Diabetes mellitus and pregnancy
the GP's role

The outcomes of pregnancy in the many young women with pregestational diabetes who are not under the regular care of specialist physicians can be optimised by GPs taking an active role in preconception counselling and ensuring good glycaemic control is established well before conception.

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Less than 50 years ago, a woman with diabetes who became pregnant could anticipate a perinatal mortality of 25 to 30%. With continued improvements in both diabetic and obstetric care, this figure has improved significantly. Unfortunately, the outcomes of pregnancies complicated by pregestational diabetes (i.e. pregnancy complicated by pre-existing type 1 or type 2 diabetes) are still considerably worse than for those in the general population. However, the outcomes can be optimised by meticulous care before and during pregnancy.

Pregestational diabetes and pregnancy outcomes

The major concerns relating to pregestational diabetes are the increased risk of congenital anomalies and perinatal mortality. There is also an increased risk of macrosomia, intrauterine growth retardation, oligo- or polyhydramnios, pregnancy-induced hypertension, prematurity, neonatal hypoglycaemia and other electrolyte abnormalities, and neonatal jaundice.

A report from England in 2002 identified a perinatal mortality in babies of women with pregestational diabetes that was five times that of the general population.[1] This study also demonstrated a fourfold increase in adverse outcome and spontaneous abortion, and a ninefold increase in major congenital malformation in women with a glycosylated haemoglobin (HbA_{1c}) concentration above 7.5% at booking.

Another nationwide prospective report, this time of 364 women with type 1 diabetes from the Netherlands, documented higher rates of maternal and perinatal mortality, pre-eclampsia, preterm delivery, congenital malformations and macrosomia compared with those of the general population.[2] A recent outcome study from Sydney also

IN SUMMARY

- **Pregnancy outcomes in patients with diabetes can be optimised by appropriate care. Preconception counselling and meticulous glycaemic control before and during pregnancy are essential.**
- **Patients need assessment for the presence of micro- and macrovascular complications of diabetes. Some of these need therapy before pregnancy (e.g. retinopathy) while others increase the likelihood of problems in pregnancy (e.g. autonomic neuropathy or nephropathy) or place the mother's health at increased risk (e.g. macrovascular disease).**
- **Postpartum counselling and adjustment of insulin therapy is required to ensure patient safety.**
- **Drug therapy, including complementary therapy, should be reviewed.**

concluded that pregnancies in women with type 1 or type 2 diabetes are more complicated than those in the general population.[3]

Roughly half of the perinatal mortality relates to major congenital malformations. The risk of major congenital malformations is largely related to the degree of hyperglycaemia around the time of conception and during the early part of the first trimester of pregnancy.

Success in optimising pregnancy outcomes is to a large extent influenced by:

- preconception counselling
- optimal glycaemic control before and during the pregnancy
- general pregnancy care by a multidisciplinary team specialising in the management of diabetes in pregnancy.

Preconception counselling

A meta-analysis of published studies of the benefits of preconception care in reducing congenital malformations demonstrated a significantly lower prevalence of major congenital anomalies in women who received prepregnancy counselling (relative risk 0.36, 95% confidence interval 0.22-0.59).[4] This concurs with our local experience that pregnancy outcomes can be improved by increased attention to detail, particularly regarding prepregnancy counselling.[5]

A considerable number of young women with type 1 diabetes are not under the regular care of specialist physicians, and there is an increasing number of women with type 2 diabetes of childbearing age who otherwise have no great need for specialist care. It is particularly in these groups of women that the generalist needs to take an active role, seeking opportunities to discuss the issue of pregnancy and reinforcing the significant benefits of preconceptional care. Even for women who see a diabetes physician, the close relationship between GPs and their patients may facilitate the discussion of pregnancy issues, and such opportunities should be used in full.

Information and counselling about the need for planning pregnancy should be provided to women with diabetes at an appropriate time after puberty or soon after diagnosis, and reinforced regularly (at least annually). The box on page 18 summarises some specific issues that should be discussed during preconception counselling.

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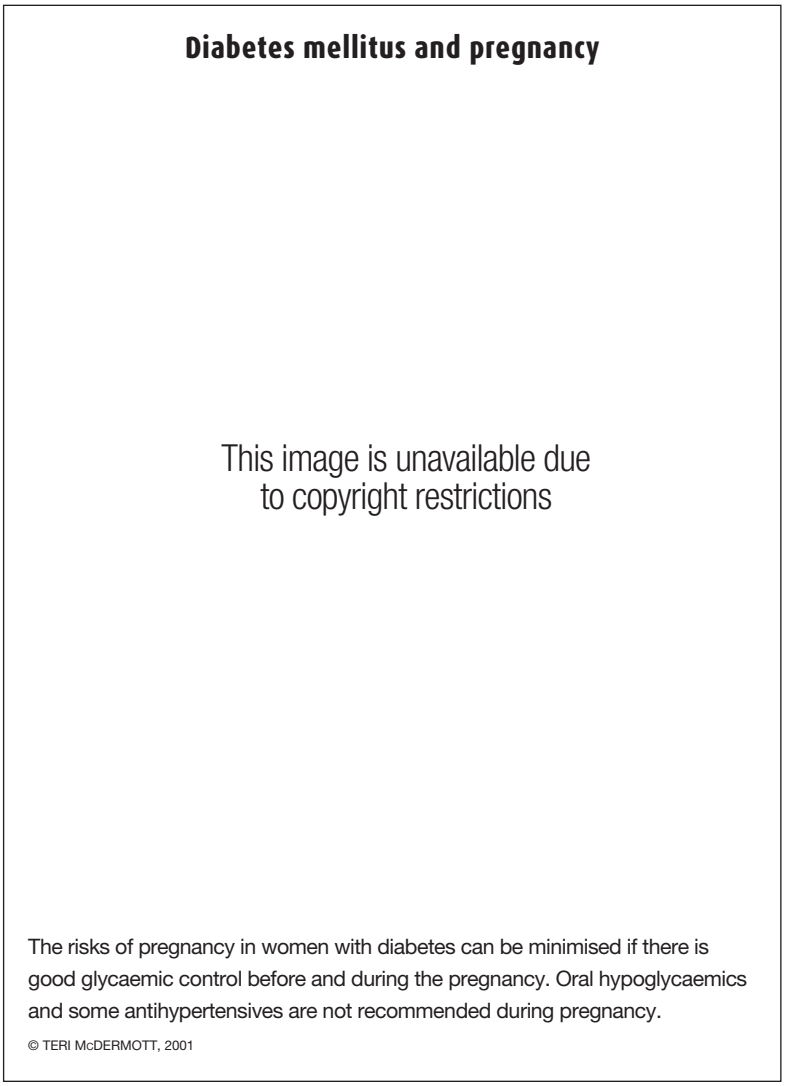

The risks of pregnancy in women with diabetes can be minimised if there is good glycaemic control before and during the pregnancy. Oral hypoglycaemics and some antihypertensives are not recommended during pregnancy.

Preconception glycaemic target

There is a widely held belief that there is a threshold HbA_{1c} concentration below which the risk of congenital malformations is not increased. Recent studies challenge this belief in both type 1 and type 2 diabetes.[6,7] These studies suggest that the risk of congenital malformation doubles when the HbA_{1c} is only slightly above the normal range. Furthermore, the congenital malformation rate in women with a HbA_{1c} less than two standard deviations above the mean of the normal range was almost double that of the control population. In the previously discussed English study, the group with better glycaemic control (i.e. HbA_{1c} less than 7.5%) had a congenital malformation

rate 2.4 times that of the background population.[1] In the Dutch study, the increased complications occurred despite 75% of the mothers having a HbA_{1c} less than 7% early in pregnancy, and the authors concluded that this level of good control (i.e. HbA_{1c} less than 7%) in early pregnancy was not adequate.[2]

The adverse effects of hyperglycaemia on pregnancy are further highlighted by the observation that an increase of one standard deviation in first trimester HbA_{1C} increased the risk of spontaneous abortion by 3%.[8]

We therefore recommend targeting the prepregnancy HbA_{1c} to a level within the normal range. Although all women with diabetes cannot achieve this, the decision to deviate from this ideal should be made on an individual basis by a physician experienced in diabetic management following discussion with the woman concerned.

Most of the other complications that may arise from pregestational diabetes, including fetal macrosomia, neonatal hypoglycaemia and pre-eclampsia, are also reduced by good glycaemic control during pregnancy.

Pregnancy care by specialised teams

Many studies from different countries have shown that centres interested in the care of pregnancy complicated by pregestational diabetes have better out - comes than do corresponding centres that do not have special interest. It is therefore recommended that the care of women with pregestational diabetes who are pregnant or contemplating pregnancy should be undertaken by people and/or units with an interest and experience in providing this care.

It would be appropriate for generalists to refer women with diabetes to obstetricians and endocrinologists or physicians experienced in the management of diabetes in pregnancy for their pregnancy care. Most larger hospitals have specialised diabetes in pregnancy clinics for this purpose. The data on the 364 women in the Dutch study were drawn from 118 hospitals,[3] and this has raised comment regarding the fragmentation of care in a country the size of the Netherlands. Other experts recommend centralised care delivery.

Ideally, referral should occur before conception for optimisation of glycaemic control and counselling. If the woman is already pregnant, she should be seen as early as possible by the specialist team.

Diabetes and pregnancy: preconception counselling discussion points

Diabetes-related issues

- The clear benefits of optimal metabolic control before conception in reducing the risk of congenital malformations and possibly other pregnancy complications.
- An outline of management during pregnancy, including medications, education, glycaemic control, complications and thyroid function monitoring.
- The importance of cessation of oral hypoglycaemic agents and the introduction of insulin.
- The most appropriate form of contraception until conception is desiredand good metabolic control has been achieved.

General prepregnancy obstetric advice

- The need for folate supplementation (5 mg folate daily should be recommended to all women with diabetes) and increased dietary intake of folate-rich foods.
- Smoking cessation.
- Reduction of alcohol intake.
- Review of all medications (including complementary and alternative) for safety in pregnancy.
- Check of immune status regarding rubella and varicella.

General principles of diabetes management in pregnancy

Medications

Oral hypoglycaemic agents are not recommended during pregnancy because their safety is not established. Oral agents being taken by women with pre-existing diabetes should be switched to insulin before conception. In special circumstances (such as in patients who absolutely refuse insulin therapy), oral agents such as metformin may be required, but they should only be continued after discussion with the patient.

Antihypertensive therapy should be optimised for pregnancy. Drugs contraindicated in pregnancy, again because of potential risk to the fetus, should be changed before conception to avoid loss of blood pressure control in early pregnancy. ACE inhibitors and angiotensin receptor blockers are contraindicated after the second trimester. We recommend that these agents be ceased before pregnancy so that the replacement therapy is adjusted before conception. Diuretics are also contraindicated, and β-blockers should be avoided unless absolutely necessary, to avoid masking hypoglycaemia.

Antihypertensive agents suitable to use in pregnancy include methyldopa (Aldomet, Hydopa), hydralazine (Alphapress, Apresoline) and verapamil (Anpec, Cordilox, Isoptin, Veracaps).

Lipid lowering therapy must be ceased before pregnancy, again because the drugs used are potentially teratogenic.

Education

Formal review is recommended, including discussion with a diabetes educator and a dietitian. The goal is to ensure adequate self-management skills, including for morning sickness and days when the patient is feeling unwell. Hypoglycaemia

management must be reviewed, and should include advice to partners of patients requiring insulin on the use of glucagon (GlucaGen). Inclusion of partners and review of their skills is essential.

Complications review

Formal assessment should be undertaken for the microvascular complications of diabetes, particularly retinopathy and nephropathy, both of which may progress in pregnancy.

Ideally, the albumin excretion rate should be quantified with a timed urine sample. Failing this the albumin:creatinine ratio (ACR) can be determined on an early morning specimen. If the ACR is more than 3.5, a timed sample should be collected to quantify the albumin excretion rate. Patients with pre-existing albuminuria are more likely to develop pregnancy-associated hypertension (pre- eclampsia) and progression of renal disease.

A person experienced in retinal examination should conduct the eye examination through dilated pupils. If retinopathy requires treatment, this should be undertaken before pregnancy.

The possibility of macrovascular disease should be considered and formally investigated if suspected.

A repeat review of microvascular complications is required during pregnancy. This is especially important for retinopathy, which may progress to become vision threatening. Routine urine testing should detect increasing proteinuria.

Glycaemic control in pregnancy

Although we recommend that specialist teams care for pregnant women with diabetes, it is important that generalists are aware of the treatment goals and targets, particularly as women may continue to seek their advice during pregnancy.

Blood glucose testing

Self-blood glucose testing is mandatory. Women should aim to test their blood glucose levels before breakfast and two hours after meals. For some women, testing before other meals is also useful. The blood glucose level targets are 3.5 to 5.5 mmol/L fasting and 3.5 to 7.0 mmol/L two hours' postprandial.

Glycosylated haemoglobin monitoring

HbA_{1c} should be monitored during pregnancy at one- to two-monthly intervals to confirm objectively the clinical impression gained from the measurements in the home monitoring record book. A HbA_{1c} level within the normal range (i.e. 4 to 6%) is desirable.

Insulin therapy

Unless the woman has diet-controlled type 2 diabetes, insulin therapy will be required. In general, a basal bolus regimen is recommended, although other regimens might be used in some circumstances. An appropriate regimen may comprise three injections of a short acting insulin (neutral-human [Actrapid, Humulin R] or neutral-bovine [Hypurin Neutral]) before meals, and a long acting or intermediate insulin (isophane-bovine [Hypurin Isophane], isophane-human [Protaphane, Humulin R], lente [Monotard, Humulin L] or ultra-lente-human [Humulin UL, Ultratard]) before bed.

There is increasing use of the newer rapid acting insulins during pregnancy. There is more published information for lispro (Humalog) than aspart (NovoRapid), although a formal multicentre study will report shortly on aspart's use in pregnancy. Both are probably safe despite early reports to the contrary. Nevertheless, their use in pregnancy should be discussed with the patient. There is little published experience with glargine (Lantus), the new long acting insulin, and it is best avoided for the moment.

Thyroid function and coeliac disease

Thyroid function should be measured before and during pregnancy. Abnormalities (especially hypothyroidism) in people with diabetes are common and associated with adverse pregnancy outcomes. Thyroid function tests in early pregnancy are often abnormal when compared with the nonpregnant normal range. Thyroid stimulating hormone (TSH) may be low, with elevated thyroxine (T4) or free triiodothyronine (T3). Specialist advice may be needed when abnormal thyroid function is discovered.

Screening for coeliac disease should be considered.

Risks to the mother

There are several conditions that are contraindications to pregnancy as they would place the mother at serious risk. These include:

- active proliferative retinopathy until treated, as retinopathy may progress rapidly in pregnancy
- renal impairment, as this also can rapidly progress; although renal function usually returns to normal postpartum, this may not be the case if the impairment is severe (creatinine greater than 200 mmol/L)
- pre-existing cardiac disease, as the physiological changes of pregnancy place additional demands on cardiac function; the ability of the heart to deal with the increased demands should be

determined before pregnancy
- pre-existing autonomic neuropathy (gastroparesis and/or postural hypo - tension), as this can make the management of pregnancy extremely difficult.

If there are contraindications, the medical practitioner needs to advise the woman of the risks she runs in undergoing a pregnancy. The decision to proceed (or not) must be made by the woman and her partner.

Risk of maternal hypoglycaemia

A word of caution is appropriate concerning glycaemic control. Good or excellent glycaemic control cannot be achieved without an increased risk of major hypoglycaemia, a life-threatening emergency. Hypoglycaemia may occasionally result in maternal death, as reported in the Dutch study, or fetal death.

There is a changing pattern of insulin requirements in pregnancy, which can make adjustment of therapy difficult and dangerous (to the women) unless there is familiarity with the metabolic changes of pregnancy. Less insulin is required early in pregnancy (up to about 18 weeks' gestation), whereas more (often two to three times more) is required between about weeks 24 and 32, after which time the requirements fall again. Any significant fall should trigger assessment by the obstetrician for fetal wellbeing and by the physician for other medical problems such as hypoadrenalism (e.g. due to lymphocytic hypophysitis), although this fall may be a normal variant.

Postpartum counselling

Insulin requirements are dramatically reduced immediately postpartum compared with that during the last few weeks of pregnancy. The patient will need advice and close monitoring to find the appropriate new dosing regimen. Postpartum is also a time of great unpredictability, given the demands of the infant, and generalists need to be aware that tight glycaemic control is almost impossible without significant hypoglycaemia. Women often need specific counselling to help them change from the intensive approach to glycaemic control followed in pregnancy. Returning to the old prepregnancy dose, as often suggested, is not appropriate in this new situation.

Oral hypoglycaemic agents should not be prescribed if the mother is breastfeeding. Therefore, for patients with type 2 diabetes who breastfeed, it may be necessary to continue insulin therapy to maintain safe glycaemic control. The care of women at this stage returns to the primary setting; GPs should be fully informed of their patients' treatment details.

The role of GPs

GPs are usually more involved with the preconception care of women with diabetes who want to become pregnant than with their care during pregnancy because most women with diabetes are referred to specialists for their pregnancy care. Rural GPs, however, are more likely than urban and suburban GPs to also be involved with the care of these women during pregnancy.

The main points to be borne in mind concerning preconception and pregnancy care of patients with pregestational diabetes is summarised in the box on this page. Rural GPs should be particularly aware of the need for specialist referral, even if this is difficult, if patients have pre-existing macrovascular disease or chronic renal failure or if glycaemic control is poor or there are pregnancy complications.

Conclusion

Although pregnancies in women with pregestational diabetes generally have a higher complication rate than those in women without diabetes, the risks can be minimised if optimal care is in place well before conception. This requires awareness of the specific problems by women's regular medical attendants, and referral to appropriate specialists or specialist teams ideally when pregnancy is being contemplated, or if pregnancy has already occurred, as soon as possible. MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: None.

Diabetes and pregnancy: guidelines for GPs

- Optimise diabetic management, including lifestyle issues, before conception. Switch from oral hypoglycaemic agents, if used, to insulin, and ensure any antihypertensive agents are appropriate for use during pregnancy.
- Check for diabetic complications:
  – ensure proliferative retinopathy is treated
  – be aware of the increased problems likely with nephropathy or autonomic neuropathy
  – the presence of macrovascular disease or chronic renal failure warrants specialist referral, even if this difficult.
- Be aware of the changing insulin requirements as pregnancy progresses.
- Maintain the best glycaemic control possible.
- Monitor closely; weekly or more frequently is appropriate in difficult cases.
- Plan for the possibility of early delivery of a premature infant at increased risk of respiratory distress and other problems.
- Consider early transfer to a referral centre if there is poor glycaemic control or emerging evidence of pregnancy complications.

Medicine Today 2004; 5(10): 16-24

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