

# Preventing the development of type 2 diabetes in women with gestational diabetes

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## Introduction

Gestational diabetes is a carbohydrate intolerance that is first detected in pregnancy and usually disappears after birth. It is characterised by fasting and post-prandial hyperglycemia. The immediate maternal and fetal consequences of gestational diabetes on pregnancy are well known. During the last decade, there has been increasing evidence suggesting that women with gestational diabetes are at increased risk of developing diabetes and metabolic syndrome in later life. A meta-analysis of 20 cohort studies involving 675 455 women reported that women with gestational diabetes had a 7.5-fold increased risk of developing type 2 diabetes compared with those women who had a normoglycemic pregnancy (RR 7.43, 95% CI 4.79-11.51).<sup>1</sup> Women with a history of gestational diabetes had a relative risk of 4.69 within 5 years of pregnancy and this risk doubled to 9.34 after 5 years.

Diabetes is a global health problem and it is estimated that 366 million people will be affected by the year 2030.<sup>2</sup> Unfortunately four-fifths of all patients with diabetes live in developing countries. One of the greatest contributors to the development of diabetes is obesity. More than 80% of cases of type 2 diabetes can be attributed to obesity. The incidence of obesity is also increasing and in the United States the life-time risk of becoming overweight and obese is 50 and 25 percent respectively.

The goals of diabetes prevention are:

- delaying the onset of diabetes
- preserving beta cell function and
- preventing microvascular complications
- preventing the associated increased risk of cardiovascular disease

## Pathogenesis of type 2 diabetes

The pathophysiology of type 2 diabetes can be explained by observing biochemical changes in patients before and after bariatric or gastric bypass surgery. Several studies have demonstrated a reversal in metabolic abnormalities following bariatric surgery.<sup>3,4</sup> Prior to bariatric surgery type 2 diabetic patients are in a state of increased energy balance. This increased energy state causes insulin resistance in muscle which in turn causes increased fat deposition in the liver. The fatty liver stimulates increased hepatic glucose output and raised plasma triacylglycerol. These high levels of fatty acids cause suppression of glucose-mediated insulin secretion by beta cells. Therefore, hepatic insulin resistance and beta cell dysfunction are directly related to ectopic fat deposition in the liver and pancreas.<sup>5</sup>

During the first week following bariatric surgery, most patients experience a significant reduction in daily energy intake. A person with a body weight of 150kg requires approximately 3 200kcal of energy per day to maintain a steady weight.<sup>6</sup> This energy intake falls close to zero from the morning of surgery for several days. Several studies have shown that this energy restriction causes liver fat levels to fall within days of surgery. Both hepatic insulin sensitivity and plasma glucose levels are also normalised.<sup>5</sup>

Therefore the aetiology of diabetes lies in a state of positive energy balance. This phenomenon is clearly demonstrated in the Pima Indians. Over a period of forty years the prevalence of diabetes has increased from 0% to 40% coinciding with a lifestyle change from subsistence farming to inactivity and surplus food.<sup>7</sup>

## Prevention

The four pillars of diabetes prevention include:

- screening
- education
- behaviour and lifestyle modification
- pharmacotherapy

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**Table 1: Steps in the pathogenesis of type 2 diabetes**

<i>Positive energy balance</i>	
Accelerated progression of insulin resistance	Lifelong or years
Increased liver fat	Years
Increased plasma triacylglycerol	Years
Unrestrained liver glucose production	Few years
Initial elevation of plasma glucose	Few years
Excess exposure of pancreas to fatty acid	Months to years
Decreased insulin secretion in response to glucose	Months to years
Hyperglycaemia	Months
Irreversible beta cell loss and dysfunction	>2 years

**Screening**

The American Diabetes Association recommends that women with gestational diabetes be screened by measuring the fasting blood glucose at 6-12 weeks postpartum, while The World Health Organisation recommends performing a 75g – 2 hour oral glucose tolerance at the 6-week postpartum visit.<sup>8</sup> Cholesterol and lipoprotein levels should also be performed at this visit to screen for metabolic syndrome. However since these risks persists for several years postpartum, continuous assessment and screening should be considered.

**Education**

Education plays an important role in diabetes prevention. Although women with previous gestational diabetes understand and are concerned by their increased risk of type 2 diabetes, only a few make positive changes to their lifestyle.<sup>9</sup> An Australian study found that maternal awareness about the role of physical activity in diabetes prevention was low.<sup>10</sup> Women who were active mentioned constraints on physical activity participation such as the demands of motherhood and the time restrictions these demands impose on their ability to take time out for themselves. These women placed the needs of their families before their own and they felt that taking time out for themselves was inappropriate in their circumstances.

**Prevention**

**Lifestyle modification**

There is sufficient evidence to suggest that lifestyle modification, aimed at reducing weight and increasing exercise will lead to a reduction in the development of type 2 diabetes in populations at risk.

**Diabetes Prevention Program** – In this trial, 3 234 subjects at risk of developing diabetes were randomised to receive either standard lifestyle plus placebo, standard

**Table 2: Postpartum care in women with gestational diabetes**

<i>Early postpartum (day 1-3)</i>	
Education	Encourage and train for healthy nutrition Plan physical activity Discuss importance of weight reduction Continue smoking cessation Facilitate breast feeding for at least 3 months Discuss appropriate contraception use Explain long-term risks of diabetes and metabolic syndrome Clarify the need for 6-8 week 2-hour glucose tolerance test Discuss the importance of planning future pregnancies
Screening	Perform fasting and post-prandial glucose test
<i>Late postpartum (6-12 weeks)</i>	
Education	Reinforce all of the above Explain the importance of yearly follow-up thereafter Discuss infant care and prevention of childhood obesity
Screening	Perform 75g 2-hour oral glucose tolerance test Monitor blood pressure, body mass index, cholesterol and lipoprotein levels
Adapted from Khandelwal M, GDM: Postpartum Management to Reduce Long-Term Risks. Current Diabetes Reports.2008	

lifestyle plus metformin or intensive lifestyle and followed for 3 years.<sup>11</sup> Subjects in the intensive lifestyle arm received counselling on the reduction of fat and calories in their diet and increased their exercise. Their aim was to reduce their body weight by 7% and increase their exercise to at least 150 minutes of moderate exercise per week. After 3 years there was a 57% reduction in the incidence of diabetes in the intensive lifestyle group compared with standard lifestyle. The incidence of diabetes was reduced by 31% in the metformin arm.

The Diabetes Prevention Program Outcome is a follow-up study which showed that the benefit of lifestyle intervention persisted over 10 years with a 34% reduction in the incidence of diabetes.<sup>12</sup>

**Finnish Diabetes Prevention Study** – Five hundred and fifty-two subjects with impaired glucose tolerance were randomised to a weight reduction and exercise program or a control -group.<sup>13</sup> After 2 years the mean weight loss in the intervention group was 3.5kg compared with 0.8kg in the control. At the end of 4 years the incidence of diabetes was significantly lower in the intervention group. (11% versus 23%)

The significance of diet should not be underestimated. A recent study showed that dietary energy restriction alone was responsible for reversal of type 2 diabetes.<sup>14</sup> Lim and co-workers demonstrated normalisation of both beta cell function and hepatic insulin sensitivity in obese type 2 diabetics after one week of a calorie restricted diet (600 kcal/day).

### **Breastfeeding**

Breastfeeding is associated with improved insulin sensitivity, increased energy expenditure and increased weight loss.<sup>15</sup> The reduction in rates of type 2 diabetes was confirmed by the Nurses' Health Study.<sup>16</sup> More than 150 000 parous women were followed up for up to 15 years post delivery. Increasing duration of lactation was associated with a reduction in risk for diabetes and for every additional year of lactation, the risk for diabetes was reduced by 15%.

Similar results were found in an Australian cohort of 52 731 patients.<sup>17</sup> The risk of developing diabetes was the greatest in parous women who did not breastfeed.

### **Pharmacological intervention**

This second-line preventative strategy should be considered for high risk patients for whom lifestyle interventions fail or are not sustainable.

### **Metformin**

Metformin is effective in reducing the risk of type 2 diabetes but it is less effective than diet and exercise. The Diabetes Prevention Program documented a relative risk reduction of 31% in the metformin group and 58% in the intensive lifestyle group.<sup>11</sup> This study showed that metformin had a greater efficacy in reducing the risk of diabetes in younger, obese subjects and particularly in women with a history of gestational diabetes. The American Diabetic Association recommends metformin for diabetes prevention for subjects who are at high risk and are younger than 60 years of age and have a BMI > 35kg/m<sup>2</sup>.<sup>18</sup>

### **Acarbose**

In the STOP-NIDDM trial subjects between the ages of 40-70 years with BMI 25-40 kg/m<sup>2</sup> were randomly allocated to acarbose or placebo.<sup>19</sup> The study duration was 3.3 years. The effects of acarbose were as follows:

- relative risk reduction of 0.75 (95% CI 0.63-0.90; p=0.0015)
- significant increase in the reversion of impaired glucose tolerance to normal glucose tolerance
- less increase in carotis intima thickness compared with placebo
- reduction in the incidence of silent myocardial infarcts
- the decrease in postprandial hyperglycemia was associated with a 49% relative risk reduction in the development of cardiovascular events
- major reduction in the risk of myocardial infarction
- 34% relative risk reduction in the incidence of new cases of hypertension.

### **Troglitazone**

In the TRIPOD study Hispanic women with previous gestational diabetes were randomised to placebo or troglitazone.<sup>20</sup> After 30 months the incidence of diabetes was 5% in the troglitazone group and 12% in the placebo group. Carotid intima thickness was 31% lower in the troglitazone group. Troglitazone has been withdrawn from the market in the United States and United Kingdom due to its serious hepatic side-effects.

### **Lipid lowering agents**

Only one study showed that pravastatin 40mg daily was associated with a relative risk reduction of newly diagnosed diabetes compared with placebo.<sup>21</sup> After 4.9 years the risk reduction was 30%. This beneficial effect was not demonstrated in other clinical studies.

### **Postmenopausal hormone replacement therapy**

The Heart and Estrogen/progestin Replacement Study (HERS) investigated the effect of hormone replacement therapy on the recurrent cardiovascular heart disease events in women with established coronary heart disease.<sup>22</sup> Combined estrogen and progestin therapy was compared with placebo. Although the primary aim of the study failed (the use of hormones is not recommended for primary prevention of cardiovascular disease) a beneficial effect was documented in a post-hoc analysis. The incidence of diabetes was 6.2% in the hormone therapy group and 9.5% in the placebo group (relative risk hazard 0.65, 95% CI 0.48-0.89, p=0.006).

Similar results were found in the Women's Health Initiative (WHI) trial.<sup>23</sup> After 5.6 years the incidence of treated diabetes was 3.5% in the hormone therapy group and 4.2% in the placebo group. (hazard ratio 0.79, 95% CI 0.67-0.93, p = 0.004)

Although combined hormone therapy may reduce the risk of type 2 diabetes, it should not be used as a primary prevention strategy.

### **Current recommendations**

The American Diabetic Association recommends lifestyle modification as the primary intervention in patients with impaired glucose tolerance, impaired fasting glucose or patients with an HbA1C of 5.7-6.4%.<sup>18</sup> At risk patients should be advised to lose 5-10% of body weight, exercise for 30 minutes each day and to stop smoking. Metformin should be considered for patients who have both impaired fasting glucose and impaired glucose tolerance. Metformin has a greater efficacy in subjects who are younger than 60 years with a BMI > 35kg/m<sup>2</sup>.

### **Conclusion**

The rate of gestational diabetes has increased by 122% in the United States between 1989 and 2004.<sup>24</sup> There is now sufficient evidence to suggest that gestational diabetes predisposes to the development of type 2 diabetes. Infants born to diabetic mothers are also at increased risk of obesity and diabetes in adolescence and adulthood. Clinicians have the unique opportunity to alter the natural course of this disease and change the future health of women and their offspring. Patients need to be educated about their future health risks. The postpartum visit should be modified to include dietary instructions aimed at reducing 7% of body weight, advice regarding exercise and breastfeeding. Early intervention may reduce the incidence of diabetes – one of the greatest contributors to the global burden of disease.

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