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Prevention of gestational diabetes mellitus: a minireview

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ABSTRACT

Gestational Diabetes Mellitus (GDM) is associated with adverse maternal, foetal and neonatal outcomes and is increasing worldwide probably for the increasing rate of overweight and obesity, being the latter a major risk factor. To these women with well recognized risk factors some interventions to prevent GDM should be offered. In this way, possible interventions are diet and/or exercise, metformin and myo-inositol. Diet and exercise are considered first line for the prevention of GDM, but in particular kind of pregnant women like obese, who usually follow unhealthy lifestyles, this type of intervention may fail. Metformin is usually used for the treatment of Diabetes Mellitus type 2 and recently also for hyper-insulinemic infertile women affected by polycystic ovary syndrome with the aim to restore ovarian cycle and ovulation. In these women, metformin was given off-label throughout pregnancy, but in prospective, randomized trials, especially when obese women are involved, metformin failed to prevent GDM. On the other hand, a supplement, myo-inositol demonstrated to reduce GDM rate when it was given since first trimester. This review analyses the effect of these three interventions for preventing GDM with the help of the most recent literature.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance that occurs for the first time or is first detected during pregnancy but does not fulfil the criteria of overt diabetes [1]. GDM is associated with adverse maternal, obstetrical, and neonatal outcomes [2]. In particular, women with GDM are more frequently affected by hypertensive syndromes and increased rate of caesarean section; furthermore, a future development of diabetes mellitus type 2 may occur. Foetuses of women with GDM are frequently large for gestational age with a higher rate of shoulder dystocia. In the newborns, hyperglycaemia may be frequent and sometimes serious, and in the childhood an increased metabolic risk has been shown, such as obesity and higher blood pressure [3]. Prevalence of GDM is increasing worldwide, principally for the increasing rate of overweight and obese pregnant women; furthermore, it may depend on different methods of diagnosis too. However, a recent meta-analysis [4] evidenced a GDM prevalence of about 11% in Europe and the same rate was in Italy too. Other risk factors are family history for diabetes

type 2, ethnicity, and advanced maternal age. In these recognized women at high risk for GDM, adequate interventions may prevent an unhealthy lifestyle like hypercaloric diet, inactivity, and excessive gestational weight gain. Among interventions for preventing GDM, at least three are considered of possible benefit: changes in lifestyle like diet and exercise, myo-inositol, and metformin, even if further high-quality studies are needed to make more robust data until now achieved [5].

DIET AND/OR EXERCISE

In a recent meta-analysis, comparing with standard care, a 23% reduction in the risk of GDM was shown as overall effect of intervention like only diet, or only exercise or mixed, showing no significant difference between these 3 types of interventions [6]. This study demonstrated that one of the most important variable that may heavily influence GDM diagnosis was the excessive weight gain through pregnancy in accordance with Institute of Medicine guidelines [7]. Furthermore, it was shown that the preventive effect of the interventions was more successful when the baseline risk of GDM was higher, like in the obese women [6], and that it was maximum when the intervention began early in pregnancy; in fact, it has been shown that pre-pregnancy physical activity may reduce GDM rate of 55% [8]. Aerobic exercise should go on for a minimum of 15 minutes, at least 3 times a week and should be increased during the second trimester up to a maximum of 30 minutes, 4 times to week [9]. A limitation of these type of GDM prevention was the adherence to the intervention, which is usually poor as reported by and Italian study [10]. It's very difficult for an obese woman with an unhealthy lifestyle to change it during pregnancy, thus the compliance of these high-risk women for these types of interventions (diet and/or exercise) is often poor. This is why a lot of them prefer assuming drug or supplement than sacrifice themselves with strict diet or deep changes in their lifestyle.

METFORMIN

Metformin is a biguanide derivative with insulin sensitizer effects. It's the most common oral drug used for the treatment of Diabetes Mellitus (DM). Metformin reduces plasma insulin concentration improving peripheral glucose uptake and reducing glucose production by the liver (gluconeogenesis). First use of metformin in non-diabetic subjects was for infertile women affected by Polycystic Ovary Syndrome (PCOS), who are very often hyperinsulinemic and this may disturb ovarian cycle preventing ovulation. Thus, metformin is currently used to improve ovulation rate in infertile women with PCOS, with beneficial effects compared to placebo [11]. Since infertile hyperinsulinemic pregnant women with PCOS were at high risk for developing GDM and other adverse pregnancy outcomes, such as miscarriages or hypertensive syndromes, researchers were encouraged to continue metformin treatment throughout pregnancy although it was off label. Some prospective cohort studies [12, 13] demonstrated a significant reduction of GDM when metformin was given from the first trimester of pregnancy. But the first randomized, double blind, controlled study didn't confirm a beneficial effect of metformin in preventing GDM [14]. Other 2 large randomized, controlled studies carried out with obese women, with a dosage of 3 g per day, failed to demonstrate a reduced rate of GDM compared to placebo [15, 16]. Furthermore, a recent Cochrane Review confirms that the use of metformin didn't prevent GDM [5]. Furthermore, gastrointestinal side effects are common when metformin is used determining sometimes a reduction of daily dosage [16]. Safety for the foetus is still questionable even if no significant differences were reported between treated and not treated women in the two large recent studies regarding foetal and neonatal outcomes [15, 16]. A follow-up study with these children at 4-7 years old is still ongoing.

MYO-INOSITOL

Myo-inositol (MI) is a polyol, and it is the most abundant of the nine isomeric forms of inositol, a ubiquitous substance in nature. MI is abundant in a lot of food like fruits and vegetables, but also in meat. Human body may produce MI from D-glucose, especially in the kidney [17]. An epimerase may convert MI in another inositol isomer, D-chiro-inositol (DCI); the conversion rate of MI to DCI in muscle and liver is almost 9% [18]. Both are contained in inositol phosphoglycans, which act as insulin mediators [19]. In particular, MI promotes glucose uptake in tissues that have high glucose utilization such as brain, heart and ovary [20], whereas DCI promotes glycogen synthesis in tissues specialized in glycogen storage, such as liver, muscle and fat [21]. As matter

of fact, MI may reduce circulating insulin with beneficial effects on Polycystic Ovary syndrome (PCOS) in which hyperinsulinemia affects ovarian cycle provoking anovulation and infertility. PCOS was the syndrome in which MI was firstly used, obtaining normal cycles and pregnancies in infertile women with amenorrhoea and anovulation [22], and recently a reduction of miscarriages too [23]. In our Unit, women affected by PCOS were treated with MI until they became pregnant, but also during whole the pregnancy [24]. Our first study was a retrospective one carried out on the charts of PCOS women treated with MI, with the aim to find out which was the GDM rate [24]. Although it was a limited number of women, the difference was statistically significant comparing GDM rate in PCOS women treated with MI (17%) and a control not treated PCOS group (54%) [24]. This first study encouraged us to perform prospective studies in which MI might be used for the prevention of GDM. Thus, we began three prospective, randomized, controlled study involving women with 3 different risk factors for GDM: a family history with DM type 2 [25]; obesity [26] and overweight women [27]. The rate of GDM in the control group of each study was obviously different, being 15%, 27% and 33%, respectively, depending on the severity of the risk factor. On the other hand, in the treated group the reduction of GDM diagnosis rate was highly significant: 6%, 11% and 14%, respectively. Interestingly, the rate of reduction of GDM diagnosis was the same, about 2/3 in the group treated with MI (4 g/day). Furthermore, in the study carried out with the obese women a reduction in insulin resistance in the group treated with MI was demonstrated [26]. A similar study [28], in which a lower dosage (1.2 g/die) of MI was used, failed to show the decrease of GDM rate in women treated with MI, suggesting that the successful result of MI is dose dependent. However, different meta-analysis demonstrated that MI may reduce GDM rate with a significant difference between groups [5, 29]. In a secondary analysis [30], databases of the 3 studies were considered all together with the aim of exploring whether MI was effective also in improving clinical outcomes of those women. Total number of women enrolled in the three studies was 660, which is underpowered in regard to clinical outcomes like hypertensive syndromes or preterm birth for which the number should be double. However, some significant statistically differences were highlighted in this secondary analysis [30]. In particular, preterm birth and rate of macrosomic and large for gestational age foetuses were significantly decreased in the group treated with MI. A very recent experimental study [31] could support inositol use for the prevention of GDM; the authors demonstrated that placental inositol content was 17% lower in women with GDM compared to controls. Fasting glycemia was associated with a reduced placental myo-inositol synthesis and with a reduced expression of inositol transporters. Furthermore, low placental inositol correlated positively with accelerated foetal growth [31]. Another important issue is the safety profile of MI and 2 recent meta-analysis [5, 29] reported no maternal adverse events and no congenital malformations in newborns. On the contrary, it's remarkable that MI has been shown to be effective in the prevention of neural tube defects [32] Furthermore, American "Food and Drug Administration" includes MI in the list of compound considered generally safe [33].

CONLUSIONS

In conclusion, lifestyle changes should be the first line of intervention for GDM prevention, but difference with no intervention is still not so clear, probably for a poor compliance of the women, in particular for overweight and obese. Metformin, the most used in DM treatment, is not so effective in GDM and women complain several side effects. MI seems to be effective and safe with a good compliance in pregnant women: it could be a promising supplement for GDM prevention.

COMPLIANCE WITH ETHICAL STANDARDS

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R.D'A entirely contributed to this work.

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Study registration

N/A.

Disclosure of interests

The author declares that he has no conflict of interests.

Ethical approval

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