Narrative review

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

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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.

Introduction

Gestational diabetes mellitus (GDM) is defined as abnormal glucose tolerance that begins during pregnancy; it increases the risk of developing preeclampsia, type 2 diabetes mellitus, fetal macrosomia, shoulder dystocia, the threat of preterm delivery; it is estimated that approximately 10% of women with GDM will require intensive care. 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. Likewise, DGM is one of the main causes of mortality and morbidity in both the mother and the fetus.

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 mioinositol como suplemento profiláctico para prevenir el desarrollo de diabetes 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 demuestra que la suplementación con mioinositol 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 hipoglucemia 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.

Conflict of interests: The authors declared there are not conflict of interests.
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.xx

The prevention of GDM is mainly based on lifestyle interventions, glycemia monitoring, and pharmacological and nutritional therapy.xx 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,xxi in addition to avoiding certain complications such as the reduction in the incidence of preterm delivery and fetal macrosomia.xxx

Consequently, the implementation of preventive strategies for GDM offers inter-generational 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.xx 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.xxx 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.xxx

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.xxx There-fore, abnormalities in its metabolism have been associated with insulin resistance.xxx

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.xxx

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.xxiv 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.xxx

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).xxv

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.xxx 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.xxx

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.xxx These complications include preterm delivery, fetal macrosomia, shoulder dystocia, among others.xxx

On the other hand, the meta-analysis performed by Sepideh et al., which included overweight and obese pregnant women, indi-
Table 1. Effects on glycemic control and neonatal and perinatal outcomes in women supplemented with myo-inositol compared to women supplemented with placebo

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


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.

From another perspective, maternal obesity and GDM have been considered risk factors for the development of neural tube defects. Facchinetti 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.

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.

Safety of myo-inositol

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

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. 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.

In contrast, Formoso et al. observed gastrointestinal adverse effects such as nausea, flatulence, and diarrhea after administration of myo-inositol.
myo-inositol at doses greater than 12 grams per day from the first trimester of gestation. 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. On the other hand, the usual pharmacological therapy for reducing the risk of GDM is metformin, a drug that can positively influence metabolic disorders. Although it has been extensively studied, more data is still required regarding its long-term safety. 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 unlike metformin which has been associated with multiple adverse effects compared to placebo.

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

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. 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 and is associated with an increased occurrence of GDM.

Probiotics

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

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.

Conclusions

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>
<thead>
<tr>
<th>Nutritional supplement</th>
<th>Effect on pregnancy</th>
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<tbody>
<tr>
<td>Vitamin D</td>
<td>High-dose vitamin D supplementation decreases insulin resistance and cholesterol levels in patients with GDM. It reduces the risk of GDM, preeclampsia and newborn complications such as low birth weight and preterm delivery.</td>
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<tr>
<td>Probiotics</td>
<td>They modulate the composition of the intestinal flora, benefit 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. 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.</td>
</tr>
<tr>
<td>Fish oil and fatty acids</td>
<td>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. Potential benefits have been seen in the fetus, reducing preterm delivery and the risk of low birth weight.</td>
</tr>
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</table>
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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