Type 2 diabetes, bariatric surgery and the risk of subsequent gestational diabetes

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Summary: Women with pre-existing abnormal glucose regulation are certain to develop gestational diabetes in pregnancy and pre-gestational type 2 diabetes will become more difficult to control. However, an increasing number of women with type 2 diabetes have had bariatric surgery. In this group, the effect of pregnancy on glucose metabolism is unknown. We report two women with type 2 diabetes who underwent laparoscopic gastric bypass surgery with normalization of plasma glucose levels. During subsequent pregnancy, maternal blood glucose levels remained completely normal throughout. This is remarkable given the predisposition to abnormal glucose tolerance and the ongoing obesity, in the face of the insulin resistance of pregnancy. Women with prior type 2 diabetes reversed by gastric bypass surgery are not at high risk for gestational diabetes.

Keywords: type 2 diabetes, obesity, bariatric surgery, pregnancy, gestational diabetes

INTRODUCTION

The obesity epidemic has led to a major increase of gestational and type 2 diabetes in pregnancy. Pre-gestational type 2 diabetes will become more difficult to control in pregnancy and women with pre-existing impaired glucose tolerance or impaired fasting glycaemia are at very high risk of developing gestational diabetes. Due to increasing rates of bariatric surgery for obesity,¹ particularly in adolescent populations,² the clinical entity of women who have had type 2 diabetes reversed by obesity surgery prior to attempted child-bearing will present increasingly to obstetricians and physicians.

The risk of gestational diabetes in previously diabetic women treated by gastric bypass surgery, the most common bariatric procedure performed worldwide,³ has not been described. We report two cases of obese women with type 2 diabetes who underwent laparoscopic gastric bypass surgery and subsequently became pregnant.

CASES

Case 1

A 26-year-old nulliparous Caucasian woman became pregnant 15 months following gastric bypass surgery for morbid obesity. She had been obese since childhood and developed type 2 diabetes at 13 years of age. Her mother and paternal grandmother also had type 2 diabetes. Problematic perineal abscesses and

poorly controlled diabetes led to requirement for insulin therapy at 22 years of age. She also had a history of oligo-amenorrhoea and hirsutism suggestive of polycystic ovarian syndrome. After bariatric surgery her weight decreased from 177 to 88 kg and she was able to discontinue insulin and all oral agents for diabetes. Her only medications were three-monthly vitamin B₁₂ injections, multivitamins, iron and folic acid supplements. Her weight of 93 kg at 10 weeks of gestation (body mass index [BMI] 30.3 kg/m²) dropped to 88.6 kg at 20 weeks and then steadily rose to 100.2 kg at 37 weeks of gestation. At 28 weeks, random blood glucose was 2.5 mmol/L. Glycosylated haemoglobin (HbA_{1c}) was 4.9% and 5.0% at 28 and 37 weeks, respectively. No oral glucose tolerance test was performed due to concerns regarding dumping syndrome. Home blood glucose monitoring was performed throughout pregnancy and pre- and postprandial blood glucose levels remained consistently below 5 mmol/L, the lowest recorded at 2 mmol/L and associated with hypoglycaemic symptoms. Urinalysis was negative for glucose throughout. Delivery was induced at 37 weeks as the infant was small for gestational age. An emergency caesarean section was required because of a deterioration in cardiotocograph. Birth weight of the infant was 2530 g and Apgar scores were 6 and 8. The only postnatal complication was that of neonatal hypothermia.

Case 2

A 37-year-old nulliparous Caucasian woman conceived spontaneously 11 months after gastric bypass surgery for morbid obesity. She was diagnosed with type 2 diabetes at 32 years of age after presentation with lethargy and was treated with oral hypoglycaemic agents (metformin and rosiglitazone). She had polycystic ovarian syndrome and had seen fertility

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specialists on two occasions. She had been deemed unsuitable for fertility treatment due to obesity. From the time of bariatric surgery her blood glucose normalized and she was able to discontinue all oral hypoglycaemic agents. Weight decreased from 200.4 kg pre-surgery to 117 kg and BMI from 73 kg/m² pre-surgery to 43 kg/m² at her booking antenatal appointment. Throughout pregnancy, pre- and postprandial home blood glucose recordings were 3.6–5.1 and 5.2–7.0 mmol/L, respectively, and HbA_{1c} was observed to be 4.8% and 5.1%. Weight gain during pregnancy was 1.8 kg. Fetal monitoring showed a large abdominal circumference (>90th centile) and delivery was induced at 39 weeks gestation. A healthy, 3.03 kg infant was delivered by spontaneous vaginal delivery with no post-natal complications.

DISCUSSION

In both women, gastric bypass surgery for severe obesity reversed type 2 diabetes prior to conception. Both women had previously been subfertile. Despite ongoing obesity and previously demonstrated predisposition to hyperglycaemia, blood glucose levels remained entirely normal throughout the pregnancies and healthy non-macrosomic infants were delivered. This is remarkable in the face of the insulin resistance associated with pregnancy and current views on pathogenesis of gestational diabetes. These observations are of major importance in understanding the pathophysiology of type 2 diabetes, both in respect of pregnancy and in the wider context.

Bariatric surgery and type 2 diabetes

The first long-term data on the effects of bariatric surgery on diabetes were from a series between 1980 and 1987.⁴ A total of 141 individuals with abnormal glucose tolerance (88 with type 2 diabetes and 53 with impaired glucose tolerance) underwent biliopancreatic diversion for morbid obesity. In all, 99% became euglycaemic within four months postoperatively and remained so over the six-year follow-up period. Another series demonstrated the differing efficacy of the various surgical procedures on the reversal of type 2 diabetes: normoglycaemia was regained in 99% after biliopancreatic diversion, 84% after gastric bypass and 48% after gastric banding.⁵ The different effects of these procedures has been claimed to reflect the direct effect of the surgery upon gut hormone secretion.⁶ The incretin hormones, including glucagon-like peptide 1 (GLP-1) and gastrointestinal peptide (GIP), are released from the gut and augment insulin secretion via effects on pancreatic beta cells. Although it has been postulated that exclusion of nutrients from the foregut or enhanced delivery of nutrients to the hindgut may enhance GLP-1 secretion and decrease GIP secretion thus improving insulin secretion, the evidence on which these theories are based is inconsistent.^{7,8} Diet alone is associated with changes in incretin hormone secretion⁹ and the negative energy balance induced by surgery could explain the reversal of diabetes.¹⁰

Glucose metabolism in normal pregnancy

The physiological and metabolic changes that occur during normal pregnancy include increased insulin resistance and a compensatory increase in meal-related insulin secretion.¹¹ These changes are thought to promote maternal fat deposition and later, to optimize fetal growth. Glucose-stimulated insulin release increases approximately three-fold by the third

trimester.¹² This is related to marked beta cell hyperplasia.¹³ Despite increasing insulin levels, postprandial glucose levels rise modestly in normal pregnancy because of the progressive reduction in maternal insulin sensitivity during pregnancy. In late pregnancy, maternal insulin sensitivity is reduced by about 50%: this decrease is comparable with that in non-pregnant people with type 2 diabetes.¹⁴ Although there is no association between frequency of hypoglycaemia and low birth weight in pregnancy in type 1 diabetes, it is interesting to note in case 1 that the infant was borderline for low birth weight after relative hypoglycaemia throughout pregnancy. Hypoglycaemia and hyperinsulinaemia are a recognized and infrequent consequence of gastric bypass surgery specifically.¹⁵ Pathology studies suggest that neither beta cell area nor turnover is increased in affected individuals.¹⁶ The aetiology is likely to be multifactorial, including dumping syndrome and inappropriately increased insulin secretion. The latter could be revealed by surgery due to the release of previous inhibition brought about by exposure to excess fat metabolites.

Gestational diabetes

In the face of decreased insulin sensitivity, the maintenance of glucose tolerance during pregnancy depends on the capacity of pancreatic beta cells to compensate and increase insulin secretion. It can therefore be appreciated that pregnancy could unmask a defect in beta cell insulin secretory capacity. In this regard, pregnancy can be considered a metabolic stress test for the future risk of diabetes. Women who develop gestational diabetes have chronic insulin resistance, the degree of which increases during pregnancy. However, serial studies of women with gestational diabetes show that insulin secretion does not increase to the same degree as in women who maintain normal glucose tolerance throughout pregnancy; the increase occurs along an insulin sensitivity curve that is approximately 50% lower.¹⁷

If pregnancy occurs in the early prediabetic stage, it is generally recognized that gestational diabetes will manifest. As progressive beta cell failure is regarded as inevitable, reduction of weight by bariatric surgery in type 2 diabetes would not necessarily prevent gestational diabetes. However, despite moderate duration diabetes, and in one woman the requirement for insulin therapy suggestive of beta cell failure, both women maintained entirely normal glucose levels throughout pregnancy.

To the best of our knowledge, this is the first detailed account of glucose homeostasis during pregnancy in women with previous type 2 diabetes following gastric bypass surgery. One study investigating cardiovascular risk factors in adolescents undergoing Roux-en-Y gastric bypass for extreme obesity incidentally reported that one subject became pregnant 11 months after surgery and had a normal plasma glucose level.¹⁸ A case series of women who had biliopancreatic diversion for severe obesity with type 2 diabetes mellitus describes normal blood glucose levels throughout subsequent pregnancy in all individuals.¹⁹ However, biliopancreatic diversion carries the highest risk of long-term complications and is used infrequently in the UK.

Implications for pathophysiology of gestational diabetes

Fat accumulation within organs is central to the pathophysiology of type 2 diabetes.^{20,21} The insulin sensitivity of the liver is closely correlated with liver fat content.²² Excess fat

deposition in the liver is uniformly present before the onset of classical type 2 diabetes,²³ and is also important in the pathophysiology of gestational diabetes.^{11,24} Either following bariatric surgery or during low calorie diets, liver fat levels fall and glucose control normalizes.^{25,26} Pancreatic fat levels are elevated in type 2 diabetes.²⁷ However, studies on pancreas fat during weight loss have until recently been limited by the accuracy of imaging techniques, due to the intra-abdominal position of the organ and its movement with respiration. It could be hypothesized that rather than gestational diabetes being primarily a problem of insulin resistance, it could be that pancreatic fat is the crucial factor preventing the compensatory increase in insulin secretion by pancreatic beta cells. There are two possible mechanisms by which excess intracellular lipid can impair insulin secretion. Firstly, although fatty acids are a requirement for the normal functioning of beta cells, there is clear *in vitro* evidence that when human pancreatic islets are exposed to chronically elevated saturated free fatty acids the acute insulin response to hyperglycaemia is significantly reduced.²⁸ Secondly, there is a relationship between beta cell triglyceride accumulation and an increase in beta cell apoptosis and this could explain the reversible decrease in beta cell number.²⁹ Whether the residual beta cell mass or level of functional capacity at the time of gastric bypass surgery limits the recovery of insulin secretion and therefore affects the future risk of gestational diabetes is as yet unknown.

CONCLUSION

It would appear that women with prior type 2 diabetes reversed by gastric bypass surgery may not be at high risk for gestational diabetes. In the cases reported, we propose that weight loss through bariatric surgery resulted in the removal of excess fat from the liver and pancreas. As well as improving insulin sensitivity this allowed beta cell recovery and capacity to hyperfunction in the face of the increasing insulin resistance associated with pregnancy.

DECLARATIONS

The authors have no conflicts of interest to declare.

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