

## Effects of zinc supplementation on glycemic control and complications of gestational diabetes

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### ABSTRACT

**Objectives:** To investigate the effects of zinc supplementation on pregnancy outcome in patients with gestational diabetes mellitus.

**Methodology:** During the randomized double blind clinical trial 60 women with gestational diabetes mellitus from 32<sup>nd</sup> of gestational age were assigned to two equal groups to receive 25mg zinc sulfate orally per day as case or placebo as control. Then, groups were compared regarding insulin dosage needs, macrosomia and preeclampsia.

**Results:** Insulin requirements and dosage changes during the investigation were lower in the case group than in the control ( $P<0.001$ ). Women in the zinc supplemental group had a lower percentage of large infants compared to control ( $P<0.01$ ). There were no significant differences between two groups regarding the rates of preeclampsia and cesarean delivery.

**Conclusions:** This study showed that zinc supplementation in gestational diabetes could reduce insulin needs and improve glycemic control of these patients and it may also reduce macrosomia.

**KEY WORDS:** Gestational diabetes, Zinc supplementation, Pregnancy outcome.

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### INTRODUCTION

Gestational diabetes is one of the most prevalent complications of pregnancy. It causes consequences to the mother and the fetus and an increased risk for subsequent overt type 2 diabetes. Diabetes may induces oxidative stress in the mother and the fetus that may lead to adverse fetal outcomes (i.e. fetal

distress, macrosomia and other congenital anomalies).<sup>1</sup> On the other hand there is evidence that in type 2 diabetes mellitus the concentration of Mg (magnesium) and Zn (zinc) levels were significantly reduced, probably suggesting lower antioxidant status in this condition.<sup>2</sup> Serum zinc levels status in diabetics is significantly lower than healthy controls.<sup>3</sup> The dietary zinc supplementation attenuated hyperglycemia<sup>4</sup> and played crucial roles in the regulation of carbohydrate and lipid metabolism.<sup>2</sup>

In gestational diabetes mellitus (GDM) like type 2 diabetes, in addition to insulin resistance, there is also secretion problem of insulin and due to importance of zinc serum levels on insulin function, the role of zinc deficiency in pregnancy is notable.<sup>2,4</sup> There are some studies about low zinc serum levels in diabetics and positive effects of zinc supplementation on glycemic control of type 2 diabetics.<sup>2,5</sup> Because of controversial results<sup>1,3,6</sup> about zinc serum levels in gestational diabetes and the scarcity of clear studies about the effect of zinc supplementation on fetal and maternal complication of gestational diabetes, this study

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was designed to investigate the effects of zinc supplementation on the outcome of pregnancy in patients with gestational diabetes mellitus.

### METHODOLOGY

All pregnant women attending Shabih Khani Hospital and other private clinics in Kashan (Iran) from May 2006 to December 2007 were routinely screened with a 50 g oral glucose tolerance test (OGTT) without regarding the time of the day or time of the last meal at 24 to 28 weeks of gestational age. All patients with positive screening results (1 h GTT  $\geq 140$  mg/dl) underwent 100 g 3 hours OGTT after an overnight fasting. GDM was diagnosed when two serum glucose values were higher than the following levels: 105 mg/dl after fasting, 190 mg/dl at 1 hour, 165 mg/dl at 2 hours or 145 mg/dl at 3 hours.<sup>7</sup>

The study included all women screened during the study period in the mentioned clinics. Pregnant women known to have diabetes mellitus or any disease affecting glucose metabolism, active infections, chronic illness or medical treatment (drugs or vitamin supplements), anemia, history of smoking or alcohol abuse, multiple pregnancies, and preterm delivery were excluded. In GDM, if fasting blood sugar (FBS) was more than 105 mg/dl and blood sugar (BS) (glucose level 2 hours after having food was more than 120 mg/dl), the patient underwent insulin therapy ( $A_2$  GDM). During the screening, 60 women with GDM were identified and after obtaining approval from Ethical Committee and written consent, they participated in this double blind clinical study.

Considering the studies of the American Diabetes Association which found that fasting

hyperglycemia may be associated with an increased risk of fetal death during the last 4 to 8 weeks of gestation<sup>7</sup>, investigators decided to commence of supplementation therapy during last 8 weeks of pregnancy, so patients from 32 weeks of gestational age randomly enrolled in two equal groups (n=30). Blocked randomization was used to choose cases. In case group (Zn group), patients received 25mg zinc sulfate orally per day as zinc containing syrup (5ml of 5mg/ml solution). Another group received 5 ml of placebo (syrup with the same features without zinc).

In both groups administration of solutions were continued until term (gestational weeks= 38-40). In both groups mean gestational age was  $39 \pm 1$  week. Both groups were checked for FBS and BS (2 hour post meal glucose) and glucose levels were maintained at level of  $< 105$  for fasting and  $< 120$  mg/dl for 2 hour after meal glucose. At the end of study each group was compared as regards insulin dosage needs, macrosomia (birth weight of more than 4000 g)<sup>7</sup> and preeclampsia (blood pressure systolic  $\geq 140$  mm Hg, or diastolic  $\geq 90$  mmHg that occurs after twenty weeks of gestation and proteinuria, excretion of protein  $\geq 0.3$  g in a 24 - hour urine specimen or  $1^+$  or greater on a random urine sample dipstick test)<sup>7</sup>. T-Test, Chi-Square, Fisher exact test and Kolmogorov-Smirnov tests were used for data analysis. Crude odds ratio also was calculated.

### RESULTS

There was no statistically significant difference between two groups at the beginning of the study regarding age, BMI and serum zinc levels. In addition, BMI changes in the two groups were not significant (Table-I). All women in both groups

Table-I: Patients' characteristics and insulin changes during the study in the case (Zn) and the control (Placebo) groups.

Variables	Zn (n=30)		Control (n=30)		P.V
	Mean	SD	Mean	SD	
Age	28.3	3.13	28.6	3.23	0.778
BMI	26.3	1.27	26.4	1.49	0.774
Insulin Dosage(IU)					
(at the start of the study)	16.36	5.47	15.23	6.86	0.482
Insulin Dosage(IU)					
(at the end of the study)	25.13	10.78	32.76	11.91	0.012
Insulin dosage changes(IU)	8.76	9.63	17.53	10.54	0.001
Serum zinc levels ( $\mu$ g/dl)	61.43	5.09	63.20	5.47	0.2

Note: Zn, Zinc -BMI, Body Mass Index-IU, International unit.

(case and control) had diabetes A<sub>2</sub> and needed insulin therapy and were treated with insulin during the study. Also there was no significant difference between the two groups regarding insulin dosage range at the beginning of the study.

At the end of the study statistical analysis showed insulin requirements and dosage changes during the investigation was significantly lower in the Zn group compared to the control one. Mean (SD) neonatal birth weight in Zn and control groups were 3729 (300) and 3867 (313) respectively ( $P=0.09$ ). Women in the Zn group had a lower percentage of large infants (macrosomia) compare to control (6.7% vs 33.3%). This difference was statistically significant. [(odds ratio (OR) =7, 95%CI: 1.38-35.487)] There were no significant differences between Zn supplemental and control regarding incidents rates of preeclampsia and cesarean delivery (Table-II).

## DISCUSSION

This study showed that Zn supplementation in gestational diabetes could reduce insulin needs and improve glycemic control of these patients and it may also reduce macrosomia incident rates. Several studies have been performed about zinc deficiency and labor complications.

Tamura et al studied the pregnancy outcome of women receiving zinc supplementation during pregnancy. They showed zinc supplementation (in non-diabetic mothers) could cause higher weight and longer head circumferences in newborns at birth.<sup>8</sup>

Finding of mentioned study does not support our results. According to our findings, in women who had received zinc supplementation, risk of macrosomia of the newborn was 7 times less than placebo receiving ones. Different results may be due to different patients' characteristics, our patients were affected by A<sub>2</sub> gestational diabetes, but the cited study was performed on non diabetic patients.

An investigation by Bo et al showed that Zinc serum levels in pregnant women (24-28 of gestational age) with abnormal GTT was lower than control group and they also showed serum levels of zinc were negatively associated with gestational hyperglycemia. They also found that hyperglycemic women with low serum zinc levels had a larger percentage of large for gestational age infants (although it was not significant) and low serum zinc levels was significantly associated with higher weight of newborn in hyperglycemic women.<sup>1</sup>

Another study which was conducted by Wang et al also showed zinc contents in serum of pregnant women with gestational diabetes decreased compared with normal pregnant women.<sup>3</sup> Assuming in gestational diabetes zinc serum levels is lower than normal and it may develop macrosomia, our results showed that zinc supplementation in diabetic mothers may reduce risk of macrosomia in newborn.

Al-Saleh et al concluded from their studies that there was no significant deference between obese gestational diabetics and non diabetic obese patients regarding zinc serum levels.<sup>6</sup> These results are against Bo and Wang's studies and the current investigation. In al-Saleh research, zinc serum levels determined at the time of delivery or cesarean section, but in Bo and Wing's studies measurement was performed at 30<sup>th</sup> week of pregnancy period. On the other hand in Al-Saleh's study, obese pregnant women (BMI>30) with or without gestational diabetes were compared. Different results in mentioned studies may be due to these methodological differences.

Use of zinc and other nutrients to prevention of preeclampsia has not been studied extensively, but the few studies have found minimal or no benefit.<sup>9</sup> Ilhan et al showed a correlation between reduction of zinc serum levels and preeclampsia.<sup>10</sup> Our study did not show any significant difference between zinc supplemented patients and placebo

Table-II: Frequency of delivery method, preeclampsia and macrosomia regarding to Zn supplementation in diabetic mothers.

Variables		Zn No (%)	Control No (%)	P.V	OR	CI
Delivery Method	NVD	14 (46.7)	8(26.7)	0.108	2.406	0.816 7.095
	C/S	16 (53.3)	22(73.3)			
Preeclampsia	Yes	4(13.3)	5(16.7)	1	1.3	0.313 5.404
	No	26(86.7)	25(83.3)			
Macrosomia	Yes	2(6.7)	10(33.3)	0.01	7	1.381 35.478
	No	28(93.3)	20(66.7)			

Note: NVD, Normal Vaginal Delivery-C/S, Cesarean Section

groups regarding weight at birth and preeclampsia incident rates.

Present study did not show significant difference regarding cesarean section delivery rates among cases selected for cesarean section due to macrosomia in two groups of study probably because of misestimating of fetal weight before delivery.

In conclusion, this study showed that zinc supplementation in gestational diabetes could reduce insulin needs and improve glycemic control of these patients and it may also reduce macrosomia incident rates.

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### Authors' contribution:

Dr. Behrashi designed and conducted the study.

Dr. Aliasgharzadeh analyzed the data.

Mr. Mahdian as the participant investigator and consultant wrote the draft. All the authors approved the manuscript for publishing.