Diabetes, menstruation, and the uterus

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Much is written about diabetes and pregnancy, but diabetes also influences other aspects of women’s health and vice versa. Failure to consider this may have serious consequences.

Menstruation in women with diabetes

Effect of menstruation on diabetes

‘Hiya – just wandered how many others suffer with high BS’s before their period and how long for beforehand? My blood sugars start to rise anything between 7–10 days before my period starts. Im on a pump and today I have needed to increase my basal rate to 120% in the morning and then 140% in the afternoon as they had climbed to 12 after tea time. The trouble is I cant just leave the rates on because the additional insulin in required at random times throughout the day/night. They are just so high and erratic – very very frustrating!!’[sic]. 1

Among women aged 18–40 years with type 1 diabetes 61% had perimenstrual changes in glucose control, mostly premenstrual hyperglycaemia. Half of them had adjusted their insulin dose accordingly. Changes in glucose control occurred in 67% of women using fixed-dose oestrogen/progesterone oral contraception.2 Women with type 1 diabetes experienced less hypoglycaemia (10.7% versus 15.8%) and more hyperglycaemia (28.5 versus 22.8%) in the luteal phase than in the follicular phase.3 Catamenial hyperglycaemia may be due to increases in circulating progesterone reducing insulin sensitivity.4 Increased appetite may contribute.

The relative insulin lack may be severe enough to precipitate diabetic ketoacidosis – catamenial diabetic ketoacidosis – which may recur before patient or diabetes team recognise the cause.5 A woman with usually well-controlled type 1 diabetes on continuous subcutaneous insulin infusion had recurrent catamenial diabetic ketoacidosis. She required a four-fold insulin dose to control premenstrual hyperglycaemia.6

If female patients have unexplained hyperglycaemia, ask if it is linked to their menstrual cycle (remembering that many diabetic women have irregular periods). Consider catamenial hyperglycaemia as a cause for diabetic ketoacidosis or recurrent diabetic ketoacidosis.

The effects of diabetes on menstruation

Among women in Wisconsin with type 1 diabetes aged <30 years diagnosed before menarche, each 1% increase in mean total glycosylated haemoglobin level in the three years before menarche delayed age at menarche by 1.3 months.7 In Chilean girls with type 1 diabetes treated with intensive insulin therapy from diagnosis, age at menarche was 12.6±1.5 years versus 12.25±1.4 years with non-diabetic peers. Haemoglobin A1c (HbA1c) or body mass index (BMI) did not affect menarche.8 In Greece, girls with type 1 diabetes were compared with non-diabetic girls also aged 12–18 years. Among those with diabetes, menarche was at 12.2±1.4 versus 11.7±1.2 years of age. Menarche occurred later among those diagnosed diabetic <10 years of age than those diagnosed after this age.9

The odds ratio for oligomenorrhoea (menstrual cycle >36 days throughout the past year [5–6/year]) in girls with type 1 diabetes was 7.8 (95% CI 3.411–17.853). Oligomenorrhoea was more likely with poor glycaemic control.10 In a US study, menarche among girls with type 1 diabetes occurred at 12.69±0.08 years. Among those with pre-existing diabetes, menarche occurred at 12.81±0.09 years versus 12.17±0.19 years in those who developed diabetes after menarche. Irregular cycles were reported by 35% of adolescent girls with diabetes.11 Adolescent Chilean girls with type 1 diabetes had a menstrual cycle of 48±39 versus 32±7 days in non-diabetic peers. Girls with type 1 diabetes were more likely to have oligomenorrhoea (58.9% versus 19.6%) and amenorrhoea (10.7% versus 1.8%). Oligomenorrhoea occurred in 53.3% of the diabetic girls who had good glycaemic balance. For each percent increase in HbA1c, the menstrual cycle duration increased by 5.1 days.12 Among French girls with type 1 diabetes aged <18 years, two years post-menarche, 44% had a menstrual disorder with higher free androgen index, total testosterone, and androstenedione levels than in the other 56%.13 Women aged <30 years with type 1 diabetes had more menstrual problems (long cycles, long menstruation, and heavy menstruation) than their sisters and control subjects.14 Women with type 2 diabetes also have menstrual problems – as many as 26.7% had polycystic ovarian syndrome in one study.15

Menopause

An American study suggested that women with type 1 diabetes have an earlier menopause than those without, losing 17% of reproductive years.16 Later research differed: ‘age at menopause in women with type 1 diabetes is not lower than that in the general population in Finland. The only statistically significant factors independently associated with earlier menopause in our study were ... end-stage renal disease and proliferative retinopathy.’17

Perimenopausal glucose control may be unstable. A review suggested that postmenopausal hormone replacement therapy reduces that risk of developing diabetes. The authors state: ‘studies suggest that postmenopausal hormone therapy has neutral or beneficial effects on glycaemic control among women already diagnosed as having diabetes mellitus. Future studies are needed to ... determine how these observations should influence recommendations for the care of postmenopausal women with diabetes mellitus.’18

Myometrial contractility in diabetes

An analysis of prenatal risk factors for Caesarean section found that diabetes (prepregnancy or gestational)
increased the risk four-fold (odds ratio 4.51; 95% CI 2.18–9.31).\textsuperscript{19} A study compared matched patients with and without diabetes undergoing elective Caesarean section. Despite controlling for confounders such as BMI, women with diabetes showed significantly decreased myometrial contraction amplitude and duration compared with controls. Diabetic women had weaker myometrial contractions with oxytocin. The authors suggest that ‘the underlying mechanism is related to reduced calcium channel expression and intracellular calcium signals and a decrease in muscle mass’.\textsuperscript{20}

**Diabetes and fibroids**

Women with diabetes may be less likely to have uterine fibroids than those without diabetes.\textsuperscript{21}

**Endometrial cancer**

A meta-analysis of prospective studies including 12 195 incident cases found that women with diabetes had an increased summary relative risk (SRR) of developing endometrial cancer (SRR 1.81; 95% CI 1.58–2.37) when compared with women without diabetes. However, diabetes was not associated with increased mortality from endometrial cancer.\textsuperscript{22} Among diabetic patients with endometrial cancer, those who did not use metformin had 1.8 times worse recurrence-free survival and 2.3 times worse overall survival than those taking metformin after adjusting for confounders.\textsuperscript{23}

**Age at menarche and risk of type 2 diabetes**

A prospective study in eight European countries compared age at menarche and the incidence of type 2 diabetes. Each year later menarche was associated with 0.32kg/m\(^2\) lower adult BMI. Women in the earliest menarche quintile had 70% higher incidence of type 2 diabetes compared with those in the middle quintile, adjusting for age at recruitment, research center, and a range of lifestyle and reproductive factors (hazard ratio [HR] 1.70; 95% CI 1.49–1.94). Adjustment for BMI partially attenuated this association (HR 1.42; 95% CI 1.18–1.71). Later menarche beyond the median age was not protective against type 2 diabetes.\textsuperscript{24}

**Caesarean section and risk of type 1 diabetes**

A meta-analysis of 20 studies found that despite accounting for confounders including maternal diabetes there was a significant increase in the risk of type 1 diabetes in children born by Caesarean section (odds ratio 1.23; 95% CI 1.13–1.32).\textsuperscript{25}

**Summary**

Menarche is delayed in girls with type 1 diabetes. Women with diabetes often have irregular periods or oligomenorrhoea. Glucose may fluctuate perimenstrually, usually rising premenstrually. Some women develop catamenial diabetic ketoacidosis. Glycaemic control may worsen premenopausally. Diabetes impairs myometrial contractility increasing the risk of Caesarean section. Diabetic women are at greater risk of endometrial cancer than those without diabetes. We must learn more about uterine complications of diabetes.

Ask female patients about their menstrual history. Consider this when reviewing glycaemic control and help women with diabetes to learn to manage their own pattern.

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**Declaration of interests**

There are no conflicts of interest declared.

**References**

1. Riri. www.diabetes.co.uk/forumThreads/for-the-ladies-high-bs-before-periods. 30313/ [accessed 1 August 2015].
4. Li Voon Ch J. Focus on catamenial hyperglycaemia. Pract Diabetes Int 2010; 27:381.