Insulin neuritis in pregnancy

Abstract
Insulin neuritis is a rare, reversible, acute, painful neuropathy which may occur after rapid improvements in glycaemic control in people with diabetes. We describe a previously unreported association of insulin neuritis occurring in early pregnancy in two Caucasian women with type 1 diabetes.

A 28 year old with diabetes for three years presented at seven weeks gestation with acute onset of severe pain and paraesthesia in both feet, worse at night. Pre-conception HbA1c was 132mmol/mol and 53mmol/mol at nine weeks gestation. The pain was managed with amitriptyline and tramadol. Her symptoms resolved by 20 weeks. Another 30 year old with diabetes of 23 years duration developed acute painful neuropathic symptoms in both feet at 12 weeks gestation. HbA1c was 147mmol/mol prior to conception and 70mmol/mol at 15 weeks gestation. She obtained some symptom relief from amitriptyline. She also required laser therapy for worsening retinopathy during this and a previous pregnancy.

Insulin neuritis (also termed treatment induced neuropathy) occurs in people with both type 1 and type 2 diabetes with rapidly improving glucose control irrespective of treatment regimen. It was first described and most commonly occurs on initiation of insulin, but here was associated with sudden improvement in glycaemia in pregnancy. Both women were non-compliant with insulin therapy outside pregnancy. The range of medications which can be used to obtain symptom relief is constrained by pregnancy. Ultimately, insulin neuritis is generally reversible after several months of maintained good glucose control. Copyright © 2016 John Wiley & Sons.

Key words
insulin neuritis; diabetes; pregnancy; neuropathy

Introduction
Insulin neuritis is a rare but reversible, acute, painful neuropathy that affects people with diabetes. It generally occurs shortly after rapid improvements in glycaemic control. It differs from the more common chronic, painful diabetic neuropathy in that its onset is abrupt, often with severe pain, but symptoms generally improve after weeks to months of maintained good glycaemic control.

Case histories
Case 1
A 28-year-old Caucasian woman with type 1 diabetes of three years’ standing was initially reviewed in the general diabetes clinic. She was non-compliant with her insulin therapy, and had previously declined attendance to a structured education programme and to counselling. Her HbA1c was 132mmol/mol. She had a history of panic attacks and had been on antidepressants a few years earlier but these had been discontinued. There was no known history of drug or alcohol misuse.

Three months later she presented to the joint diabetes/antenatal clinic at nine weeks gestation. She had started taking folic acid 5mg tablets daily at six weeks gestation. She had already made drastic improvements to her glycaemic control and the clinic HbA1c was 53mmol/mol. However, she described severe pain (score 10/10) and paraesthesia in both feet at 12 weeks gestation. HbA1c was 147mmol/mol prior to conception and 70mmol/mol at 15 weeks gestation. She obtained some symptom relief from amitriptyline. She also required laser therapy for worsening retinopathy during this and a previous pregnancy.

Case 2
Another 30 year old with diabetes of 23 years duration developed acute painful neuropathic symptoms in both feet at 12 weeks gestation. HbA1c was 147mmol/mol prior to conception and 70mmol/mol at 15 weeks gestation. She obtained some symptom relief from amitriptyline. She also required laser therapy for worsening retinopathy during this and a previous pregnancy.

The pain was worse at night, with allodynia, and only relieved by keeping her feet cold. She had a poor quality of life as the pain kept her awake most of the night every night. Neurological examination was intact. The HbA1c levels before and during pregnancy are shown in Figure 1. Her thyroid function tests in first trimester had been normal with TSH 1.1mU/L (0.3–5.5).

She was started on amitriptyline and tramadol. She maintained good glycaemic control and the pain began to improve from around 13 weeks of gestation and had completely resolved at 20 weeks. Her HbA1c was 42mmol/mol in the third trimester. She delivered by elective caesarean section for breech presentation at 34 weeks gestation, with the baby weighing 3245g. She had...
discontinued the amitriptyline and tramadol by the time of her delivery and opted to have her diabetes followed up in the community.

**Case 2**
A 30-year-old Caucasian woman with type 1 diabetes mellitus of 23 years duration and a history of depression on antidepressants was reviewed in the antenatal clinic at 15 weeks into her fifth pregnancy. Her HbA1c prior to conception was 147mmol/mol and she was known to be non-compliant with her insulin outside pregnancy. During her fourth pregnancy two years earlier, she had required laser therapy for worsening proliferative retinopathy after she had re-established insulin therapy. There was no prior history of neuropathy.

In the current pregnancy, having discovered that she was pregnant at eight weeks gestation with an HbA1c of 120mmol/mol, she had tightened up her control and started taking folic acid. She then developed very painful sharp shooting pains and continuous tingling sensation in both of her feet at 12 weeks gestation. These symptoms were particularly severe at night, and seriously interfered with her sleep and therefore the ability to care for her other four children. Her HbA1c on review in clinic at 15 weeks gestation was 70mmol/mol; see Figure 2.

She was started on amitriptyline and noticed more than 50% improvement in her symptoms by 28 weeks gestation. However, the symptoms had not completely resolved by the time of delivery by emergency caesarean section at 35 weeks gestation for pre-eclampsia. She had a live birth with the baby weighing 3000g.

During the course of this pregnancy, she again developed proliferative retinopathy which required laser therapy at 20 weeks gestation. She was also admitted with high blood pressure and proteinuria at 24 weeks gestation.

Her painful neuropathic symptoms continued post-partum, and she remained on amitriptyline – and gabapentin had also been introduced to try to alleviate her symptoms.

Her diabetes control has deteriorated again with the HbA1c having risen to 124mmol/mol at 12 weeks post-partum. She, however, is more open to input from the diabetes specialist nurses to help manage her diabetes outside pregnancy.

**Discussion**
The women described here both had a history of poor compliance with their diabetes management outside pregnancy, reflected by strikingly high HbA1c levels. Neither of the pregnancies was planned, but the discovery of pregnancy precipitated a major improvement to glycaemic control followed in both cases by the rapid onset of an acute painful neuropathy. The burden of lack of sleep and severity of pain had a significant adverse impact on the quality of life in each case. The second woman, who had previously demonstrated worsening retinopathy due to tightened glycaemic control, again required laser therapy for proliferative retinopathy.

Insulin neuritis is a rare, reversible, acute painful neuropathy that generally occurs after rapid improvements in glycaemic control. It was first described by Caravati in 1933, in a woman with diabetes who developed numbness, tingling and shooting pains in the lower extremities four weeks after the initiation of insulin therapy. The pain failed to improve with simple analgesia and sedatives, but resolved within three days of stopping the insulin therapy. The symptoms recurred on reintroduction of insulin and hence the term ‘insulin neuritis’ was coined.1

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1 Caravati E (1933) Neuritis in diabetes mellitus unresponsive to stimulation of the sympathetics. JAMA 99, 1305–1311.
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Its acute onset and reversibility distinguish insulin neuritis from the more common, chronic, painful diabetic neuropathy.

In several small observational studies, insulin neuritis has been described in people with both type 1 and type 2 diabetes and treated with either insulin or oral hypoglycaemic agents.2,3 In all cases reported, there is a history of a rapid improvement in pre-existing poor chronic glycaemic control prior to the onset of symptoms. It is not insulin itself that causes the condition, but rather the rapid improvement in glycaemic control. The condition has therefore alternatively and perhaps more accurately been termed ‘treatment induced neuropathy of diabetes’. Insulin neuritis can occur irrespective of the duration of diabetes (cf. the two patients in this report) and has been described in association with other symptoms, particularly autonomic symptoms or unexplained weight loss, although none were noted here. Insulin neuritis typically runs a monophasic course but can on occasions be recurrent.

The principal symptom is that of severe pain in the lower limbs – characteristically burning in nature – which may be severe enough to prevent walking.4 Pain can affect other areas including the hands, trunk and abdomen, or be more generalised. Patients may also describe hypersensitivity to tactile (allodynia) and painful stimuli (hyperalgesia) with nocturnal exacerbations.

The neurological examination findings in patients with insulin neuritis may demonstrate reduced pain and thermal sensation in a stocking distribution but may be normal. Vibration sense and motor strength usually remain intact. A recently proposed algorithm to aid in the diagnosis and management of patients with insulin neuritis suggests testing for thyroid function, vasculitis screen, vitamin B12 and B1. In one prospective case series, all patients described significant life events that triggered the rapid improvement in the control.6 There is a correlation between the percentage drop in HbA1c and risk of developing insulin neuritis, with a fall of more than two percentage points (22mmol/mol) in HbA1c over three months being suggested as a trigger.7

The pathophysiology underlying insulin neuritis is incompletely understood. It has been suggested that prominent epineurial arteriovenous shunting and new vessel formation result in ectopic generation of impulses in regenerating axon sprouts. This is analogous to the deterioration of a pre-existing retinopathy which may occur following rapid improvement in glycaemic control.8

The principles for managing insulin neuritis include good glycaemic control, regular foot care and the use of pharmacological therapy to control the pain until the symptoms improve.9 This approach is similar to that used for chronic neuropathy where recommended pharmacological treatments include anticonvulsants, antidepressants and opioid analogues.10 There is, however, concern about using gabapentin, pregabalin and other anticonvulsants in pregnancy. Relaxing glycaemic control may help with symptom relief temporarily, but this is not a realistic option in pregnancy and, if good glycaemic control is maintained, symptoms generally eventually resolve.11

Rapidly improving glycaemic control in people with diabetes is associated with a risk of developing insulin neuritis. We report a seemingly novel association of two cases of insulin neuritis occurring in early pregnancy in young women with type 1 diabetes. Pain control in this situation poses particular challenges as tight glycaemic control must be maintained and there are constraints on the range of acceptable drug therapies.

**Declaration of interests**

There are no conflicts of interest declared.

**References**


**Key points**

- Insulin neuritis remains a rare, reversible, acute, painful neuropathy which may occur after rapid improvements in glycaemic control in people with diabetes.
- Insulin neuritis has not previously been documented to occur in pregnancy and here we report a seemingly novel association of two cases of insulin neuritis occurring in early pregnancy in young women with type 1 diabetes.
- Pain control in this situation poses particular challenges as tight glycaemic control must be maintained and there are constraints on the range of acceptable drug therapies in early pregnancy.