

Exercise in the prevention and treatment of maternal–fetal disease: a review of the literature

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Abstract: Evidence-based guidelines indicate that regular prenatal exercise is an important component of a healthy pregnancy. In addition to maintaining physical fitness, exercise may be beneficial in preventing or treating maternal–fetal diseases. Women who are the most physically active have the lowest prevalence of gestational diabetes (GDM), and prevention of GDM may decrease the incidence of obesity and type 2 diabetes in both mother and offspring. However, few studies have investigated the effectiveness of exercise in delaying or preventing GDM in at-risk women, and exercise prescriptions that optimize outcomes for women with GDM are lacking. Physically active women are also less likely to develop pre-eclampsia, and we have proposed the following 4 mechanisms that may explain this protective effect: enhanced placental growth and vascularity, reduced oxidative stress, reduced inflammation, and correction of disease-related endothelial dysfunction. Exercise may also prevent reproductive complications associated with maternal obesity. Obesity increases the risk of infertility and miscarriage, and weight loss programs that incorporate diet and exercise are a cost-effective fertility treatment that may also reduce the probability of obesity-related complications during pregnancy. Regular exercise following conception may prevent excessive gestational weight gain and reduce post-partum weight retention.

Key words: exercise, pregnancy, disease prevention.

Résumé : La littérature scientifique nous apprend que, pour une grossesse en santé, la pratique régulière de l'activité physique se révèle une composante importante. En plus de contribuer au maintien de la condition physique, l'activité physique contribue à la prévention et au traitement de maladies materno-fœtales. Les femmes les plus actives physiquement présentent moins d'incidence de diabète gestationnel (GDM) et la prévention du GDM concourt à réduire l'incidence de l'obésité et du diabète de type 2, et ce, autant chez la mère que chez l'enfant. Il y a cependant peu d'études sur l'efficacité de l'activité physique à retarder ou prévenir le GDM chez des femmes à risque et il n'y a pas assez d'études sur les programmes d'activité physique visant à optimiser les bienfaits sur la santé chez des femmes présentant un GDM. Les femmes physiquement actives sont aussi moins à risque de prééclampsie; nous proposons 4 mécanismes à l'appui de cette thèse : développement amélioré du placenta et de sa vascularisation, réduction du stress oxydatif, diminution de l'inflammation et réduction des maladies associées à la dysfonction endothéliale. L'activité physique prend part à la prévention de problèmes de reproduction associés à l'obésité maternelle. L'obésité accroît le risque d'infertilité et d'avortement spontané; en ce qui concerne le traitement de la fertilité, les programmes de perte de poids et d'exercice physique présentent aussi un bon rapport coût-efficacité et contribuent à réduire les complications associées à l'obésité durant la grossesse. La pratique régulière de l'activité physique après la conception est un bon moyen de prévenir un gain excessif de poids durant la grossesse et de réduire la rétention de poids post-partum.

Mots clés : activité physique, grossesse, prévention des maladies.

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Introduction

Recent evidence-based guidelines indicate that regular prenatal exercise is an important component of a healthy pregnancy (Davies et al. 2003). In addition to allowing expectant mothers to maintain cardiovascular and muscular fitness, regular exercise is associated with a lower incidence of conditions such as varicose veins, deep vein thrombosis, dyspnea, and low-back pain (Davies et al. 2003). Exercise is a critical component of prevention and treatment strategies for diabetes, hypertension, cardiovascular disease, and obesity in non-pregnant patients (Albright et al. 2000; American College of Sports Medicine 1994; Pescatello et al. 2004). This review examines emerging evidence that regular prenatal exercise is similarly important in the treatment and prevention of gestational diabetes, pre-eclampsia, and maternal obesity, and explores the resulting implications for maternal and fetal health.

The value of prenatal exercise in treating or preventing gestational diabetes: background

Gestational diabetes (GDM) is defined as a glucose intolerance that is first recognized or diagnosed during pregnancy (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003). Muscular insulin resistance reduces the uptake of glucose into muscle cells, causing an elevation in maternal blood glucose concentrations. Insulin resistance during mid-pregnancy is a normal response to the cascade of hormonal events that ensures an adequate maternal blood glucose concentration to support fetal growth and development (Artal 2003). In women with GDM, this increase in insulin resistance is exacerbated, extending metabolic compensations for adequate fetal growth and development beyond the normal range resulting in maternal hyperglycemia.

Uncontrolled maternal hyperglycemia, such as that which occurs with GDM, gives rise to many adverse outcomes. Women with GDM are more likely to have a difficult labour and delivery, delivery by Caesarean section, and other birth complications (Jovanovic 2001). Common fetal complications include shoulder dystocia and newborn lethargy due to very low blood glucose concentrations at birth (Jovanovic 2001).

Risk factors for GDM include a history of diabetes in the immediate family (including maternal grandmother), previous diagnosis of GDM, belonging to a high-risk ethnic group (Aboriginal, Hispanic, South Asian, Asian, or African descent; Dornhorst and Rossi 1998), age equal to or greater than 35 years, being overweight (body mass index (BMI) ≥ 25 kg/m²), being obese (BMI ≥ 30 kg/m²), or a history of insulin resistance (American College of Obstetricians and Gynecologists 2001; Ben-Haroush et al. 2004; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003). Women diagnosed with GDM have an increased risk of pre-eclampsia and, later in life, developing type 2 diabetes. (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003; Goldman et al. 1991; Yogeve et al. 2004). Babies born to women with GDM are more likely to weigh more than 4000 g (macrosomia; Catalano et al. 2003) and are at increased risk for obesity during childhood (Catalano et al. 2003) and future development of diabetes (Canadian Diabetes Association Clin-

ical Practice Guidelines Expert Committee 2003). Thus, GDM leads to large babies, increasing the risk of obesity, which leads to an increased risk for type 2 diabetes, thereby increasing the risk for GDM, and the cycle continues.

The prevalence of GDM in Canada may be higher than previously thought, ranging up to 4% in the general population (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003), and as high as 18% in the Aboriginal population (Dyck et al. 2002; Godwin et al. 1999; Harris et al. 1997; Rodrigues et al. 1999). New screening recommendations to detect GDM suggest that all pregnant women be screened at 25 to 28 weeks gestation (American College of Obstetricians and Gynecologists 2001; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003). The screening test is determined from plasma and is a random (non-fasting) 1 h blood draw (1hPG) after ingestion of a 50 g glucose load. If 1hPG ≥ 10.3 mmol/L, GDM is diagnosed (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003). If 1hPG ≥ 7.8 mmol/L, a fasted oral glucose tolerance test (OGTT) with a 75 g glucose load is warranted. The fasting plasma glucose (FPG), 1hPG, and 2 h plasma glucose (2hPG) concentrations after the glucose load are measured. Plasma glucose concentrations are screened for the following: FPG ≥ 5.3 mmol/L, 1hPG ≥ 10.6 mmol/L, and 2hPG ≥ 8.9 mmol/L. Impaired glucose tolerance during pregnancy is diagnosed if one of these criteria is met or exceeded, and GDM is confirmed if 2 of these criteria are met or exceeded (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003).

After GDM is diagnosed, primary treatment is through nutritional management by a registered dietitian. The 2 goals of nutrition intervention are to achieve normal blood glucose concentrations through good food choices and to provide sufficient energy and nutrients for meeting the needs of pregnancy (Dietitians of Canada and American Dietetic Association 2000). The dietary plan should include smaller, more frequent meals, ingestion of complex carbohydrates with an increase in fiber and elimination of simple sugars (Gunderson 1997).

Women with GDM are encouraged to self-monitor their capillary blood glucose concentrations using a glucometer. Capillary blood glucose concentrations should be <5.3 mmol/L while fasting, <7.8 mmol/L 1 h post-prandial, and <6.7 mmol/L 2 h post-prandial (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003). Capillary blood glucose concentrations are assessed after 2 weeks of dietary intervention, and daily insulin injections are initiated if the values listed above are continuously exceeded (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003). A variety of insulin protocols are used, with multiple injections being the most effective (Nachum et al. 1999). The course of insulin treatment and adjustment are based on fasted and post-prandial capillary glucose concentrations (Hadden 2001).

Exercise as an adjunctive therapy for GDM

Exercise is currently considered an adjunctive therapy for women with GDM. The Canadian Diabetes Association (CDA) recommends physical activity for women with GDM

be encouraged; however, the frequency, intensity, type, and duration of activity should be based on each individual's obstetric risk (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003). The American College of Obstetricians and Gynecologists (ACOG) (2001) recommends that women with GDM who lead an active lifestyle be encouraged to continue an exercise program approved for pregnancy. These vague recommendations make it difficult for health professionals to give sound advice other than to increase physical activity. In examining the etiology of GDM in Saskatchewan, Dyck et al. (2002) found that women who were the most physically active had the lowest prevalence of GDM. A recent review in this area would concur (Dempsey et al. 2005). However, an optimal physical activity prescription required to achieve the best possible outcomes for women with GDM is lacking. This may be due to inconsistency in the success rate of exercise programs in controlling maternal blood glucose concentrations to delay or prevent insulin therapy. The mixed success rate may be due to confounding factors such as inadequate randomization, poor compliance to the exercise program, and the time at which maternal blood glucose concentrations are measured after the exercise bouts. The exercise programs that were successful in delaying or preventing insulin therapy in women with GDM had adequate subject attendance, measured maternal blood glucose within 30 min after exercise, and had an exercise intensity that was $\leq 55\% \text{ VO}_2 \text{ max}$ (Table 1).

Measurement of A1c has been considered an objective marker of chronic glycemic control (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2003) in diabetes (Homko and Khandelwal 1996). Those studies in which maternal blood glucose concentrations were normalized due to exercise in GDM women also showed decreases in A1c values (Jovanovic-Peterson et al. 1989), whereas, no change in blood glucose concentrations over time indicated no alteration in A1c values (Avery et al. 1997; Table 1).

Conclusions drawn from Lesser et al. (1996) (Table 1) must be interpreted with caution, as it has been shown that an acute bout of exercise (regardless of intensity) did not change insulin sensitivity as measured by a fasted oral glucose tolerance test within 17 h after exercise in sedentary non-pregnant women (Ben-Ezra et al. 1995). Examining the effects of a mixed meal with or without a single bout of exercise performed 14 h previously in GDM women (Lesser et al. 1996) may have missed the time frame for maximal effect of the exercise.

The failure of researchers to develop an accessible, cost-effective evidence-based program (including guidelines for exercise frequency, intensity, duration, and modality) that is optimal for glucose control may explain why exercise is not consistently used to treat GDM patients. Although exercise is still considered a valuable adjunctive therapy, the effectiveness of specifically structured exercise interventions will remain untapped until guidelines are available from well-controlled research studies. Until such studies are conducted, the available evidence would suggest that women who wish to include exercise as part of their GDM therapy should consider including low-intensity exercises such as walking or stationary biking (Table 1) and following the guidelines

set out in the PARmed-X for Pregnancy recommendations (Wolfe and Mottola 2002).

Preliminary evidence-based information on prenatal exercise in preventing GDM

GDM is considered a significant initiating factor in the type 2 diabetes epidemic (especially in high-risk ethnic groups) and thus prevention of GDM may lead to decreased rates of type 2 diabetes in successive generations (Dyck et al. 2002). Higher recurrence of GDM has been associated with greater pre-pregnancy weight, BMI, and pregnancy weight gain (Damm et al. 1992). In addition, high BMI and pre-pregnancy obesity have been identified as predictors of postpartum type 2 diabetes (Pallardo et al. 1999). Thus, prevention of GDM, particularly in women at risk for this disease, may decrease the incidence of obesity and type 2 diabetes in specific population groups. To date, few studies have investigated the effectiveness of exercise in delaying or preventing GDM in women at risk. A pilot project from Saskatchewan examined the feasibility of using exercise initiated before 21 weeks gestation to prevent GDM among Aboriginal women (Dyck et al. 1999). The target exercise intensity was 70% of the age-predicted maximal heart rate. Unfortunately, recruitment and compliance to the study were minimal, with only 8 women participating over the 2 year period. This moderate exercise intensity may have been too difficult for sedentary women, resulting in low compliance despite incentives to remain in the program. Because of the low compliance, it is difficult to assess whether or not the exercise program truly prevented GDM in this population (Dyck et al. 1999).

In a more recent case-control study, Dempsey et al. (2004) found that women who participated in any recreational physical activity within the first 20 weeks of gestation experienced a 48% reduction in the risk of GDM, after adjusting for potential confounding factors. Women who participated in any recreational physical activity during the previous year before pregnancy had a 51% decrease in the risk of GDM (Dempsey et al. 2004). In addition, women who participated in recreational physical activity during the previous year and during the first 20 weeks of pregnancy had a 60% reduction of GDM risk after controlling for confounding variables (Dempsey et al. 2004). The authors suggested that although their physical activity information was measured using a self-reported questionnaire, the relationship between physical activity and GDM risk is robust, and was detected even though physical activity was measured using a relatively imprecise tool (Dempsey et al. 2004).

Preliminary research on women with low-risk pregnancy has shown that mild exercise ($30\% \text{ VO}_2 \text{ peak}$) on a stationary bike was better at promoting glucose tolerance in response to an oral glucose load after exercise than moderate-intensity exercise ($70\% \text{ VO}_2 \text{ peak}$) in late gestation (Mottola et al. 1998b). The cycle ergometer program was initiated at 16–20 weeks gestation and continued until delivery (Mottola et al. 1998a; Mottola et al. 1998b). Biopsies of the vastus lateralis muscle in late gestation showed that GLUT 4 (insulin sensitive glucose transporter) protein was higher in women who completed mild exercise training than in women who performed moderate-intensity training (Mottola et al.

Table 1. Studies examining the success of exercise in reducing blood glucose in GDM women.

Authors	Subjects	Methods	Conclusions
Jovanovic-Peterson et al. (1989)	19 GDM women (28 weeks gestation) randomized to 6 week diet or diet + exercise intervention	Three 20 min arm ergometer sessions/week at $\leq 50\%$ $VO_{2\max}$	Women in diet + exercise lower A1c values, fasting plasma glucose than dietary intervention
Avery and Walker (2001)	12 GDM women (30 – 34 weeks gestation)	Acute response to 30 min of exercise at 35% or 55% estimated $VO_{2\max}$.	Blood glucose decreased following exercise at both intensities; exercise at $\leq 55\%$ $VO_{2\max}$ decreases blood glucose.
Garcia-Patterson et al. (2001)	20 GDM women (30.7 \pm 5 weeks gestation)	Postprandial walking at 2.52 km/h; 9 beats/min increase from resting HR	Decreased post-exercise blood glucose excursion; light postprandial exercise prevents or delays insulin therapy
Lesser et al. (1996)	Six GDM and 5 normal women (28–38 weeks gestation); randomized cross-over design	30 min stationary cycling ($\sim 60\%$ $VO_{2\max}$) 14 h before a mixed meal (600 kcal; 50% carbohydrate, 20% protein, 30% fat)	Exercise failed to improve postprandial glycemic response to mixed meal 14 h later
Avery et al. (1997)	GDM women randomized to exercise ($n = 15$; 28 weeks gestation) or control ($n = 14$; 26 weeks gestation)	Partially home-based exercise program (70% estimated max HR, 30 min, 3–4 \times /week) and dietary therapy	Exercise group: increased cardiovascular fitness, metabolic control not different compared to the control group; both groups: no change in blood glucose, HbA1c, incidence of newborn hypoglycemia
Brankston et al. (2004)	GDM women (29 weeks gestation), randomized to diet alone group ($n = 16$) or diet + resistance training ($n = 16$).	2.0 \pm 0.9 sessions circuit-type resistance exercise/week, HR \leq 140 beats/min	Number of women requiring insulin not different between groups; overweight women: lower incidence of insulin use in the exercise group
Bung et al. (1993)	Randomly assigned 41 GDM-A2 patients (1 week failure of intensive dietary therapy) into diet + exercise or diet + insulin	Three 15 min bouts and two 4 min rests of recumbent cycling 3 \times /week; 50% of maximum aerobic capacity	No between-group differences in blood glucose, delivery complications or neonatal outcomes; exercise facilitates avoidance of insulin therapy

Note: HR, heart rate.

1998a). In a subsequent study, nutritional intake was controlled during pregnancy (8350 kJ/d, 200 g/d carbohydrate) and exercise was conducted on a stair climber at 30% $VO_{2\text{ peak}}$. The combination of nutritional control and mild exercise (30% $VO_{2\text{ peak}}$) was better than mild exercise alone in controlling blood glucose concentrations as indicated by a fasted OGTT in late pregnancy and was also superior in preventing excessive gestational weight gain (Mottola et al. 1999). The effects of the combination of nutritional control and mild exercise during pregnancy persisted at 2 months postpartum, in that the area under the curve for a fasted OGTT was lower, and more of the women were at or below their pre-pregnancy body mass (Mottola et al. 1999). These studies provided the ground-work for development of a Nutrition and Exercise Lifestyle Intervention Program (NELIP), in which a mild walking program (30% $VO_{2\text{ peak}}$) is combined with nutritional control (8350 kJ/d; 200 g carbohydrate) for women at risk for GDM (Sopper et al. 2004). Preliminary results indicate that women at risk for GDM do not develop this disease while on the NELIP ($n = 23$), and glucose tolerance remains normal at 2 months post-partum (Batada et al. 2003). When combined with nutritional control, mild exercise (30% $VO_{2\text{ peak}}$, regardless of modality) appears to be a key factor in helping women at risk for GDM control blood glucose concentrations and to prevent excessive weight gain during pregnancy. Although these re-

sults are preliminary, they are the first to provide evidence that a controlled, structured, mild NELIP appears to prevent GDM in women at risk for this disease. If these results are supported by future research, this combined strategy may be a powerful tool for diabetes prevention among pregnant and postpartum women.

The value of prenatal exercise in pre-eclampsia prevention

Pre-eclampsia is a serious maternal–fetal disease that is diagnosed after 20 weeks gestation based on persistent hypertension (blood pressure $>140/90$ mmHg) and proteinuria (24 h urinary protein level ≥ 0.3 g/d) (American College of Obstetricians and Gynecologists 2002). This condition affects 2%–7% of healthy, nulliparous pregnant women (Weissgerber et al. 2004), and complications include pre-term birth, abruptio placentae, renal failure, pulmonary edema, cerebral hemorrhage, circulatory collapse, eclampsia, and the necessity for immediate delivery regardless of gestational age (Roberts and Lain 2002; Weissgerber et al. 2004). As has been reviewed previously (Weissgerber et al. 2004), underlying causes of pre-eclampsia include abnormal placental development, predisposing maternal constitutional factors, oxidative stress, immune maladaptation, and genetic susceptibility. Each of these potentially interactive factors

Table 2. Epidemiological studies examining the relationship between physical activity and pre-eclampsia risk.

Authors	Subjects	Methods	Conclusions
Saftlas et al. (2004)	2422 NPW, 172 women with GH, 44 women with PE	Interview concerning occupational and LTPA prior to 16 weeks gestation	Any LTPA reduced the risk of PE (aOR = 0.66)
Sorensen et al. (2003)	201 preeclamptic women without HELLP, 356 NPW controls	Post-partum interview; self-reported PA used to calculate weekly energy expenditure during the first 20 weeks of pregnancy and the year prior to conception	Any PA in the first 20 weeks of pregnancy decreased PE risk by 34%; light/moderate PA reduced risk by 24%; vigorous PA reduced risk by 54%; maximal intensity and number of sessions per week inversely related to PE risk
Irwin et al. (1994)	5605 active-duty US Navy personnel, including women with GH ($n = 244$), mild ($n = 182$) and severe ($n = 33$) PE, eclampsia ($n = 7$), unspecified hypertension ($n = 28$)	Diagnosis and occupation determined from database; occupations classified according to physical activity exposure	Nulliparous women: high levels of occupational lifting significantly reduced PE risk (RR = 0.68); non-significant trend towards reduced PE risk among women whose jobs required more standing, lifting, exertion, and industrial machinery use; parous women: moderate occupational exertion and lifting increased PE risk
Marcoux et al. (1989)	Women with PE ($n = 152$) and GH ($n = 251$), 505 NPW controls	Post-partum interview and questionnaire	The RR of PE decreased as hours of PA per week increased; inverse relationship between the RR of PE and maximal LTPA intensity.

Note: aOR, adjusted odds ratio; GH, gestational hypertension; LTPA, leisure-time physical activity; NPW, normotensive pregnant women; PA, physical activity; PE, pre-eclampsia; RR, relative risk.

promotes endothelial dysfunction, which leads to late-stage symptoms of pre-eclampsia (Weissgerber et al. 2004). This section will review the evidence that the incidence of pre-eclampsia is reduced among physically active women. We will then propose 4 mechanisms that may explain the observed protective effect. Finally, the importance of assessing exercise safety in preeclamptic women will be discussed, and we will critique existing studies that have examined exercise safety in pregnancy-induced hypertensive disorders.

Epidemiology of prenatal physical activity and pre-eclampsia risk

Large-scale clinical trials examining the hypothesis that regular prenatal exercise is beneficial to prevent, delay the onset, or reduce the severity of pre-eclampsia have not yet been conducted. However, epidemiologic studies indicate that regular leisure-time physical activity (LTPA) in early pregnancy is associated with a reduced risk of pre-eclampsia (Table 2) (Marcoux et al. 1989; Saftlas et al. 2004; Sorensen et al. 2003). Although some studies indicate that women who engage in the highest-intensity exercise (Sorensen et al. 2003) or have the greatest weekly energy expenditure for LTPA (Marcoux et al. 1989) demonstrate the lowest incidence of pre-eclampsia, others show no change in risk with increasing activity (Saftlas et al. 2004). Daily physical activity such as frequent walking (Marcoux et al. 1989), stair climbing (Sorensen et al. 2003), or lifting in nulliparous women (Irwin et al. 1994) were also associated with a reduced incidence of pre-eclampsia. The consistency of results despite differing methodologies, populations, and imprecise quantification of physical activity suggest a robust protective effect when exercise is performed regularly (Sorensen et al. 2003).

Postulated mechanisms for a protective effect

Physical conditioning has beneficial effects on many physiological systems that are adversely affected in pre-

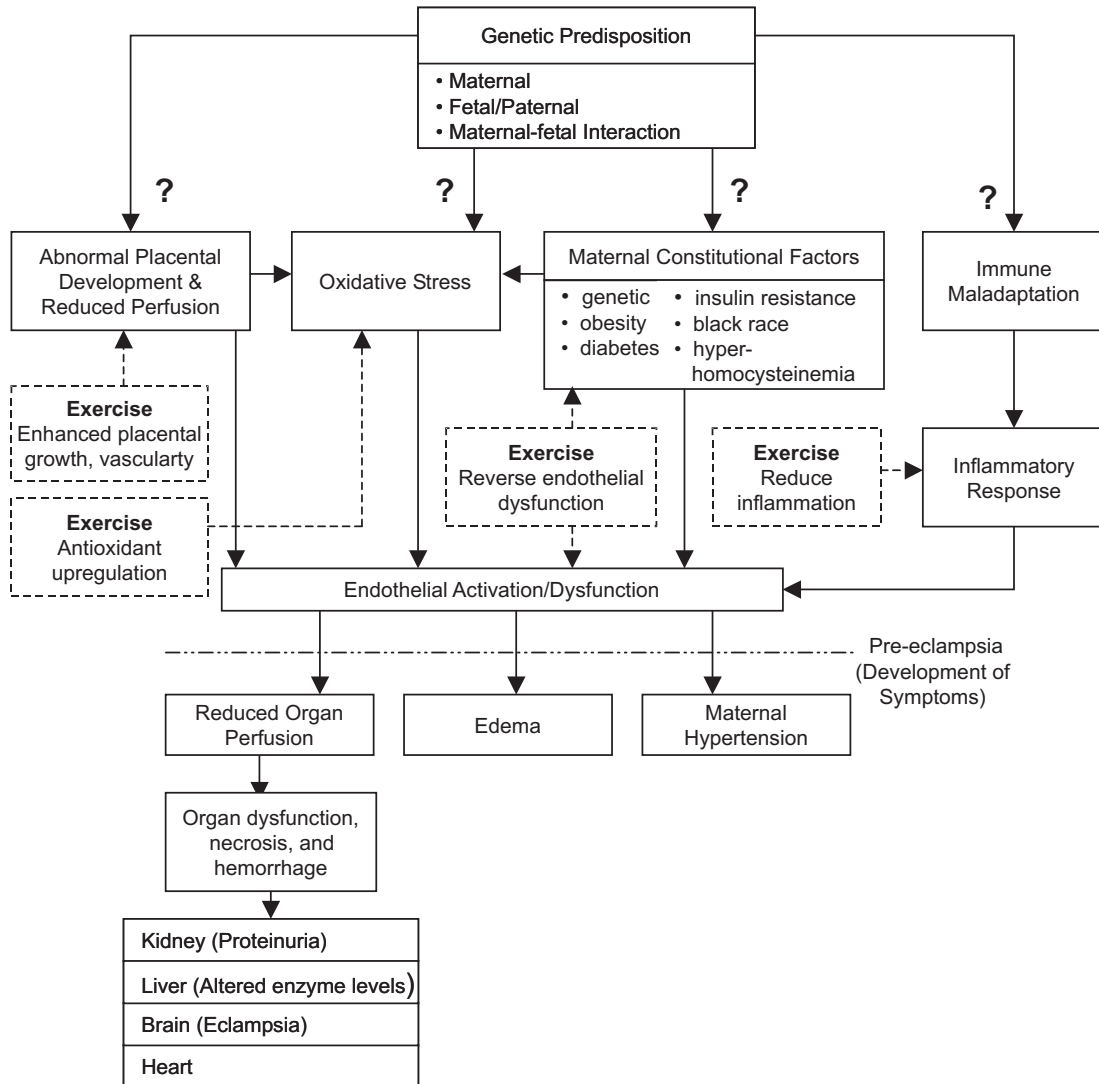
eclampsia. We hypothesized that 4 separate but potentially interactive mechanisms may protect against pre-eclampsia in active women (Fig. 1; Weissgerber et al. 2004).

Enhanced placental growth and vascularity

Abnormal placental development is an underlying cause of pre-eclampsia in some women, particularly those with growth-restricted fetuses. Inadequate trophoblastic invasion of the uterine spiral arteries in early pregnancy may lead to an incomplete loss of sensitivity to vasoconstrictors in uteroplacental vessels, causing intermittent hypoxia and reperfusion (Hung et al. 2002). The underperfused placenta may respond by releasing cytokines or lipid peroxides into the maternal circulation (Redman and Sargent 2001). Repeated hypoxia and reperfusion also increases pro-oxidant production, and anti-oxidant deficiency may impair the mother's ability to dispose of large quantities of reactive oxygen species (ROS) released following reperfusion (Roberts and Lain 2002). ROS may also cause placental villous tissue fragments to break off (Hung et al. 2002), triggering systemic inflammation and endothelial activation (Redman and Sargent 2001). Release of any of these substances (cytokines, lipid peroxides, ROS, villous tissue fragments) into the maternal circulation may cause the systemic oxidative stress that contributes to endothelial dysfunction and pre-eclampsia (Roberts and Lain 2002).

Regular exercise in early pregnancy stimulates placental growth and may protect against the pathophysiological placental changes that lead to pre-eclampsia. Women who begin an exercise program in early pregnancy demonstrate increased placental volumes and growth rates (Clapp 2003), a reduced fraction of non-functional tissue and an increased volume of villous tissue (Jackson et al. 1995). These adaptations are still evident at term even when the mother stopped exercising by 20 weeks gestation, suggesting that early pregnancy is a critical period for promoting placental growth

Fig. 1. Postulated etiology of pre-eclampsia and proposed benefits of exercise (Weissgerber et al. 2004). Solid-line boxes represent effects of pre-eclampsia; dashed-line boxes represent effects of exercise; question marks (?) indicate pathways by which genetics may influence pre-eclampsia risk. (From Weissgerber et al. 2004, reproduced with permission of Med. Sci. Sports Exerc., Vol. 36(12), p. 2028, © 2004 Lippincott Williams & Wilkins.)



(Jackson et al. 1995). Mothers who continue to exercise until term demonstrate modest additional increases in placental volume and surface area (Jackson et al. 1995). Enhanced placental growth and vascularity improves perfusion and transport capacity, and this adaptive response to exercise may prevent reductions in fetal substrate and oxygen supplies during intermittent decreases in placental blood flow (Clapp 2003).

Prevention and (or) reduction of oxidative stress

Regular exercise enhances antioxidant defense systems, limiting cellular damage from exercise-induced oxidative stress (Powers et al. 1999). Animal models indicate that exercise training up-regulates antioxidants in the liver, heart (Venditti and Di Meo 1997), and skeletal muscle, while increasing the activities of the antioxidant enzyme superoxide dismutase (SOD) and the non-enzymatic antioxidant glutathione peroxidase (Powers et al. 1999). Among healthy men and women, a 16 week aerobic training program increased

whole-blood glutathione peroxidase activity and plasma glutathione reductase activity without altering erythrocyte SOD activity (Elosua et al. 2003). The training program also increased low-density lipoprotein (LDL) resistance to oxidation, resulting in a decrease in oxidized LDL concentration (Elosua et al. 2003). Elevated energy expenditure for low-intensity physical activity in Spanish women is associated with high erythrocyte SOD activity, whereas elevated energy expenditure or high-intensity activity is associated with high glutathione peroxidase activity (Covas et al. 2002). Although erythrocyte activities of the antioxidant enzymes SOD, glutathione peroxidase, and catalase do not differ between active and sedentary pregnant women prior to delivery, SOD and catalase activities increase dramatically 1 h post-partum in active women (Kobe et al. 2002). This increase is not observed in sedentary women, and appears to prevent labor-induced increases in malondialdehyde (an indicator of lipid peroxidation) (Kobe et al. 2002). These results suggest that regular exercise training may enhance

maternal antioxidant responses to increased oxidative stress in normal pregnancy (Kobe et al. 2002), which may prevent endothelial dysfunction and the resulting symptoms of pre-eclampsia.

Reduction of inflammation

Although the effects of physical activity on inflammatory markers during pregnancy are not known, the majority of available evidence supports an anti-inflammatory effect of regular exercise (Kasapis and Thompson 2005) in non-pregnant individuals and patients with heart failure (Adamopoulos et al. 2001) and coronary artery disease (Goldhammer et al. 2005). Women in the highest quintile of physical activity demonstrated a 68% reduction in C-reactive protein (CRP) levels in comparison with women in the lowest quintile (Pischon et al. 2003). Moderate associations between physical activity and both CRP and interleukin-6 were markedly attenuated after adjustment for BMI and leptin, an indicator of fat mass, suggesting that the anti-inflammatory effects of exercise are mediated through changes in body composition (Pischon et al. 2003). The effects of exercise training on CRP may also depend on baseline CRP levels (Lakka et al. 2005). A 20 week training program decreased CRP in white and black women with high CRP levels (>3.0 mg/L); however, there were no changes in women with baseline CRP < 3.0 mg/L (Lakka et al. 2005). Although reductions in CRP following 12 weeks of exercise training in men and women with coronary artery disease were greater among diabetic patients than among non-diabetic patients, this difference was likely due to a 36% greater mean baseline CRP in diabetic patients (Goldhammer et al. 2005). The training program also decreased interleukin-1, interleukin-6, and interferon- γ , while increasing the anti-inflammatory cytokine interleukin-10 (Goldhammer et al. 2005). If exercise training has similar anti-inflammatory effects in pregnant women, this could prevent or attenuate the systemic inflammatory response that occurs in pre-eclampsia (Redman and Sargent 2004).

Correction of endothelial dysfunction

Although the effects of exercise training on endothelial function in healthy pregnant women and women at risk for pre-eclampsia have not been examined, regular exercise improves endothelial function in non-pregnant individuals with endothelial dysfunction resulting from a variety of conditions. Aerobic conditioning increases local endothelium-dependent dilation in patients with endothelial dysfunction resulting from aging (DeSouza et al. 2000) and type 2 diabetes (Maiorana et al. 2001), while large muscle mass exercise improves systemic endothelial function in heart failure patients (Maiorana et al. 2000). Enhanced endothelial function may provide short-term compensation for exercise-induced increases in shear stress (Laughlin 1995). Repeated exposure to shear stress causes structural remodeling of the vasculature to reduce shear stress, and endothelial function in healthy subjects returns to pre-training levels (Kingwell et al. 1997). In contrast, exercise training causes long-term improvements in endothelial responses in patients with endothelial dysfunction resulting

from a variety of conditions (Maiorana et al. 2001; Maiorana et al. 2000). If similar results are observed in women at risk for pre-eclampsia, training-induced correction of disease-related endothelial dysfunction may prevent the main pathological process leading to this disease.

Exercise safety and the potential role of exercise as an adjunct therapy in pregnancy-induced hypertensive disorders

Treatment guidelines for gestational hypertension and mild pre-eclampsia have traditionally recommended bed rest to prevent blood pressure increases associated with daily activity. However, as many as one third of women fail to comply with bed rest recommendations (Josten et al. 1995), and compliance does not effect pregnancy outcome among women who develop mild pre-eclampsia in late gestation (Magee et al. 1999). Recent recommendations have therefore shifted towards ambulatory management with careful patient monitoring (Lenfant 2001; Moutquin et al. 1997). The patient is advised to incorporate additional rest into her normal routine, and is carefully monitored to ensure that her condition is stable (Lenfant 2001). Exertion associated with activities of daily living is highly variable, however, and research is therefore needed to assess the safety of moderate-intensity physical activity for both the hypertensive mother and her fetus. Research is also needed to determine if the blood pressure lowering effects of acute exercise extend to women with gestational hypertension, mild pre-eclampsia, and chronic hypertension in pregnancy. Although exercise is a recommended adjunct therapy in non-pregnant hypertensive patients (Pescatello et al. 2004), it is not known if this is a safe or effective adjunct therapy in pregnancy-associated hypertensive disorders.

Six studies have conducted brief exercise interventions in women with gestational hypertension and pre-eclampsia (Hackett et al. 1992; Morris et al. 1956; Nisell et al. 1985; Nisell et al. 1987; Rafla 2000; Rafla and Cook 1999). Comparison of sodium clearance rates in pre-eclamptic and normotensive pregnant women at rest and during 10–16 min of supine cycling suggested that exercise-induced increases in leg blood flow are accompanied by small decreases in uterine blood flow (Morris et al. 1956). The authors speculated that the magnitude of the observed reductions would not adversely effect the fetus unless the mother was severely pre-eclamptic (Morris et al. 1956). Pre-eclampsia, however, was defined exclusively by hypertension with no criteria for multisystem organ involvement (Morris et al. 1956).

Uteroplacental resistance increases during supine cycling in women with normal pregnancies, pregnancy-induced hypertension, and small for gestational age fetuses (Hackett et al. 1992). The authors postulated that this could be detrimental to the fetus, particularly in mothers with an abnormal resting uteroplacental waveform (Hackett et al. 1992). However, fetal responses were not directly measured and uteroplacental resistance rapidly returned to baseline levels following exercise (Hackett et al. 1992). Differences between complicated and uncomplicated pregnancies may have reflected between-group differences in physical fitness and a failure to standardize the exercise protocol, as cycling tests were completed at the same absolute work rate and exercise duration was not reported (Hackett et al. 1992).

Only one study evaluated fetal responses following exercise in hypertensive pregnant patients. Examination of fetal heart rate tracings after 5 min of cycle ergometry in 44 women with high-risk pregnancies (diabetes ($n = 9$), intrauterine growth restriction (IUGR) ($n = 18$), and hypertension ($n = 17$)) revealed 9 cases of fetal bradycardia (Rafla and Cook 1999). Unfortunately, the diagnoses of these women were not reported, and it is unclear if hypertensive and diabetic women were also screened for IUGR (Rafla and Cook 1999). Post-exercise bradycardia may be more likely in growth-restricted fetuses (MacPhail et al. 2000), as the chronic placental blood flow deficiency can be exacerbated by diversion of blood from the uterus to the exercising muscles. A subsequent publication evaluating changes in umbilical artery blood flow after 5 min of cycle ergometry in 17 in-patients with hypertension and 2+ proteinuria concluded that 5 min of moderate-intensity cycle ergometry was not harmful to the hypertensive mother or fetus (Rafla 2000). Changes in heart rate, blood pressure, stroke volume, cardiac output, and vascular resistance during 3 min of isometric handgrip exercise do not differ between healthy pregnant controls and women with gestational hypertension (Nisell et al. 1985) and mild pre-eclampsia (Nisell et al. 1987).

Existing research has several limitations that should be addressed. First, available studies (Hackett et al. 1992; Morris et al. 1956; Nisell et al. 1985; Nisell et al. 1987; Rafla 2000; Rafla and Cook 1999) have not adequately distinguished between gestational hypertension, chronic hypertension, and pre-eclampsia. The etiology of these disorders may differ, and the effects of exercise in each condition should be examined separately. Second, fetal monitoring is needed to directly assess fetal exercise safety in each of these conditions. Third, the potential benefits of exercise as an adjunct anti-hypertensive therapy have not been examined. The maximum exercise duration was 10–16 min (Morris et al. 1956) and the 5 min exercise bouts used in most studies (Nisell et al. 1985; Nisell et al. 1987; Rafla 2000) are substantially less than the 30 min minimum recommended to reduce blood pressure in non-pregnant hypertensive patients (Pescatello et al. 2004). Observations that diastolic blood pressure in pregnant hypertensive patients fell below pre-exercise levels after supine cycling (Morris et al. 1956) should be evaluated by ambulatory blood-pressure monitoring. The effects of longer duration, large muscle mass exercise on maternal blood pressure, fetal heart rate, and pregnancy outcome have important implications for the management of women with gestational hypertension, chronic hypertension, and mild pre-eclampsia.

Pre- and post-natal exercise to prevent maternal obesity

The percentage of overweight women of childbearing age (ages 20–39 y) in the United States nearly doubled between 1988 to 1994 and 1999 to 2000, reaching 49% among white women and 70% among black women (Okosun et al. 2004). The percentage of obese white women (ages 20–39 y) increased from 15% between 1988 and 1994 to 24% in 1999–2000, and values for black women were nearly double those

for white women (Okosun et al. 2004). Although the implications of these trends for cardiovascular disease and diabetes have received considerable attention, the reproductive effects are less commonly understood. This section therefore examines the risks of being overweight or obese before, during, and after pregnancy, and presents evidence that lifestyle interventions that include regular aerobic exercise may reduce the risk of obesity-related reproductive complications (Fig. 2).

Risks of obesity and benefits of exercise prior to conception

Women who are overweight or obese before conception have an increased risk of complications, including polycystic ovarian syndrome (PCOS) (Yen 1980), menstrual irregularity, and infertility (Rich-Edwards et al. 1994), that reduce the probability of conception. The relative risk of ovulatory infertility increases progressively with increasing BMI at 18 years of age, with values ranging from 1.7 in women with a BMI of 26–27.9 kg/m² to 2.7 in women with a BMI > 30 kg/m² (Rich-Edwards et al. 1994). Increases in menstrual irregularity were also observed among overweight and obese women, reaching a relative risk of 1.75 in those with a BMI > 32 kg/m² (Rich-Edwards et al. 1994). Body fat distribution may influence fertility, as a 0.1 unit increase in the waist–hip ratio of women enrolled in a donor insemination program decreased the probability of conception by 30% per cycle (Zaadstra et al. 1993). Obesity may also account for increased spontaneous abortion rates in women with PCOS (Wang et al. 2001).

In addition to reducing the probability of conception, obesity negatively affects fertility treatment outcomes. Obese women are less likely to conceive when using clomiphene citrate, and the dose required for successful conception increases with increasing BMI (Dickey et al. 1997). Conception rates are similar in lean and obese women with anovulatory PCOS following gonadotropin treatment; however, obese women are more likely to miscarry and require larger gonadotropin doses to induce ovulation (Hamilton-Fairley et al. 1992). Women with a BMI greater than 25 kg/m² are 1.77 times more likely to miscarry in early pregnancy after in vitro fertilization or intracytoplasmic sperm injection than women with a BMI less than 25 kg/m² (Fedorcsak et al. 2000). Obese women are more likely to require fertility treatments to conceive (Rich-Edwards et al. 1994); however, they are less likely to successfully conceive and give birth as a result of these treatments.

The effectiveness of group weight loss programs that include regular exercise in restoring fertility in obese women (BMI ≥ 30 kg/m²) was recently demonstrated by a 6 month lifestyle intervention study (Clark et al. 1998). Subjects ($n = 67$) had been infertile for at least 2 y, were able to exercise, and had no endocrine condition other than PCOS. Women attended a 2 h weekly session (1 h of aerobic exercise and 1 h of educational seminars on weight-related topics) in a supportive group environment, and were instructed to complete at least 2 additional exercise sessions per week. Women who completed the intervention lost an average of 10.2 ± 4.3 kg (range 3.5–15 kg), in contrast to an average yearly increase in BMI of 1 kg/m² before the intervention. Eighty percent of participants were anovulatory before the

Fig. 2. Reproductive risks associated with obesity and benefits of exercise prior to conception, during pregnancy, and post-partum. Solid-line boxes represent reproductive risks associated with obesity (note that excessive weight gain and weight retention are not risks of obesity per se; however, they may increase the risk of future problems with body mass in some women); dashed-line boxes represent effects of weight loss before conception (exercise and dietary intervention) and exercise on reproductive risks associated with obesity.

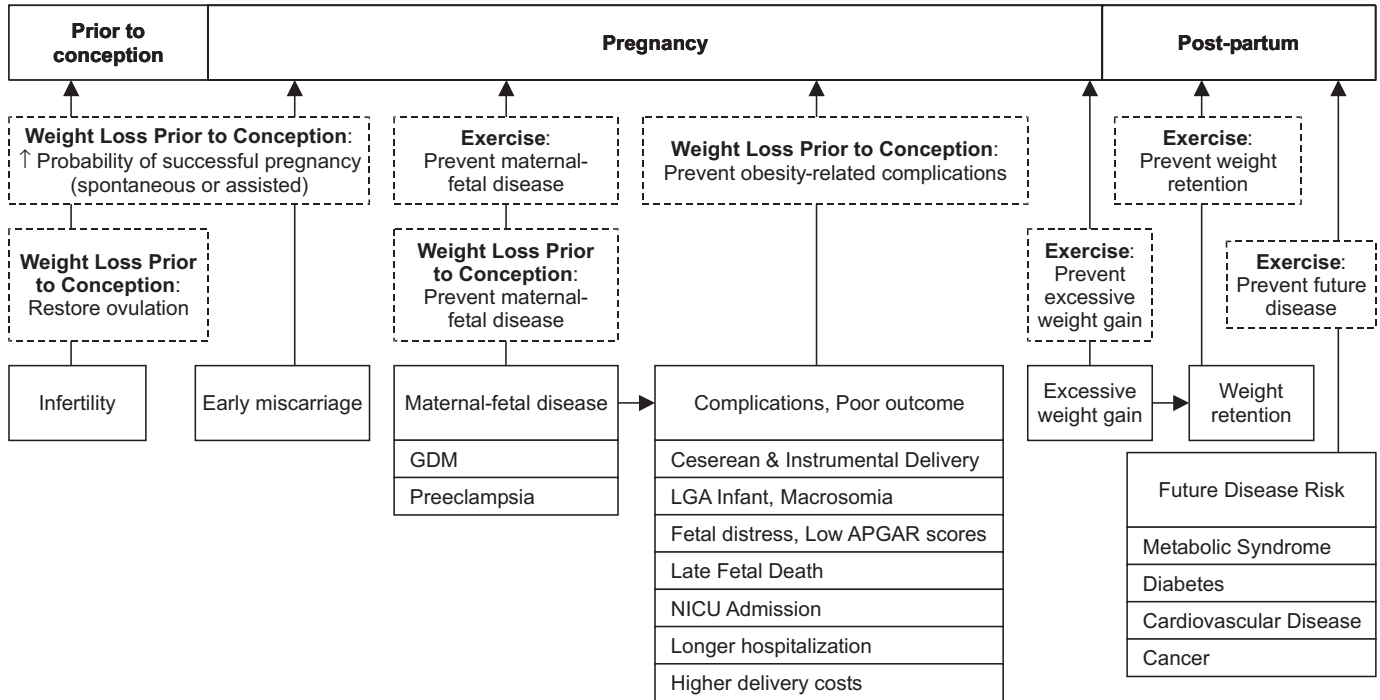


Table 3. Relative risk of complications in overweight and obese women.

	Relative risk for overweight women	Relative risk for obese women	References
Maternal outcomes			
Pre-eclampsia	2.0 (1.8, 2.2)*	3.3 (3.0, 3.7)*	Baeten et al. 2001
Pre-eclampsia and PIH	1.7 (1.0, 2.8)†	5.6 (3.5, 9.0)†	Jensen et al. 2003
GDM	2.4 (2.0, 2.9)*	5.2 (4.3, 6.2)*	Baeten et al. 2001
Induced labour	1.5 (1.1, 2.2)†	3.2 (2.2, 4.6)†	Jensen et al. 2003
Caeserean delivery	1.6 (1.2, 2.3)†	2.7 (1.9, 3.8)†	Jensen et al. 2003
	1.8 (1.6, 1.9)*	2.7 (2.5, 2.9)*	Baeten et al. 2001
Fetal outcomes			
Macrosomia	1.5 (1.4, 1.6)*	2.1 (1.9, 2.4)*	Baeten et al. 2001
	1.4 (1.0, 1.9)†	2.2 (1.6, 3.1)†	Jensen et al. 2003
LGA infant	1.1 (0.8, 1.5)†	2.5 (1.8, 3.6)†	Jensen et al. 2003
Late fetal death	1.6 (1.1, 2.3)*	2.6 (1.7, 3.7)*	Cnattingius et al. 1998

Note: Overweight was defined as a pre-pregnancy BMI of 25.0–29.9 kg/m², whereas obese was defined as a pre-pregnancy BMI ≥ 30 kg/m². Late fetal death was defined as stillbirth occurring after 28 weeks gestation. GDM, gestational diabetes mellitus; LGA, large for gestational age; PIH, pregnancy-induced hypertension.

*Relative risk compared with a reference group with a BMI < 20 kg/m².

†Relative risk compared to women with a BMI between 18.5 and 24.9 kg/m².

intervention, whereas 90% were ovulating spontaneously after the intervention. All subjects had been infertile for at least 2 y before the intervention; however, 77% of subjects conceived successfully during or after the intervention. Sixty-seven percent delivered live infants, and 40% of these births resulted from spontaneous conception. The miscarriage rate was also dramatically reduced, from 75% before the intervention to 18% during the intervention and the fol-

lowing year. Women who did not conceive spontaneously or give birth to a live infant were either smokers, attended less than 66% of weekly sessions, or were not successful in reducing BMI below 40 kg/m² by the end of the intervention. The authors hypothesized that improved fertility resulted from beneficial effects of reduced insulin resistance and lower insulin concentrations on reproductive hormone pro-

The diet and exercise intervention described above (including fertility treatments) cost 210 000 Australian dollars (AUD) and resulted in 45 live births, a cost of AUD 4600 per baby (Clark et al. 1998). Traditional infertility treatments in the same women before the intervention cost AUD 550 000 and resulted in 2 live births, a cost of AUD 275 000 per baby. The intervention was 60 times more cost-effective and yielded a success rate of 67% (versus 3% with traditional treatment), demonstrating that weight loss through diet and regular exercise before conception should be a cornerstone of infertility treatment for obese women.

Risks of obesity and benefits of exercise during pregnancy

Overweight and obese women who conceive have an increased risk of maternal and fetal complications, which contribute to longer hospitalization (Galtier-Dereure et al. 1995) and higher delivery costs (Galtier-Dereure et al. 2000). The risk of maternal and fetal complications increases with the degree of obesity. The incidence of pre-eclampsia doubles with every 5–7 kg/m² increase in pre-pregnancy BMI, with each 1 kg/m² increase in BMI resulting in a 0.54% increase in pre-eclampsia risk for women with BMIs between 18 and 36 kg/m² (O'Brien et al. 2003). The risk of gestational diabetes also increases progressively in overweight, obese, and morbidly obese women (Table 3) (Baeten et al. 2001; Cedergren 2004). Overweight and obese women are more likely to deliver large for gestational age and macrosomic infants (Catalano et al. 2003), even after controlling for higher rates of gestational diabetes and pre-eclampsia (Baeten et al. 2001; Jensen et al. 2003). Infants of obese women are more likely to experience neonatal intensive care unit admission (Rosenberg et al. 2003), caesarean section (Galtier-Dereure et al. 2000) and instrumental delivery. Those of morbidly obese mothers (BMI ≥ 40 kg/m²) are twice as likely to demonstrate fetal distress and low APGAR (activity, pulse, grimace, appearance, and respiration) scores (Cedergren 2004). The high incidence of complications in overweight and obese women increases the cost of prenatal hospital care 5 fold (Galtier-Dereure et al. 1995).

Regular prenatal exercise, which includes exercise conducted before conception and during pregnancy, may act through several mechanisms to prevent obesity-related complications and adverse pregnancy outcomes. First, exercise-induced weight loss before conception, ideally resulting in a healthy BMI, may prevent obesity-related increases in the risk of complications described above. Second, the research contained in earlier sections of this review suggests that regular aerobic exercise initiated during pregnancy may prevent gestational diabetes (Batada et al. 2003) and pre-eclampsia (Weissgerber et al. 2004). Lowering the incidence of these 2 conditions among overweight and obese women may also prevent the resulting complications and adverse pregnancy outcomes associated with these maternal–fetal diseases. Third, exercise during pregnancy may assist women in preventing excessive weight gain (Polley et al. 2002). Excessive gestational weight gain is associated with increased post-partum weight retention, and hence prenatal exercise may also be beneficial to facilitate return to pre-pregnancy weight after delivery (Rooney and Schauburger 2002).

Post-partum risks of obesity and benefits of exercise

Early observations that the average maternal BMI and the prevalence of obesity increase with increasing parity suggested that post-partum weight retention might contribute to obesity, particularly in women who have had at least 5 children (Heliövaara and Aromaa 1981). More recent analyses indicate that mean post-partum weight retention is negligible after controlling for measurement error and weight gain attributable to aging, suggesting that pregnancy does not lead to obesity in most women (Gunderson and Abrams 1999). Variation in pregnancy-induced weight retention is large, however, and pregnancy can contribute to unhealthy weight increases in up to 20% of women (Gunderson and Abrams 1999).

Women who become overweight or obese as a result of excessive gestational weight gain and post-partum weight retention have an increased risk of future health problems and co-morbid conditions. As has been reviewed extensively elsewhere, obesity increases the risk of developing the metabolic syndrome, hypertension, coronary artery disease, stroke, type 2 diabetes, and arthritis (Haslam and James 2005). Many of these conditions demonstrate dose–response relationships, with the most obese individuals demonstrating the greatest increase in risk (Haslam and James 2005). Excess body mass and physical inactivity are also known to increase the risk of cancer (Haslam and James 2005) in the breast, colon, kidney, esophagus, and endometrium (Modesitt and van Nagell 2005). The increased incidence of co-morbid conditions decreases life expectancy in obese individuals (Haslam and James 2005). Structured weight-loss programs that include physical activity are therefore important to assist women in attaining a healthy weight post-partum. This may prevent future morbidity and mortality, while reducing the risk of developing reproductive complications associated with obesity in subsequent pregnancies. Women who do not achieve a healthy weight may still benefit from increasing physical activity, which can lower adiposity and reduce the risk of mortality (Hu et al. 2004) and endometrial cancer (Modesitt and van Nagell 2005) in obese women.

Two studies have examined the effectiveness of regular exercise and caloric restriction in promoting post-partum weight loss (Lovelady et al. 2000; O'Toole et al. 2003). In the first study, overweight, sedentary, non-smokers who were exclusively breast feeding were randomly assigned to a control group ($n = 19$) or a diet and exercise intervention ($n = 26$) (Lovelady et al. 2000). Subjects in the intervention were prescribed an energy intake of 500 kcal (1 kcal = 4.184 kJ) less than the average of the baseline energy intake and calculated energy requirements, and participated in four 45 min exercise sessions per week at 65%–80% of heart rate reserve. Women who completed the 10 week intervention demonstrated significant reductions in weight (4.8 ± 1.7 kg), BMI (1.8 ± 0.6 kg/m²), and fat mass (4.0 ± 2.0 kg) with no adverse effects on infant growth. There were no significant changes among women in the control group.

Although the lifestyle intervention resulted in short-term weight loss and improved body composition (Lovelady et al. 2000), the results have limited implications for health care providers. Women in the control group did not attempt to lose weight, whereas women in the intervention group were given personalized programs and carefully monitored

to ensure compliance (Lovelady et al. 2000). Outside of the research setting, however, most women do not have access to personalized programs and ongoing monitoring to ensure success. The ability of overweight and obese women to lose weight under these circumstances has important implications for post-natal care.

This issue was examined in a second study conducted on women who delivered 1.5–6 months before entering the study and had a pre-pregnancy BMI of 25–29.9 kg/m² (O'Toole et al. 2003). Subjects had gained at least 15 kg during pregnancy, were at least 5 kg above their pre-pregnancy weight upon enrollment, and were not regularly exercising or participating in a weight loss program. Subjects were randomly assigned to either a structured ($n = 21$) or self-directed ($n = 19$) intervention. Women completing the structured intervention attended regular group education sessions, and received a personalized 12-week diet and exercise program designed to increase energy expenditure by 150 kcal/d while creating a dietary caloric deficit of 350 kcal/d. During a 1 h session with a dietician and exercise physiologist, subjects completing the self-directed intervention received basic diet and exercise information and instructions to create a 500 kcal/d caloric deficit. Subjects who completed the structured intervention lost an average of 5.6 kg and 4.9% body fat over 12 weeks, and these changes persisted 1 y post-partum. There were no changes at either time point among women completing the self-directed intervention. These results clearly indicate that structured, personalized programs with regular follow-up are important to facilitate post-partum weight loss in women with excessive weight gain during pregnancy and post-partum weight retention.

Future directions

Well-controlled research studies are urgently needed to develop exercise guidelines for the prevention and treatment of GDM. Intervention studies should focus on the benefits of low-intensity exercise in improving blood glucose control and pregnancy outcomes for women with this condition. Research is also needed to determine if exercise protects against pre-eclampsia through the proposed mechanisms (enhanced placental growth and vascularity, reduced oxidative stress, and correction of disease-related endothelial dysfunction), and to assess the potential benefits of exercise as an adjunct treatment for mild hypertension in pregnancy. Finally, future studies should assess the relative importance of dietary changes, regular exercise, and weight loss in protecting against obesity-related complications. The effects of regional fat distribution on fertility, pregnancy outcome, and the effectiveness of exercise in preventing these complications should also be examined. Large-scale lifestyle interventions that lower the prevalence of obesity are urgently needed to reduce the incidence of reproductive complications and improve maternal and fetal well-being.

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