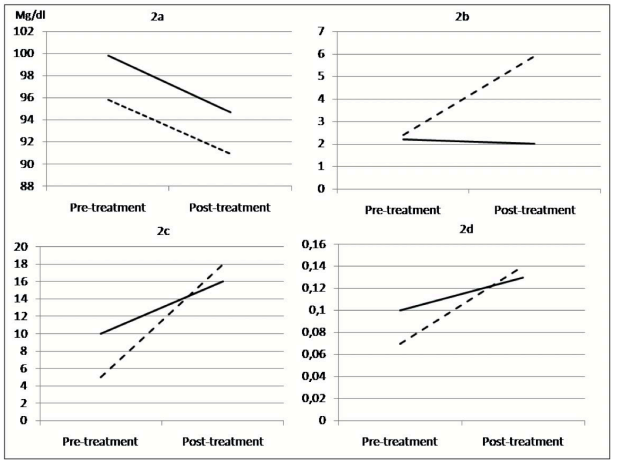
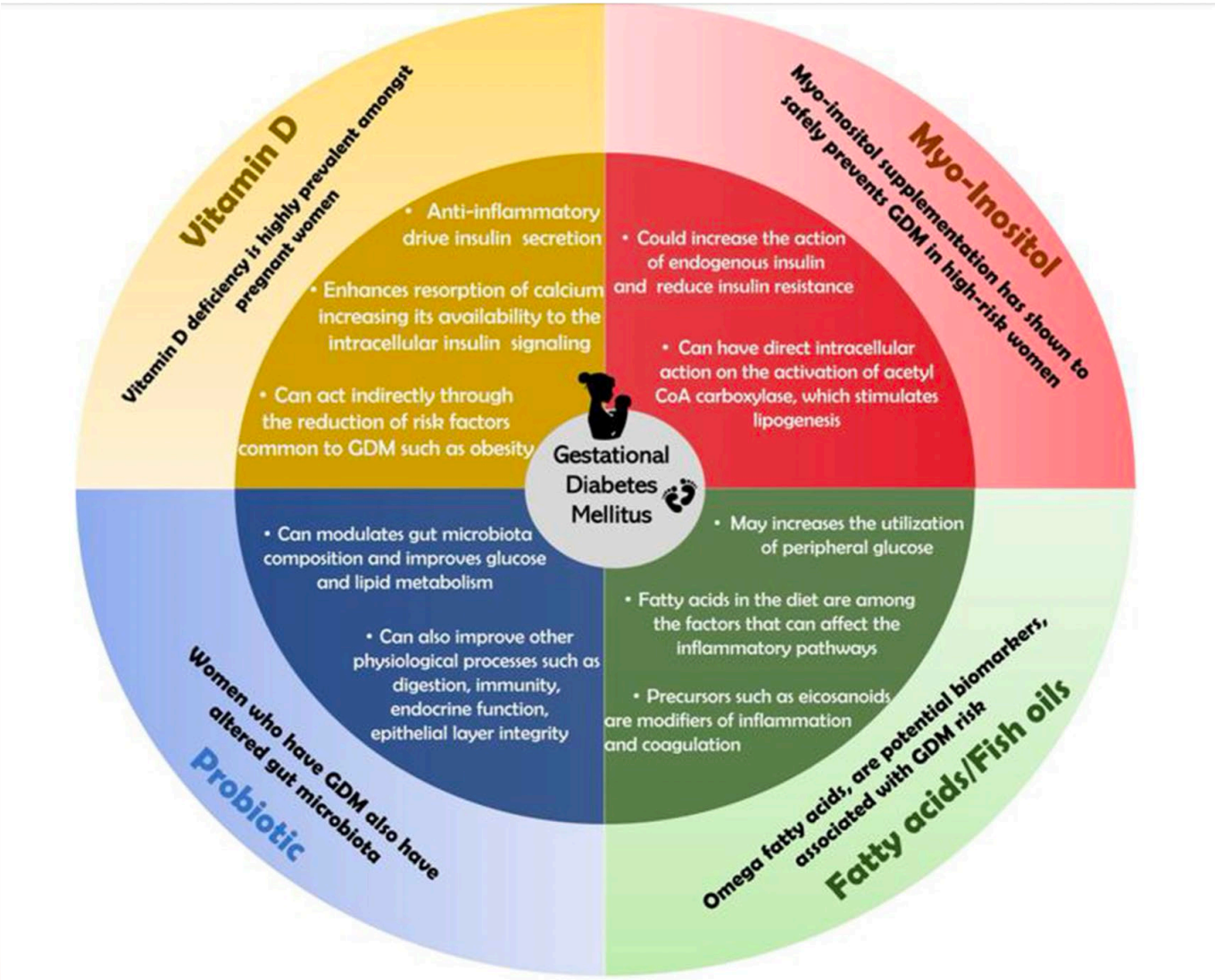


Figure 2. Overall mean glucose levels *(2a)*, MAGE *(2b)*, Standard Deviation *(2c)* and variability coefficient *(2d)* differences between the period before and after the treatment was started.Continue lines are women treated with myo-inositol; dotted lines are controls.

TABLE 1 | Summary of systematic reviews and meta-analyses of RCTs on the effects of nutritional supplementation during pregnancy.

References	Study type	Intervention	Inclusion criteria	Significant results
Probiotics Chen et al. (8)	Meta-Analysis (7 RCTs)	Probiotic supplementation	Pregnant women with GDM	Reduction in FBG and inflammatory markers
Zhang et al. (9)	Meta-analysis (11 RCT)	Probiotic supplementation	Pregnant women with GDM	Reduction in newborn's hyperbilirubinemia, maternal HDL- and inflammatory and oxidative stress biomarkers
Taylor et al. (10)	Meta-analysis) (4 RCT)	Probiotic supplementation	Pregnant women with GDM	Reduction in (HOMA-IR)
Omega 3 Amirani et al. (11)	Systematic review and meta-analysis (14 RCTs)	Omega-3 supplementation	GDM, overweight or obese women.	Improvement in HDL levels.
Middleton et al. (12)	Cochrane Review(70 RCTs)	Omega-3 supplementation	Pregnant women	Reduction in preterm delivery (<37 weeks); early preterm delivery (<34 weeks), & risk of low birth weight
Vitamin D Ojo et al. (13)	Systematic Review and Meta-Analysis of 5 RCTs	Vitamin D supplementation	Pregnant women with GDM	Lower FBG, HbA1c, and serum Insulin concentration
Yin et al. (14)	Meta-Analysis (16 RCTs)	Vitamin D Supplementation	Pregnant women with GDM	Reduced FBG, reduced fasting Insulin, improved HOMA-IR, and HOMA-β, and (QUICKI)
Jin et al. (15)	Systematic Review and Meta-Analysis (13 RCTs)	Vitamin D supplementation	Pregnant women with GDM	Reduced FBG, and reduced HOMA-IR
Myoinositol Crawford et al. (16)	Cochrane systematic review (4 RCTs)	Myo-Inositol supplementation	Pregnant women with GDM	Reduction in the incidence of GDM
Zhang et al. (17)	Systematic Review and Meta-Analysis (5 RCTs)	Myo-Inositol supplementation	Pregnant women with GDM	Reduction in the incidence of GDM and preterm delivery

| The effect of nutritional supplementation on glucose metabolism during pregnancy.



Therefore, at present, nutritional medical therapy and lifestyle intervention are considered the cornerstone for the prevention and treatment of GDM.

Nonetheless, larger studies in populations of different ethnic groups are needed in order to assess the optimal dosage, frequency, and timing of supplementation, as well as the safety and long-term effects on maternal, neonatal, and childhood outcomes.

Grazie per l'attenzione