Diabetes and the breast

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To most women, their breasts are an essential part of their femininity but breast disorders are forgotten by many health care professionals. Yet the breast is important in diabetes care.

Breast feeding and future diabetes
In the Nurses’ Health Study, for every additional year of lactation, women who had given birth in the previous 15 years had a 15% (95% confidence interval [CI] 1–27%) reduced risk of developing type 2 diabetes.1

Nulliparous women without metabolic syndrome at baseline were followed for 20 years. Among those who became pregnant, longer duration of breast feeding was associated with a reduced risk of metabolic syndrome. Risk reduction was greater in women who had had gestational diabetes.2

Breastfed subjects were significantly less likely to develop type 2 diabetes in later life than those fed formula mixtures (odds ratio [OR] 0.78 [0.73, 0.84]). Breastfed infants had lower premeal blood glucose and insulin levels than those given formula feeds.3

The more often a mother breast-feeds her baby, the lower the infant insulin concentration, even at nine months old. Insulin concentration correlates with infant waist circumference. Glucose concentration correlates with skinfold thickness.4

Breast feeding in women with diabetes
Plasma glucose levels influence milk glucose concentrations in diabetic women. Maternal milk and plasma glucose levels were measured in lactating diabetic and non-diabetic women. After a rise in plasma glucose, the milk glucose rose with a lag time of 40–90 minutes. There was a linear relationship between plasma and milk glucose levels. The milk glucose level was about a third of the plasma glucose. Baseline milk insulin levels were elevated in hyperinsulinaemic women. After an intravenous insulin dose, milk insulin concentrations of insulin rose with a lag time of 60–80 minutes.5

Among offspring of diabetic mothers fed either their mothers’ milk or non-diabetic banked donor breast milk, the volume of diabetic breast milk consumed correlated with their weight at two years old. The volume of non-diabetic donor milk and weight correlated inversely. The more non-diabetic donor milk neonates drank, the lower the risk of impaired glucose tolerance in childhood.6

This suggests that glucose control during breast feeding should be good.

However, this risks hypoglycaemia. In Spanish women with type 1 diabetes, insulin requirements for two months post-partum were below preconception doses whether they breastfed or not, with no difference in hypoglycaemic episodes. Breast-feeding women had lower blood glucose levels during the first week post-partum.7

Diabetes drugs and breast feeding
Insulin is found in breast milk5 but will be digested so should not affect infant blood glucose. Although advocated by NICE,8 metformin is not licensed for use during lactation. Most summaries of product characteristics leave the decision up to the prescriber. NICE guidance and the licensing situation should be explained to the patient before she starts breast feeding. Make a note of the conversation.

In seven breast-feeding women taking metformin (median dose 1500mg orally daily): ‘The mean milk-to-plasma ratio for metformin was 0.35 (0.2–0.5)...’ The concentrations of metformin in breast milk were generally low and the mean infant exposure to the drug was only 0.28% of the weight-normalized maternal dose. As this is well below the 10% level of concern for breastfeeding, and because the infants were healthy, we conclude that metformin use by breastfeeding mothers is safe. Nevertheless, each decision to breastfeed should be made after conducting a risk/benefit analysis for each mother and her infant.9

Glibenclamide and glipizide were not found in breast milk after a single dose given to eight women.10 NICE supports using glibenclamide during lactation.8 However, concern that sulphonylureas may make infants hypoglycaemic may remain without larger studies. Other glucose-lowering drugs are not recommended during lactation.

Breast abscess and undiagnosed diabetes
Breast abscesses are uncommon in non-lactating women. A review of abscesses in non-lactating women (89% black) found that 64% had known diabetes and 8% new diabetes. Diabetic women had longer abscess resolution time and hospital stay than those without diabetes. Glucose control was poor – improving this could improve healing.11

Diabetic mastopathy/fibrous breast disease/lymphocytic mastitis
Finding one or more firm irregular breast lumps in a person with diabetes leads to concern about cancer. While this must be excluded, so must diabetic mastopathy which occurs in women and men, insulin-treated or not, unilaterally or bilaterally, with single or multiple lumps. It may be recurrent. Similar lesions have been found in people without diabetes, for example, those with autoimmune disease. Histology shows ‘lymphocytic ductitis and lobulitis... keloidal fibrosis, vasculitis, epithelioid fibroblasts, and lymphoid nodule formation.’12 The lymphoid infiltrates are B-cell predominant although a study found no lymphomas.13

Imaging is complex and mastopathy is diagnosed after biopsy. Recurrence requires further biopsies to exclude malignancy which has rarely been described within mastopathy.14
Diabetes and breast cancer
Several components of the metabolic syndrome are associated with an increased risk of breast cancer. Visceral adiposity, insulin resistance, hyperglycemia and hyperinsulinemia, with or without clinically manifest diabetes mellitus, low serum high-density lipoprotein cholesterol and hypertension have all been related to increased breast cancer risk.15

A meta-analysis found that diabetes is associated with an increased risk of breast cancer (relative risk 1.20; 95% CI 1.12–1.28) with an increased mortality from breast cancer among women with diabetes.16

A later study of women with breast cancer confirmed that those with diabetes were more likely to die (pooled hazard ratio [HR] 1.49; 95% CI 1.35–1.65) than non-diabetic women. Pre-existing diabetes was associated with more advanced cancer stage at presentation. Women with diabetes were more likely to have altered breast cancer treatment regimens and increased toxicity from chemotherapy.

A Canadian study found that, in the five years after diagnosis of breast cancer, having diabetes reduced the survival rate by nearly 40% compared with non-diabetic breast cancer patients. As the mortality rate was similar in diabetic women with or without breast cancer, the authors felt that diabetes factors might explain the increased risk of death.18

A major mortality study showed that having diabetes is associated with a greater risk of death from breast cancer than in non-diabetic people (HR 1.25; 95% CI 1.02–1.52).19

Metformin treatment seems to improve the results of chemotherapy in breast cancer. Metformin-treated diabetic women with breast cancer receiving neoadjuvant chemotherapy had a higher pathologic complete response rate (24%) than diabetic patients not receiving metformin (8.0%) or non-diabetic women (16%).20

Long-term metformin treatment was found to reduce the risk of breast cancer in UK women with type 2 diabetes (OR 0.44; 95% CI 0.24–0.82). This effect was not found with other hypoglycaemic therapy.21

Cowden syndrome, PTEN, and insulin sensitivity
Phosphatase and tensin homolog (PTEN) influences cell growth and metabolic signalling. It is a protein and lipid phosphatase that antagonises the phosphatidylinositol 3-kinase pathway. PTEN also acts as a tumour suppressor. Mutations impairing PTEN function have been found in Cowden syndrome – a rare autosomal dominantly inherited hamartomatous condition with an increased risk of cancer. Major criteria for diagnosis of Cowden syndrome are macrocephaly and thyroid, breast or endometrial cancer.

Diabetes, obesity and breast cancer are linked. Cowden syndrome patients are obese so one would expect them to have insulin resistance. Yet a study of Cowden patients with PTEN haploinsufficiency found that they are highly insulin sensitive, with low fasting insulin levels.22 We need a better understanding of the relationship between metabolic pathways involving insulin and obesity, and those affecting cell growth and malignancy.

Summary
Breast feeding may reduce the risk of future diabetes in both mother and child. Breast milk from a sugary diabetic mother may risk obesity in her child. Insulin doses are lower post-partum than preconception. The risk of maternal hypoglycaemia from breast feeding seems small. Metformin passes into breast milk in such small quantities that it seems unlikely that they would harm the baby. Check non-lactating women with breast abscesses for diabetes. A breast lump in a diabetic woman could be diabetic mastopathy but women with diabetes are at greater risk of breast cancer than non-diabetic women, with poorer outcomes. Metformin might improve this. There is still a lot we don’t know about the complex link between diabetes, obesity, and breast cancer. More research is needed.

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References