



Published in final edited form as:

Am J Perinatol. 2016 November ; 33(13): 1291–1299. doi:10.1055/s-0036-1586504.

Windows of Opportunity for Lifestyle Interventions to Prevent Gestational Diabetes Mellitus

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Abstract

Gestational diabetes mellitus (GDM) is linked with several acute maternal health risks and long-term development of type 2 diabetes, metabolic syndrome, and cardiovascular disease. Intrauterine exposure to GDM similarly increases offspring risk of early life health complications and later disease. GDM recurrence is common, affecting 40–73% of women, and augments associated maternal/fetal/child health risks. Modifiable and independent risk factors for GDM include maternal excessive gestational weight gain and pre-pregnancy overweight and obesity. Lifestyle interventions that target diet, activity, and behavioral strategies can effectively modify adiposity. Randomized clinical trials testing the effects of lifestyle interventions during pregnancy to reduce excessive gestational weight gain have generally shown mixed effects on reducing GDM incidence. Trials testing the effects of postpartum lifestyle interventions among women with a history of GDM have shown reduced incidence of diabetes and improved cardiovascular disease risk factors. However, the long-term effects of inter-pregnancy or pre-pregnancy lifestyle interventions on subsequent GDM remain unknown. Future adequately powered and well-controlled clinical trials are needed to determine the effects of lifestyle interventions to prevent GDM and identify pathways to effectively reach reproductive-aged women across all levels of society, before, during, and after pregnancy.

Keywords

Lifestyle intervention; gestational diabetes mellitus; postpartum; preconception; inter-pregnancy

INTRODUCTION

Gestational diabetes mellitus (GDM) is rapidly rising in prevalence and could soon impact one in ten women.¹ Women with GDM have elevated risk of preeclampsia, cesarean deliveries, induced labor, and preterm birth^{2,3} and long-term risk of type 2 diabetes, metabolic syndrome, renal disease,⁴ and cardiovascular disease.^{5–10} An estimated 15–25% of women with prior GDM will develop type 2 diabetes within 1–2 years after pregnancy,^{11–14} and 35–70% will develop type 2 diabetes 10–15 years after pregnancy.^{7,8,15,16} Moreover, recurrence of GDM in a subsequent pregnancy is common, affecting 40–73% of women overall^{17–26} and 66–80% of women with overweight or

obesity.^{18,27,28} Women with additional pregnancies complicated by GDM experience three-fold increases in health risks.^{4,29,30} Identification and treatment of GDM in women exacts a high cost to the health care system.^{31–33}

Intrauterine exposure to maternal diabetes also conveys high risk of several short and long-term health problems in offspring.^{34–36} Exposure to GDM has been linked with birth trauma, respiratory distress syndrome, and neonatal death.^{37,38} GDM increases risk of excess fetal growth in utero,³⁹ higher infant fat mass,⁴⁰ neonatal macrosomia, and greater childhood prevalence of obesity (> 90th percentile) through adolescence.^{41,42} Offspring of women with GDM also have increased risk of type 2 diabetes. In a series of longitudinal studies of Pima Indians, most of the increased prevalence of childhood type 2 diabetes occurring over a 30 year time frame was attributable to increasing exposure to maternal diabetes during pregnancy.⁴³ Other long-term, prospective research has shown adolescent offspring of mothers who had diabetes during pregnancy had a significantly higher prevalence of impaired glucose tolerance (19.3 vs. 2.5%, respectively) and obesity (50% vs. 20%, respectively) than the age- and sex-matched controls,⁴⁴ and females born with obesity had increased risk of later obesity⁴¹ and doubled risk for delivering an obese infant themselves.⁴⁵

Preventing GDM has the potential to reduce the incidence of diabetes and obesity and halt the transgenerational cycle of disease.³⁶ GDM prevention has been identified as a national health priority^{46,47} Several approaches have been studied for GDM prevention, including effects of metformin,^{48,49} probiotics⁵⁰, myoinositol supplementation,^{51,52} and bariatric surgery.⁵³ This review focuses on the effects of lifestyle interventions targeting maternal weight, eating, and activity.

Obesity: A Modifiable Risk Factor for GDM

Arguably the strongest modifiable risk factor for GDM is pre-pregnancy overweight or obesity.^{54,55} Obesity affects approximately 36% of adult women overall⁵⁶ and 20% of women entering pregnancy.⁵⁷ Kim et al.⁵⁸ estimated that half of GDM cases could be prevented by reducing pre-pregnancy obesity alone. In epidemiologic studies, the risk of GDM is four to eight times higher in women with overweight or obesity than normal weight women.⁵⁸ Similarly, a meta-analysis concluded that for every 1 kg increase in pre-pregnancy BMI, the prevalence of GDM was increased by 0.92%.⁵⁹ Reducing prenatal obesity may also have impacts on offspring health. Honein et al⁶⁰ estimated that if 10% of women with pre-pregnancy obesity achieved a healthy weight before pregnancy, nearly 300 congenital heart defects and 700 fetal deaths per year could be prevented each year. Independent of GDM, pre-pregnancy obesity is also associated with several adverse maternal/infant outcomes, including preeclampsia, sleep apnea, macrosomia, induction of labor, cesarean delivery, and post-surgical wound infection.^{61,62} Independent of pre-pregnancy obesity, excessive gestational weight gain during pregnancy is also an independent risk factor for development of GDM.⁶³ Thus, reducing pre-pregnancy obesity and excessive gestational weight gain both have the potential to reduce GDM but also significantly improve other obesity-related complication and risks of disease.

Effective Lifestyle Interventions for Weight Control

Fortunately, there are effective means of promoting healthy weight loss in women. Research in obesity treatment and prevention has identified several dietary, physical activity, and behavioral strategies effective in promoting long-term weight loss (Table 1). Well-controlled randomized trials over the past 30 years have painted a consistent picture of the effective treatment components.^{64–67} The most effective weight control programs combine calorie restriction, high levels of physical activity, and behavioral strategies, including frequent self-monitoring of diet and body weight. Structured meal plans, partial meal-replacement programs, and ongoing patient-provider contact also appear to improve both short and long-term weight loss outcomes. Moreover, treatment can be delivered over many modalities (in-person, phone-based, internet).⁶⁸

Clinical trials testing the effects of comprehensive behavioral programs have found weight losses averaging about 10.7 kg (11% of body weight) over 30 weeks.^{66,69} Nonetheless, even with comprehensive behavioral treatment, gradual weight regain is often observed overtime, resulting in modest (~5%) overall weight losses at 3–4 years.^{64,70} Even with weight regain, however, improvements in long-term health occur.⁶⁴ The Diabetes Prevention Program (DPP) Research Group conducted a large, randomized clinical trial involving adults (> 25 y) in the US who had a BMI ≥ 24 and elevated glucose concentrations, making them at high risk for the development of type 2 DM.^{64,71} The DPP lifestyle intervention produced a 5.6 kg weight loss at 3 years and reduced the risk of developing diabetes by 58%; the intervention also reduced high blood pressure and metabolic syndrome.⁶⁴ Similarly, other research has shown that lifestyle interventions that promote modest weight loss prevent or delay development of type 2 diabetes in adults with impaired glucose tolerance.⁷² In a study of patients with type 2 diabetes, the Look AHEAD trial's lifestyle intervention produced an 8.6% weight loss at 1 year and a nearly 5% weight loss maintained at 8 years.⁷³ The intervention did not reduce cardiovascular events, such as heart attack and stroke,⁷⁴ but was associated with improved diabetes control and reduction in cardiovascular disease risk factors and medication use.^{70,75} Overall, comprehensive lifestyle interventions can promote sustained, modest weight losses that translate into significant health benefits and hold potential for improving the health of women at risk for GDM and its recurrence.

Lifestyle Interventions: Before, During, and/or After pregnancy

During Pregnancy—The National Academy of Science Institute of Medicine (IOM) has formulated specific recommendations based on maternal pre-pregnancy BMI for gestational weight gain ranges that are associated with optimal maternal/child health outcomes.⁷⁶ However, approximately 35% of normal weight women and 60% of obese women gain more than recommended.⁷⁷ Excessive gestational weight gain prior to glucose screening is a consistent predictor of GDM, independent of maternal pre-pregnancy BMI.⁶³ Thus, efforts to prevent GDM have focused extensively on testing lifestyle interventions to prevent excessive gestational weight gain and promote healthy eating and activity early during pregnancy.^{78–84}

Randomized clinical trials testing the effects of prenatal interventions to reduce excessive gestational weight gain and incidence of GDM have generally found no significant effects of

lifestyle interventions vs. control conditions for the prevention of GDM.^{79,81,83,84} Thus, a 2015 Cochrane review concluded no significant differences in the risk of GDM between women receiving prenatal diet and exercise interventions vs. standard care;⁸⁵ this conclusion has been echoed in other reviews.^{86,87} A meta-analysis of randomized controlled trials testing prenatal physical activity intervention concluded that physical activity in pregnancy provided only a slight protective effect against the development of GDM.⁸⁸ GDM prevention interventions that begin during pregnancy may have reduced efficacy due to: 1) low intervention intensity during pregnancy out of concerns over effects on growing fetus; 2) biological changes in pregnancy creating added barriers to adherence (e.g., craving, nausea, edema, weight gain); and, 3) a very short intervention window (2 months) to intervene prior to GDM diagnosis. Notably, the scientific literature to date has been limited by lack of power, variability in interventions, and lack of intervention uptake.^{86,87}

More recently, the RADIEL trial in Finland reported that lifestyle intervention early in pregnancy (< 20 weeks gestation) targeting diet, activity, and weight control significantly reduced gestational weight gain (−0.58 kg) and the incidence of GDM relative to a control group (incidence was 13.9% vs. 21.6%, respectively).^{89,90} The RADIEL intervention enrolled only women with obesity and was innovative in encouraging no weight gain in the first two trimesters. Ongoing trials are further testing the efficacy of interventions during pregnancy to prevent GDM^{91,92,90,93} including two US-based studies.^{94–96} The results of these trials will provide critical information on the efficacy of intervening during pregnancy to prevent GDM.

Postpartum interventions—The time period after pregnancy has also been proposed as an opportune time for intervention to reduce risk of developing type 2 diabetes and related comorbidities in women with a history of GDM. Postpartum diet and exercise interventions specifically for women with prior GDM have shown promise in reducing insulin resistance and diabetes and cardiovascular disease risk factors (Table 2).^{94,95,97–106} For example, the Tianjin GDM Prevention Program in China enrolled 1180 women (normal and overweight/obese) with prior GDM and randomized participants to a lifestyle intervention targeting diet, activity, and weight control or a control group.¹⁰⁰ After 1 year, average weight losses as a percentage of study entry weight were 2.1% in the intervention group vs 0.3% in the control group, and the decrease was more significant among overweight/obese women in the intervention (4.2%) compared with the control group (0.7%). Importantly, the intervention's modest weight losses significantly reduced diabetes risk factors, including fasting insulin and insulin resistance. Other work from the DPP study found similar - albeit more dramatic - results. The DPP included women with previous histories of GDM,¹⁰³ and, consistent with the full sample results, the behavioral weight loss intervention significantly reduced the incidence of type 2 diabetes in women with prior GDM by 50% compared with the placebo group.^{103,64}

Interconception or preconceptional interventions—Of course, the postpartum period may also be conceptualized as an interconception or preconceptional period in mothers who are planning (or who will) have additional children (Figure 1). Inter-pregnancy weight gain has been shown to significantly augment risk of GDM and its recurrence. An

analysis of 22,351 women in the Kaiser Permanente Northern California Pregnancy Glucose Tolerance Registry found that a gain of 1 to 2 body mass index (BMI) unit between the first and second pregnancy increased risk of GDM by 71%; higher gains doubled and tripled risk of GDM.¹⁰⁷ Conversely, a loss of more than 2 BMI units between the first and second pregnancy reduced odds of GDM by 68%. Other epidemiological research suggests that even modest weight losses (> 10 pounds)^{108–110} or less weight gain^{111–113} prior to pregnancy reduces risk of GDM development compared to women who maintain weight or gain >10 pounds. Retrospective data from bariatric surgery populations also suggest that weight loss in obese women prior to pregnancy may reduce the risk of GDM^{114–116} and prevent transmission of obesity to children.¹¹⁷ While the findings from observational studies are intriguing, no known clinical trials to date (Table 2) have examined the effect of postpartum weight control interventions on subsequent pregnancy and maternal/child health outcomes among women with prior GDM.

Barriers and Motivators for Lifestyle Change

Several barriers exist in intervening in the postpartum/inter-pregnancy period among women with a history of GDM.^{118,119} In addition to usual barriers that mothers face after having a baby (fatigue, unpredictable schedules, childcare demands, return to work, financial concerns), women with prior GDM are more likely to also be managing infant health issues, lactation failure, elevated depressive symptoms, and feelings of frustration with healthcare.^{118–120} However, timing interventions after pregnancy may also capitalize on a “teachable moment” for promoting long-term behavior change in women with prior GDM. “Teachable moments” are naturally occurring life transitions or health events thought to augment motivation for adopting risk-reducing health behaviors.^{121,122} Women with prior GDM report high motivation to change behaviors to protect their health and/or the health of their future child.^{119,123,124} Data from populations at high-risk of type 2 diabetes, such as Pima Indians¹²⁵ and Mexican Americans, indicate that some women with a history of GDM may be unaware that GDM poses risks after pregnancy, underscoring another potential motivational target for interventions in the postpartum period.

Future Directions

This is an exciting time for research in prevention of GDM and associated adverse maternal/child health outcomes. The evidence in support of lifestyle interventions after GDM to reduce type 2 diabetes and other disease risk factors is compelling, and some preliminary and ongoing studies suggest the potential for early interventions in pregnancy to reduce incidence of GDM. Several questions merit further investigation.

1. Can lifestyle interventions during the inter-pregnancy/pre-pregnancy period prevent GDM? As reviewed above, optimizing maternal weight and the intrauterine environment before pregnancy holds promise for preventing GDM recurrence and improving short and long-term maternal/child health outcomes. Postpartum weight loss interventions in women with prior GDM may reduce insulin resistance and diabetes and cardiovascular disease risk factors,^{94,95,97–106} but effects of postpartum interventions on subsequent maternal/child outcomes have not been investigated. Intervening in the immediate postpartum period may

be too distal from subsequent pregnancy to exert a protective effect on GDM recurrence; alternatively, timing interventions soon after a pregnancy complicated by GDM may capitalize on heightened motivation for mothers to reduce GDM recurrence. Although an estimated 45% of pregnancies are unplanned,¹²⁶ some studies suggest that pre-pregnancy lifestyle weight loss intervention is feasible among women planning pregnancy.^{127–134} Future research should test whether and how optimizing maternal weight before pregnancy can prevent GDM and its recurrence.

2. What are the most effective postpartum interventions to reach women after pregnancies complicated by GDM? Postpartum women face several challenges to attending traditional face-to-face weight loss interventions; this may explain the high attrition rates (30–40%) seen in many postpartum weight loss programs.^{135–138} Delivering weight loss intervention via telephone and/or other modalities (i.e., internet, mobile technology) may offer an alternative to face-to-face interventions⁶⁸ and may be particularly useful for postpartum women.¹³⁹ Regardless of modality, sufficient “dose” of treatment and incorporation of evidence-based weight control strategies are likely more important in determining postpartum intervention efficacy.⁶⁸
3. Can we envision a future healthcare model that conceptualizes a continuum of care? Most women in the US have access to health care and insurance during pregnancy but may lose coverage postpartum. The expansion of Medicaid in some states and the Affordable Care Act has increased the number of women who have access to insurance coverage for postpartum and preconception healthcare visits. The Affordable Care Act requires insurance coverage of at least one preconception visit without charging a co-payment. Nevertheless, we are far from a model of care that views pre-pregnancy, prenatal, and postpartum care as a continuum of opportunity for disease prevention interventions in mothers and the next generation. Only 48% of women with prior GDM receive postpartum screening for type 2 diabetes mellitus.¹⁴⁰ A continuation of services is likely needed to facilitate greater screening for diabetes, weight control counseling, and follow-up of social, behavioral, or physical health problems that may have been identified during pregnancy. Systems are in place that reach reproductive aged women before, during, and after pregnancy. The Maternal, Infant and Early Childhood Home Visiting Program and the Women, Infants, and Children (WIC) Food Supplementation program serves millions of women and young children in the US each month. However, until a larger evidence base shows significant maternal and child health benefit to preconception, prenatal, and postnatal lifestyle interventions, healthcare systems will have little mandate to create an affordable and accessible continuum of care for women and children.

CONCLUSION

More than 200,000 women in the US receive a diagnosis of GDM each year¹⁴¹ and are likely to experience acute pre- and perinatal complications and long-term development of

type 2 diabetes, metabolic syndrome, and cardiovascular disease. Children exposed to GDM similarly experience increased risk of early life complications and long-term development of disease. GDM disproportionately impacts women of low socioeconomic status and those of Hispanic, Native-American, Asian, and African-American descent.^{18,27,28,142–144} Since GDM exerts strong transgenerational effects on obesity and diabetes in offspring, a vicious cycle of social disparities in disease may be promulgated via exposure to GDM.

Comprehensive weight loss programs after GDM can reduce diabetes and other disease risk factors. The American College of Obstetrics and Gynecology and the American Diabetes Association both recommend that women with prior GDM be counseled about the benefits of diet, exercise, and weight loss in an effort to prevent the development of type 2 diabetes. However, a critical next step in research is to develop and test innovative methods to reach and improve the health status of reproductive-aged women before pregnancy and across all levels of society.

Acknowledgments

This was funded, in part, by a grant from *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (1RO1HD084282)

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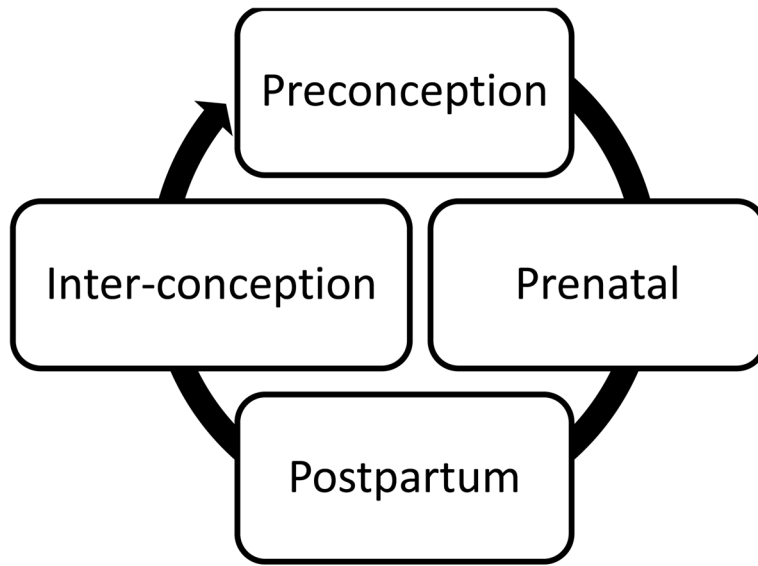


Figure 1.
Continuum of care model for health of mothers

Table 1

Variables associated with successful weight control

Calorie prescription
Meal replacements/structured meal plan
High physical activity goals (60–90 min/d)
Daily self-weighing of body weight
Daily monitoring of food intake
Behavior therapy
Continued patient-provider contact (2/mo)

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Table 2
Randomized controlled trials of lifestyle interventions after gestational diabetes mellitus

Study reference	Setting & Study duration	Intervention targets		Modality	Impact on weight	Impact on DM biomarkers
		Activity	Diet			
Ratner et al., 2008 ¹⁰³	US 3 y	Y	Y	In person	Y	Y (T2DM)
Hu et al., 2012 ¹⁰⁰	China 1 y	Y	Y	In person	Y	Y (insulin)
Shyam et al., 2013 ¹⁴⁵	Malaysia 6 mo	N	Y	In person/text message/email	Y	N
Wein et al., 1999 ¹⁴⁶	Australia 1–5 y	N	Y	Telephone/mailing	N/A	Y (T2DM)
PILOT STUDIES						
Reinhardt et al., 2012 ¹⁴⁷	US 6 mo	Y	Y	Motivational interviewing/Telephone/mailing	Y	NA
Cheung et al., 2011 ¹⁴⁸	Australia 1 y	Y	N	In person/telephone/mailing	N	NA
Ferrara et al., 2011 ⁹⁷	US 1 year	Y	Y	In person/telephone	N	NA
Kim et al., 2012 ¹⁴⁹	US 3 mo	Y	N	Web	N	N
McIntyre et al., 2012 ¹⁵⁰	Australia 3 mo	Y	N	In person/telephone	N	N

Y=yes; N=no; N/A=non applicable; mo=months; y=years; T2DM= type 2 diabetes mellitus; US= United States; GI= Glycemic index