Hrana u zdravlju i bolesti, znanstveno-stručni časopis za nutricionizam i dijetetiku (2021) 10 (2) 97-103
Food in Health and Disease, scientific-professional journal of nutrition and dietetics (2021) 10 (2) 97-103

THE ROLE OF INOSITOL, FOLIC ACID AND POLYUNSATURATED FATTY ACIDS IN PREGNANCY AND FETAL DEVELOPMENT

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review paper

Summary

Historical reasons have led to knowledge that would not have been possible to obtain through research without gross violations of ethical norms. Quantification of macro- and micro-nutrient intake is hampered by a number of barriers. It has been observed that changes in fetal nutrition and its endocrine status can result in developmental adjustments that permanently alter the structure, physiology, and metabolism of children, thus exposing individuals to the risk of metabolic, endocrine, and cardiovascular diseases in adulthood. In research on the process better known as "fetal programming", the influence of the *in utero* environment on the epigenetic mechanisms of the fetus has been observed. Decreased or increased amounts of food intake may interfere with placental function and interfere with fetal growth. Altered placental function can lead to endothelial dysfunction, leading to changes in fetal growth and development. More recently, there has been increasing research on the impact of dietary supplementation on pregnant women and perinatal outcome. Among the more frequently examined variables are micronutrients such as folic acid, antioxidants, iron, magnesium and zinc, but also polyunsaturated fatty acids. The Covid-19 pandemic further highlighted the need to create disease registries and systematically monitor data, especially given the differences in health care availability on one hand and the incredible global differences in nutrient availability on the other.

Keywords: gestational diabetes, fetal development, inositol, folic acid, polyunsaturated fatty acids, supplementation, perinatal outcome

Introduction

There is a growing number of studies on the impact of certain nutrients that could prevent the development of pregnancy-related diseases. These are primarily metabolic diseases that can be treated by changing lifestyle. If healthy habits were to be accepted, with the possibility of using nutrients that in some way preserve the health homeostasis of the organism, it is likely that the perinatal outcome would be improved. Some nutrients have been studied more frequently, such as myoinositol, folic acid, and omega fatty acids and deserve consideration for their impact on the prevention of a very common metabolic disease in pregnancy - gestational diabetes mellitus (GDM).

The role of inositol in fetal development through the prevention of gestational diabetes mellitus

During pregnancy, significant metabolic and hormonal changes occur in pregnant women, which are necessary for normal fetal growth and development (Bozzetti et al., 1988). One of the important physiological hormonal changes is the occurrence of maternal hyperinsulinemia and insulin resistance (Hadden et al., 2009). Insulin resistance increases with gestational age and is the highest in the third trimester (Catalano et al., 1991). This physiological change enables and improves the fetal glucose supply during pregnancy. However, if this condition is not accompanied by adequate insulin secretion it may contribute to an increased risk of developing gestational diabetes (*GDM*) (Phelps et al., 1981). In addition, certain conditions such as overweight and obesity may increase insulin resistance due to increased endocrine activity of increased visceral adipose tissue in such patients and thus increase the risk for *GDM* (Catalano et al., 1991). *GDM* is the most common metabolic complication in pregnancy and it is defined as any degree of glucose intolerance with an onset during pregnancy (ADPSG, 2010). It is a risk factor for the cardiometabolic disorders development in both mother and their child later in life (Bellamy et al., 2009; Schwartz et al., 2015; Teh et al., 2011). In addition, there are other multiple risk factors for *GDM*; they are the following: pre-gestational obesity (*BMI*≥ 30 kg/m^2), weight gain during pregnancy in overweight or obese women (Hedderson et al., 2010; Morisset et al., 2010), physical inactivity (Chasan-Taber et al., 2008), older maternal age (Morisset et al., 2010), diets low in fiber

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and with a high glycemic load (Zhang et al., 2006), previous history of macrosomic baby or *GDM* (Petry, 2010), family history or first-degree relative with diabetes, or polycystic ovarian syndrome (Reece, 2010).

Systematic review of 23 randomized controlled trials (*RCT*s) on the prevention of *GDM* by combined diet and exercise interventions has shown 15% reduced risk for *GDM* in 19 *RCT*s, 5% reduced risk of caesarean section in 14 *RCT*s, and in 16 *RCT*s less gestational weight gain (mean difference (MD) -0.89 kg) in the diet and exercise intervention group compared to the control (no intervention) group (Shepherd et al., 2017). Further, there were no significant differences between aforementioned groups (moderate- to very low- quality evidence) in hypertensive pregnancy disorders, large-for-gestational age, neonatal hypoglycemia, perinatal mortality and childhood adiposity (Shepherd et al., 2017). The authors of this Cochrane review concluded that currently available evidence suggests that combined diet and exercise interventions may be effective for preventing *GDM*, but due to the variability of the diet and exercise components tested in the *RCT*s included in the review, the evidence is limited for clear recommendations in clinical practice (Shepherd et al, 2017). Recently, there is increasing number of interventional studies of some potentially effective and safe supplements in preventing the onset of *GDM* in high-risk pregnant women, or in improving glucose homeostasis in pregnant women with preexisting diabetes. One of these supplements with insulin-sensitizing properties is inositol (Corrado et al., 2011; D'Anna et al., 2013; Larner et al., 2010). Inositol (cyclohexane-1,2,3,4,5,6-hexol) is a sugar alcohol that can be synthesized by humans from glucose (National Center for Biotechnology Information, 2021). There are nine possible stereoisomers of which myo-inositol (*MI*) and D-chiro-inositol (*DCI*) are the most abundant in nature (Thomas et al., 2015; Turneret al., 2002). MI is naturally found in food of plant origin, predominantly in fresh fruits and vegetables, or of animal origin, such as meat, fish and milk (Clements et al., 1980). Inositol is a phospholipid structural component of the cell membrane. Moreover, it mediates osmoregulation (Murthy, 2006). Inositol forms the structural base for a number of signaling molecules and secondary messengers thus participating in a number of biological processes. Its phosphorylated derivatives participate in protein phosphorylation (Saiardi et al., 2004), control of gene transcription (Odom et al., 2000), chromatin remodeling (Shen et al., 2003), and facilitate the export of *mRNA* from the nucleus (York et al., 1999). Further, *MI* and *DCI* are involved in glucose and insulin metabolism (Larner, 2002; Larner et al., 2010; Nacimento et al., 2006). Thus, inositol imbalance can result with the development of different diseases (Chhetri, 2019).

In our review we will present the results of interventional studies on *MI* supplementation alone or in combination with other isomers such as *DCI*, or with folic acid (*FA*) in prevention of *GDM*. In *RCT* on pregnant women (n=200) with *GDM* risk factors Amaeful et al. (2018) have found that *MI* supplementation (4 g daily) from early 2nd trimester until the end of pregnancy resulted in reduction of macrosomia and 60% reduction of *GDM* compared to placebo. In *RCT* on non-obese singleton pregnant women (n=180, pre-gestational *BMI* $\leq$25 kg/m^2) at risk for *GDM* (elevated fasting glucose in the first or early second trimester) on different inositol stereoisomers (*MI*, *DCI*, combined *MI* and *DCI*) supplementation Celentano et al. (2020) have found that those on *MI* alone had a lower incidence of abnormal oral glucose tolerance test (*OGTT*) compared to placebo group. Moreover, all exposed groups required less insulin for glycemic control compared to placebo, and this effect was the most pronounced in the group on *MI*. Further, singleton GDM patients (n=80, BMI not specified) at different dosages of inositol isomers (*MI* group - 4g *MI* plus 400 mg *FA*; *DCI* group - 500 mg *DCI* plus 400 mcg *FA*, *MI plus DCI* group - 1100/27.6 mg *MI/DCI* plus 400 mcg *FA*) showed a significant decrease in *HOMA-IR* index and lower variation in average weight gain (at delivery vs. pre-pregnancy and *OGTT* period) in *MI* group compared to control group (*FA* 400 mcg only) after 8 weeks of treatment. In addition, women on *MI* and *MI plus DCI* treatment required significantly less intensified insulin treatment. Interestingly, women treated with inositol had lower birth weight compared to the control group (Fraticelli et al., 2018). In a small RCT on non-obese singleton pregnant women (n=75, BMI <30 kg/m^2) with *GDM* risk factors Matarrelli et al. (2013) found that women randomized to receive *MI* (n=36) from the first or early second trimester to delivery had significantly lower incidence of *GDM* in mid-pregnancy, required less insulin therapy, delivered at a later gestational age, had significantly smaller babies with fewer episodes of neonatal hypoglycemia compared to placebo. In another *RCT* on pregnant non-obese but overweight women (n=220, pre-pregnancy body mass index (BMI) $\geq$ 25-30 kg/m^2) supplementation with *MI* (4 g daily) together with *FA* (400 mcg daily) from the first trimester to delivery resulted in significantly lower incidence of *GDM* compared to control group on *FA* only. Further, *MI plus FA* treatment was associated with a 67% risk reduction of developing *GDM* (OR

0.33; 95% CI 0.15–0.70), but with no effect on macrosomia, hypertensive pregnancy disorders, shoulder dystocia and pre-term delivery (Santamaria et al., 2016). In another *RCT*, *MI* plus *FA* supplementation (4g *MI* plus 400 mcg *FA* daily) from the first trimester to delivery in pregnant obese women (n= 220, pre-pregnancy *BMI*≥30 kg/m^2) resulted in significantly reduced *GDM* rate compared to control group on *FA* only. Further, women on *MI plus FA* treatment showed a significantly greater reduction in *HOMA-IR* index compared with the control group (D'Anna et al., 2015). In meta-analysis on pregnant women at risk for *GDM* (n=965, patients' heterogeneity: variable *BMI*, singleton and unspecified pregnancies, most Caucasians) inositol supplementation (*MI* 4 g daily or *MI* 1100 mg plus *DCI* 27.6 mg daily) was associated with 51% lower rate of *GDM* (OR 0.49, 95% CI 0.24–1.03, p = 0.01) and 65% lower preterm delivery rate (OR 0.35, 95% CI 0.17–0.74, p = 0.006). After adjustment for the type of intervention (*MI* vs. *MI plus DCI*) significant effect was found only in patients receiving *MI*. In the study there was no adverse effects reported (Vitagliano et al., 2019). In the Cochrane systematic review Crawford et al. (2015) showed a potential benefit of antenatal dietary supplementation with *MI* during pregnancy (first and second trimesters to delivery, n = 567) in reducing the incidence of *GDM*, while it was not possible to conclude on perinatal outcomes (neonatal morbidity and mortality) due to lack of data about the same. Based on the recent evidence presented in this review, preventing *GDM* with antenatal inositol supplementation we improve early maternal and perinatal outcome (except for lower birth weight compared to the control group) and prevent the development of chronic diseases later in life for both mother and their offspring.

Impact of folic acid and omega fatty acids on fetal growth and development

Pregnancy is a period of rapid tissue growth, cell differentiation and organogenesis, processes crucial for normal fetal development. Consequently, it is a period of altered and increased need for dietary supply for both mother and the fetus. If micro and/or macronutrients are given at an inappropriate time of fetal development (different organs develop at different times during pregnancy) and/or inappropriate dose, they may be ineffective and even harmful. Therefore, inappropriate nutrition leads to an increased risk of death *in utero*, but also to alterations in birth weight and functional changes in the neonatal organs (McArdle et al., 1999). Therefore, in interpreting impact of nutrition on fetal growth and development, it should be borne in mind that inadequate nutrition may be due to socio-economic factors, inappropriate eating habits, or failure to fully absorb nutrients.

For several decades, folate has been known to be associated with a reduction in pregnancy complications including neural tube defects, congenital malformations (congenital heart diseases), haemorrhage, pre-eclampsia, spontaneous abortions, and fetal growth restriction (Jonker et al., 2020; Ramakrishnan et al., 1999). Because of its role in nucleic acid synthesis, the need for folate increases during times of rapid dividing of cells, such as in fetal development. Therefore, situations with folate deficiency may lead to alterations in DNA synthesis with variety of problems in fetal growth and development.

Long-chain omega-3 polyunsaturated fatty acids (*PUFA*) are essential fatty acids and nutrients which mostly derive from fish and other seafood. They cannot be synthesized by humans and must be ingested through the diet or from supplements. The most biologically active *PUFA* are eicosapentaenoic acid (*EPA*) and docosahexaenoic acid (*DHA*). During pregnancy, *PUFA* requirements increase to support fetal growth, particularly of the brain and eyes. There is evidence that deprivation of *PUFA* during pregnancy is associated with visual and behavioral deficits that cannot be reversed with *PUFA* postnatal supplementation (Coletta et al., 2010).

In this paper we review the effect and impact of prenatal and/ or antenatal *PUFA*, lipid-based nutrient and *FA* supplementation with or without other micronutrient(s) on fetal growth and development. Most of the studies included in this review are from socially deprived, mostly low-income countries. Thus, there is poor or inadequate *PUFA* dietary intake worldwide, especially in low-income countries. Effect of wealth on response to different nutrient supplementation during pregnancy on perinatal outcomes (birth weight, duration of gestation and perinatal mortality) was investigated in the double-blind *RCT* in rural China (Zeng et al., 2011). The assessment of wealth was based on the inventoried household assets. Pregnant women from the poorest households on multimicronutrient (*MMN*) supplementation had significantly increased birth weight by 68 g, reduced low birth weight by 60% and tended to have reduced early neonatal mortality by 52% compared with *FA* group. Further, women in poorest households on iron plus *FA* supplements had significantly increased duration of gestation by 0.41 weeks, reduced pre-term birth by 45% and reduced early neonatal mortality by 90% compared with those on *FA* alone. In this study, pregnant women from the

poorest households had the most improved perinatal outcomes by *MMN* supplementation, while iron plus *FA* supplementation in these women provided more protection for neonatal survival than the *MMN* one. Interestingly, no significant effects of iron plus *FA* and *MMN* supplementation on perinatal outcomes were observed in women from wealthier households in this study (Zeng et al., 2011). In socially deprived, multi-ethnic population from East London, *MMN* supplementation including iron and *FA*, from the first trimester to delivery resulted in higher mean hemoglobin, higher median concentrations of serum ferritin, erythrocyte folate and 25-hydroxyvitamin D later in gestation compared to controls. Moreover, placebo treated women had more small-for-gestational age (*SGA*) infants than treated ones (Brough et al., 2010). Further, another interventional study on undernourished pregnant women in India showed that additional *MMN* supplementation (29 vitamins and minerals once a day) to FA and iron supplements, from second or early third trimester (24 to 32 weeks of gestation) until delivery resulted in lower incidence of low birth weight (a 70% decrease; relative risk, 0.30; 95% CI, 0.13-0.71; P=.006) and lower incidence of early neonatal morbidity (a 58% decrease; relative risk, 0.42; 95% CI, 0.19-0.94; P=.04) compared to placebo (FA plus iron) (Gupta et al., 2007). Maternal *MMN* supplementation in rural Burkina Faso showed significantly higher both birth weight (52 g; 95% CI: 4, 100; P = 0.035) and birth length (3.6 mm; 95% CI: 0.8, 6.3; P = 0.012) compared to those exposed to iron and FA alone. Further, in *MMN* group the risk of large-for gestational-age infants was higher (OR:1.58; 95% CI: 1.04, 2.38; P = 0.03), and this affected mainly primiparous women (OR: 3.44; 95% CI: 1.1, 10.7; P for interaction = 0.11) (Roberfroid et al., 2008). In another study the same group of authors investigated association between cumulative micronutrient intake (*CMI*) and fetal growth. They found moderate improvement in fetal growth. *MMN* supplementation increased birth weight by 69 g compared to iron plus FA alone. Similar results were observed for thoracic and cephalic circumferences. In the same study, *MMN* supplementation together with iron plus *FA* intake during pregnancy showed cumulative effect on fetal growth (Roberfroid[a] et al., 2012). Further, the same authors in another study demonstrated that prenatal *MMN* supplement for singleton pregnant women when compared with the iron and *FA* supplement (*IFA*) treated women, resulted in a 27% (HR: 0.73; 95% CI:0.60, 0.87; P = 0.002) reduction of stunting over the whole observation period. This difference was lost by age of 30 months. The effect of *MMN* supplementation on postnatal growth continued over the observation period with 14% reduction in reported episodes of fever. No other differences in childrens' morbidity and mortality compared to *IFA* group were observed (Roberfroid[b] et al., 2012). Sebayang et al. (2011) showed that maternal *MMN* supplementation increased mean birthweight by 33 g and significantly reduced low birth weight by 21% compared to infants whose mothers received *IFA* supplements. In contrast to previous studies, Ramakrishnan et al., (2016) demonstrated that preconceptional weekly supplementation with *IFA* or the same amount of aforementioned nutrients plus other *MMN* had no effect on birth outcomes (birth weight, gestational age, preterm delivery and small for gestational age) compared to *FA* alone in Vietnamese women.

Prenatal lipid-based nutrient supplementation *(LNS*, 20g daily) for primiparous women in Ghana resulted in greater mean birth length, weight, *BMI* and head circumference than the groups treated with *IFA* (60 mg iron/400 mg FA) or with *MMN* (18 micronutrients including 20 mg iron) (Adu-Afarwuah et al., 2015). The same group of authors demonstrated that maternal *LNS* supplementation during pregnancy and 6 months postpartum together with their infant *LNS* supplementation from 6 to 18 months of their age resulted in significantly greater baby mean length and weight, but not head or midupper arm circumference, compared to those treated with *IFA* or with *MMN*. Further, the prevalence of stunting in the *LNS* group was lower compared to the aforementioned groups (Adu-Afarwuah et al., 2016). In another study maternal fish-oil supplementation from 22nd gestational week until delivery significantly increased maternal *PUFA* stores (*DHA* and *EPA*) after adjustment for maternal baseline *DHA* and *EPA*. In addition, it increased cord blood *DHA* thus improving fetal *PUFA* status. Folate supplementation of pregnant women was significantly associated with increased maternal *DHA*. Andrés Catena et al. (2016) demonstrated that children born to mothers supplemented during pregnancy with *FA* alone solved the response conflict more quickly than those on the placebo or on supplementation with FA and long-chain polyunsaturated fatty acid.

Regarding birth defects, Wehby et al. (2013), investigated effects of different doses of *FA* supplementation (0.4 and 4 mcg per day) before pregnancy and throughout the first trimester on oral cleft recurrence and fetal growth. Cleft rates were compared to historic recurrence rates. The recurrence rates in both treated groups were similar (2.9 and 2.5% in the 0.4 and 4 mg groups) and significantly lower compared to historic rate (6.3%). In addition, there was no difference in fetal growth complications between the two FA groups. Based on the above results, mostly from low-income countries, prenatal

and/ or antenatal *MMN*, *IFA* supplementation with or without lipid-based nutrient supplementation improved perinatal outcomes mainly in malnourished and/ or primiparous pregnant women except in one study. Due to the increased dietary needs of the mother and the fetus during pregnancy, adequate energy and macro and micronutrients, including folic acid and iron, intake through food and supplements are required for normal fetal growth and development. Some studies have shown cumulative effect of those nutrients on fetal growth.

Conclusion

Pregnancy is characterized by significant changes in the hormonal and metabolic status of the pregnant woman, but also by increased needs for macro and micronutrients necessary for normal fetal growth and development. Adequate prenatal and antenatal nutrition and supplementation can improve perinatal outcome and prevent the development of chronic diseases of the mother and offspring later in life.

References

Adu-Afarwuah, S., Lartey, A., Okronipa, H., Ashorn, P., Zeilani, M., Peerson, J.M., Arimond, M., Vosti, S., Dewey, K.G. (2015): Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana. *Am J Clin Nutr.* 101 (4), 835-846.

Adu-Afarwuah, S., Lartey, A., Okronipa, H., Ashorn, P., Peerson, J.M., Arimond, M., Ashorn, U., Zeilani, M., Vosti, S., Dewey, K.G. (2016): Small-quantity, lipid-based nutrient supplements provided to women during pregnancy and 6 mo postpartum and to their infants from 6 mo of age increase the mean attained length of 18-mo-old children in semi-urban Ghana: a randomized controlled trial. *Am J Clin Nutr*. 104 (3), 797–808.

Amaefule, C.E., Drymoussi, Z., Dodds, J., Sweeney, L., Pizzo, E., Daru, J., Robson, J., Poston, L., Khalil, A., Myers, J., Harden, A., Hitman, G.A., Khan, K., Zamora, J., Huda M.S.B. Thangaratinam, S. (2018): Effectiveness and acceptability of myo-inositol nutritional supplement in the prevention of gestational diabetes (EMmY): a protocol for a randomised, placebo-controlled, double-blind pilot trial. *BMJ Open.* 8 (9), e022831.

Bellamy, L., Casas, J.P., Hingorani, A.D., Williams, D. (2009): Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet.* 373 (9677), 1773–1779.

Bozzetti, P., Ferrari, M.M., Marconi, A.M., Ferrazzi, E., Pardi, G., Makowski, E.L., Battaglia, F.C. (1988): The relationship of maternal and fetal glucose concentrations in the human from midgestation until term. *Metabolism*. 37 (4), 358–363.

Brough, L., Rees, G.A., Crawford, M.A., Morton, H.R., Dorman, E.K. (2010): Effect of multiple-micronutrient supplementation on maternal nutrient status, infant birth weight and gestational age at birth in a low-income, multi-ethnic population. *Br J Nutr.* 104 (3), 437–445.

Catalano, P.M., Tyzbir, E.D., Roman, N.M., Amini, SB., Roman, N.M. (1991): Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol*. 165 (6 Pt 1), 1667–1672.

Catena, A., Muñoz-Machicao, J.A., Torres-Espínola, F.J., Martínez-Zaldívar, C., Diaz-Piedra, C., Gil, A., Haile, G., Györei, E., Molloy, A.M., Decsi, T., Koletzko, B., Campoy, C. (2016): Folate and long-chain polyunsaturated fatty acid supplementation during pregnancy has long-term effects on the attention system of 8.5-y-old offspring: a randomized controlled trial. *Am J Clin Nutr.* 103 (1), 115-127.

Celentano, C., Matarrelli, B., Pavone, G., Vitacolonna, E., Mattei, P.A., Berghella, V., Liberati, M. (2020): The influence of different inositol stereoisomers supplementation in pregnancy on maternal gestational diabetes mellitus and fetal outcomes in high-risk patients: a randomized controlled trial. *J Matern Fetal Neonatal Med*. 33 (5), 743-751.

Chasan-Taber, L., Schmidt, M.D., Pekow, P., Sternfeld, B., Manson, J.E., Solomon, C.G., Braun, B., Markenson, G. (2008): Physical activity and gestational diabetes mellitus among hispanic women. *J Womens Health (Larchmt).*17 (6), 999–1008.

Chhetri, D.R. (2019): Myo-Inositol and Its Derivatives: Their Emerging Role in the Treatment of Human Diseases. *Front Pharmacol.* 10, 1172.

Clements, R.S. Jr., Darnell, B. (1980): Myo-inositol content of common foods: development of a high-myo-inositol diet. *Am J Clin Nutr.* 33 (9), 1954–1967.

Coletta, J.M., Bell S.J., Roman, A.S. (2010): Omega-3 Fatty Acids and Pregnancy. *Rev Obstet Gynecol.* 3 (4), 163–171.

Corrado, F., D'Anna, R., Di Vieste, G., Giordano, D., Pintaudi, B., Santamaria, A., Di Benedetto, A. (2011): The effect of myoinositol supplementation on insulin resistance in patients with gestational diabetes. *Diabet Med.* 28 (8), 972–975.

Crawford, T.J., Crowther, C.A., Alsweiler, J., Brown, J. (2015): Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. *Cochrane Database Syst Rev*. (12), CD011507.

D'Anna, R., Scilipoti, A., Giordano, D., Caruso, C., Cannata, M.L., Interdonato, M.L., Corrado, F., Di Benedetto A. (2013): Myo-Inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes. *Diabetes Care.* 36 (4), 854–857.

D'Anna, R., Di Benedetto, A., Scilipoti, A., Santamaria, A., Interdonato, M.L., Petrella, E., Neri, I., Pintaudi, B., Corrado, F., Facchinetti, F. (2015): Myo-inositol Supplementation for Prevention of Gestational

Diabetes in Obese Pregnant Women: A Randomized Controlled Trial. *Obstet Gynecol.* 126 (2), 310-315.

Fraticelli, F., Celentano, C., Zecca, I.A., Di Vieste, G., Pintaudi, B., Liberati, M., Franzago, M., Di Nicola, M., Vitacolonna, E. (2018): Effect of inositol stereoisomers at different dosages in gestational diabetes: an open-label, parallel, randomized controlled trial. *Acta Diabetol*. 55 (8), 805-812.

Hadden, D.R., McLaughlin, C. (2009): Normal and abnormal maternal metabolism during pregnancy. *Semin Fetal Neonatal Med*. 14 (2), 66–71.

Hedderson, M.M., Gunderson, E.P., Ferrara, A. (2010): Gestational weight gain and risk of gestational diabetes mellitus. *Obstet Gynecol*. 115 (3), 597–604.

Gupta, P., Ray, M., Dua, T., Radhakrishnan, G., Kumar, R., Sachdev, H.P. (2007): Multimicronutrient Supplementation for Undernourished Pregnant Women and the Birth Size of Their Offspring. *Arch Pediatr Adolesc Med.* 161 (1), 58-64.

International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger, B.E., Gabbe, S.G., Persson, B., Buchanan, T.A., Catalano, P.A., Damm, P., Dyer, A.R., Leiva, Ad., Hod, M., Kitzmiler, J.L., Lowe, L.P., McIntyre, H.D., Oats, J.J., Omori, Y., Schmidt, M.I. (2010): International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 33 (3), 676–682.

Jonker, H., Capelle, N., Lanes, A., Wen, SW., Walker, M., Corsi, D.J. (2020): Maternal folic acid supplementation and infant birthweight in low- and middle-income countries: A systematic review. *Matern Child Nutr*. 16 (1), e12895.

Larner, J. (2002): D-chiro-inositol – Its functional role in insulin action and its deficit in insulin resistance. *Int J Exp Diabetes Res.* 3 (1), 47–60.

Larner, J., Brautigan, D.L., Thorner, M.O. (2010): D-chiro-inositol glycans in insulin signaling and insulin resistance. *Mol Med.* 16 (11–12), 543–552.

Murthy, P.P.N. (2006): Biology of inositol and phosphoinositide. In: Subcellular Biochemistry, Majumder A.L., Biswas, B.B. (ed.), Boston, USA: Springer, pp. 1-19.

Matarrelli, B., Vitacolonna, E., D'Angelo, M., Pavone, G., Mattei, P.A., Liberati, M., Celentano, C. (2013): Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes mellitus and fetal outcomes: a randomized controlled trial. *J Matern Fetal Neonatal Med.* 26 (10), 967-972.

McArdle, H.J., Ashworth, C.J. (1999): Micronutrients in fetal growth and development. *Br Med Bull.* 55 (3), 499-510.

Morisset, A.S., St-Yves, A., Veillette, J., Weisnagel, S.J., Tchernof, A., Robitaille, J. (2010): Prevention of gestational diabetes mellitus: a review of studies on weight management. *Diabetes Metab Res Rev*. 26 (1), 17–25.

Nascimento, N.R., Lessa, L.M., Kerntopf, M.R., Sousa, C.M., Alves, R.S., Queiroz, M.G., Price, J., Heimark, D.B., Larner, J., Du, X., Brownlee, M., Gow, A., Davis, C., Fonteles, M.C. (2006): Inositols prevent and reverse endothelial dysfunction in diabetic rat and rabbit vasculature metabolically and by scavenging superoxide. *Proc Natl Acad Sci U S A.* 103 (1), 218–223.

Odom, A.R., Stahlberg, A., Wente, S.R., York, J.D. (2000): The role of nuclear inositol 1,4,5-trisphosphate kinase in transcription control. *Science.* 287 (5460), 2026–2029.

Petry, C.J. (2010): Gestational diabetes: risk factors and recent advances in its genetics and treatment. *Br J Nutr.* 104 (6), 775–787.

Phelps, R.L., Metzger, B.E., Freinkel, N. (1981): Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol, and individual amino acids in late normal pregnancy. *Am J Obstet Gynecol.* 140 (7), 730–736.

National Center for Biotechnology Information. PubChem Compound Summary for CID 892. 2021 *Inositol*. https://pubchem.ncbi.nlm.nih.gov/compound/Inositol. Accessed October 28, 2021.

Ramakrishnan, U., Manjrekar, R., Rivera, J., Gonzáles-Cossío, T., Martorell, R. (1999): Micronutrients and pregnancy outcome: A review of the literature. *Nutrition Research.* 19 (1), 103–159.

Ramakrishnan, U., Nguyen, P.H., Gonzalez-Casanova, I., Pham, H., Hao, W., Nguyen, H., Truong, T.V., Nguyen, S., Harding, K.B., Reinhart, G.A., Neufeld, L.M., Martorell, R. (2016): Neither Preconceptional Weekly Multiple Micronutrient nor Iron–Folic Acid Supplements Affect Birth Size and Gestational Age Compared with a Folic Acid Supplement Alone in Rural Vietnamese Women: A Randomized Controlled Trial, *J Nutr.* 146 (7), 1445S-1452S.

Reece, E.A. (2010): The fetal and maternal consequences of gestational diabetes mellitus. *J Matern Fetal Neonatal Med.* 23 (3), 199–203.

Roberfroid, D., Huybregts, L., Lanou, H., Henry, M.C., Meda, N., Menten, J., Kolsteren, P.; MISAME Study Group. (2008): Effects of maternal multiple micronutrient supplementation on fetal growth: a double-blind randomized controlled trial in rural Burkina Faso, *Am J Clin Nutr.* 88 (5), 1330–1340.

Roberfroid, D., Huybregts, L., Lanou, H., Habicht, J.P., Henry, M.C., Meda, N., Kolsteren, P. (2012): Prenatal Micronutrient Supplements Cumulatively Increase Fetal Growth. *J Nutr.* 142 (3), 548–554.

Roberfroid, D., Huybregts, L., Lanou, H., Ouedraogo, L., Henry, M.C., Meda, N., Kolsteren, P.; MISAME study group. (2012): Impact of prenatal multiple micronutrients on survival and growth during infancy: a randomized controlled trial, *Am J Clin Nutr.* 95 (4), 916–924.

Saiardi, A., Bhandari, R., Resnick, A.C., Snowman, A.M., Snyder, S.H. (2004): Phosphorylation of proteins by inositol pyrophosphates. *Science.* 306 (5704), 2101–2105.

Santamaria, A., Di Benedetto, A., Petrella, E., Pintaudi, B., Corrado, F., D'Anna, R., Neri, I., Facchinetti, F. (2016): Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial. *J Matern Fetal Neonatal Med.* 29 (19), 3234-3237.

Schwartz, N., Nachum, Z., Green, M.S. (2015): The prevalence of gestational diabetes mellitus recurrence-effect of ethnicity and parity: a metaanalysis. *Am J Obstet Gynecol.* 213 (3), 310–317.

Sebayang, S.K., Dibley, M.J., Kelly, P., Shankar, A.V., Shankar, A.H. (2011): Modifying effect of maternal nutritional status on the impact of maternal multiple micronutrient supplementation on birthweight in Indonesia. *Eur J Clin Nutr*. 65 (10), 1110–1117.

Shen, X., Xiao, H., Ranallo, R., Wu, W.H., Wu, C. (2003): Modulation of ATP-dependent chromatin-remodeling complexes by inositol polyphosphates. *Science*. 299 (5603), 112–114.

Shepherd, E., Gomersall, J.C., Tieu, J., Han, S., Crowther, C.A., Middleton, P. (2017): Combined diet and exercise interventions for preventing gestational diabetes mellitus. *Cochrane Database Syst Rev*. 11 (11), CD010443.

Teh, W.T., Teede, H.J., Paul, E., Harrison, C.L., Wallace, E.M., Allan, C. (2011): Risk factors for gestational diabetes mellitus: implications for the application of screening guidelines. *Aust N Z J Obstet Gynaecol.* 51 (1), 26–30.

Thomas, M.P., Mills, S.J., Potter, B.V.L. (2015): The "Other" Inositols and Their Phosphates: Synthesis, Biology, and Medicine (with Recent Advances in myo-Inositol Chemistry). *Angew Chem Int Ed Engl.* 55 (5), 1614-1650.

Turner, B.L., Papházy, M.J., Haygarth, P.M., McKelvie, I.D. (2002): Inositol phosphates in the environment. *Philos Trans R Soc Lond B Biol Sci.* 357 (1420), 449–469.

Vitagliano, A., Saccone, G., Cosmi, E., Visentin, S., Dessole, F., Ambrosini, G., Berghella, V. (2019): Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. *Arch Gynecol Obstet.* 299 (1), 55-68.

Wehby, G.L., Félix, T.M., Goco, N., Richieri-Costa, A., Chakraborty, H., Souza, J., Pereira, R., Padovani, C., Moretti-Ferreira, D., Murray, J.C. (2013): High dosage folic acid supplementation, oral cleft recurrence and fetal growth. *Int J Environ Res Public Health.* 10 (2), 590-605.

York, J.D., Odom, A.R., Murphy, R., Ives, E.B., Wente, S.R. (1999): A phospholipase C-dependent inositol polyphosphate kinase pathway required for efficient messenger RNA export. *Science*. 285 (5424), 96–100.

Zeng, L., Yan, H., Cheng, Y., Dibley, M.J. (2011): Modifying effects of wealth on the response to nutrient supplementation in pregnancy on birth weight, duration of gestation and perinatal mortality in rural western China: double-blind cluster randomized controlled trial. *Int J Epidemiol.* 40 (2), 350-362.

Zhang, C., Soloman, C.G., Liu, S., Hu, F.B. (2006): Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. *Diabetes Care*. 29 (10), 2223–2230.