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Are Novel Lifestyle Approaches to Management of Type 2 Diabetes Applicable to Prevention and Treatment of Women with Gestational Diabetes Mellitus?

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ABSTRACT

Background: Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance first recognized in pregnancy. GDM is associated with maternal and fetal adverse outcomes. Dietary approaches, including energy restriction, have the potential to prevent and treat GDM. The aim of the two systematic reviews is to evaluate the effect and safety of energy-restricted dietary approaches on both prevention and management of GDM.

Methods: The Medline database was searched for relevant articles and reference lists of retrieved studies. Randomized controlled trials, clinical trials and observational studies related to energy-restricted diets were included in the two systematic reviews.

Results: Eight RCTs assessing the effect and safety of energy-restricted intervention compared to non-energy-restricted intervention on GDM prevention were included in the first systematic review (1792 women and their babies). Only two were found to significantly reduce GDM incidence, but all were found to reduce gestational weight gain (GWG). No difference on maternal and fetal adverse outcomes was reported. Three RCTs assessing the effect and safety of energy-restricted intervention compared to non-energy-restricted intervention on GDM management were included in the second systematic review (437 women and their babies). Furthermore, one clinical trial and one observational study related to energy restriction were also added. Three studies reported improved glycemic control in women with GDM receiving energy-restricted diet, but without increasing the risk of adverse outcomes.

Conclusion: The results indicate that there may be some benefits of energy restriction on reducing GWG on women without GDM and improving glycemic control in women with GDM, without increasing the risk of adverse maternal and fetal outcomes.

KEYWORDS

Gestational Diabetes Mellitus, Type 2 Diabetes, Women, Glucose, Insulin

ABBREVIATIONS

ADA	:	American Diabetes Association
BMI	:	Body Mass Index
CHO	:	Carbohydrates
EGWG	:	Excessive Gestational Weight Gain
FIWC	:	Fifth international Workshop Conference
GAD	:	Glutamic Acid Decarboxylase
GDM	:	Gestational Diabetes Mellitus

GI	:	Glycemic Index
GWG	:	Gestational Weight Gain
HAPO	:	Hyperglycemia and Adverse Pregnancy Outcomes
IAA	:	Insulin Auto Antibodies
IADPSG	:	International Association of Diabetes and Pregnancy Study Group
IL-6	:	Interleukin 6
IOM	:	Institute of Medicine
LGA	:	Large for Gestational Age
MNT	:	Medical Nutrition Therapy
MODY	:	Maturity-Onset Diabetes of the Young
NICE	:	National Institute for Health and Care Excellence
OGTT	:	Oral Tolerance Glucose Test
PPAR-γ	:	Peroxisome Proliferator-activated receptor γ
RCT	:	Randomized Controlled Trial
SIGN	:	Scottish Intercollegiate Guidelines Network
TNF-a	:	Tumor Necrosis Factor a
WHO	:	World Health Organization

INTRODUCTION

Gestational Diabetes Mellitus

Introduction and definition: According to American Diabetes Association, Gestational Diabetes Mellitus (GDM) is a complication of pregnancy that is defined as any degree of glucose intolerance with onset or first recognition during pregnancy and it occurs when the body is unable to produce enough insulin to meet the increased insulin requirements of pregnancy [1]. Women with undiagnosed preexisting diabetes and those whose diagnosis occur during the second and the third trimester of pregnancy, are diagnosed with GDM. It is associated with high risk of adverse maternal, fetal and offspring outcomes.

Epidemiology: One of the most common pregnancy complications globally is Gestational diabetes mellitus. The prevalence of GDM varies and depends on the diagnostic criteria and the differences in the characteristics of the population that were studied. A recent review reported wide variations in the prevalence, affecting up to 5% and 25% of pregnancies in England and Asia, respectively [2]. It is estimated that GDM complicates up to 14% of all pregnancies, accounting for approximately 200.000 new cases in the United States annually. Of all types of diabetes, GDM accounts for 87.5% of all cases of diabetes in pregnancy [1].

Pathophysiology: Pregnancy is a diabetogenic state characterized by impaired insulin sensitivity. During normal pregnancy, relative insulin resistance develops in the second trimester and increases to maximum at the end of the third trimester [3]. Transport of glucose is promoted physiologically across the placenta to induce normal fetal growth and development. The mechanism is due to the production of hormones by the placenta such as human placental lactogen, cortisol, growth hormone and prolactin and cytokines released from adipocytes such as IL-6 and TNF-a [4]. This results in reduced postprandial glucose disposal by up to 60% [5].

In pregnancy, insulin secretion normally increases up to 200% to 250% to maintain maternal glycemia in the face of increased insulin resistance [6]. However, in contrast to healthy women, GDM women have greater reductions in insulin sensitivity during pregnancy and are unable to maintain normal glucose levels [7, 8]. Barbour et al. (2007) compared skeletal muscle fibers of obese GDM with those of obese nonpregnant women and investigated the mechanisms for insulin resistance of pregnancy compared with the nonpregnancy state. Evidence suggests that the majority of women with GDM appear to have β-cell dysfunction prior to pregnancy with an already established chronic insulin resistance and decreased insulin secretory capacity [9]. The combined underlying pre-pregnancy pathology and pregnancy-associated insulin resistance results in GDM occurrence.

In GDM, increased inflammation (TNF-a) and decreased adiponectin levels promote impaired insulin signaling, resulting in increased insulin resistance. Other defects, such as impaired insulin-stimulated glucose transport and reduced expression of PPARγ have been found in muscle and fat cells of women with GDM. However, it is currently unknown whether these features are primary or the result of insulin action [10]. It has been demonstrated from expression studies that altered insulin signaling is stimulated by the maternal environment and not by fetus. In addition, it has been shown that women with diabetes and obesity have a post-receptor deficiency in the insulin signaling pathway in the placenta [11].

In a small proportion of women (5-10%), the defects in β-cell have been attributed to autoimmune process. This is characterized by increased levels of immune markers against pancreatic islets (Anti-islet antibodies) or β-cell antigens (GAD, IAA). These women do not have typical risk factors for GDM and they have an increased risk for developing type 1 diabetes. Another cause for β-cell dysfunction is gene mutations that cause maturity-onset diabetes of the young (MODY) [10].

Diagnosis: There are currently no universally accepted diagnostic criteria for GDM. It is recognized that these criteria are concluded from the association between glycemic cut-off points and the increased risk for adverse maternal and perinatal outcomes. GDM is generally diagnosed using an Oral Tolerance Test (OGTT) with glucose measured fasting and post-challenge. There is significant variation nationally and internationally between the oral glucose load (75 g or 100 g), the post-challenge time points and the cut-off points for determining abnormal values (Table 1).

Table 1: Diagnostic criteria for GDM by a 75 g OGTT

Reference	Plasma Glucose (mmol/L)				
	Fasting	1 hour	2 hours	3 hours	OGTT
WHO (1999)*	≥ 7.0	-	≥ 7.8	-	75 g
IADPSG (2010)*	≥ 5.1	≥ 10.0	≥ 8.5	-	75 g
NICE (2015)*	≥ 5.6	-	≥ 7.8	-	75 g
ACOG (2013)**	≥ 5.3	≥ 10.0	≥ 8.6	≥ 7.8	100 g

World Health Organization (WHO); International Association of Diabetes and Pregnancy Study Group (IADPSG); National Institute for Health and Care Excellence (NICE); American College of Obstetrics and Gynecology (ACOG);*One abnormal value required; **Two abnormal values required

In 1999, World Health Organization (WHO) recommended a 75 g OGTT between the 24th and 28th week of gestation with cut-off points of venous plasma glucose levels ≥7.0 mmol/L (fasting glucose) and/or ≥7.8 mmol/L (2-h glucose) [12]. Later in 2008, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was the first to report the linear and continuous association of elevated maternal glucose levels with GDM-associated adverse outcomes [13]. However, there was no clear threshold at which the risk increased substantially to establish new cut-off diagnostic points [13]. The International Association of Diabetes and Pregnancy Study Group (IADPSG) suggested new diagnostic criteria based on the perinatal outcomes of the HAPO study [14]. It has been estimated that applying IADPSG diagnostic criteria, compared with other criteria, would increase the prevalence of GDM, resulting in major economic consequences [15]. Current NICE guidelines recommend criteria between of those from WHO and IADPSG criteria [16], while the Scottish Intercollegiate Guidelines Network (SIGN) and American Diabetes Association (ADA) recommend IADPSG criteria. Global debate concerning the pregnancy outcomes and the cost/benefit ratio of the existing cut-off points is still ongoing [17].

Risk factors: There are many risk factors associated with increased risk of developing GDM. Not surprisingly, medical conditions that results in metabolic and hormonal dysfunction, such as pregnancy obesity (BMI >30 kg/m^2), family history of type 2 diabetes, polycystic ovary disease and high blood pressure during pregnancy, are associated with increased the risk of GDM [18]. Other risk factors are advance maternal age, multiple pregnancies, maternal short stature, previous pregnancy with GDM and excessive Gestational Weight Gain (GWG). Presence of adverse outcomes in previous pregnancies including prior neonatal death, prior caesarian delivery, previous stillbirth, congenital malformations or previous macrosomic baby (≥4.5 kg) can also increase the risk [15]. There is a strong correlation of Type 2 diabetes and gestational diabetes, in terms of risk factors (Obesity, family history) and pathophysiology (Increased insulin resistance, β-cell dysfunction), suggesting that gestational period can affect the development of metabolic diseases both in the mother and the offspring [19].

Complications

Fetal Complications

In response to maternal hyperglycemia, the fetus increases insulin secretion, resulting in an increased growth-promoting environment [20]. The commonest fetal complication associated with GDM is macrosomia or infants Large for Gestational Age (LGA), which is defined as a weight of more than 4.000 g or a weight above the 90th percentile for the gestational age. The prevalence ranges between 18 and 29% [20,21]. The excessive fetal growth leads to fetal pancreatic hyperplasia resulting in hyperinsulinemia. Thus, hypoglycemia is a major adverse complication with approximately 24% of infants reaching very low levels of blood glucose during their first period of life. Another consequence of growth-promoting activity is the excessive development of subcutaneous adipose tissue mass and broad shoulders, resulting in shoulder dystocia at birth, where anterior shoulder of the infant cannot pass below and fail to deliver shortly after the head [5,21]. Increased risk of perinatal mortality, including still birth and neonatal death, has been associated with GDM [5,22].

Maternal Complications

Women with GDM have an increased long-term risk for developing type 2 diabetes after delivery, due to the underlying pathophysiology. It has been estimated that approximately 10% of women with GDM suffer from T2D after pregnancy and there is a 40% risk of developing T2D the next 10 years after delivery [23]. Markers of vascular diseases such as impaired endothelial function are also increased, suggesting an increased risk for metabolic syndrome. Other maternal complications include pre-eclampsia and cesarean section [10].

Gestational Diabetes Mellitus Management

Blood Glucose Monitoring

Blood glucose monitoring is required to achieve normal blood glucose concentrations and metabolic control. The Fifth international Workshop Conference (FIWC) suggests the following targets for capillary blood glucose levels: pre-prandial ≤ 95 mg/dL (<5.3 mmol/L) and either <140 mg/dL (<7.8 mmol/L) 1 h postprandial or 120 mg/dL (<6.7 mmol/L) 2 h postprandial [24]. Recommendations from American Diabetes Association (ADA) of slightly higher capillary blood glucose concentrations suggest pre-prandial ≤105 mg/dL (<5.8 mmol/L) and either <155 mg/dL (<8.6 mmol/L) 1 h postprandial or 130 mg/dL (<7.2 mmol/L) 2 h postprandial. Achieving postprandial glycemic targets is more important than pre-prandial because it has been shown that it correlates better with adverse neonatal outcomes, including macrosomia, hypoglycemia and malformations [25].

Medication

Insulin

Insulin therapy is the gold standard medication when medical nutrition therapy fails to achieve glycemic control and it does not cross the placenta. It has been suggested that insulin therapy needs introduction after failure of MNT to achieve normal blood glucose levels. Insulin dose depends on the maternal BMI before pregnancy and the present maternal weight and varies between 0.7-1.0 Units/kg [26]. It is recommended a basal-bolus insulin regimen, including a basal injection (long-acting insulin) once per day and a bolus injection (Rapid-acting insulin) before each meal. A recent systematic review suggests that administration of any type of insulin (Regular, NPH or one of the analogs) can be both safe and effective in the management of GDM with respect to the specific needs of the pregnant women [27].

Oral hypoglycemic medication

Use of oral anti-diabetic drugs, with exception of Glyburide and metformin, designed to manage type 2 diabetes is not recommended to treat GDM due to concerns about crossing the placenta and causing fetal complications, including teratogenicity and neonatal hyperinsulinemia and hypoglycemia. These drugs are generally used as the second option after insulin therapy. Glyburide and metformin are the two classes of oral drugs that have been widely used in GDM [5].

Glyburide, a second-generation sulfonylurea agent, increases insulin secretion and reduces insulin resistance. In contrast to other sulfonylureas, studies have shown that glyburide do not cross the human placenta [28,29]. Langer et al., (2000) conducted a randomized open-label clinical trial enrolling woman with GDM, assigned to receive either glyburide or insulin. Glyburide was found to be similarly effective to insulin in improving glycemic control and with fewer hypoglycemic episodes than with insulin. There were no significant differences in macrosomia or in maternal outcomes, such as pre-eclampsia and caesarian section, between the two groups [30]. On the other hand, many recent small RCTs have showed increased neonatal hypoglycemia and/or fetal growth with glyburide. Although the current evidence and NICE guidelines are in agreement with the use of glyburide in pregnancy, there remain concerns about the maternal glycemic control and fetal development [15].

Metformin is the second line agent for treatment of GDM. Although it increases insulin sensitivity and does not cause weight gain or hypoglycemia, it crosses the human placenta. However, evidence suggests that it is safe in pregnancy. The Metformin and Gestational Diabetes (MIG) trial randomized women with GDM to either metformin or insulin. Metformin was found to reduce severe neonatal hypoglycemia and gestational weight gain compared to insulin. Approximately half of women in metformin group (46%) did not reach the glycemic targets requiring addition of insulin part from metformin. There were no differences in adverse pregnancy outcomes between the two groups [31]. Although this and other studies have reported the beneficial results of metformin, it can cross the placenta and the long-term effects on offspring are not yet known [5].

Lifestyle Interventions

It has been shown that the pathophysiology behind type 2 diabetes is correlated with that of gestational diabetes, including the underlying insulin resistance and the relative β-cell dysfunction. Lifestyle approaches, including nutrition therapy and physical activity are key components for type 2 diabetes management and diabetes complications prevention, with established recommendations [32-34].

Many studies have shown that energy restriction and modest weight loss can provide improved glycemia and clinical benefits in patients with diabetes. The greatest weight loss was achieved in Look AHEAD trial [35] and in DiRECT study [36], 8.4 kg and 10.0 kg, respectively. In these studies, the improvements in HbA1c were also significant in the intervention group compared to the control and equal to -0.64% and -0.94%, respectively. It has been shown that a weight loss equal to 7-8.5% of initial body weight can be achieved by eating patterns that result in reduced energy intake and it is an important component of weight loss interventions [37].

The quantity and quality of carbohydrates seems to affect glycemic response and diabetes management. Concerning the quantity of CHO, the evidence is inconclusive. Many studies have demonstrated that decreased CHO intake (Ranging from 20 g per day up to 40% of energy requirements) improved glycemic control and insulin sensitivity compared to increased CHO intake [38-42]. Three RCTs did not show any significant differences in glycemic control between low and high-CHO diets [43-45]. In many of these studies, weight loss occurred, which is a major confounding factor and many of them were small and with short duration. One recent systematic review of 9 RCTs demonstrated a significant reduction of HbA1c levels by 0.44% with low-CHO compared to high-CHO diets. Although it is the first study focused on patients with diabetes type 2, they reported that only five studies were of high quality and the CHO intake ranged from 5% to 20% of the daily energy requirements [46].

Concerning the quality of carbohydrates, two systematic reviews and meta-analysis have demonstrated that low-GI diets compared to high-GI diets decreased HbA1c levels by 0.43% [47] and 0.4% [48]. Both reviews included trials based on strict criteria, including randomized control design, comparable difference of outcome, quality control data and a control of confounding factors in most studies (weight loss, energy intake). However, many of the studies included in these two meta-analyses were of short duration and had small number of subjects and there is no agreement in the definition of "low-GI" (Range 35-77) or "high-GI" (Range 56-100) and both ranges were wide, where foods can be ranked based on a scale from 0 to 100 according to the extent they raise blood glucose, compared to a reference food, such as white bread [33]. Some organizations suggest that substituting low-GI for high-GI diets can improve glycemic control [33,49,50].

Thus, lifestyle strategies designed to manage type 2 diabetes can have an important effect both on the prevention and management of gestational diabetes mellitus. Lifestyle approaches have been studied the past few years and it has been established that the majority of pregnant women with GDM (70-85%) can control blood glucose levels with lifestyle modification only and without any medication, emphasizing its importance [51].

Current evidence from systematic reviews and meta-analysis examining the effect of lifestyle interventions, including dietary (dietary advice, low-GI diet, energy-restriction diet, low-CHO diet) and combined diet and physical activity interventions, on both prevention and treatment of GDM are presented below.

Prevention of GDM

Dietary interventions: It has been shown in a systematic review of RCTs by Facchinetti et al., (2014) that dietary counseling compared to standard care reduced the incidence of GDM by 5% and the gestational weight gain. However, there were no differences in fetal outcomes and the authors stated that the interventions were of poor quality and there were high rates of heterogeneity in the inclusion criteria [52].

A recent Cochrane systematic review (2017) has assessed the effect of dietary advice interventions in pregnancy on the incidence of GDM and on maternal and fetal outcomes. They included randomized control trials where dietary advice interventions were compared with no dietary advice intervention and to different types of dietary advice (low-GI vs high-GI dietary advice and high-fiber vs standard advice). The review included 6 trials in the first arm (Dietary advice vs standard care) and demonstrated a trend towards a reduction in the risk of GDM (8.6% vs 12.6%, 5 trials with available data), a reduction in hypertension (2.88% vs 9.79%, 2 trials with available data) and in gestational weight gain (4.70 kg less, 5 trials with available data) in women who received dietary advice intervention. There were no differences in pre-eclampsia and perinatal mortality between the two groups. In the 4 trials in the second arm (low-GI vs high-GI dietary advice), no differences were demonstrated in the GDM incidence and large-for-gestational age or in the maternal and fetal outcomes. Women in the low-GI dietary advice group had lower fasting blood glucose at 32 to 36 weeks, compared to the high-GI group (0.27 mmol/L lower, 2 trials with available data). No differences were found in blood glucose after OGTT or birth weight between the high-fiber group and standard dietary advice in one trial at the third arm [53].

The same year, another systematic review of 8 clinical trials (Diet intervention, in 6 trials and supplements interventions, in 2 trials) and 20 prospective cohort studies examined the effect of nutritional factors (Diet and supplements) on the prevention of GDM. The review found no differences in the incidence of GDM in the 6 trials comparing dietary intervention, but demonstrated a reduction in the rates of GDM in 2 trials that used probiotics and muo-inositol compared to placebo. Data from the observational studies showed that decreased incidence of GDM can be achieved through a healthier dietary pattern, including Mediterranean dietary plan, less consumption of sugar sweetened beverages, fatty foods and sweets [54].

Another systematic review by Morisset et al., (2010) examined the effect of reduced gestational weight gain on the prevention of GDM. The review revealed that women with excessive gestational weight gain, above IOM recommendations, have an increased risk of developing GDM and adverse maternal and fetal outcomes, including preterm delivery, macrosomic neonates and cesarean section. The review included studies that used energy-restricted dietary interventions (1200-1800 kcal or 35 kcal/kg of ideal body weight) and they demonstrated that dietary restriction can reduce gestational weight gain and improve the glycemic control without inducing adverse effects on fetal growth [55].

Tanentsapf et al., (2011) conducted a systematic review on dietary interventions designed to prevent excessive gestational weight gain through dietary interventions, including dietary advice, energy-restricted, low-fat and low-CHO diets. The review revealed that all types of interventions achieved to reduce gestational weight gain by almost 2 kg and reduce the incidence of caesarian section. Although the interventions reduced the incidence of GDM, pre-eclampsia and macrosomia, the differences between the intervention and control groups did not reach statistical significance [56].

Combined diet and physical activity: A recent Cochrane systematic review (2017) has assessed the effect of interventions that combined any type of dietary advice and exercise compared with no intervention in pregnancy on the incidence of GDM and on maternal and fetal outcomes. The review included 23 RCTs where the dietary advice provided varied with main recommendations being about energy restriction, healthy eating pattern, less fat and carbohydrates intake and the exercise components included advice about daily walking, increased mild and moderate-intensity exercise 3 times per week and resistance training. The review demonstrated an average reduction from all the available trials in the incidence of GDM (15% reduction, 19 trials with available data) and in the incidence of caesarean section (5% reduction, 14 trials with available data) in women who received the combined lifestyle intervention. Although there were no differences in pre-eclampsia, perinatal mortality, neonatal hypoglycemia or large-for-gestational age between the

two groups, the combined intervention groups significantly reduced gestational weight gain (0.89 kg less, 16 trials with available data) [57].

Many systematic reviews and meta-analysis assessed the effect of either diet alone, exercise alone or combined lifestyle intervention in pregnancy outcomes.

Rogozinska et al., (2015) conducted a systematic review of randomized studies, including diet-based advice (5 RCTs), combined interventions (13 RCTs) and nutritional supplements (2 RCT). They demonstrated that only diet-based interventions reduced the risk of GDM by 33%, whereas there was no difference between groups for the combined interventions. Although there was a trend towards a reduction of pre-eclampsia and hypertension in the diet intervention, there were no differences in other maternal or fetal outcomes for any of three intervention groups [58].

Similarly, Song et al., (2016) conducted a systematic review of 29 RCTs comparing diet only (5 RCTs), combined interventions (10 RCTs) and physical activity only (8 RCT) with control group. Although, they demonstrated that all the interventions achieved to reduce GDM risk before the 15th gestational week by 18%, lifestyle intervention initiated after the 15th was not able to decrease the risk. This systematic review did not report any maternal or fetal outcomes [59].

The most recent systematic review by Bennett et al., (2018) examined the effect of 45 lifestyle intervention studies (diet, physical activity or combined interventions) designed to reduce excessive gestational weight gain in prevention of GDM. They showed that dietary and physical activity intervention alone significantly reduced the risk of GDM by 44% and 38%, respectively. However, there were no differences in the incidence of GDM between the combined lifestyle intervention and control groups [60].

Management of GDM

Dietary interventions: A recent Cochrane systematic review (2017) has assessed the effect of different dietary advice interventions on pregnancy outcomes in women with GDM. The review among others, included RCTs that compared low-GI with high-GI diet (4 trials), energy-restricted with no-energy-restricted diet (3 trials) and low-CHO with high-CHO diets (2 trials). They demonstrated that there was a benefit for glycemic control (2-h postprandial glucose for women in the low-GI diet group (0.71 mmol/L lower, 1 trial with available data), but without any differences in other maternal or fetal and neonatal outcomes for the women in the low-GI compared to the high-GI diet group. Although, women in restricted-energy group had lower fasting glucose (0.23 mmol/L lower, 1 trial with available data), 24-h mean plasma glucose (1.3 mmol/L lower, 1 trial with available data) and 1-h postprandial glucose (0.5 mmol/L lower, 1 trial with available data), there were more neonates with hypoglycemia born in the energy-restricted diet group compared with the control (1 trial with available data). One trial reported less gestational weight gain (0.9 kg less) for women receiving the low-CHO diet compared with those in high-CHO diet, but without any other differences in maternal/fetal outcomes [61].

Viana et al., (2014) conducted a systematic review of RCTS of dietary interventions in women with GDM, including low-GI (4 trials), total energy restriction (2 trials) and low-CHO (2 trials). They demonstrated that low-GI diet group used less insulin by 23% and the new-born weight was reduced (0.42 kg less) compared to the control group. There were no differences in GWG or caesarean section between the two groups. There were no differences in frequency of insulin use, number of cesarean sections, frequency of macrosomia or neonatal hypoglycemia for any of the other two intervention groups [62].

Combined lifestyle intervention: A recent Cochrane systematic review (2017) has assessed the effect of lifestyle interventions compared with usual care on pregnancy outcomes in women with GDM. Lifestyle interventions varied among the 15 RCTs, including a combination of at least two or more of the following: diet, exercise, behavioral change techniques and blood glucose monitoring. The review demonstrated no differences for pre-eclampsia, caesarean section, induction of labor or development of type 2 diabetes (Up to 10 years follow-up) between lifestyle interventions and control groups. More women in lifestyle groups achieved their postpartum weight goals one year after birth compared to control. Although, there were no differences in perinatal death or neonatal hypoglycemia between groups, lifestyle interventions reduced the risk of large-for-gestational age babies (40% reduction, in 6 trials) and the incidence of macrosomia compared to control groups [8].

Objectives

Previous reviews have attempted to summarize the available evidence of the effect of different dietary interventions on the prevention or management of GDM. However, there are no reviews that focus entirely on studies that assessed the effect of energy-restricted approaches compared to non-energy-restricted approaches on either the prevention or management of GDM. An energy-restricted approach is defined as a diet containing calories less than the required amount for pregnancy.

The aim of the first systematic review is to assess the effect and safety of energy-restricted dietary approaches on prevention of gestational diabetes mellitus, measured by the GDM incidence and associated adverse maternal/fetal outcomes. The aim of the second systematic review is to assess the effect and safety of energy-restricted dietary approaches on management of gestational diabetes mellitus, measured by the glycemic control and associated adverse maternal/fetal outcomes.

METHODS

Prevention of GDM

Literature search: A literature review was performed in electronic database (Medline). The following strategy was used: "gestational diabetes OR GDM" AND "RCT OR randomized controlled trial" AND "energy OR energy intake OR caloric restriction OR energy-restricted diet OR low-calorie diet OR hypocaloric diet OR diet OR dietary intervention" AND "prevention OR GDM incidence". Additional articles were identified from the reference lists of relevant studies and reviews.

The initial search resulted in 196 titles. After titles and abstracts were screened and irrelevant articles were excluded, 86 possibly relevant articles remained for further full text review. Of these 86, only 8 articles met the inclusion criteria and included in the systematic review (Figure 1).

Study selection: The inclusion criteria included RCTs that included an energy-restricted diet as part of the intervention in pregnant women, difference on caloric intake between intervention and control group, women with a singleton pregnancy, outcomes were the incidence of GDM and other maternal and fetal complications; exclusion criteria were presence of type 1 or 2 prior to pregnancy or previous GDM, women taking any medication, studies with only an exercise-based intervention, presence of other diseases requiring dietary treatment, studies in animals.

Outcome measures: The primary outcome was the incidence of GDM. The secondary outcomes were divided into maternal and fetal outcomes. Maternal outcomes included total GWG, pregnancy-induced hypertension, preeclampsia, cesarean section and labor induction. The fetal outcomes included LGA, macrosomia (>4000 g) and preterm delivery.

Quality of studies and risk of bias: The risk of bias assessed using the criteria outlined in the Cochrane risk of bias tool [63]. Each criterion categorized as low, high or unclear risk of bias, depending on the available information from each study.

Allocation concealment and random sequence generation

Five studies had low risk of bias for both allocation concealment and random sequence generation [65,66,68-70]. In four of these trials a computer-generated random sequence was used [66, 68-70] and in the fourth one a random number table was used [65]. All of these five used a numbered, scaled envelope as concealing allocation method. Although, two trials [64,71] used a proper method for

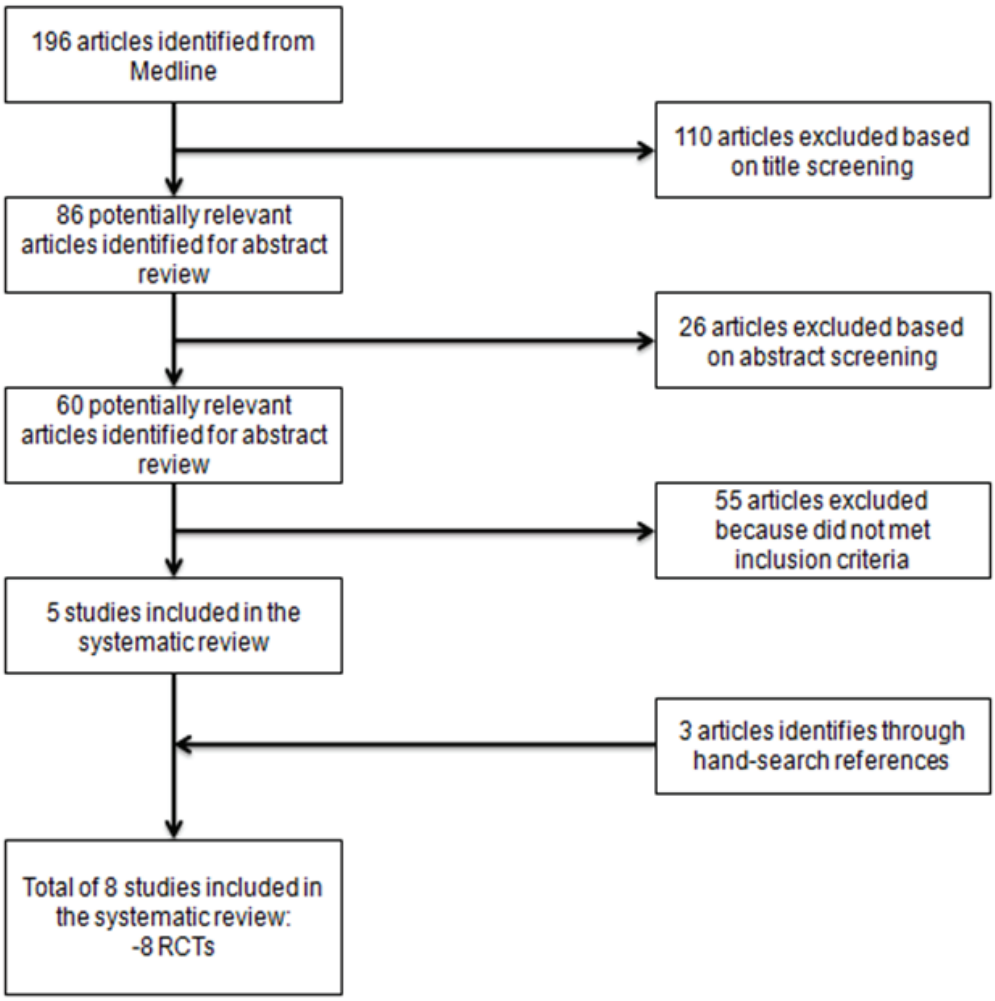

Figure 1: Flow chart outlying study selection in the systematic review assessing the effect and safety of energy restriction on prevention of GDM

sequence generation (Computer randomization), the first one did not clearly report the allocation method and the second one allocated the participants by age and BMI. Similarly, the risk of selection bias was high in Poston et al., (2013) [67], where the participants were allocated by maternal age and BMI and the randomization method was not reported.

Blinding

All 8 trials [64-71] were at a high risk of performance bias, because blinding study participants and study personnel is difficult in dietary intervention studies.

However, blinding of outcome assessors involved in the analysis was assessed as a quality criterion. The blinding of outcomes assessors was adequate in two studies [64,70]. In Hui et al., (2014) [70] student assistants without knowledge of the study collected and manipulated the data and in Wolf et al., (2008) [64], women were asked not to reveal their assignment groups to physicians. All the other studies were judged to be at unclear risk of detection bias [65-70].

Incomplete outcome data

Four trials were judged to be at low risk of attrition bias [66, 67, 70, 71]. In four studies the reasons for loss to follow up were reported and they were similar in all groups. Specifically, the drop-out rate was 5% in Walsch et al., (2014) [66], 15% in Poston et al., (2013) [67], 4% in Vesco et al., (2014) [71] and in Hui et al., (2014) [2014] there were no withdraws. Two trials were at unclear risk of attrition bias, because there were no available data regarding withdraws or with unbalanced reasons for losses across the groups (65, 68). Specifically, in Thorton et al., (2009) [65] the drop-out rate was 6% in the control group and 12% in the intervention group without any reasons reported and in Petrella et al., (2014) [68] there were no reasons or drop-out rates reported. Two trials were at high attrition bias [64,69], where in Wolf et al., (2008) [64] the drop-out rate was extremely high and equal to 38% with missing data about main outcomes, including weight measurements. In Hui et al., (2011) [69], only half of women completed both the 3-day food record at baseline and 2 months after.

Management of GDM

Literature search: A literature review was performed in electronic database (Medline). The following strategy was used: "gestational diabetes OR GDM" AND "RCT OR randomized control trial" AND "energy OR energy intake OR caloric restriction OR energy-restricted diet OR low-calorie diet OR hypocaloric diet OR diet OR dietary intervention" AND "management OR treatment" AND" prospective OR observational OR Randomized controlled trial". Additional articles were identified from the reference lists of relevant

Studies and reviews: The initial search resulted in 494 titles. After titles and abstracts were screened and irrelevant articles were excluded, 71 possibly relevant articles remained for further full text review. Of these 71, only 4 articles met the inclusion criteria and included in the systematic review and another one was added from reference lists (Figure 2).

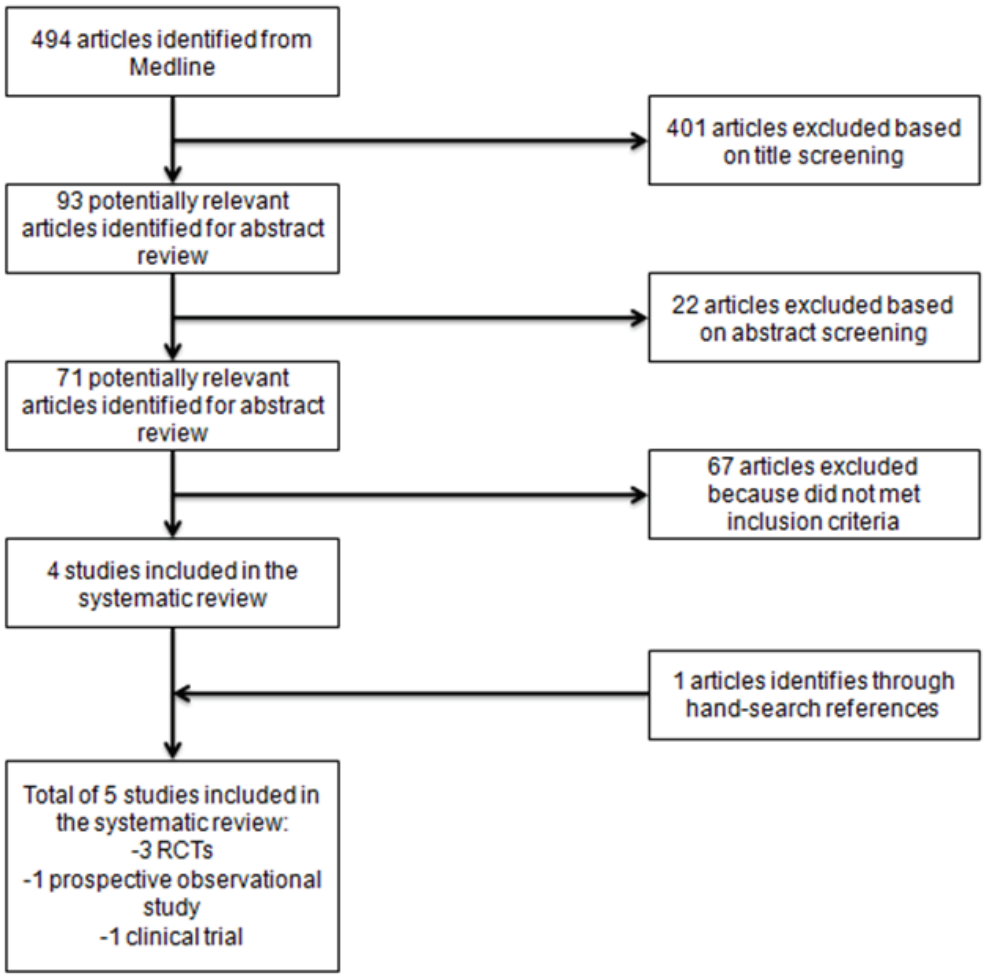

Figure 2: Flow chart outlying study selection in the systematic review assessing the effect and safety of energy restriction on management of GDM

Study selection: The inclusion criteria included clinical trials and adjusted prospective cohort studies that assessed the effect of an energy-restricted diet on maternal and fetal outcomes in women with gestational diabetes mellitus. Other inclusion criteria were difference on caloric intake between intervention and control group, women with a singleton pregnancy; exclusion criteria were presence of type 1 or 2 prior to pregnancy or previous GDM, women taking any medication, studies with an exercise-based intervention, presence of other diseases requiring dietary treatment, dietary characteristics not available, no reported outcomes of interest.

Outcome measures: The primary outcome was the glycemic control measured by fasting glucose, postprandial, pre-prandial and 24-h mean glucose. The secondary outcomes were divided into maternal and fetal outcomes. Maternal outcomes included total GWG, pregnancy-induced hypertension, preeclampsia, cesarean section and maternal ketonemia. The fetal outcomes included LGA, macrosomia (>4000 g) and neonatal hypoglycemia.

Quality of Studies

Randomized Control Trials

The risk of bias for the RCTs was assessed using the criteria outlined in the Cochrane risk of bias tool [63]. Each criterion categorized as low, high or unclear risk of bias, depending on the available information from each study. One study had low risk of selection bias for random sequence generation, using random numbered tables [72]. The remaining two did not provide sufficient information for the randomization method and they were characterized to be at unclear risk of bias [73,74]. In two of them the selection bias was at unclear risk where they did not report method for concealing allocation. Rae reported that women were allocated using opaque numbered envelopes. Regarding blinding participants and study personnel, Rae reported that women and study stuff were blinded, so the risk of performance bias was low. In one study, participants were not blinded so the risk of performance bias was high [72] and one was at unclear risk [74]. Regarding blinding of outcome assessors, there was no available information in the three studies and they were at unclear risk of detection bias. All studies were judged to be at low risk of attrition bias. In two, the number of women lost to follow-up was small (6.4%, in Rae, 0.3%, in Garner) and in one there were no losses to follow-up [74].

Non-Randomized Control Trials

The risk of bias for the non-randomized control trials was assessed using the ROBINS-I tool for assessing risk of bias in non-randomized studies of interventions [75]. Each criterion categorized as low, moderate, serious, critical or unclear risk of bias, depending on the available information from each study.

Concerning bias due to confounding, in Dornhorst et al., (1991) [76], the risk was serious due to significant differences between the baseline characteristics of GDM women and general population. In Ho et al., (2005) [77] there were no differences in confounding factors between the caloric tertiles and the risk was low. The risk of

bias in measurement of intervention in Dornhorst et al., (1991) [76] was unclear because there was no assessment dietary method for the intervention. In Ho et al., (2005) [77], the risk of bias was low due to adequate assessment of dietary intake by a 5-day food record. The risk of bias due to departures from intended interventions was low in Dornhorst et al., (1991) [76], because of the study design. All women were assigned to diet depending on their needs and then were categorized by their average daily intake without any specific intervention. In Ho et al., (2005) [77], the risk was low. Dornhorst et al., (1991) [76] reported the number of women that were excluded from the final survey and the reasons and the risk of bias due to missing data was low. There was no information about the drop-out rate or any missing data in the study of Ho et al., (2005) [77] and the risk was judged as unclear. The risk of measurement of outcomes in both studies was unclear due to insufficient information about the blinding of assessors of the outcomes.

RESULTS

Prevention of GDM

Description of studies: The eight RCTs in this review involved a total of 1792 pregnant women and their babies and were published between 2008 and 2014. They conducted across a variety of countries including two in Canada [69,70], two in USA [65,71] and one each in England [67], Denmark [64], Ireland [66] and Italy [68]. Five RCTs included obese or/and overweight women (BMI ≥ 25 kg/m^2) [64-68, 71]. One study used a 7-day food record as the dietary assessment method [64], three a 3-day food record [66,69,70], one a Food Frequency Questionnaire (FFQ) [68], one a 24-h recall [67], one a daily food record [65] and one did not report the dietary assessment method [71].

Description of intervention: All the studies included a dietary intervention that contained an energy-restricted diet compared to the control group. Of eight studies, five demonstrated the data from the energy intake and reported statistically significant difference on energy intake between the intervention and the control group (64,66,67,69,70). The same studies reported a caloric intake below 2000 kcal for the intervention group. Specifically, the differences on energy intake (kcal) at the end of the studies between the intervention and the control groups were 1700 vs 2000 (64), 1816 vs 1935 (66), 1613 vs 1842 (67), 1996 vs 2416 (69) and 1983 vs 2551 (70). All studies, except for two [64, 66], included physical activity advice in the intervention. Although all studies included energy-restricted diet in the intervention group, a range of dietary interventions were assessed.

In Wolf et al., (2008) [64] women attended 10 consultations of 1 h each with a trained dietitian. The energy restriction was estimated based on each woman's energy requirements and the energetic cost of fetal growth. Women in the intervention group of Thornton et al., (2009) [65] were placed on an 18 to 24 kcal/kg energy-restricted dietary plan. In Walsh et al., (2012) [66] women attended a 2-h group dietary session where advised to increase the intake of low-GI foods and reduce the total caloric intake. Women in Poston et al., (2013) [67] were encouraged to increase consumption of foods with low-GI and decrease energy intake of saturated fats. In Petrella et al., (2013) [68], women assigned to an energy-restricted diet with a low-GI dietary advice. In both Hui et al., (2011) [69] and (2014) [70], dietitian provided personalized dietary counseling twice to each participant based on their Food Choice Map interview results, pregnancy week and weight gain aiming at reducing the caloric intake. In Vesco et al., (2014) [71], women were asked to follow an energy reduced eating plan, based on DASH dietary pattern. The energy intake was estimated based on 30 kcal/kg/day of pregnancy weight for non-obese women and then reduced by 30%.

Incidence of GDM: All the studies assessed the effect of intervention on the incidence of GDM. Four studies reported the diagnostic criteria: two used to Canadian Diabetes Association criteria (2008) [69, 70], one used the International Association of Diabetes and Pregnancy Study Group's (IADPSG) criteria (2010) [67] and one used both Carpenter-Coustan's and American Diabetes Association's criteria [66]. Only one study reported statistical significant difference on the incidence of GDM between the intervention and the control group (23% vs 57%, in Petrella) [68]. Although in Thornton et al., (2009) [65] the difference was not significant (9.5% vs 16.4%), women who did not adhere to the nutritional regimen had significantly higher risk of developing GDM (2.2% vs 34.6%). In the six remaining studies, intervention group showed a trend towards a reduction in the incidence of GDM compared to control group, but it did not reach statistical significance (0% vs 10%, in Wolf [64]; 3% vs 5%, in Walsh [66]; 28% vs 32%, in Poston [67]; 2% vs 2.4%, in Hui 2011 [69]; 1% vs 3%, in Hui 2014 [70]; 11% vs 12%, in Vesco [71]).

Maternal and fetal outcomes

Maternal outcomes

All the trials evaluated the effect of intervention on GWG. Six out of eight studies reported that intervention group reduced GWG significantly compared to control group: (6.6 kg vs 13 kg, in Wolf [64]; 9 kg vs 14 kg, in Thornton [65]; 12.3 kg vs 13.7 kg, in Walsh [66]; 6.7 kg vs 16.1 kg, in Petrella [68]; 12.9 kg vs 16.2 kg, in Hui 2014 [70]; 5 kg vs 8.4 kg, in Vesco [71]).

Four reported the incidence of pregnancy-induced hypertension [64,65,68,71] and only two reported a significant difference between the two groups [65, 68]. Three reported the effect of intervention on pre-eclampsia [64,65,71] and six on caesarean section (64-66,69-71). There was no significant effect of intervention on these outcomes.

Only two reported the incidence of labor induction. Walsh et al., (2008) [64] reported a significantly higher incidence of labor induction in the intervention group. Although in Thornton et al., (2009) [65] the difference was not significant, women who did not adhere to the nutritional regimen had significantly higher risk of inducing their labor.

Fetal outcomes

Four studies evaluated the effect of intervention on large-for-gestational age (LGA) [67, 69, 70, 71] and three on macrosomia (>4000 g) (65, 67, 71). Only in Vesco et al., (2014) [71] the intervention group reduced significantly the risk of LGA. Although intervention groups of all studies demonstrated a trend towards a reduction in the risk of both outcomes, only in Thornton et al., (2009) [65] the difference between the two groups was statistically significant, taking into consideration the adherence of dietary plan. Three studies reported the incidence of preterm delivery [66,68,71]. The results from the first systematic review are presented in Table 2.

Management of GDM

Description of studies: Three studies were randomized control trials [72-74], one was clinical trial [76] and one was prospective observational study [77]. The three RCTs involved a total of 437 mothers and their babies and they were published between 1991 and 2000. They conducted in Canada [72], Australia [73] and USA [74]. Two included obese women (BMI ≥ 30 kg/m^2) [73,74] and one women of any BMI [72]. One study used a 5-day food record as kcal/day the dietary assessment method [73], one included hospitalization during the study and the meals were given by the hospital [74] and one did not report the assessment method [72]. The three RCTs randomized women with GDM into intervention group that included an energy-restricted diet or into control group. In Rae et al., (2000) [73], women in the intervention group assigned to a diet with moderate energy restriction consisting of 1590-1776 kcal/day compared to unrestricted diet with 2010-2220 kcal/day. In Garner et al., (1997) [72], intervention group was placed on an energy-restricted diet of 35 kcal/kg of ideal body weight per day and women were also taught glucose monitoring techniques. In Magee et al., (1990) [74], the intervention group assigned to 1200 kcal and the control group to 2400 kcal per day.

The one clinical trial conducted in UK [76] and compared maternal and fetal outcomes among gestational diabetic women (n=35), general population (n=2337), high risk for GDM group

Table 2: Main outcomes in the systematic review assessing the effect and safety of energy restriction on prevention of GDM

	Study design	Outcomes (energy-restricted vs no energy-restricted diet group)							
		GDM incidence (%)	GWG (kg)	Pregnancy-induced hypertension (%)	Pre-eclampsia (%)	Caesarean section (%)	LGA (%)	Macrosomia (%)	Preterm delivery (%)
Wolf [64] (2008)	RCT	0 vs 10	***6.6 vs 13 ****	4 vs 15	0 vs 4	9 vs 11	NR	NR	NR
Thornton [65] (2009)	RCT	***9.5 vs 16.4 ****	***9 vs 14 ****	***2.6 vs 8.6 ****	9.5 vs 6	71.6 vs 78.4	NR	3.4 vs 7.8	NR
Walsh [66] (2012)	RCT	3 vs 5	***12.3 vs 13.7 ****	NR	NR	10.3 vs 9.2	NR	NR	0 vs 0
Poston [67] (2013)	RCT	28 vs 32	NR	NR	NR	NR	8 vs 8	15 vs 19	NR
Petrella [68] (2014)	RCT	2 vs 2.4	***6.7 vs 16.1 ****	***3 vs 25 ****	NR	NR	NR	NR	***0 vs 35.7 ****
Hui [69] (2011)	RCT	***23 vs 57 ****	14.1 vs 15.2	NR	NR	2 vs 3.4	11.8 vs 17	NR	NR
Hui [70] (2014)	RCT	1 vs 3	***12.9 vs 16.2 ****	NR	NR	4 vs 10	10 vs 7	NR	NR
Vesco [71] (2014)	RCT	11 vs 12	***5 vs 8.4 ****	9 vs 10	9 vs 10	38 vs 45	***9 vs 26 ****	11 vs 22	4 vs 5

Data are presented as mean
*Statistically significant difference between the intervention and control group, $p<0.05$
NR, Not Reported; GDM, Gestational diabetes mellitus; GWG, gestational weight gain

(n=35) and low risk for GDM (n=35). Intervention group included the GDM women who were prescribed an energy-restricted diet of 1200-1800 kcal.

The one prospective observational study included 32 women with GDM and was conducted in China [77]. They explored the relationship between energy intake (3 tertiles; 1863, 1692 and 1384 kcal) and glycemic control using a 5-day food record as a dietary assessment.

Glycemic control: All the RCTs assessed the effect of intervention on glycemic control. In Rae et al., (2000) [73], there were no differences in mean blood glucose levels (Fasting, postprandial, pre-prandial) or HbA1c between the groups. In Garner et al., (1997), although there were no differences in mean plasma glucose after the OGTT, the intervention group had significantly reduced pre-prandial (80.4 vs 84.6 mg/dL) and 1-hour postprandial (126.1 vs 135.3 mg/dL) blood glucose levels during the 36^{th}-38^{th} week compared to the control group. In Magee et al., (1990) [74], although there were no differences in pre-prandial, fasting glucose or 24–h mean plasma glucose levels during the intervention between the two groups, women in the intervention group had significantly lower 24-hour mean plasma glucose levels at the end of intervention compared to control. In the observational study by Ho et al., (2005) [77], although there were no differences between post-breakfast and post-lunch glucose levels between the caloric groups, the post-dinner and mean postprandial glucose levels were significantly correlated with the highest tertile group.

Maternal and Fetal Outcomes

Maternal outcomes

Rae et al., (2000) [73] did not find any differences on pre-eclampsia between the intervention and control group. Two studies [72,73] reported on the incidence of cesarean section but without any differences. Two studies commented on gestational weight gain. Although Rae et al., (2005) [73] did not find any differences in GWG, in Dornhorst et al., (1991) [76], GWG was significantly reduced for women with GDM (mean ± SD 4.6 ± 4.9 kg), compared with the general prenatal population (mean ± SD 9.3 ± 5.3 kg) or women in control low-risk (mean ± SD 9.7 ± 5.3 kg) and high-risk groups (mean ± SD 9.7 ± 5.4 kg). Magee et al., (1990) [74] demonstrated that women in who assigned to the energy-restricted diet had significantly increased urine ketones and decreased insulin levels compared to control.

Fetal

Two studies reported on LGA. In Ho et al., (2005) [76], the incidence of LGA did not correlated significantly with the caloric intake. Rae showed no difference for babies born to mothers from the intervention versus the control group. Three studies reported on macrosomia [72,73,76] but none of them showed any significant difference between the intervention and the control group except in Dornhorst where babies born from women in the intervention group had significantly reduced rates of macrosomia compared to high risk control group. Two studies evaluated the effect of the energy-restricted diet on neonatal hypoglycemia [72,73], but only in Garner et al., (1997) [72] the difference was significantly different between the two groups. Two studies reported on perinatal mortality, but the number of incidents was zero [72,73]. The results from the first systematic review are presented in Table 3.

DISCUSSION

Summary of findings: The first review included 8 randomized controlled trials (Involving 1792 women and their babies) assessing the effect of energy-restricted interventions on GDM prevention. Only two studies demonstrated that intervention significantly reduced the incidence of GDM compared to control [65,68] and the remaining

Table 3: Main outcomes in the systematic review assessing the effect and safety of energy restriction on management of GDM

	Study design	Outcomes (energy-restricted vs no energy-restricted diet group)						
		Glycemic control (mg/dL)	GWG (kg)	Caesarean section (%)	Pre-eclampsia (%)	LGA (%)	Macrosomia (%)	Neonatal Hypoglycemia (%)
Garner [72] (1997)	RCT	***-Preprandial (80.4 vs 84.6) * -1-h postprandial (126.1 vs 135.3) ****	NR	20. 1 vs 18.6	NR	NR	16.1 vs 18.7	***14.4 vs 8.1 ****
Rae [73] (2000)	RCT	No differences	9.6 vs 11.5	18.5 vs 21.4	22.2 vs 22.4	28 vs 24.6	16.7 vs 10.7	37 vs 50
Magee [74] (1990)	RCT	***-Mean 24-h glucose (97.2 vs 122.5) ****	NR	NR	NR	NR	NR	NR
Dornhorst [76] (1991)	Clinical trial	NR	***4.6 vs 9.7 ****	NR	NR	NR	***9.3 vs 20.9 ****	NR
Ho [77] (2005)	Prospective observational	***Caloric restriction was significantly correlated with reduced post-dinner and mean postprandial glucose***	NR	NR	NR	Caloric restriction was not correlated with LGA	NR	NR

Data are presented as mean
*Statistically significant difference between the intervention and control group, $p<0.05$
NR, Not Reported; GDM, Gestational diabetes mellitus; GWG, gestational weight gain

six showed only a trend towards a reduction in the risk of GDM [64,66,67,69-71]. Significant reductions in gestational weight gain were observed in six trials for women who received energy-restricted diets [64-68,70,71]. Four studies reported on pregnancy-induced hypertension [64,65,68,71] and only two showed a significant difference between the two groups [65,68]. No clear differences were observed for other maternal outcomes pre-eclampsia and caesarean section between the two groups. Similarly, although intervention groups of studies demonstrated a trend towards a reduction in the risk of LGA [67-71] and macrosomia [65,67,71], there were no significant differences between the groups.

The second review included 5 studies (Involving 539 women and their babies) assessing the effect of energy-restricted interventions on GDM management. Three studies reported significant differences on glycemic control for women who received energy-restricted diets [72,74,77]. While no difference was shown for pre-prandial fasting glucose or 24–h mean plasma glucose levels during the intervention, women receiving dietary intervention had significantly lower 24-hour mean plasma glucose levels at the end of intervention compared to control [74]. Significant differences in pre-prandial and 1-hour postprandial glucose levels between the groups were also observed [72]. Post-dinner and mean postprandial glucose levels were significantly correlated with the highest tertile energy group in the observational study [77]. No clear differences were observed between the energy-restricted and the control group, when considering the secondary outcomes pre-eclampsia, GWG, LGA and macrosomia. One study demonstrated that women who assigned to the energy-restricted diet had significantly increased urine ketones and decreased insulin levels compared to control [74] and one showed a significant increased number of neonates with hypoglycemia born to women in the intervention compared to control group [72].

Relevance to current evidence: The majority of studies in the first systematic review showed that energy-restricted diets reduced GWG significantly. It has been demonstrated in a recent systematic review that current recommendations for increased energy intake during pregnancy can lead to excessive weight gain and increase the risk for GDM and adverse pregnancy outcomes [78]. The Institute of Medicine (IOM) has published in 2009 gestational weight gain guidelines in order to optimize maternal and fetal outcomes based on BMI [79]. Excessive gestational weight gain (EGWG) can occur when GWG exceeds IOM recommendations and can result in various adverse consequences. Women who gain an excessive GWG may be at increased risk for having a cesarean section [79,80] and develop type 2 diabetes and cardiovascular disease in the future [81]. Infants born to mothers who gained excessive GWG may be at increased risk of LGA and macrosomia [82,83]. In addition, another systematic review suggested that energy restriction can reduce GWG, improving glycemic control and reducing the risk for pregnancy outcomes [55]. However, only two studies demonstrated a reduction in the incidence of GDM, despite the reduced GWG. Similarly, in another systematic review by Tanentsapf et al., (2011), dietary interventions, including caloric restriction, reduced GWG significantly, but it showed only a trend towards a reduction in the risk for GDM [56]. Findings from another systematic review assessing combined diet and exercise interventions for preventing GDM suggest that there is no clear benefit in the risk of developing GDM, but the difference between the intervention and control group on GWG is significant [84].

In the second systematic review, no differences were observed in GWG in women with established GDM, but benefits were observed for glycemic control. Similarly, 2 other systematic reviews demonstrated that dietary interventions can improve glycemic control, but without reducing GWG [61,62]. It has been suggested that dietary interventions to reduce weight gain, such as caloric restriction, may need to be initiated before pregnancy in order to prevent adverse pregnancy outcomes [85]. The Position Statement of American Dietetic Association and the American Society of Nutrition recommends that all women should receive dietary counseling before, during and after pregnancy in order to reduce the risk of adverse pregnancy outcomes, including GDM [86].

Concerning the safety of energy-restricted diets, the first review

conducted on women without GDM demonstrated a beneficial effect of intervention on pregnancy-induced hypertension, LGA and macrosomia, but the difference between the groups was not significant. Only one study showed that intervention caused adverse effect and specifically increased the risk of labor induction. The second review conducted on women with GDM demonstrated that intervention did not have an effect on pre-eclampsia or caesarean section, but one study showed that women in intervention group had increased urine ketones compared to control. Excessive calorie restriction can increase maternal ketones [24] and many studies have demonstrated that increased ketonemia can affect fetal development, including mental development and neurological function [87,88]. Although these reports have raised concerns about the safety of energy-restricted diets, evidence recommends caloric restriction, highlighting the small risk-benefit ratio [89,90]. There were no differences on fetal outcomes between the two groups, but babies from women in the intervention group had increased neonatal hypoglycemia in one study. Similarly, in a recent Cochrane systematic review under a comparison of energy-restricted diet versus control in women with GDM, there were no differences for fetal outcomes or neonatal hypoglycemia [62].

Strengths and Limitations: The majority of studies included in the two systematic reviews was randomized control trials and compared significant different amounts of energy intakes between the intervention and control group. The risk of bias was assessed based on the Cochrane tool and it was mainly low in most of the criteria. Although all the included studies in the first review reported on the incidence of GDM, some had methodological limitations, such as lack of outcome assessors, small number of participants and doubt concerning dietary compliance. In the second review, only three studies were RCTs and the remaining two did not report clear results or reported only the correlation between energy intake and pregnancy outcomes. Despite limiting these systematic reviews to studies including energy-restricted dietary approaches less than 2000 kcal in the intervention group, there still appears to be much variation in the amount of energy used on each study. Women in the intervention group had more than one intervention, such as advice for low-GI foods, saturated fats, DASH dietary pattern, making it difficult to depict the beneficial impact of energy restriction. The majority of studies included advice about a certain extent of physical activity. It is possible that a publication bias may have occurred as many studies assessing the effect of energy-restricted diets on prevention or management of GDM have not presented the energy intake among the groups or were not identified and therefore were not included in the current systematic reviews. In addition, there is a limited amount of publications related to the study of prevention or management of GDM through energy restriction. Another limitation was the different level of heterogeneity in some studies, due to differences in ethnicity, characteristics of participants and diagnostic criteria for GDM used, making it difficult to generalize to the general population of pregnant women.

Future research: In the light of limitation associated to the current evidence, further randomized controlled trials are required to assess the effect of energy-restricted dietary interventions during pregnancy either on preventing or managing GDM and determine their safety in terms of adverse maternal and fetal outcomes. Future trials must be sufficiently powered and well designed to assess the clear benefit of energy restriction, without the existence of other dietary interventions. The optimal amount, duration and timing of energy restriction need to be identified. Furthermore, future trials should evaluate the effect of energy restriction before women get pregnant.

CONCLUSIONS

Results from 8 randomized controlled trials suggested no clear difference in GDM risk, pre-eclampsia or hypertension between women receiving energy-restricted diet and those receiving no energy-restricted diet and no clear difference for their babies in the risk of being born LGA or with macrosomia, but a potential benefit for reducing GWG. Results from 5 studies suggest that energy-restricted diet can improve glycemic control (1-h postprandial glucose, 24-h mean plasma glucose and end of intervention fasting glucose) in women with GDM, without increasing the risk of having caesarean section for mothers and LGA and macrosomia for infants. A potential risk for increased neonatal hypoglycemia may exist in infants born to women receiving energy-restricted diet.

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