Diabetes and pregnancy

practice points for GPs

A woman who now has type 2 diabetes after her first pregnancy was complicated by gestational diabetes comes to see you about having another child. How should you advise her?

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Case study

Mary is 34 years old and is seeing you about her planned second pregnancy. Her first pregnancy was at age 30 and was complicated by gestational diabetes at 25 weeks (see *Medicine Today*, August 2001 issue).[1] Insulin therapy was required but all went well and her son Timothy was delivered vaginally at 38 weeks, with a birthweight of 3.2 kg.

Twelve months after delivery her follow up fasting plasma glucose was 6.9 mmol/L – that is, just below the diabetes diagnostic value of fasting plasma glucose (≥7.0 mmol/L).[2] Despite Mary's adherence to healthy lifestyle recommendations, her blood

IN SUMMARY

- Pregnancy outcomes for women with diabetes and their babies have improved dramatically over the past 50 years.
- Pre-pregnancy planning helps minimise the teratogenic effects of poorly controlled diabetes in the first weeks of pregnancy, when most organ systems are being formed and when pregnancy may not yet have been diagnosed.
- During pregnancy, the priorities are to minimise the effects of diabetes on the pregnancy and the effects of pregnancy on the diabetes, and to monitor for complications, hypoglycaemia and urinary tract infections.
- After delivery, breastfeeding offers special benefits to women with diabetes and an opportunity for you to offer advice about the risk of diabetes to the baby (and its siblings) and about planning future pregnancies.
- The GP plays a key role throughout all stages of pregnancy and counselling for supporting the woman. The GP is the health professional most likely to trigger appropriate pregnancy planning beforehand and to offer the necessary follow up afterwards.

glucose levels progressively rose over the next 12 months and she began oral hypoglycaemic therapy two years ago.

Mary is now taking metformin 850 mg twice daily and blood glucose control has been reasonable with a recent glycated haemoglobin (HbA_{1c}) of 8.4%.

Her complication risk factor profile is relatively benign with her nonsmoking habit, healthy lifestyle, weight 69 kg, blood pressure 115/67 mmHg and normal lipid profile. She is 2.5 kg heavier now than she was before her first pregnancy, and her body mass index (BMI) of 27 kg/m^2 indicates that she is slightly overweight (a BMI between 25 and 30 is considered overweight).

She has no evidence of microvascular complications, with normal fundoscopy and normoalbuminuria on last check a year ago.

She asks if it is safe for her to become pregnant again and if the baby would be likely to be all right. She and her partner are currently using condoms for contraception. She asks if this is enough protection and whether there is anything she should do before trying to become pregnant.

How should you advise Mary?

The outcomes of pregnancy in women with diabetes have improved enormously over the past 50 years as more effective methods to control maternal glycaemia have been implemented. While diabetes can adversely affect the pregnancy – predisposing to congenital malformation and obstetric complications – the pregnancy can also affect the diabetes, increasing insulin requirements and hyperglycaemia and accelerating microvascular complications. However, with careful planning and active management, outcomes for mothers with diabetes and their babies are similar to equivalent pregnancies not complicated by diabetes.

The usual contraception recommended for women with diabetes is the oral contraceptive because of its effectiveness and convenience, but there are pros and cons with all contraceptive methods. Mary is unlikely to have problems from the oral contraceptive as she is a nonsmoker and her blood pressure and lipid profile are normal. Oestrogen may increase glycaemia but hypoglycaemic medication can be modified accordingly. Condom use (especially without a spermicide) is less effective than oral contraception (88% compared with 98% for the combined pill or 94% for the progestogen only pill) in reducing the risk of an unplanned pregnancy.

Apart from reviewing contraceptive practice, Mary could consider a 'diabetes overhaul' leading up to her planned pregnancy. This would involve an update of self-care skills, review of current lifestyle and blood glucose profile, and a re-check for microvascular complications. Her medication schedule should also be reviewed, checking for potentially teratogenic medications (Table 1), changing to insulin in place of oral hypoglycaemic agents and taking folate supplements.[3]

Further case information

Pre-pregnancy planning

Mary and her partner return a few days later saying they have decided to try to have a second child. Mary is happy to switch to an oral contraceptive and to start insulin therapy. On the advice of an endocrinologist you suggest a twice

Table 1. Risks in pregnancy of medications which may be used to treat diabetes[3]

Medication	ADEC rating*
Hypoglycaemic agents	
Insulin†	A
Acarbose	B3
Miglitol	B3
Metformin	C
Sulfonylureas	C
Antihypertensive agents	
Guanethidine, methyldopa	A
Clonidine	B3
Prazosin	B2
Spironolactone	B3
Amiloride, triamterine	C
Thiazides, loop diuretics	C
ACE inhibitors and angiotensin receptor antagonists‡	D
Calcium channel blockers	C
Hypolipidaemic agents	
Gemfibrozil	B3
Statins (HMG-CoA reductase inhibitors)	C

* Australian Drug Evaluation Category (ADEC) – categorisation of risk of drug use in pregnancy.
† There have been isolated reports of congenital abnormalities associated with the lispro insulin analogue (Humalog).[6]
‡ Use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists in the first trimester does not appear to present a risk to the fetus.

continued

Table 2. Mary's blood glucose profile

	Blood glucose (mmol/L)					
	Breakfast		Lunch		Dinner	
	Before	After	Before	After	Before	After
Pre-pregnancy, one week after starting insulin						
Monday	5.0		6.2		6.9	
Tuesday	4.6	7.0	6.4	8.4		
Wednesday						
Thursday	4.9				7.3	9.4
10 weeks' gestation						
Monday	4.2		6.3	8.7		
Tuesday					4.5	
Wednesday	5.2	9.4			4.1	6.8
Thursday	4.6	9.7	6.5			

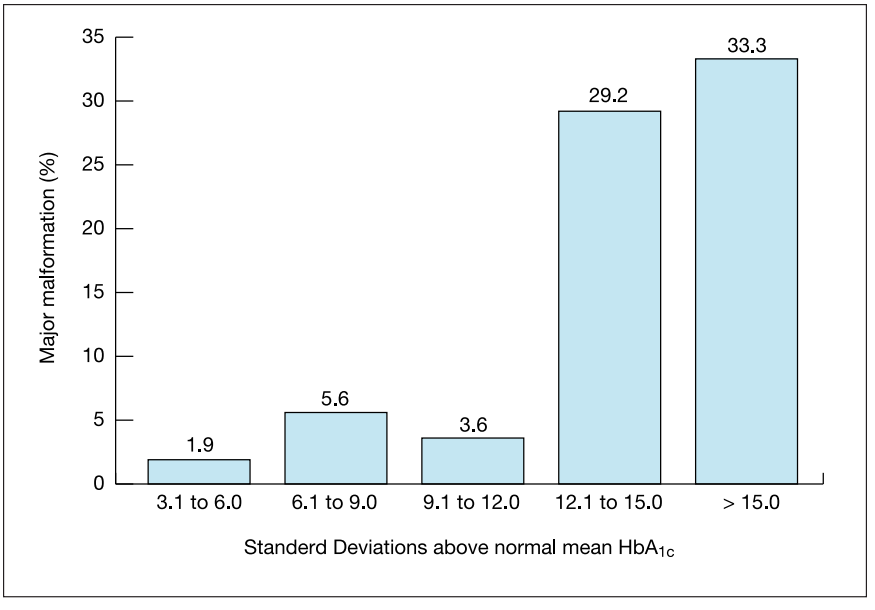


Figure 1. Congenital malformations and prevailing glycaemia during the first trimester.

daily intermediate insulin schedule (isophane, NPH [Humulin NPH, Protaphane]; 16 units before breakfast and 8 units before the evening meal), using a pen injector. As a rough guide, starting insulin doses are half to one-third of the healthy weight split into a twice daily schedule, two-thirds in the morning and the remainder in the evening. At 160 cm tall, Mary's healthy weight is approximately 60 kg so her recommended total daily dose of insulin is 20 to 25 units per day.[4]

The following week her blood glucose profile is as shown in Table 2.

What glycaemic targets should be set?

The risk of congenital malformation increases dramatically with increasing prevailing glycaemia (Figure 1) and pre-pregnancy planning includes trying to achieve ideal glycaemic control during fetal development.[5] If the woman waits until she knows she is pregnant before trying to optimise diabetes management, the fetus will have been exposed to hyperglycaemia for approximately eight weeks – a major proportion of the time of organogenesis.

Recommended glycaemic targets before and during pregnancy are:[2]

- preprandial blood glucose level of 3.5 to 5.5 mmol/L
- 2-hour postprandial blood glucose level of 3.5 to 7.0 mmol/L
- HbA_{1c} <7%.

What insulin changes should be recommended?

Mary's fasting values are on target but most of the daytime values are high. She should increase her morning intermediate insulin, continue to measure blood glucose and liaise with you and the diabetes centre to adjust her insulin schedule according to the blood glucose profile.

The doses of intermediate insulin are adjusted to bring values before breakfast and dinner into the target range. If these values are on target and healthy meals are eaten, high values after meals suggest the need to start or increase quick acting insulin (neutral; clear) before that meal. Although there is no definite evidence, reports of adverse fetal outcomes with a new quick acting insulin analogue (lispro; Humalog) have prompted the conservative recommendation to use recombinant human insulin (Actrapid, Humulin R) for the time being.[6] There are various insulin schedules providing background longer acting insulin (basal) and meal time

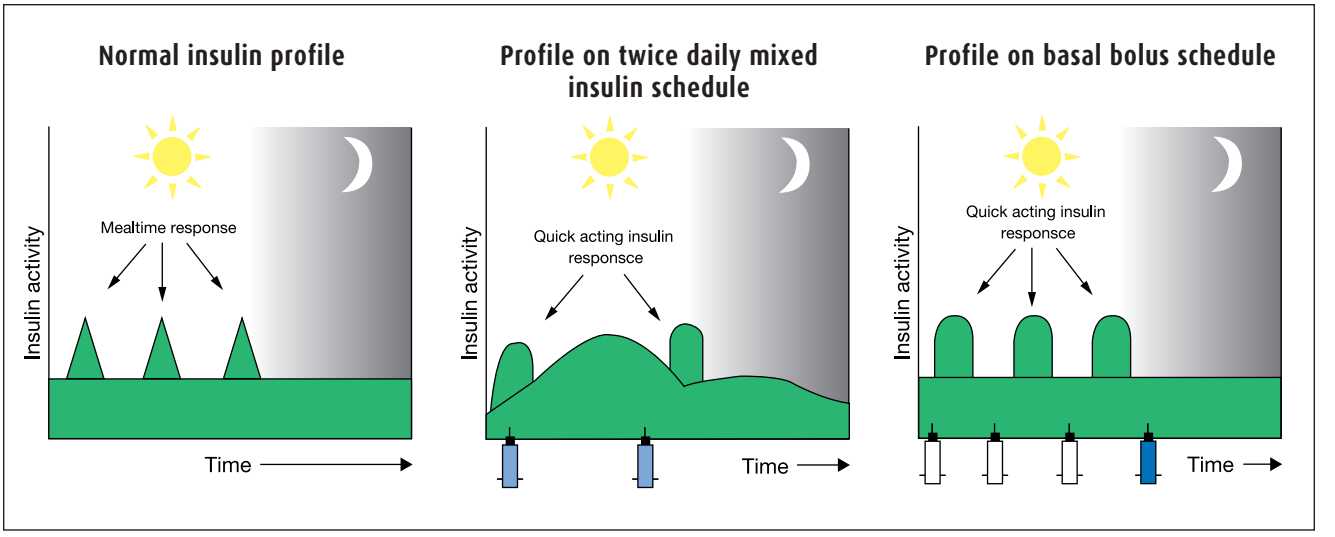


Figure 2. Insulin profiles in pregnancy.

extra insulin (bolus), if necessary (Figure 2). In general, the usual KISS principle applies ('keep it safe and simple') in type 2 and gestational diabetes, and these are often controlled by twice daily schedules. In most women with type 1 diabetes, the full basal bolus schedule of four or more injections per day is usually adopted.

Further case information

Becoming pregnant

Mary responds positively to your advice, begins taking the oral contraceptive pill and folate supplements, and visits the diabetes centre and also the obstetrician and endocrinologist who had helped her through her first pregnancy. She quickly gains tight control of her blood glucose profile and has a positive pregnancy test four months later.

10 weeks' gestation

She sees you at 10 weeks' gestation because she has just had an ultrasound to check for gross fetal malformations and as a baseline to monitor growth, during which she overheard the technologist commenting on 'high risk pregnancy' and the need to check carefully the baby's size and development. Although the technologist showed her the ultrasound, gave her a copy and told her everything was fine, she is concerned that something will happen to her baby. She is especially worried because she has not been able to keep her blood glucose profile within the target range and feels that she may be harming her baby or herself. Her blood glucose profile is shown in Table 2.

What can diabetes do to the pregnancy and the pregnancy to the diabetes?

Mary is quite right to be concerned as her diabetes can affect her pregnancy and vice versa (see the box on page 40). However, with the patient's diligence in keeping control of her diabetes and co-operation between the multidisciplinary professional team, most women with type 1 or type 2 diabetes will have a busy but uneventful pregnancy and a healthy baby.

During the pregnancy, the diabetes priority is to stabilise blood glucose in the desired range (fasting, 3.5 to 5.5 mmol/L; 2-hour postprandial, 3.5 to 7.0 mmol/L) and thus avoid the risks of hyperglycaemia – that is, congenital malformations in the first trimester, toxaemia and hydramnios in the second and macrosomia in the third. This also minimises the risks of hypoglycaemia (which is potentially lethal for the mother and associated with growth retardation in the fetus) and ketosis (which is suspected of being associated with fetal neurological abnormalities or with termination of the pregnancy if severe).

A schedule should be established for close monitoring of pre-existing microvascular complications, retinopathy and nephropathy to allow for early intervention, and also to monitor fetal growth and wellbeing and maternal health (especially for pre-eclampsia, polyhydramnios and urinary tract infections).

What insulin changes should be recommended?

This time the values before breakfast and dinner are on target, indicating the background intermediate insulin dose is correct. It is the values after breakfast that are high. More intermediate insulin before breakfast will not help because it would not act quickly enough and would probably cause hypoglycaemia in the afternoon and before dinner. Mary needs some quick acting insulin before breakfast. This could be given using a second pen injector, or by mixing the intermediate and quick acting insulin in a syringe before injecting them. This may be a good time to see if

Mary would like to switch to a basal bolus schedule with more injections but more flexibility (night-time intermediate or long acting insulin, and mealtime quick acting insulin).

Further case information

12 weeks' gestation

Mary decided to use a second pen with a quick acting insulin. She gradually increased the dose to 10 units, which kept blood glucose levels after breakfast and before lunch under control. She found that injecting the insulin 20 to 30 minutes before breakfast resulted in better blood glucose control than injecting it immediately before eating. (This is as expected for human insulin because insulin absorption from the subcutaneous depot will then be well under way by the time glucose from breakfast is being absorbed; the quick acting analogues [Humalog, NovoRapid] are absorbed more quickly and can be given immediately before eating in nonpregnant patients.)

At this stage Mary is using:

- intermediate insulin – 30 units in the morning and 15 at night
- quick acting insulin – 10 units in the morning.

28 weeks' gestation

Review by Mary's ophthalmologist at 28 weeks showed no change in the condition of her eyes. Her albumin excretion rate has stayed normal (8 μg/min; range <20), and she is now taking a twice daily mixed insulin schedule:

- intermediate insulin – 44 units in the morning and 20 at night
- quick acting insulin – 20 units in the morning and 15 in the evening.

The ultrasound at 28 weeks shows a well formed baby boy (Mary was a bit upset because she would have preferred a girl) whose biparietal head circumference was on the 90th percentile. The obstetrician discussed the possibility of inducing an early delivery if the baby's size increased much more.

31 weeks' gestation

At 31 weeks into the pregnancy, all is going well. Mary's weight has increased by 4 kg, her blood pressure has not increased and her HbA_{1c} has been consistently 6 to 7.5%. Mary is now seeing you because she is having multiple hypoglycaemic episodes in the middle of the night. Fortunately she wakes up and is able to check her blood glucose and take extra carbohydrate. However, she and her partner are concerned that one night she might not wake up and she and the baby might get into trouble. She thinks her insulin dose may be too high since she is using a lot more now than when she started (99 units per day *v.* 24 units per day, respectively).

Will Mary need to be induced or have a caesarean section?

It is true that the rates of induction or caesarean section for women with diabetes are higher than those for women without diabetes. It is also true that there are often good reasons for this, such as macrosomia as an indication of risk of complications or fear of intrauterine death (especially in a complex pregnancy). However, it is now recognised that the rates of intervention in the past may have been too high, and these days most women (>80%) with diabetes deliver vaginally at term and without intervention.

Mary has already had one successful spontaneous vaginal delivery at 36 weeks, her pregnancy has been uncomplicated so far and ultrasound may not accurately predict the risk of macrosomia at birth. Her situation and preference could be discussed with the obstetrician who may agree to try for a spontaneous vaginal delivery.

Why is she getting nocturnal hypoglycaemia and is she taking too much insulin?

The maternal glycaemic response to pregnancy reflects the antioestrogen effects of the placenta and glucose utilisation by the fetus. As the pregnancy progresses, placental size, fetal size and glucose utilisation increase.

At night, fetal glucose utilisation continues but there is no exogenous carbohydrate intake. In women without diabetes, insulin secretion falls and hepatic glucose output increases to meet the extra demand. In women treated with insulin, insulin absorption from the subcutaneous site continues during the

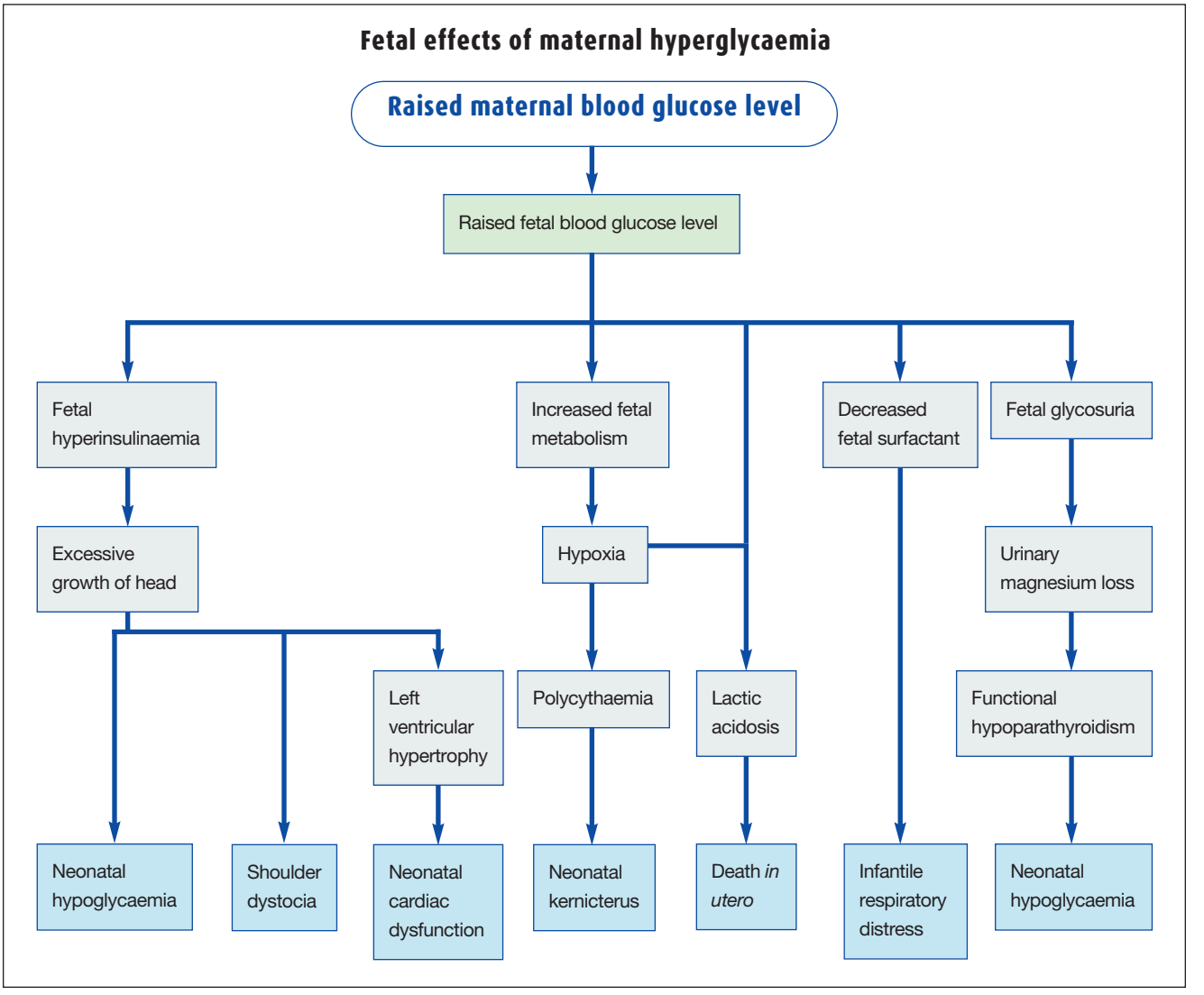
Interactions of diabetes and pregnancy

Effects of pregnancy on diabetes

- Placental lactogen is the major contributor to increasing insulin resistance and to predisposing to hyperglycaemia and ketosis
- Fetal glucose utilisation predisposes to hypoglycaemia (especially nocturnal)
- Pregnancy associated hypertension (pre-eclampsia) may accelerate micro- and macrovascular complications (especially renal and retinal)
- Obstetric interventions in premature labour (beta-2-agonists, corticosteroids) predispose to hyperglycaemia and ketosis
- Placental delivery dramatically reduces insulin resistance and insulin requirements

Effects of diabetes on pregnancy

- Hyperglycaemia increases congenital malformations (first trimester), predisposing to pre-eclampsia and polyhydramnios (second trimester) and to macrosomia and intrauterine death (third trimester)
- Prolonged severe hypoglycaemia may cause fetal growth retardation
- Micro- and macrovascular complications predispose to hypertension and pre-eclampsia and to placental insufficiency, fetal growth retardation and intrauterine death



night and stops the liver from releasing extra glucose. In the last trimester, the rapidly increasing fetal size and glucose utilisation mean that night-time hypoglycaemia increases in these women.

Some women manage the problem by adjusting their eating schedule and taking an extra bedtime carbohydrate snack; others set the alarm and snack in the middle of the night. Alternatively, the insulin schedule could be changed to reduce the night-time level – for example, by using a background (basal) insulin with a flatter absorption profile (such as ultralente [Humulin UL, Ultratard]).

Further case information

The delivery

Mary has no maternal or fetal complications of diabetes in pregnancy and James is delivered vaginally at 39 weeks, with a birthweight of 3.2 kg. Mary's partner rings to tell you the good news and you visit Mary the next day.

Mary is still worried. She is concerned that something may have happened in the delivery that required the special intervention of a drip, and that there is something wrong with the baby that required him to spend his first six hours in the neonatal nursery. She is also worried about breastfeeding James (she didn't succeed in breastfeeding Timothy, her first child).

Why did Mary have a drip?

Several things affect glucose homoeostasis during delivery. The increased physical work of labour uses glucose, the pain of labour mobilises glucose and the delivery of the placenta dramatically decreases insulin resistance. An infusion of insulin and glucose adjusted using blood glucose measurements smooths out these fluctuations.

A high maternal blood glucose will increase fetal glycaemia and insulin levels

and thus put the baby at risk of hypoglycaemia when it is deprived of its maternal glucose supply through the placenta. The drip also allows glucose to be given to the mother if her blood glucose level falls as the placenta separates and insulin resistance decreases.

Why did her baby go to the neonatal intensive care unit?

Maternal hyperglycaemia predisposes a whole range of neonatal problems (see flowchart on page 43). Many women with diabetes deliver in hospitals with neonatal intensive care units so that their babies can spend some time in the unit under observation to see if any of these problems occur.

Should she breastfeed James?

In addition to the usual benefits, breastfeeding helps the mother with diabetes to control her weight and reduces the baby's risk of developing type 1 diabetes if either parent has type 1 diabetes (possibly because cow's milk contains antigens that sensitise the baby's immune system and predispose to the development of autoimmune destruction of pancreatic beta cells – that is, type 1 diabetes).

Further case information

Three weeks' post-delivery

Three weeks after the delivery, Mary looks tired and a bit flat, and she bursts into tears when you comment on this. She is finding it hard managing her newborn baby James, her toddler Timothy, her diabetes, the house, her partner…Breastfeeding is difficult because she has a cracked nipple, James is very restless, Timothy is very demanding, her diabetes is not well controlled, she has had a series of hypoglycaemic episodes and she has put on weight!

She is now taking 24 units of intermediate insulin in the morning and another 12 units in the evening.

She also wonders about the risk of diabetes for her sons and is feeling very down about not coping and for passing on 'bad genes' to her children. She wonders if she has depression, and asks if you can help.

Should you prescribe an antidepressant?

A woman with diabetes may feel a great sense of relief after a successful delivery. However, she must then cope with any complications of the delivery, the usual postpartum turmoil, a crying 'bundle of joy' and changed family relationships, as well as her diabetes – which often becomes more difficult to control after the pregnancy than during it. At this time, a great deal of psychological, emotional and physical support are required.

Mary's thyroid function should be checked because autoimmune thyroid disease often 'flares' after pregnancy (postpartum thyroiditis is painless, unlike subacute thyroiditis). Assuming the thyroid function tests are normal, Mary will probably feel better able to cope if she gets more support. There are few antidepressants that are considered safe during lactation, and at this stage it is probably better to wait and monitor her progress.

Can Mary switch back to oral hypoglycaemic agents?

As noted earlier, the available oral hypoglycaemic agents are not recommended for use during pregnancy because their safety is not established (they are generally not recommended during lactation for similar reasons – especially the sulfonylureas, which can cause hypoglycaemia in the baby). Also, Mary is taking 36 units of insulin per day – in general, people

Table 3. Risks of developing diabetes for children whose mothers have diabetes[7]

Maternal diabetes	Child's risk of diabetes
Type 1	1%*
Type 2	10%†
Maturity onset diabetes of the young	50%‡

*If the father also has type 1 diabetes, the risk is much higher (approx. 10%).
†If the father also has type 2 diabetes, the risk is doubled (approx. 20%).
‡A rare familial form of diabetes.

requiring more than 30 to 40 units per day find it difficult to achieve glycaemic control with oral hypoglycaemic agents unless major changes are possible in their lifestyle (for example, losing weight if obese, becoming more active if inactive).

Mary is overweight but not obese, she is already probably fairly active and might find it difficult to fit a strenuous exercise program into her already crowded day. The situation may change as she gets more control over her life and re-establishes her regular schedule; however, trying to switch at this stage may add to her problems rather than solving them.

What is the future risk of diabetes for her sons?

Type 2 diabetes is inherited more strongly than type 1 diabetes (table 3).[7] The two types are genetically distinct with no genetic interaction. The risk of Mary's sons developing type 2 diabetes is increased compared to the general population, but not enormously. Her children are also at increased risk of the other components of the metabolic syndrome (Syndrome X), namely hypertension, hyperlipidaemia, central obesity and cardiovascular problems. Mary should be encouraged to apply her healthy lifestyle prescription to the whole family.

Further case information

The future

The following week Mary says that she is coping much better. Her mother, with whom she gets on well, has moved in to help. Her partner is doing more around the house, looking after Timothy and even changing the baby's nappy occasionally! Her thyroid function tests are normal and her diabetes seems a bit more stable.

She feels much more positive but she and her partner both think a family of two children is enough and he is considering a vasectomy.

Conclusion

With careful planning and active management, outcomes for mothers with diabetes and their babies are similar to equivalent pregnancies not complicated by diabetes. Pre-pregnancy planning is important and includes review of contraceptive practice, diabetes management, complication status and medication. MT

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