Narrative review

Use of myo-inositol and other nutritional supplements for the primary prevention of gestational diabetes *mellitus*

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Lorena Guadalupe Menjívar Ponce[1]*, Andrea Sofía Herrera Orantes[2], César Gerardo Tario Amaya[3], Kenny Lissette Abrego de Rodríguez[4]

1-3. Dr. José Matías Delgado University, Antiguo Cuscatlán, La Libertad, El Salvador.
4. San Rafael National Hospital, Santa Tecla, La Libertad, El Salvador.

*Correspondence
lorena.menjivar15@gmail.com

1. 0000-0003-3031-2585 2. 0000-0002-6829-7731
3. 0000-0002-4156-9565 4. 0000-0003-1453-1227

Abstract
Gestational diabetes *mellitus* is the abnormal carbohydrate tolerance that begins during pregnancy and is considered a risk factor for the development of complications in the mother and fetus during pregnancy. Its prevention is based on lifestyle interventions, glycemia monitoring, and pharmacological and nutritional therapy. Nutritional supplements are presented as a promising alternative to treat and prevent this phenomenon. This literature review aims to determine the efficacy of myo-inositol as a prophylactic supplement to prevent the development of gestational diabetes *mellitus* and its complications, as well as to mention other alternative supplements. A search was conducted in Pubmed, SciELO, Elsevier, and Hinari databases, including original articles published between 2019 and 2023. The evidence found showed that myo-inositol supplementation in pregnancy increases insulin sensitivity, reduces low-density lipoprotein levels, reduces pregnancy-induced hypertension, and reduces the incidence of preterm delivery, fetal macrosomia, episodes of fetal hypoglycemia and neural tube defects, being its implementation safe in pregnancy. However, it is necessary to conduct research with a larger number of participants, with standardized doses that allow for establishing the efficacy of this supplement for its use as an alternative in the prevention of gestational diabetes.

Keywords
Primary Prevention, Gestational Diabetes, Myo-inositol.

Resumen
La diabetes *mellitus* gestacional es la tolerancia anormal a los carbohidratos que inicia durante el embarazo y a su vez se considera un factor de riesgo para el desarrollo de complicaciones en la madre y el feto durante el embarazo. Su prevención se basa en intervenciones en el estilo de vida, monitoreo de la glicemia, terapia farmacológica y nutricional. Los suplementos nutricionales se presentan como una alternativa prometedora para tratar y/o prevenir dicho fenómeno. Esta revisión bibliográfica tiene por objetivo determinar la eficacia del mio-inositol como suplemento profiláctico para prevenir el desarrollo de diabetes *mellitus* gestacional y sus complicaciones, así como mencionar otros suplementos alternativos. Se realizó una búsqueda bibliográfica en las bases de datos Pubmed, SciELO, Elsevier e Hinari, incluyendo artículos originales publicados entre el año 2019 hasta 2023. La evidencia encontrada demostró que la suplementación con mio-inositol en el embarazo, aumenta la sensibilidad a la insulina, reduce los niveles de lipoproteínas de baja densidad, disminuye la hipertensión inducida por el embarazo, reduce la incidencia de parto pretérmino, macrosomía fetal, episodios de hipoglicemia fetal y defectos del tubo neural, siendo su implementación segura en el embarazo. Sin embargo, es necesario realizar investigaciones con un mayor número de participantes, con dosis estandarizadas que permitan establecer la eficacia de este suplemento para su uso como alternativa en la prevención de la diabetes gestacional.

Palabras clave
Prevención primaria, Diabetes gestacional, Mioinositol.

Introduction

Gestational diabetes *mellitus* (GDM) is defined as abnormal glucose tolerance that begins during pregnancy;[i] it increases the risk of developing preeclampsia, type 2 diabetes *mellitus*,[ii] fetal macrosomia, shoulder dystocia, the threat of preterm delivery; it is estimated that approximately 10 % of women with GDM will require intensive care.[iii]

GDM has a prevalence of 6 to 13 % worldwide, and in Central and South America, approximately 11 %. Because of this, it is considered a growing public health problem.[iv] Likewise, DGM is one of the main causes of mortality and morbidity in both the mother and the fetus.[v]

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Uso de mio-inositol y otros suplementos nutricionales para prevención primaria de la diabetes *mellitus* gestacional

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According to data recorded in the Morbidity, Mortality, and Vital Statistics System, 529 cases of GDM were reported in El Salvador between January and December 2022.[vi]

The prevention of GDM is mainly based on lifestyle interventions, glycemia monitoring, and pharmacological and nutritional therapy.[vii] However, in recent years, the use of nutritional supplements for the prevention of complications derived from GDM has become an object of study of growing interest since it could be a safe, affordable, and effective strategy,[viii] in addition to avoiding certain complications such as the reduction in the incidence of preterm delivery and fetal macrosomia.[ix]

Consequently, the implementation of preventive strategies for GDM offers intergenerational benefits by reducing future chronic diseases in both the mother and her child. Some nutritional supplements represent options with a practical and safe approach for preventing GDM. These include myo-inositol, vitamin D, and fatty acids.[x]

A narrative literature review was carried out, including original articles, narrative reviews, systematic reviews and meta-analyses in English and Spanish, with less than five years of publication. The search was carried out in databases such as PubMed, Elsevier, SciELO and Hinari. The following Boolean operators and search terms were used: "Prevention" AND "Gestational diabetes" AND "Myo-inositol supplementation". This review aims to describe the efficacy of myo-inositol as a prophylactic supplement for the prevention of gestational diabetes *mellitus* and its complications, as well as to mention alternative supplements for the prevention and treatment of gestational diabetes *mellitus*.

Discussion

Inositol is a cyclic carbohydrate isolated from muscle extracts in 1850 by Johan Joseph Scherer, initially considered an essential nutrient belonging to the vitamin B family.[xi] It has nine structural isomers; myo-inositol and D-chiro-inositol are the most studied; myo-inositol is incorporated within the cell membrane and acts as a secondary messenger in the transduction of endocrine signals, including follicle-stimulating hormone, thyroid-stimulating hormone and insulin.[xii]

In recent years, inositol has played an important role in modulating the pathogenesis of inflammation, oxidative stress, and insulin resistance, acting as a mediator of insulin action and is necessary to activate key enzymes in glucose metabolism.[xiii] Therefore, abnormalities in its metabolism have been associated with insulin resistance.[xiv]

Myo-inositol is synthesized endogenously from glucose-6-phosphate; the body is capable of producing up to 4 g per day of inositol, with the kidneys and liver being the main producers. Exogenously, it is obtained from cereals, legumes, and seeds from which up to 1 g per day is obtained from these sources.[xv]

Recent research has shown that supplementation with inositols correlates with a healthy pregnancy, achieving adequate glucose levels, and preventing possible maternal/fetal alterations and complications.[xvi] Comparative studies have evaluated the efficacy of different inositol stereoisomers for the prevention of GDM, showing that the greatest benefit is found in the myo-inositol group.[xvii]

Glycemic control

Guarnotta *et al.* in their study conducted in Italy included 330 women with GDM, 150 supplemented with myo-inositol at a dose of 4 g per day, and the remaining 180 supplemented with placebo, showed that women with GDM supplemented with myo-inositol had better glycemic control and lower insulin requirements, and also had a lower incidence of low birth weight and hypoglycemic events in the newborn, compared to women who did not receive myo-inositol supplementation (Table 1).[xviii]

Likewise, Gambioli *et al.* compared the effectiveness of myo-inositol and metformin in glycemic control and lipid profile. In this study, they demonstrated that myo-inositol was more effective in increasing insulin sensitivity, thus reducing serum insulin levels and low-density lipoprotein levels in women with polycystic ovary syndrome.[xix] Numerous studies have established that a dose of 2 g of myo-inositol twice daily resulted in a decrease in the risk of developing GDM, such as the study by McVay *et al.*, where this administration schedule was associated with a 66 % decrease in the incidence of GDM.[xx]

Overweight and obesity

Overweight and obesity have become a growing public health problem since their presence before pregnancy increases the risk of complications during that period.[xxi] These complications include preterm delivery, fetal macrosomia, shoulder dystocia, among others.[xxii]

On the other hand, the meta-analysis performed by Sepideh *et al.*, which included overweight and obese pregnant women, indi-

cated that supplementation with myo-inositol showed that it was a new and safe preventive strategy to reduce the incidence of GDM through the regulation of fasting glucose levels and in the oral glucose tolerance test one and two hours postprandially. In addition, a decrease in the development of hypertension during pregnancy was evidenced,[xxiii] as stated by Salvatore G, in his study of 223 women, of whom 110 women were supplemented with myo-inositol and 113 with placebo; the former showed a significant reduction in the overall incidence of pregnancy-induced hypertension (7.3 %), while in the latter group, it was higher (21.2 %).[xxiv]

Maternal-fetal miscarriages

A study carried out at the University d'Annunzio in Italy with non-obese patients but with elevated fasting glucose in the first and second trimester of pregnancy included a total of 73 women, 35 of whom were supplemented with myo-inositol and 38 with placebo; as a result, a decrease in the incidence of GDM was evidenced in women who received myo-inositol as a supplement, with an absolute risk reduction of 66.3 %. In addition, it was shown that this group required a lower dose of insulin compared to the placebo group (placebo group 21 % versus myo-inositol group 3 %). Likewise, the incidence of preterm delivery, fetal macrosomia, and episodes of neonatal hypoglycemia was significantly lower in the myo-inositol-supplemented group (Table 1). Because of this, the authors concluded that myo-inositol supplementation during pregnancy reduces the incidence of GDM in women at high risk of this disorder.[xxv]

From another perspective, maternal obesity and GDM have been considered risk factors for the development of neural tube defects.[xxvi] Facchhinetti *et al.* concluded that myo-inositol supplementation, initiated in the first trimester in obese pregnant women, appears to reduce the incidence of GDM through a reduction in insulin resistance and also appears to reduce the risk of recurrence of neural tube defects.[xxvii]

In addition, a meta-analysis conducted in February 2023, which included seven studies with 1319 pregnant women, states that the use of myo-inositol can reduce GDM and hypertensive disorders in pregnancy and preterm delivery. However, its use does not generate a reduction in the risk of a large-for-gestational-age newborn. These reviewed studies were performed with small samples, which do not allow the necessary statistical power to evaluate perinatal mortality and severe infant morbidity.[xxviii]

Safety of myo-inositol

Myo-inositol has been used for decades in many studies related to both polycystic ovary syndrome and insulin resistance.[xxix] Studies in animal models and multiple clinical trials have been conducted to evaluate the safety of the supplement.[xxx] Preclinical data indicate no toxic effects in terms of renal function, cognitive functions or carcinogenesis.[xxxi]

Reyes *et al.* analyzed five randomized clinical studies and found no adverse effects in pregnant patients who consumed myo-inositol at a dose of 2 g twice daily.[xxxii] In addition, in the meta-analysis developed by Vitagliano A and Saccone G, it was concluded that there were no differences in secondary outcomes such as incidence of cesarean section, shoulder dystocia, perineal tears, newborn birth weight, neonatal hypoglycemia and admission to the neonatal intensive care unit with the use of this supplement.[xxxiii] In contrast, Formoso *et al.* observed gastrointestinal adverse effects such as nausea, flatulence, and diarrhea after administration of

Table 1. Effects on glycemic control and neonatal and perinatal outcomes in women supplemented with myo-inositol compared to women supplemented with placebo

	Group supplemented with myo-inositol (N=150)	Placebo-supplemented group (N= 180)
Effects on glycemic control		
Fasting glucose (mg/dL)	95.7 ± 9.81	95.1 ± 10.9
1-hour postprandial glycemia (mg/dL)	150.7 ± 36.5	163.5 ± 52.1
2-hour postprandial glycemia (mg/dL)	115.8 ± 30.8	122.4 ± 37.6
Neonatal and perinatal outcomes (in years)		
Birth weight (grams)	3.241 ± 443	3.361 ± 406
Hypoglycemia (%)	11 (7.3 %)	36 (20 %)

Source: Adapted from Guarnotta V, Cuva G, Imbergamo MP, Giordano C. Myo-inositol supplementation in the treatment of gestational diabetes mellitus: effects on glycaemic control and maternal-fetal outcomes. BMC Pregnancy Childbirth. 2022 Jun 26; 22 (1): 516. http://creativecommons.org/licenses/by/4.0/

myo-inositol at doses greater than 12 grams per day from the first trimester of gestation.[xxxiv]

In addition, myo-inositol is part of the list of compounds generally recognized as safe for the general population by the FDA (Food and Drug Administration); however, further studies are still required to confirm its efficacy and safety in pregnancy.[xxxv] On the other hand, the usual pharmacological therapy for reducing the risk of GDM is metformin,[xxxvi] a drug that can positively influence metabolic disorders.[xxxvii] Although it has been extensively studied, more data is still required regarding its long-term safety.[xxxviii] As demonstrated by Shokrpour M *et al.* who conclude that when comparing the risk-benefit ratio of myo-inositol and metformin, myo-inositol represents a valid alternative given its greater safety and tolerability,[xxxix] unlike metformin which has been associated with multiple adverse effects compared to placebo.[xl]

However, the studies neither report on other relevant maternal and newborn outcomes nor provide data on long-term outcomes.[xli]

Other Nutritional Supplements for the Prevention of GDM

Nutritional supplements are presented as a safe and generally well-tolerated alternative for the treatment and prevention of GDM.[xlii] These supplements include probiotics, vitamin D and polyunsaturated fatty acids, among others. Some of their effects are detailed in Table 2.

Vitamin D

Vitamin D deficiency is common during pregnancy due to fetal requirements, inadequate intake, and limited sun exposure[xliii] and is associated with an increased occurrence of GDM.[xliv]

Probiotics

Probiotic supplementation during pregnancy has been associated with improved glucose and lipid metabolism, being beneficial in the prevention or control of GDM.[xlv]

Polyunsaturated fatty acids

The antilipidic effects of these fatty acids are of particular interest during pregnancy due to the existence of an increase in total cholesterol, triglycerides, and lipoproteins from week eight of gestation; in addition, it has been seen that women with GDM present even higher levels of these lipids compared to women with normal glucose tolerance.[xlvi]

Conclusion

Most studies suggested that using myo-inositol could prevent GDM and its complications in both the mother and the fetus due to the reduction in fasting glucose levels and the oral glucose tolerance test one and two hours postprandial. However, it is unclear whether supplementation is associated with a decrease in the incidence of GDM because the existing studies are small enough to detect differences in maternal-fetal outcomes. Myo-inositol has been associated with a reduction of hypertensive disorders during pregnancy. There are variations in the dosage of the supplement between studies and the characteristics of the pregnant patients, such as ethnicity; most of

Table 2. Comparison of the effectiveness of nutritional supplements for the prevention of GDM

Nutritional supplement	Effect on pregnancy
Vitamin D	High-dose vitamin D supplementation decreases insulin resistance and cholesterol levels in patients with GDM.[xlvii]
	It reduces the risk of GDM, preeclampsia and newborn complications such as low birth weight and preterm delivery.[xlviii]
Probiotics	They modulate the composition of the intestinal flora, benefits the immune system and improves glucose and lipid levels, as well as markers of inflammation and oxidative stress, subsequently reducing the risk of gestational diabetes.[xlix]
	Supplementation for four to eight weeks in women with GDM reduced insulin resistance, improved HDL cholesterol levels, markers of inflammation and oxidative stress, and decreased the incidence of hyperbilirubinemia in the newborn.[l]
Fish oil and fatty acids	Omega-3 supplementation for six weeks in women with GDM demonstrated benefits in the expression of genes that regulate insulin function, decreased triglyceride levels and increased LDL and HDL cholesterol levels.[li]
	Potential benefits have been seen in the fetus, reducing preterm delivery and the risk of low birth weight.[lii]

these studies were conducted on the European continent. Being a natural component, synthesized in the body and present in many foods in the regular diet, studies suggest that the component does not pose a risk to the mother or fetus, so its use is considered safe during pregnancy.

The reviewed studies suggest that supplementation with vitamin D, probiotics, fish oil, and fatty acids can reduce insulin resistance and improve cholesterol levels in patients with GDM. However, there is a lack of significant studies comparing the effects of myo-inositol with these supplements. It is necessary to conduct well-designed research with a larger number of participants using standardized doses to establish the efficacy of myo-inositol in preventing GDM. Subsequent research that compares the effectiveness of myo-inositol with other nutritional supplements is also required.

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