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Myo-inositol may prevent gestational diabetes in PCOS women. Preliminary data.

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TITLE: **Myo-inositol may prevent gestational diabetes in PCOS women. Preliminary data.**

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ABSTRACT

AIMS: To evaluate retrospectively the prevalence of gestational diabetes (GD) in pregnancies obtained with myo-inositol administration in PCOS women.

METHODS: A total of 98 pregnancies in PCOS women obtained in a three-year period, either with myo-inositol (n. 54), or with metformin (n. 44) were considered. While myo-inositol was assumed through the whole pregnancy, the group of women treated with metformin stopped the drug assumption after pregnancy diagnosis, and was considered as a control group. After having eliminated cases of miscarriages and twin pregnancies, a definitive number of 46 women in the myo-inositol group and 37 in the control group was taken in account to be retrospectively evaluated. The primary outcome measure was GD occurrence in both groups; whereas secondary outcome measures were pregnancy outcomes: hypertensive disorders, pre-term birth, macrosomia and caesarean section occurrence.

RESULTS: Prevalence of GD in the myo-inositol group was 17.4% versus 54% in the control group, with a highly significant difference also after adjusting for covariates. Consequently, in the control group the risk of GD occurrence was more than double compared to the myo-inositol group, with an OR 2.4 (CI 95% , 1.3- 4.4). There was no difference between the groups in relation to secondary outcome measures.

CONCLUSIONS: This study suggests a possible effect of myo-inositol in the primary prevention of gestational diabetes in PCOS women.

KEY WORDS: PCOS, myo-inositol, gestational diabetes

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a disorder characterized by polycystic ovaries at ultrasound evaluation, oligomenorrhoea and hyperandrogenism, affecting approximately 5 to 17% of Caucasian women in fertile age (1). Menstrual irregularities such as oligo-amenorrhea are frequently the effects of chronic anovulation, which is one of the reasons of female infertility. The pathogenesis of PCOS is unknown although insulin resistance, which affects about 70% of the PCOS patients, seems to be the main cause (2). Consequently, insulin sensitizing substances have been proposed as putative treatments for hyperinsulinemia-induced ovarian dysfunction in order to restore ovulation and regular menstrual cycles (3). All women with preconception hyperinsulinaemia who become pregnant had impairment of glucose metabolism during pregnancy (4), because pregnancy increases requirements for insulin secretion while increasing insulin resistance. In particular, PCOS patients were reported to be at higher risk of developing carbohydrate abnormalities during pregnancy than a normal population of similar reproductive age; it has been reported that about 30% of women affected by PCOS develop gestational diabetes (GD) (5).

Inositol was described as a second messenger system that may exert an insulin-like effect on metabolic enzymes (6); for this action, inositol has been reported to improve insulin sensitivity and ovulatory function in young women affected by PCOS, both in the isoform D-chiro-inositol (7), and in the isoform myo-inositol (8). Our group has recently demonstrated that also in GD pregnancies, myo-inositol may improve markers of insulin resistance (9). In this study, we retrospectively evaluated the outcome of pregnancies obtained after myo-inositol administration in PCOS women, highlighting the prevalence of GD in these high risk pregnant women.

METHODS

We considered retrospectively 98 pregnancies obtained in the Centre of Reproductive Medicine of Messina (Italy) University Hospital, on a three-year period (01/01/2007 to 31/12/2009) from anovulatory and hyperinsulinemic PCOS non diabetic women treated with myo-inositol (n. 54): at a dosage of 4 g/die plus folic acid (400 mcg/die) *(inofolic, LO.LI Pharma, Italy)*, or with metformin (n. 44): at a dosage of 1.5 mg/die plus folic acid (400 mcg/die). Myo-inositol treatment was begun before pregnancy and then was continued throughout the whole pregnancy until delivery; whereas metformin treatment was continued until a positive pregnancy test occurred and then was stopped; so we considered this latter group as the control group. There were six miscarriages in the myo-inositol group and 5 in the metformin group. Furthermore, 2 twin pregnancies occurred in both groups and were not taken into account, leaving 46 as the final number of single pregnancies studied in the myo-inositol group and 37 in the control group. At the beginning of treatment, fast glucose and insulin were assessed and insulin resistance was calculated by Homeostasis Assessment Ratio (HOMA-R).The length of treatment until pregnancy was from 3 to 9 months, with a mean of 6 months, in the myo-inositol group; and it was from 2 to 6 months, with a mean of 4 months, in the metformin group. At 24-28 weeks gestation, all the women studied performed a Glucose Challenge Test (GCT) (10) and, if positive, a complete 100 g oral glucose tolerance test (OGTT) for the diagnosis of GD was done. We considered as a primary outcome measure the prevalence of GD in both groups; secondary outcome measures were: gestational hypertension (GH), pre-term birth (< 37 weeks gestation), macrosomia (foetal weight > 4.000 g) and caesarean section (CS) occurrence.

Statistical analysis:

Data are expressed as means +/- SD or n (%). To compare the two groups, the unpaired t test (parametric distributions) or the Mann-Whitney U test (nonparametric distributions) was used. Categorical variables were compared using the X^2 test. Prevalence of GDM was considered as a dichotomous variable and reported as odds ratio (OR) with 95% CIs. Statistical analyses were

performed using SPSS version 17.0 software (SPSS, Inc. Chicago, IL). P values <0.05 were considered to be statistically significant.

RESULTS

Between the groups, there were no statistical differences in percentage of diabetic parents, body mass index (BMI), fast glucose, fast insulin and HOMA at the beginning of the treatment, but also no difference in age, percentage of nulliparous, gestational age at delivery and birth weight (tab 1). Prevalence of GD in the myo-inositol group was 17.4% (8 cases out of 46), of whom 6 needed insulin and the other two were treated only by diet. In the control group, in 20 women out of 37 (54%) GD occurred, and only in 2 cases insulin was needed. The difference of GD occurrence comparing the groups was highly significant (p=0.001), also after adjustment for covariates (age, BMI, percentage of nulliparous, diabetic parents). Furthermore, the prevalence of gestational diabetes occurrence was more than double in the control group: OR 2.4, (CI 95% , 1.3- 4.4) compared to the myo-inositol group; and no side effect was reported by the patients during myo-inositol treatment. Differences between the groups in relation of secondary outcomes were not significant (table 2).

DISCUSSION

Even if retrospectively and in a small series, this is the first report about the effect of myo-inositol on GD occurrence in PCOS infertile women. Gestational diabetes prevalence in PCOS women ranges from 16.9% in Vanki E et al (11) and 20% in Katthab S et al (12) to 30% in Glueck CG et al (13), until 42% in Veltman-Verhulst SM et al (14). These studies were different both for the number of the women studied, and for the methods used to diagnose GD, which might be responsible for the high differences in the outcomes. In this study the prevalence of GD in the PCOS non treated group was the highest among the trials reported in literature: 54%, probably because it was only a small group. However, myo-inositol supplementation, acting as an insulin sensitizing drug, was able to reduce the risk of GD; indeed, in the control group there was more than a double risk of being affected by GD compared to the PCOS women treated with myo-inositol. This supplementation was well tolerated through the whole pregnancy, with no harm for the foetus and the mother reported. This data about safety was not surprising because we had already used myo-inositol in GD women for about 8 weeks, without any side effects, obtaining an improvement of insulin resistance markers (9). Also metformin was used throughout the pregnancy in PCOS women, but with conflicting results; someone found a significant difference compared to placebo in GD occurrence: 7% vs 30% in the Glueck et al study (13), in which metformin was given with a hypocaloric diet; or in the Khattab S et al (12) study, in which a significant difference in GD occurrence was highlighted between the metformin group (4%) and the control group (20%). Instead in Vanki et al study (11), GD prevalence in women treated with metformin (17.6%) was similar to the control group (16.9%). In this study, we also considered some secondary outcome measures, such as hypertensive disorders, pre-term birth, macrosomia and CS occurrence, but no differences were highlighted between cases and controls. Similar results were obtained in a larger multicenter study in which metformin was used (11); whereas in the Katthab et al study (12) a significantly reduced prevalence of preeclampsia was shown. In this study, the limited number of the study population, couldn't

really give definitive data about clinical outcome measures in the group treated. Larger studies are needed to confirm this preliminary data about the possible effect of myo-inositol in the primary prevention of gestational diabetes in PCOS women.

Declaration of Competing Interests: Nothing to declare

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Table 1: Clinical characteristics of the study groups

	Control group (n. 37)	Myo-inositolo group (n. 46)	p
Age (years)	30.6 ± 4.2	29.2 ± 3.8	0.12
Body Mass Index	24.7 ± 3.9	26.2 ± 5.8	0.17
Nulliparous (%)	89.2	91.3	0.91
Fast glucose (mg/dl)	87.7 ± 8.1	86.9 ± 7.7	0.65
Fast insulin (µU/ml)	12.3 ± 5.5	9.8 ± 10.5	0.19
HOMA-IR	2.4 ± 1.1	1.9 ± 2.1	0.21
Parents with diabetes (%)	42.4%	28.2%	0.09
G. A. at delivery (w)	39.4 ± 1.1	38.8 ± 1.7	0.8
Birth weight (g)	3231±350	3089±424	0.1

G.A.= gestational age; w = weeks; g = grams

Table 2: Secondary outcomes measures in the study groups

	Control group (n. 37)	myo-inositolo group (n. 46)	p
Macrosomia	1 (2.7%)	3 (6.5%)	0.7
Hypertensive disorders	3 (8.1%)	3 (6.5%)	0.8
Pre-tem delivery	2 (5.4%)	2 (4.3%)	0.7
Cesarean section	25 (67%)	23 (50%)	0.07