The Effectiveness of D-Chiro Inositol Treatment in Gestational Diabetes

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Abstract

Background: Purpose of this study was to evaluate the role of D-chiro-inositol (DCI) in the metabolic control of women affected by gestational diabetes mellitus (GDM) and to examine the impact on pregnancy and fetal outcome.

Methods: A prospective, randomized, open-label, single-center, pilot study was conducted between December 2013 and December 2015 on pregnant women with GDM attending the outpatient clinic. Patients were randomized to receive or not DCI (500 mg twice a day). We evaluated maternal medical condition, fetal growth parameters and obstetric complications.

Results: A total of 137 pregnant women were enrolled and randomized to receive (n=67) or not (n=70) DCI. We found a reduction in post-prandial glucose (breakfast, lunch and dinner; p=0.005, p=0.003, p=0.005 respectively) in the DCI group. The median weight gain was 11.5 kg in the control group compared to a median increase of 9 kg in the DCI group (p=0.015). The two groups differ significantly in the number of insulin doses (on average 3 daily doses in the control group compared with 2 in the DCI group; p=0.026). The median abdominal circumference of newborns in the control group was 339 mm compared to 332 mm in the DCI group (p=0.001); the median value of head circumference of newborns in the control group was 338.8 mm compared to 333 mm (p=0.012). We do not find a significant difference in neonatal birth weight (3.360 kg DCI versus 3.262 kg in the control group; p=0.067) but the neonatal PI at birth was significantly lower in DCI group.

Conclusion: Our results suggest that DCI supplementation improves glucose metabolism during pregnancy, controls maternal weight gain and fetal growth. Therefore, dietary supplementation with DCI during pregnancy may be an appealing strategy for treating GDM, but should be further explored.

Keywords: Gestational diabetes mellitus; Dietary supplementation; D-chiro-inositol

Introduction

Gestational diabetes mellitus (GDM) is defined as a condition of carbohydrate intolerance with onset or first recognition during the second or third trimester of pregnancy [1]. Incidence of GDM varies from 2% to 14% worldwide and is growing [2] and hyperglycaemia has been independently associated with a risk for mother, foetus and neonate, both in the short and long term [3,4]. Although GDM usually disappears after delivery, women who have been previously diagnosed with GDM are at a greater risk of developing gestational diabetes in subsequent pregnancies, and type 2 diabetes (T2DM) later in life [5,6].

GDM commonly develops when maternal glucose metabolism is unable to compensate for the progressive development of insulin resistance, mainly due to the increasing of diabetogenic placental hormones. Theoretically, since insulin resistance is the main culprit in its pathogenesis, insulin sensitizers would be the ideal treatment.

Inositol (INS), also known as cyclohexane-1,2,3,4,5,6-hexol, is a polyol which belongs to vitamin B complex, and exists under nine stereoisomeric forms depending on the spatial orientation of its six hydroxyl groups. Myo-inositol (MYO-INS) and D-chiro-inositol (DCI) are stereoisomers of inositol which have been shown to exert insulin-mimetic action and to lower postprandial glucose. In particular, DCI plays a key role in the insulin pathway, acting as insulin sensitizing through the enhancement of glucose peripheral tissue uptake and glycogen synthesis [7-11]. Thanks to these effects, they have been used for the treatment of insulin resistance states as polycystic ovary syndrome (PCOS), T2DM or GDM [12,13].

The purpose of this study was to evaluate the role of DCI in the metabolic control of women affected by GDM and to examine the impact on pregnancy and fetal outcome.

Materials and Methods

A prospective, randomized, open-label, two-arm, single-center, pilot study was designed and conducted on pregnant women with GDM attending the pregnancy outpatient clinic in the period of enrollment.

Diagnosis of GDM was obtained according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [14] criteria after the 24th week of pregnancy performing a 75 g Oral Glucose Tolerance Test (OGTT). Pregnant women with diagnosis of gestational diabetes before the 24th week of pregnancy were excluded.

Primary objective was the evaluation of the metabolic control in women enrolled, using blood glucose monitoring as primary endpoint.

Secondary endpoints were the impact of treatment on maternal insulin need, weight gain, obstetric complications, fetal growth parameters such as abdominal circumference (AC), head circumference (HC), biparietal diameter (BPD), femur length (FL), head to abdominal circumference ratio (HC/AC), humerus length (HL) and neonatal parameters such as birth weight and ponderal index (PI=weight/height x 100) at birth.

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For both groups a therapeutic educational program has been created for food choices and diet prescription. In order to maintain the overweight women above the ketonuria threshold, the caloric intake was fixed at 24 kcal/kg/die with 40% to 50% of carbohydrates. Patients were educated to self-monitoring of capillary blood glucose, to keep a diary about the glycemic parameters and about food intake.

Morning fasting and 1 hour postprandial blood glucose values registered on diaries were evaluated at baseline (T0) and every 3 weeks (T1, T2 and T3). Maternal weight was measured before pregnancy and during the last visit (between 38 and 40 weeks). Ultrasound monitoring was performed at 32 and 38 weeks of gestation to evaluate fetal growth parameters.

Insulin therapy has been started if glycaemia was over the normal range (92 mg/dL upon waking up, 140 mg/dL 1 hour after meal, confirmed at least in two ambulatorial visits, detected at a distance of a week) without discontinuing DCI (if used). During the subsequent visits in the group of patients undergoing insulin therapy the number of administration, the units and the type of insulin (long active or short active) were evaluated. Continuous data are presented by listing the average value, standard deviation (SD), median, first quartile (Q1) and third quartile (Q3), minimum (min) and maximum (max) values. Dichotomous or categorical variables are presented through absolute number (N) and the corresponding percentage.

Quantitative variables (e.g. age, weight, glycemic values, neonatal parameters) were compared between the two groups using the Student’s t-test for unpaired data or Mann Whitney’s non-parametric test. The Chi-squared test, or Fisher’s exact test when necessary, was used to evaluate possible associations between categorical variables.

To evaluate the association between the need for insulin and the treatment groups adjusted for the effect of age, a logistic regression model was performed. The results were expressed in Odds Ratio (OR) and its 95% confidence interval (95% CI).

A survival analysis was conducted to assess the association between insulin therapy and treatment group, taking into account the time without insulin therapy. The log rank test was used to determine any differences in the curves between the two groups.

A p value <0.05 was considered statistically significant. All analyses were done with STATA 14.1.

The study was approved by the Ethics Committee of San Pietro Hospital. All participants provided written informed consent, and the Ethics Committee approved the consent procedure.

Results

Between December 2013 and September 2015, 137 patients were enrolled and randomized to receive one tablet of 500 mg twice a day of DCI (n=67) or no treatment (n=70).

The baseline characteristics were similar in the two groups (Tables 1a and b). All women enrolled followed the same diet and none of them were smokers or physically active. In the control group, 46 patients had a body mass index (BMI) equal to or greater than 25 and 43 in the DCI group.

With regard to glycemic values (upon waking up, after breakfast, after lunch and after dinner) no significant differences were detected in the two groups at baseline (Table 1b). At T1, 47.8% of women in the DCI group had a good metabolic control compared to 42.9% in the control group; at T2 the percentage was higher in both groups, 62.9% in the control group and 62.7% in the group of treated patients; at T3 all patients in the DCI group had a good metabolic control compared to 95.7% in the control group (Table 2). In both groups, 42 patients had good metabolic control throughout the period of pregnancy (respectively 62.7% in the DCI group and 60% in the control group; \( p_{\text{Mann-Whitney}} = 0.747 \)). No statistically significant differences were revealed between the two groups of patients, except in the blood glucose measurements after breakfast, after lunch and after dinner at T3, in which patients in the treatment group showed lower values than those in the control group. In general, there was a reduction in blood glucose values from T1 to T3. Comparing the two groups, the reduction was not statistically significant, except for values after dinner: in particular, the median change in the control group was -7 mg/dL (25\(^{th}\), 75\(^{th}\) percentile=-16 mg/dL; 4 mg/dL) while the median change in the DCI group was -13 (25\(^{th}\), 75\(^{th}\) percentile=-20 mg/dL; -3 mg/dL; \( p_{\text{Mann-Whitney}} = 0.013 \)).

At the end of the study, it was observed that in the control group 65.7% (95% CI: 53.4% - 76.65%) did not need insulin while in the DCI group the percentage was 74.6% (95% CI: 62.5% - 84.5%). However, there was no statistically significant association between the type of treatment and the need for insulin therapy (\( p_{\text{adjOR DCI vs. control}} = 0.65, 95\% \text{ CI: 0.31 to 1.36; } p=0.249 \)).

The association remained not significant even adjusting data for age (adjOR DCI vs. control=0.65, 95% CI: 0.31 to 1.36; p=0.249).

Taking into account the time that women spent before starting the treatment groups adjusted for the effect of age, a logistic regression model was performed. The results were expressed in Odds Ratio (OR) and its 95% confidence interval (95% CI). The association remained not significant even adjusting data for age (adjOR DCI vs. control=0.65, 95% CI: 0.31 to 1.36; p=0.249).

Table 1(a): Variables at baseline (T0).

| Variables | Control Group N=70 | Chiroinositol N=67 | p-value |
|-----------|---------------------|--------------------|---------|
| BMI classes | | | | 0.655 |
| BMI_class_2 | 24 | 34.3 | 24 | 35.8 |
| BMI_class_3 | 33 | 47.1 | 27 | 40.3 |
| BMI_class_4 | 13 | 18.6 | 16 | 23.9 |
| Glycemia upon waking up | | | | 0.879 |
| ≤92 mg/dL | 43 | 61.4 | 42 | 62.7 |
| >92 mg/dL | 27 | 38.6 | 25 | 37.3 |
| Glycemia after breakfast | | | | 0.377 |
| ≤140 mg/dL | 52 | 74.3 | 54 | 80.6 |
| >140 mg/dL | 18 | 25.7 | 13 | 19.4 |
| Glycemia after lunch | | | | 0.999* |
| ≤ 140 mg/dL | 63 | 90.0 | 60 | 89.6 |
| >140 mg/dL | 7 | 10.0 | 7 | 10.4 |
| Glycemia after dinner | | | | 0.780* |
| ≤140 mg/dL | 62 | 88.6 | 61 | 91.0 |
| >140 mg/dL | 8 | 11.4 | 6 | 9.0 |

Table 1(b): Metabolic variables at baseline (T0).

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treatment, through an analysis of survival, it has been observed that in the control group the median “survival time” for insulin therapy was 41 weeks (25th percentile equal to 39 weeks), while in the treatment group it was not possible to determine the median value but only the 25th percentile equal to 40 weeks (Figure 1).

The number of insulin daily doses was 3 for patients in the control group and 2 for patients treated with insulin in the DCI group (pT-Test=0.026; Table 4).

Considering the maternal weight variation, patients in the control group at baseline had a median weight of 70 kg (25th to 75th percentile: 65 kg to 78 kg) and patients in the treatment group had a median weight of 72 kg (25th to 75th percentile: 65 kg to 84 kg; Table 5). At the end of the study there was an increase in weight in both groups, with a median variation of 11.5 kg (25th to 75th percentile: 8 kg to 15 kg) in the control group compared to 9 kg (25th to 75th percentile: 7 kg to 12 kg) in the DCI group. The difference between the two groups was statistically significant (pT-Test=0.048).

In both groups there are very similar percentages of women who had a spontaneous delivery (75.7% in the control group vs. 70.2% in the DCI group).

### Table 2: Variations in glycemic values after 3 weeks (T1) and 9 weeks (T3).

| Variables                  | N  | Mean  | SD   | Median | Q1  | Q3  | Min  | Max  | p         |
|---------------------------|----|-------|------|--------|-----|-----|------|------|-----------|
| Glycemia upon waking up T1|    |       |      |        |     |     |      |      |           |
| Control Group             | 70 | 11.7  | 2.9  | 11.5   | 7   | 15  | 5.0  | 15.0 | 0.687*    |
| Chiroinositol             | 67 | 11.8  | 2.9  | 11.3   | 8.5 | 14.5| 4.5  | 18.5 |           |
| Glycemia upon breakfast T3|    |       |      |        |     |     |      |      |           |
| Control Group             | 70 | 11.0  | 2.8  | 11.0   | 8.3 | 15  | 4.3  | 15.0 | 0.624*    |
| Chiroinositol             | 67 | 11.0  | 2.8  | 11.0   | 8.0 | 15  | 4.3  | 15.0 |           |
| Glycemia after lunch T1   |    |       |      |        |     |     |      |      |           |
| Control Group             | 70 | 11.7  | 2.8  | 11.5   | 8.0 | 15  | 4.3  | 15.0 | 0.596*    |
| Chiroinositol             | 67 | 11.7  | 2.8  | 11.5   | 8.0 | 15  | 4.3  | 15.0 |           |
| Glycemia after dinner T1  |    |       |      |        |     |     |      |      |           |
| Control Group             | 70 | 12.0  | 2.9  | 11.5   | 8.5 | 15  | 4.5  | 18.5 | 0.612*    |
| Chiroinositol             | 67 | 12.0  | 2.9  | 11.5   | 8.0 | 15  | 4.3  | 15.0 |           |

### Table 3: Number of patients treated with insulin and metabolic control between the two groups.

| Variables                  | Control Group N: 70 | Chiroinositol N: 67 |
|---------------------------|---------------------|---------------------|
| Insulin                   |                     |                     |
| No                        | 46                  | 65.7                |
| Yes                       | 24                  | 34.3                |
| p                         | 0.255*              |                     |
| Metabolic Control T1      |                     |                     |
| No                        | 40                  | 57.1                |
| Yes                       | 30                  | 42.9                |
| p                         | 0.564               |                     |
| Metabolic Control T2      |                     |                     |
| No                        | 26                  | 37.1                |
| Yes                       | 44                  | 62.9                |
| p                         | 0.984               |                     |
| Metabolic Control T3      |                     |                     |
| No                        | 3                   | 4.3                 |
| Yes                       | 67                  | 95.7                |
| p                         | 0.087               |                     |

*Chi-squared test
Table 6: Fetal growth parameters (in mm) and variations between week 32 and 38.

| Variables | N  | Mean  | SD   | Median | Q1   | Q3   | Min  | Max  | p          |
|-----------|----|-------|------|--------|------|------|------|------|------------|
| Control Group | 70 | 84.2  | 3.4  | 84.0   | 82.0 | 87.0 | 77.0 | 90.0 | 0.071*     |
| Chiroinositol | 67 | 82.7  | 4.4  | 83.0   | 81.0 | 86.0 | 68.0 | 92.0 |            |
| **BPD week 32** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 92.8  | 3.0  | 92.0   | 91.0 | 94.0 | 83.0 | 100.0| 0.112*     |
| Chiroinositol | 67 | 92.0  | 2.8  | 92.0   | 91.0 | 94.0 | 84.0 | 98.0 |            |
| **BPD variation** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 8.7   | 3.7  | 8.0    | 6.0  | 11.0 | 2.0  | 19.0 | 0.416*     |
| Chiroinositol | 67 | 9.2   | 4.8  | 9.0    | 6.0  | 12.0 | -4.0 | 21.0 |            |
| **AC week 32** |     |       |      |        |      |      |      |      | 0.138*     |
| Control Group | 70 | 291.9 | 15.4 | 290.0  | 282.0| 304.0| 262.0| 322.0|            |
| Chiroinositol | 67 | 286.8 | 17.4 | 286.0  | 279.0| 297.0| 226.0| 319.0|            |
| **AC variation** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 15.1  | 3.8  | 14.5   | 14.0 | 16.0 | 10.0 | 20.0 | 0.613*     |
| Chiroinositol | 67 | 15.0  | 3.8  | 14.5   | 14.0 | 16.0 | 10.0 | 20.0 |            |
| **HC week 32** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 336.7 | 12.4 | 333.0  | 325.0| 335.0| 280.0| 368.0|            |
| Chiroinositol | 67 | 329.8 | 12.4 | 333.0  | 325.0| 335.0| 280.0| 368.0|            |
| **HC variation** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 4.8   | 2.0  | 4.5    | 4.0  | 5.0  | 3.0  | 6.0  | 0.374*     |
| Chiroinositol | 67 | 4.7   | 1.9  | 4.5    | 4.0  | 5.0  | 3.0  | 6.0  |            |
| **HL week 32** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 86.0  | 1.6  | 86.0   | 84.0 | 88.0 | 77.0 | 92.0 | 0.793*     |
| Chiroinositol | 67 | 84.6  | 1.8  | 84.0   | 82.0 | 86.0 | 75.0 | 92.0 |            |
| **HL variation** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 14.7  | 1.2  | 14.5   | 14.0 | 15.0 | 11.0 | 17.0 | 0.678*     |
| Chiroinositol | 67 | 14.7  | 1.2  | 14.5   | 14.0 | 15.0 | 11.0 | 17.0 |            |
| **FL week 32** |     |       |      |        |      |      |      |      | 0.937*     |
| Control Group | 69 | 62.6  | 4.3  | 63.0   | 61.0 | 65.0 | 36.0 | 71.0 |            |
| Chiroinositol | 67 | 62.3  | 5.4  | 63.0   | 60.0 | 65.0 | 32.0 | 70.0 |            |
| **FL variation** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 1.7   | 1.0  | 1.7    | 1.0  | 2.0  | 0.0  | 4.0  | 0.719*     |
| Chiroinositol | 67 | 1.7   | 1.0  | 1.7    | 1.0  | 2.0  | 0.0  | 4.0  |            |
| **AC week 32** |     |       |      |        |      |      |      |      |            |
| Control Group | 70 | 11.5  | 0.7  | 12.0   | 11.0 | 12.0 | 9.0  | 15.0 | 0.357*     |
| Chiroinositol | 67 | 11.5  | 0.7  | 12.0   | 11.0 | 12.0 | 9.0  | 15.0 |            |
| **AC variation** |     |       |      |        |      |      |      |      | 0.176*     |
| Control Group | 67 | 1.0   | 0.0  | 1.0    | 1.0  | 1.0  | 0.9  | 1.1  | 0.176*     |
| Chiroinositol | 65 | 1.0   | 0.0  | 1.0    | 1.0  | 1.0  | 0.9  | 1.1  |            |
| **HC/AC variation** |     |       |      |        |      |      |      |      | 0.896*     |
| Control Group | 67 | -0.0  | 0.0  | -0.0   | -0.1 | -0.0 | -0.2 | 0.1  |            |
| Chiroinositol | 65 | -0.0  | 0.0  | -0.0   | -0.1 | -0.0 | -0.2 | 0.1  |            |

Considering the fetal growth parameters there were no significant differences between the two groups, except in the AC and HC values observed at the end of the study (Table 6). Children born from patients in the control group had a median AC of 339 mm at week 38 (25th to 75th percentile: 328-345 mm) while children born from patients in the treatment group had a median AC of 332 mm (25th to 75th percentile: 326-332 mm). The median value of HC of 333 mm (25th to 75th percentile: 328-345 mm) while children born from patients in the treatment group had a median HC of 332 mm (25th to 75th percentile: 330-335 mm; pMann-Whitney=0.001); the median value of HC in the control group was 338.5 mm at week 38 (25th to 75th percentile: 328-345 mm) while children born from patients in the treatment group had a median value of HC of 333 mm (25th to 75th percentile: 328-345 mm; pMann-Whitney=0.012). Between the first and the second measurement we observed an increase in all the fetal growth parameters but differences between the two groups were no statistically significant.

We did not find any significant difference between two groups about neonatal birth-weight (3.360 kg in the DCI group vs. 3.262 kg in the control group; p=0.067) but the neonatal PI was significantly lower in the DCI group (median DCI group=338.5 mm at week 38 (25th to 75th percentile: 328-345 mm) vs. 325-335 mm pMann-Whitney=0.001); the median value of HC of the control group was 338.5 mm at week 38 (25th to 75th percentile: 328-345 mm) while children born from patients in the control group had a median AC of 339 mm at week 38 (25th to 75th percentile: 328-345 mm) vs. 330-335 mm. Between the first and the second measurement we observed an increase in all the fetal growth parameters but differences between the two groups were no statistically significant.

The ALI of the control group was 338.5 mm at week 38 (25th to 75th percentile: 328-345 mm) while children born from patients in the treatment group had a median AC of 332 mm (25th to 75th percentile: 326-332 mm). The median value of HC of 333 mm (25th to 75th percentile: 328-345 mm) while children born from patients in the treatment group had a median value of HC of 333 mm (25th to 75th percentile: 328-345 mm; pMann-Whitney=0.001). Between the first and the second measurement we observed an increase in all the fetal growth parameters but differences between the two groups were no statistically significant.

Statistical Analysis

Subgroup analysis: BMI ≥ 25

Analyzing data related to the subgroup of patients with a BMI ≥ 25, none of the variables at baseline were different between the two groups (Tables 8a and b), except the median value of blood glucose after lunch which was lower in the DCI group (median DCI group=119 gr/dL vs.
The association remained not significant even adjusting data for age (adjOR DCI vs. control=0.51; 95% CI: 0.20 to 1.31; p=0.163).

The number of insulin daily doses was 3 for patients in the control group and 2 for patients treated with insulin in the DCI group (pT Test=0.019; Table 9). Taking into account the time that women spent before starting the treatment, through an analysis of survival, a difference between the two groups was not observed (Log Rank test p =0.323; Figure 2).

Patients in the DCI group weighed more than the patients in the control group both pre- and post-pregnancy, but the difference was not statistically significant. The weight gain in women in the control group was greater than in women in the DCI group, but the difference was not statistically significant.

Almost all patients in the control group did not have neonatal complications (97.8%), and the same was in DCI group (97.1%; p=0.659). In both groups, there were very similar percentages of women who had a spontaneous birth (control group 71.7% vs. DCI group 67.4%; p=0.035).

Considering the fetal growth parameters, there were no significant differences between the two groups, except in the AC2 and HC2 values (p=0.323; Figure 2). Almost all patients in the control group did not have neonatal complications (97.8%), and the same was in DCI group (97.1%; p=0.659). In both groups, there were very similar percentages of women who had a spontaneous birth (control group 71.7% vs. DCI group 67.4%; p=0.035).

**Discussion**

During pregnancy, mother's metabolism undergoes extensive alteration to support fetal development and growth. Insulin resistance becomes particularly severe during the second half of pregnancy, when insulin secretion increases by 200% to 250% to maintain euglycemia. If insufficient insulin is secreted, hyperglycemia and GDM develop. The prevalence of GDM has rapidly increased in recent years, in parallel with the obesity, cardiovascular disease, and T2DM epidemics [2]. GDM is a major concern because of the various short- and long-term health consequences it poses for both the mother and the child. Women with GDM are more likely to experience further pregnancy complications, such as pre-eclampsia [15], and to develop T2DM later in life [3,6]. Babies born from pregnancies complicated by GDM are more likely to be large for gestational age (LGA), and to be affected by obesity and T2DM in the future [4]. The adverse programming of beta cells may also be transmitted to subsequent generations.

DCI is a carbohydrate consumed and produced within the body and is a precursor for various phosphorylated derivatives, such as phosphatidylinositol trisphosphate (PIP)-a downstream effector of insulin signalling. DCI therefore acts as an insulin-sensitizing agent, and has shown promise as a treatment for diseases with glucose intolerance, such as polycystic ovarian syndrome (PCOS) and T2DM [8-11].

Our results are encouraging considering the statistically significant differences between the two groups observed in the blood sugar level measurements after lunch and after dinner at the T3. Patients in the treatment group had lower values compared to the control group in all three measurements after three weeks of treatment with DCI. These data were also confirmed when we considered pregnant women with BMI ≥ 25. Moreover, DCI group received a number of doses of insulin significantly lower compared to the control group.

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**Table 9:** Number of doses of insulin in the sub-sample of patients with BMI ≥ 25.

| Variables | Control Group N: 46 | Chiroinositol N: 43 | p-value |
|-----------|---------------------|--------------------|---------|
| No        | N | % | N | % | p               |
| Previous pregnancies | 32 | 68.3 | 25 | 58.3 | 0.262 |
| No       | 14 | 59.1 | 18 | 51.4 | 0.663 |
| Yes      | 17 | 40.9 | 14 | 48.6 | 0.139* |

*Fisher Exact test

**Table 8(b):** Metabolic variables at baseline (T0) in the sub sample of patients with BMI ≥ 25.

**Table 9:** Number of doses of insulin in the sub-sample of patients with BMI ≥25.
Table 10: Fetal growth parameters (in mm) and variations between week 32 and 38 in the sub sample of patients with BMI ≥ 25.

| Variables        | N  | Mean  | SD   | Median | Q1  | Q3  | Min  | Max  | p   |
|------------------|----|-------|------|--------|-----|-----|------|------|-----|
|                  |    |       |      |        |     |     |      |      |     |
| BPD week 32      | 4   | 92.7  | 3.0  | 92.0   | 83.0| 94.0| 94.0 | 93.0 | 0.190|
| Chiroinositol    | 43  | 92.3  | 2.8  | 92.0   | 84.0| 94.0| 94.0 | 94.0 | 0.666|
| BPD week 38      | 46  | 8.5   | 3.2  | 8.0    | 7.0 | 10.0| 2.0  | 19.0 | 0.336|
| Chiroinositol    | 43  | 9.2   | 4.8  | 8.0    | 7.0 | 12.0| -4.0 | 21.0 | 0.310|
| AC week 32       | 46  | 293.4 | 15.1 | 283.0  | 304.0| 263.0| 322.0| 0.210|
| Chiroinositol    | 43  | 288.5 | 18.4 | 280.0  | 304.0| 226.0| 319.0| 0.190|
| AC week 38       | 46  | 339.3 | 13.9 | 340.5  | 329.0| 348.0| 313.0| 0.002|
| Chiroinositol    | 43  | 330.0 | 13.5 | 333.0  | 327.0| 335.0| 280.0| 0.366|
| AC variation     | 46  | 45.9  | 19.7 | 44.5   | 35.0| 58.0| 9.0  | 102.0| 0.360|
| Chiroinositol    | 43  | 41.5  | 20.4 | 45.0   | 30.0| 54.0| -5.0 | 107.0| 0.863|
| HC week 32       | 46  | 303.5 | 9.8  | 307.5  | 300.0| 212.0| 282.0| 0.035|
| Chiroinositol    | 43  | 302.4 | 15.1 | 306.0  | 300.0| 212.0| 254.0| 0.630|
| HC week 38       | 46  | 337.5 | 14.4 | 340.5  | 329.0| 348.0| 300.0| 0.002|
| Chiroinositol    | 43  | 333.5 | 10.2 | 336.0  | 331.0| 338.0| 300.0| 0.690|
| HC variation     | 46  | 34.0  | 15.0 | 33.5   | 23.0| 44.0| -1.0 | 84.0 | 0.257|
| Chiroinositol    | 43  | 31.1  | 14.0 | 31.0   | 22.0| 35.0| -3.0 | 70.0 | 0.444|
| FL week 32       | 45  | 62.9  | 2.7  | 63.0   | 61.0| 65.0| 54.0 | 68.0 | 0.860|
| Chiroinositol    | 43  | 62.6  | 3.9  | 63.0   | 60.0| 65.0| 53.0 | 70.0 | 0.718|
| FL week 38       | 46  | 71.3  | 1.5  | 71.0   | 70.0| 72.0| 69.0 | 75.0 | 0.444|
| Chiroinositol    | 43  | 69.7  | 9.5  | 72.0   | 70.0| 73.0| 12.0 | 75.0 | 0.860|
| FL variation     | 45  | 8.5   | 2.8  | 9.0    | 7.0 | 10.0| 3.0  | 18.0 | 0.785|
| Chiroinositol    | 43  | 7.1   | 9.7  | 8.0    | 6.0 | 10.0| -51.0| 18.0 | 0.860|
| HL week 32       | 8   | 53.6  | 11.5 | 57.0   | 54.5| 59.0| 26.0 | 62.0 | 0.785|
| Chiroinositol    | 12  | 56.2  | 3.3  | 56.5   | 55.0| 58.0| 48.0 | 61.0 | 0.780|
| HL week 38       | 5   | 62.4  | 1.3  | 63.0   | 61.0| 63.0| 61.0 | 64.0 | 0.480|
| Chiroinositol    | 6   | 62.0  | 2.4  | 62.0   | 60.0| 64.0| 59.0 | 65.0 | 0.860|
| HL variation     | 1   | 4.0   | 4.0  | 4.0    | 4.0 | 4.0 | 4.0  | 4.0  | 0.117|
| Chiroinositol    | 4   | 5.8   | 2.5  | 5.5    | 4.0 | 7.5 | 3.0  | 9.0  | 0.117|
| HC/AC week 32    | 43  | 1.04  | 0.04 | 1.02   | 1.0 | 1.07| 0.97 | 1.16 | 0.030|
| Chiroinositol    | 42  | 1.05  | 0.05 | 1.16   | 1.0 | 1.08| 0.95 | 1.17 | 0.030|

In conclusion, dietary supplementation with DCI during pregnancy may be an appealing strategy for treating GDM, but should first be further explored.

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