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

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Abstract. – OBJECTIVE: Myo-inositol supplementation prevents gestational diabetes (GDM) in women at risk and reduces insulin resistance in women with GDM. No data are available about its effect on glucose variability. The aim of this study was to evaluate the effects of a supplementation of myo-inositol on glucose variability in women with GDM.

PATIENTS AND METHODS: Myo-inositol effect on glucose variability was studied in a pilot case-control study involving 12 consecutive pregnant women (median age 34 years, 25.0% insulin-treated) with GDM. Six women received myo-inositol 2 g plus 200 mg folic acid twice a day, the others received only folic acid. Information on side effects was collected. A continuous glucose monitoring system was wore before and at the beginning of the supplementation. Mean amplitude of glucose excursion (MAGE), standard deviation (SD) and variability coefficient were the indexes of glucose variability.

RESULTS: Myo-inositol lowered glucose levels in the first days after the treatment was started. However, pre-post supplementation overall mean glucose difference was similar between groups (-4.8 *vs.* 5.0 mg/dL for controls and treated, respectively; $p = 0.79$). Pre-post differences in SD (13.7 *vs.* 6.0; $p < 0.001$), MAGE (3.5 *vs.*-1.5; $p < 0.001$) and variability coefficient (0.14 *vs.* 0.02; $p < 0.001$) were improved in myo-inositol group. No side effects were recorded.

CONCLUSIONS: Myo-inositol is effective in reducing glucose variability in women with GDM. It could be a useful strategy for treating GDM.

Key Words:
Myo-inositol, Gestational diabetes, Glucose variability.

Introduction

Gestational diabetes mellitus (GDM) is defined as a glucose impairment first detected in pregnancy[1]. In the last years, its prevalence is steeply increasing with relevant consequences[2]. GDM is associated with some adverse maternal and neonatal outcomes[3-5]. For these reasons, the detection and the care of GDM are very important. Prevention strategies have been proposed. The supplementation with myo-inositol, a stereoisomer of inositol that is a cyclitol present in animal and plant cells, has been demonstrated to be effective in reducing GDM occurrence in several categories of women at risk for GDM. Particularly, a preventive role was reported for women with a family history of diabetes[6], women with impaired fasting blood glucose[7], obese[8] or overweight[9]. A Cochrane Review reported a reduction of almost 57% in the incidence of GDM in women at high risk after supplementation of myo-inositol compared to controls[10]. When used in women with GDM, myo-inositol was effective in reducing insulin resistance levels and insulin treatment requirement[11-13]. Despite this strong clinical effect, a comprehensive investigation of the inositol mechanism of action in GDM was not performed. Data already published report a reduction of insulin resistance in women treated with myo-inositol. Although this is the likely mechanism, we cannot exclude different inositol effects on glucose metabolism[14]. A more accurate and deeper exploration of inositol effect on glucose status could be possible with the use of a continuous glucose monitoring (CGM) system. CGM can give a detailed picture

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of glucose variation, providing also glucose variability indexes. To the best of our knowledge, no study has reported data on glycemic profiles detected with CGM in women with GDM taking inositol. The aim of this research was to investigate the effect of the supplementation of myo-inositol on glucose profiles and glucose variability in women with GDM.

Patients and Methods

This is a pilot case-control study approved by the local Ethics Committee, involving a total of 12 Caucasian pregnant women with GDM consecutively referred to the Clinic of Diabetes and Pregnancy of the University of Messina, Italy, from 1st January 2014 to 31st July 2014. All the participants gave informed consent. The investigation was conducted in accordance with the Declaration of Helsinki. All the participants underwent a 75 g 2-h Oral Glucose Tolerance Test (OGTT) between 24 and 28 weeks of gestation. The diagnosis of GDM was made according to the International Association of Diabetes and Pregnancy Study groups (IADPSG) recommendations[15]. Briefly, the IADPSG suggests conducting a 75 g-OGTT, with plasma glucose measurements at fasting and at 1-h and 2-h after the glucose load, at 24-28 weeks of gestation in women not previously diagnosed with overt diabetes. The diagnosis of GDM is made when any of the following plasma glucose values are exceeded: at fasting ≥5 .1 mmol/L, at 1-h ≥ 10.0 mmol/L, and at 2-h ≥ 8.5 mmol/L. After the diagnosis, all women received specific dietary advice and self-monitoring blood glucose was started as usual care. A supplementation with 2 g myo-inositol plus 200 mg folic acid (Inofolic, Lo.Li. Pharma srl, Rome, Italy) was administered twice a day to the first six consecutive women (treated). Supplementation started from the 30th gestational week until delivery. Only 200 mg folic acid was administered twice a day in the same period of pregnancy to the others 6 consecutive women (controls). Information on the occurrence of side effects caused by treatments was collected during follow-up visits. In particular, the presence of nausea, flatulence, diarrhea, headache, insomnia, uterine contractions, and tiredness was assessed. At gestational week 28, when women followed only the diet, a CGM system (iPro2 Medtronic) in holter-like mode was wore by all the participant women. At week 30, after the beginning of the supplementation, the CGM was repeated both in the treated and in controls. A professional CGM system, such as iPro2, is a clinician-owned device that collects glucose data without patient interaction for retrospective review. Data are masked to maintain regular behavior. Professional CGM is used by healthcare providers to reveal glucose excursions. These excursions often go unnoticed with traditional glycated hemoglobin (HbA1c) tests and standard glucose meter measurements. The system automatically records 288 glucose values per day and is capable to give several parameters such as glucose means, specific glucose trends, glucose variability indexes, and many others. CGM did not substitute self-monitoring, it was instead an additional tool used for the detection of glucose variability. As indexes of glucose variability, we considered: the mean amplitude of glucose excursion (MAGE), that is calculated as the arithmetical mean of differences between consecutive glycemic peaks and nadirs, only including changes of more than 1 standard deviation (SD) in the glycemic values[16], the SD and the variability coefficient. The SD is calculated by CGM system for the overall period of measurement. This is one of the simplest and most effective parameters for assessing glycemic variability, being closely correlated with most of the other glucose variability parameters. The following parameters were collected from the medical clinical records: maternal age, pre-pregnancy Body Mass Index (BMI), BMI at delivery, weight gain at delivery, fasting plasma glucose values of the first trimester of pregnancy, history of previous GDM, previous macrosomia (birth weight ≥4500 g), family history of diabetes (first-degree relative with diabetes), origin of family from areas with a high prevalence of diabetes, HbA1c levels of the third trimester of gestation, OGTT glucose values, third trimester fetal ultrasound parameters, insulin treatment and insulin doses, gestational weeks at delivery and type of delivery, newborn gender, and weight.

Statistical Analysis

Data are reported as medians for continuous variables and percentages for categorical variables. The characteristics of the study population were categorized by myo-inositol treatment (yes/no) and were compared using the χ^2-statistic for categorical variables and the Mann-Whitney U

test for continuous variables. Hierarchical linear models for repeated measurements were used to assess changes over time in glucose levels and glucose variability indexes[17].

For statistical significance, a p-value < 0.05 was considered. The analyses were carried out using SAS version 9.2 (SAS Institute Inc.).

Results

Clinical characteristics of the enrolled women in this study, according to the treatment group, are reported in Table I. The two groups were not statistically different for anthropometric, anamnestic, laboratory and ultrasound parameters. The rate of insulin in treated women was similar. Moreover, neonatal parameters were not significantly different between groups. Figure 1 shows daily mean glucose values recorded by continuous glucose monitoring system. Women treated with inositol showed a reduction of glucose levels in the first days post-treatment compared with controls. Results of the analyses of glucose variability from CGM are reported in Figure 2. Overall mean glucose reduction between the period before and after the beginning of supplementation was similar between the two groups (-4.8 *vs.* -5.0 mg/dL for controls and treated, respectively; $p = 0.79$) (Figure 2a). Women treated with myo-inositol had a better MAGE, being the pre-post difference of 3.5 and -1.5 for controls and treated, respectively ($p < 0.001$) (Figure 2b). The SD increased in both groups, but the difference was lower in treated patients compared to controls (13.7 *vs.* 6.0 for controls and treated, respectively; $p < 0.001$) (Figure 2c). When looking at the variability coefficient, it was lower in the group of women treated with myo-inositol, being the pre-post difference of 0.14 and 0.02 for controls and treated respectively ($p < 0.001$) (Figure 2d). No side effects linked to the treatment were recorded during the study.

Discussion

This is the first study exploring the effect of the supplementation of myo-inositol on glucose variability in women with GDM. Myo-inositol treatment led to a reduction of mean daily glucose values in the first days after the beginning

Table I. Clinical characteristics of the studied women according to the treatment group.

	Overall	Controls	Cases	p
N	12	6	6	
Age (years)	34.0 (33.0-35.0)	35.0 (27.0-41.0)	34.0 (33.0-35.0)	0.99
Family history of diabetes mellitus (%)	44.4	33.0	50.0	0.63
Pre-gestational BMI (kg/m^2)	23.3 (21.1-26.3)	26.8 (26.8-26.8)	22.0 (21.1-24.6)	0.29
BMI at delivery (kg/m^2)	27.0 (23.7-28.5)	29.2 (27.0-29.5)	25.0 (23.7-28.7)	0.37
Weight gain (kg)	6.7 (5.0-12.0)	4.5 (2.5-6.5)	8.5 (6.0-14.0)	0.28
Previous GDM (%)	50.0	50.0	50.0	0.99
First trimester fasting glycemia (mg/dl)	89 (84-92)	89 (84-95)	89 (82-92)	0.90
OGTT fasting glucose (mg/dl)	90 (83-94)	85 (76-89)	93 (92-96)	0.18
OGTT-1-h-post-load glucose (mg/dl)	168 (150-188)	192 (140-204)	165 (161-172)	0.40
OGTT-2-h-post-load glucose (mg/dl)	120 (104-147)	149 (105-170)	105 (104-136)	0.22
Glycemia at first visit (mg/dl)	96 (90-106)	98 (79-110)	94 (92-102)	0.99
HbA1c of the third trimester (%)	5.6 (5.2-5.8)	5.0 (5.0-5.1)	5.7 (5.6-5.8)	0.10
Third trimester fetal ultrasound examination (weeks)	31 (27-34)	32 (26-34)	33 (31-35)	0.09
Biparietal diameter (mm)	69.0 (53.5-80.0)	51.0 (48.0-70.0)	78.0 (68.0-82.0)	0.18
Abdominal circumference (mm)	270.0 (198.0-285.0)	188.0 (162.0-270.0)	284.0 (253.0-294.0)	0.13
Head circumference (mm)	265.0 (212.0-282.0)	212.0 (177.0-247.0)	269.5 (262.0-293.0)	0.28
Femur length (mm)	60.0 (39.0-61.0)	37.0 (33.0-60.0)	60.0 (60.0-62.0)	0.17
Insulin treated (%)	25.0	10.0	33.0	0.26
Gestational weeks at delivery (week)	38.5 (38.0-39.0)	38.0 (37.0-39.0)	38.5 (38.0-39.5)	0.65
Cesarean section rate (%)	50.0	33.0	60.0	0.46
Gender of newborn (%)				0.43
Male	30.0	50.0	20.0	
Female	70.0	50.0	80.0	
Neonatal weight (g)	3290.0 (2960.0-3490.0)	3245.0 (3200.0-3290.0)	3300.0 (2960.0-3490.0)	0.85

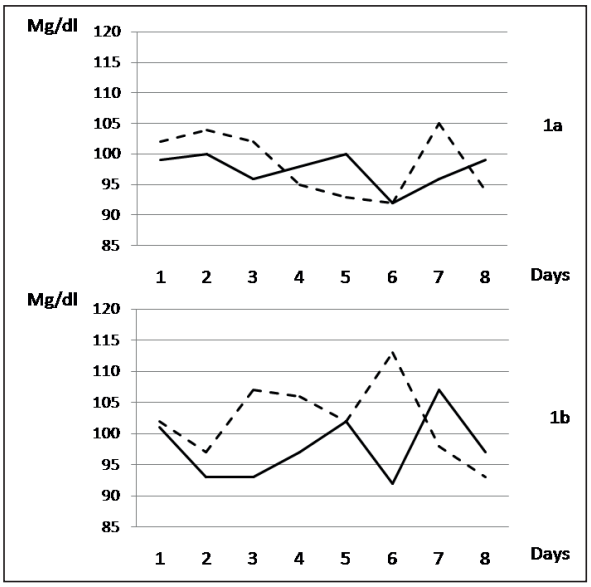

Figure 1. Daily mean glucose values recorded by continuous glucose monitoring system. Figure 1a reports data of the period before the treatment was started. Figure 1b reports data after the beginning of the treatment. Continue lines are women treated with myo-inositol; dotted lines are controls.

of treatment compared with controls. Glucose variability was improved after the treatment was started. Standard deviation, MAGE and variability coefficient, three of the main glucose variability indexes, were lower in the treated group than in the controls. None of the treated women reported side effects related to the supplement. A direct comparison with existing studies in the literature is not possible, being, our work, the first looking at the effect of myo-inositol on glucose variability. So far, few studies[18-21] analyzing the use of CGM in women with GDM have been published. Modern CGM systems can catch the direction and the magnitude of short-lived changes in interstitial glucose levels. This can assess glucose variability more accurately than self-monitoring blood glucose. CGM can detect also hypoglycemic episodes and hypoglycemia is a major barrier for optimal glycemic control in women with GDM on insulin. Naik et al[22] found a higher incidence of masked hypoglycemia (glucose < 2.77 mmol/L for ≥ 30 min) in pregnant women with GDM than controls by

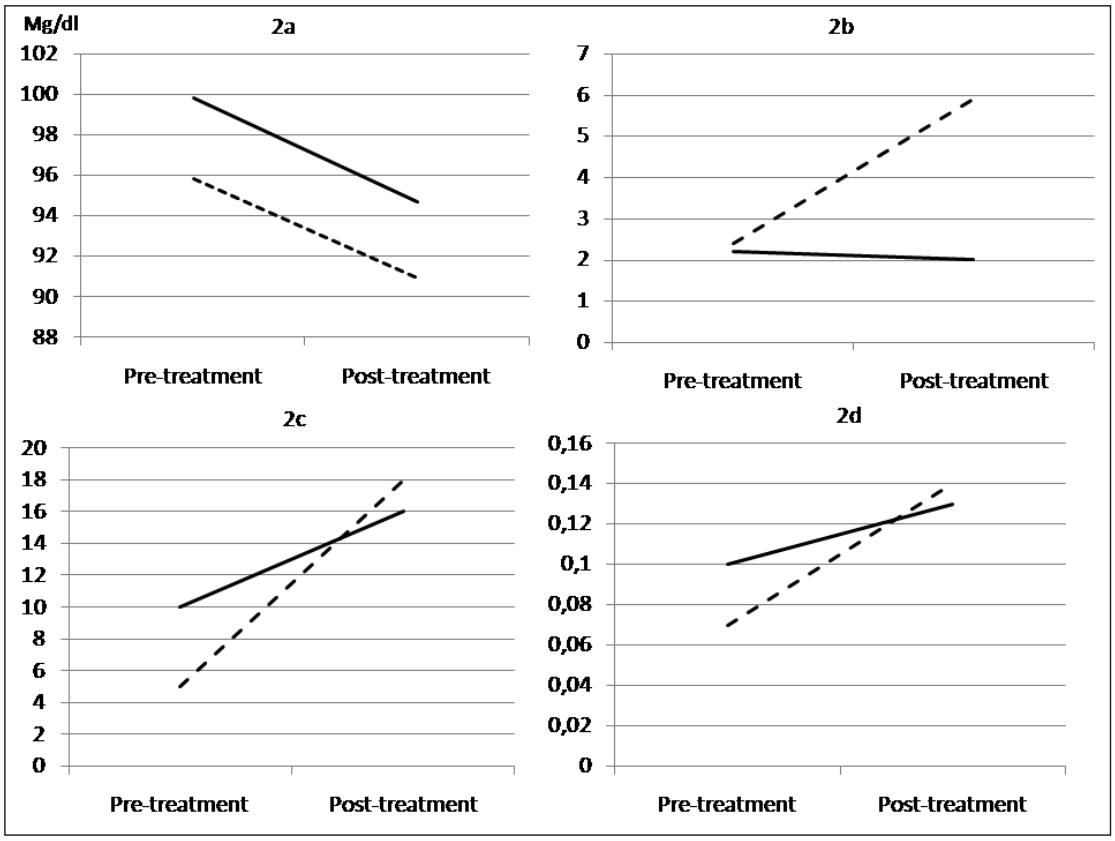

Figure 2. Overall mean glucose levels ***(2a)***, MAGE ***(2b)***, Standard Deviation ***(2c)*** and variability coefficient ***(2d)*** differences between the period before and after the treatment was started.Continue lines are women treated with myo-inositol; dotted lines are controls.

using a CGM system. Moreover, glucose values over the targets established for pregnancy (that are < 95 mg/dL for fasting and < 140 for 1-h after meal) are to be avoided. In this context CGM has been demonstrated to be capable to detect differences in time spent with glucose levels above 140 mg/dL between women with GDM and healthy pregnancies, highlighting the positive influence of diet counseling on glucose variability[23]. In our study, we have reported the positive effect of an intervention, represented by a supplement of myo-inositol, on glucose variability. Following these results, several key points useful in the clinical practice can be highlighted. First, myo-inositol supplementation was confirmed to be safe[24]. The occurrence of side effects caused by treatments was collected during follow-up visits and none of the treated women reported related-problem symptoms. The other important finding of our research confirmed the specific role of myo-inositol in reducing blood glucose levels. The preventive role of myo-inositol on the occurrence of GDM was explored by others researchers and clinicians. However, this capability has been documented only for the OGTT glucose values, constantly showing lower values in subjects treated with myo-inositol respect to controls[10]. Other authors[11,12] reported a glucose-lowering effect of inositol when it was used after the diagnosis of GDM. Our research provided more details of glucose levels trends in the days after the beginning of treatment. We found a significant effect in lowering glucose levels, particularly in the first three days after the beginning of the supplementation. After this period the effect was more mitigated, probably as a consequence of the stabilization of glucose levels. Knowing that myo-inositol treatment is able to reduce glucose variability could be an important consideration in the clinical management of GDM. Indeed, it is actually unlikely that healthcare professionals use CGM for women with GDM in usual care and this mainly for related costs and for the lack of scientific evidence. Information coming from this study could represent a useful knowledge to understand the mechanisms leading to and characterizing hyperglycemia in pregnancy and could guide therapeutic approach. A lower glucose variability potentially could lead to less insulin treatment and to an easier drug intervention. However, as already published, the use of supplementary CGM, combined with routine antenatal care, could improve glycemic control and pregnancy outcomes of patients with GDM[25]. Glycemic variability in GDM is higher than in normal pregnant women and glycemic variability, evaluated by MAGE, correlates well with impaired early-phase insulin secretion in GDM[26]. The reduction observed in MAGE could be a reflection of a treatment-induced improvement of early-phase insulin secretion. Limits of the study are firstly the case-control design that does not allow to test cause-effect. A randomized controlled trial design could explain more. Secondly, the low number of studied women did not allow to generalize the findings to all the categories of women; however, this is the first study investigating the effect of myo-inositol on glucose variability in women using CGM. The last limit is the lack of information on the association between glucose variability indexes and pregnancy outcomes.

Conclusions

We found that myo-inositol treatment is a useful strategy not only in lowering mean glucose levels but also in reducing glucose variability in women with GDM. For its role in reducing both insulin resistance and glucose variability, it could be a valuable approach for treating GDM.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care 1998; 21 Suppl 2: B161-167.

2) Corrado F, Pintaudi B, Di Vieste G, Interdonato ML, Magliarditi M, Santamaria A, D'Anna R, Di Benedetto A. Italian risk factor-based screening for gestational diabetes. J Matern Fetal Neonatal Med 2014; 27: 1445-1448.

3) Casey BM, Lucas MJ, McIntire DD, Leveno KJ. Pregnancy outcomes in women with gestational diabetes compared with the general obstetric population. Obstet Gynecol 1997; 90: 869-873.

4) Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, Australian Carbohydrate Intolerance Study in Pregnant Women Trial G. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005; 352: 2477-2486.

5) Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp JM Jr., Sciscione A, Catalano P, Harper M, Saade G, Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB, Eunice Kennedy Shriver National Institute of Child H, Human Development Maternal-Fetal Medicine Units N. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009; 361: 1339-1348.

6) D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, Corrado F, Di Benedetto A. Myo-inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: a prospective, randomized, placebo-controlled study. Diabetes Care 2013; 36: 854-857.

7) Matarrelli B, Vitacolonna E, D'Angelo M, Pavone G, Mattei PA, Liberati M, Celentano C. 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 2013; 26: 967-972.

8) D'Anna R, Di Benedetto A, Scilipoti A, Santamaria A, Interdonato ML, Petrella E, Neri I, Pintaudi B, Corrado F, Facchinetti F. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial. Obstet Gynecol 2015; 126: 310-315.

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

10) Crawford TJ, Crowther CA, Alsweiler J, Brown J. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. Cochrane Database Syst Rev 2015: CD011507.

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

12) Lubin V, Shojai R, Darmon P, Cosson E. A pilot study of gestational diabetes mellitus not controlled by diet alone: first-line medical treatment with myo-inositol may limit the need for insulin. Diabetes Metab 2016; 42: 192-195.

13) Costabile L, Unfer V. Treatment of gestational diabetes mellitus with myo-inositol: analyzing the cutting edge starting from a peculiar case. Eur Rev Med Pharmacol Sci 2017; 21: 73-76.

14) Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. Biochimie 2013; 95: 1811-1827.

15) Weinert LS. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy: comment to the International Association of Diabetes and Pregnancy Study Groups Consensus Panel. Diabetes Care 2010; 33: e97; author reply e8.

16) Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970; 19: 644-655.

17) Raudenbush SW, Bryk AS, Bryk SWRAS, Coaut BAS. Hierarchical linear models: applications and data analysis methods. SAGE Publications, 2002.

18) Dalfra MG, Chilelli NC, Di Cianni G, Mello G, Lencioni C, Biagioni S, Scalese M, Sartore G, Lapolla A. Glucose fluctuations during gestation: an additional tool for monitoring pregnancy complicated by diabetes. Int J Endocrinol 2013; 2013: 279021.

19) Yogev Y, Ben-Haroush A, Chen R, Kaplan B, Phillip M, Hod M. Continuous glucose monitoring for treatment adjustment in diabetic pregnancies--a pilot study. Diabet Med 2003; 20: 558-562.

20) Chen R, Yogev Y, Ben-Haroush A, Jovanovic L, Hod M, Phillip M. Continuous glucose monitoring for the evaluation and improved control of gestational diabetes mellitus. J Matern Fetal Neonatal Med 2003; 14: 256-260.

21) Mazze R, Yogev Y, Langer O. Measuring glucose exposure and variability using continuous glucose monitoring in normal and abnormal glucose metabolism in pregnancy. J Matern Fetal Neonatal Med 2012; 25: 1171-1175.

22) Naik D, Hesarghatta Shyamasunder A, Doddabelavangala Mruthyunjaya M, Gupta Patil R, Paul TV, Christina F, Inbakumari M, Jose R, Lionel J, Regi A, Jeyaseelan PV, Thomas N. Masked hypoglycemia in pregnancy. J Diabetes 2017; 9: 778-786.

23) Carreiro MP, Lauria MW, Naves GN, Miranda PA, Leite RB, Rajao KM, de Aguiar RA, Nogueira AI, Ribeiro-Oliveira A, Jr. Seventy two-hour glucose monitoring profiles in mild gestational diabetes mellitus: differences from healthy pregnancies and influence of diet counseling. Eur J Endocrinol 2016; 175: 201-209.

24) Carlomagno G, Unfer V. Inositol safety: clinical evidences. Eur Rev Med Pharmacol Sci 2011; 15: 931-936.

25) Yu F, Lv L, Liang Z, Wang Y, Wen J, Lin X, Zhou Y, Mai C, Niu J. Continuous glucose monitoring effects on maternal glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus: a prospective cohort study. J Clin Endocrinol Metab 2014; 99: 4674-4682.

26) Su JB, Chen T, Xu F, Wang XQ, Chen JF, Wu G, Jin Y, Wang XH. Glycemic variability in normal glucose regulation subjects with elevated 1-h postload plasma glucose levels. Endocrine 2014; 46: 241-248.