Chapter 1

Type 2 diabetes mellitus

Catherine Henry and William M. Hague

Clinical history

Mrs. N. was a 35-year-old process worker who was diagnosed with type 2 diabetes mellitus 2 years previously (random serum glucose 11.4 mmol/L). Both her parents were diabetic. She had two children by a previous partner: the younger was 4 years old, and during that pregnancy the patient experienced gestational diabetes (GDM), which was managed with insulin. Her husband had oligospermia and IVF/ICSI was required. Mrs. N. was maintained on metformin 500 mg tds and daily gliclazide 30 mg: $HbA1_c$ was 8.6%. Her body mass index (BMI) was 31 kg/m^2 and her blood pressure was 130/85 mmHg. She had background minor retinopathy. Urine dipstick analysis showed 1+ protein and serum creatinine 85 μmol/L (upper limit of normal). The couple presented for preconception counseling.

Introduction

Type 2 diabetes mellitus (T2DM) is a common condition that is increasingly diagnosed in younger patients [1, 2]. Its occurrence in women of reproductive age is as much as 20% in some populations [3]. These observations are linked with the rising obesity epidemic in developed countries, associated with more sedentary lifestyles and increased intake of energy-dense food [1, 2].

T2DM is characterized by hyperglycemia secondary to impaired pancreatic beta-cell function and peripheral insulin resistance [1]. End-organ effects, particularly micro- and macrovascular complications during pregnancy may impact both mother and fetus directly and in the longer term [4]. T2DM is associated with increased perinatal mortality, congenital malformations, preeclampsia, birth trauma, and operative delivery [5]. Additionally, the hormonal milieu of pregnancy worsens maternal glycemic control and may accelerate preexisting complications. Although traditionally considered a "less serious" form of diabetes in pregnancy, T2DM is associated with equally poor or worse gestational outcomes than T1DM,with a 4-fold increase in perinatal mortality and a 2-fold increase in congenital malformations. It is crucial that women with T2DM receive effective multidisciplinary care preconception and during pregnancy [1, 2, 4].

Preconception management

Preconception counseling and active management of women with T2DM has been reported to reduce significantly the risk of major congenital malformations[3]. Care focuses on optimizing glycemic control, medication review, identification and treatment of complications, counseling, and reduction of associated risk factors [4, 5]. Effective contraception is advised during the pregnancy-planning period [4]. See Figure 1.1.

History/screening examination

Review of Mrs. N.'s diabetic, obstetric, and personal history was undertaken to identify issues that required correction. Diabetic history must focus on timing of diagnosis, previous and current management, glycemic control, and any active complications [3]. Obstetric history should elucidate previous preeclampsia, intrauterine growth restriction/macrosomia, birth trauma (shoulder dystocia/genital tract injury), and neonatal complications related to diabetes [3]. Modifiable factors include physical inactivity, a high BMI, and poor diet. Nonmodifiable risk factors include ethnicity and a strong family history [5]. GDM carries a 50% risk for the development of T2DM over the next 10 years, so previous care should have incorporated counseling to avert its development. Annual screening of blood glucose is recommended following GDM pregnancy to facilitate early recognition and treatment of T2DM.

Counseling and psychological support

Prepregnancy counseling forewarns about the effects of pregnancy on T2DM and vice versa [2]. It empowers women and promotes uptake of effective management strategies. It should incorporate discussion on the risk of deterioration of diabetic complications, and the potential development of preeclampsia, polyhydramnios, infection, and/or dystocia [4, 5]. Pertinent to this case were concerns regarding deterioration of her sight and renal function, as well as her obesity. Potential fetal complications include miscarriage, stillbirth, and neonatal death [3]. The risk of congenital malformations, including cardiac anomalies, is increased: this is closely related to glycemic control [3, 5]. Strict diabetic control is vital for the long-term health of offspring, as intrauterine programming from exposure to maternal hyperglycemia is associated with higher rates of obesity, metabolic syndrome, and T2DM in later life [1, 5]. Although not all malformations are preventable, careful planning can lessen the potential for many conditions.

T2DM in pregnancy will require heightened monitoring and multidisciplinary involvement [4]. The possibility of preterm or operative delivery (e.g., cesarean section for macrosomia, shoulder dystocia, or previous perineal trauma) should be raised [4]. Discussion should cover increased neonatal risks of hypoglycemia, jaundice, polycythemia, respiratory distress syndrome, hypocalcemia, and the potential for admission to the special care nursery/neonatal intensive care unit [4].

Despite the hazards, it is important to stress that a woman with T2DM can improve the outcome through preventative activities, such as effective blood glucose control and building in gentle exercise.

Medication review

Patients planning pregnancy should undergo medication review to identify potential teratogens [4]. Those pertaining to T2DM include antihyperglycemic, antihypertensive, and lipid-lowering agents [3].

There is long experience with insulin in pregnancy. Its short- and long-term effects (including adverse impacts) have been established over many years [3]. A small number of trials of insulin analog support their safe use in pregnancy [3]. These include insulin lispro and aspart (short-acting analogues) and insulin detemir (long-acting) [3, 5]. Although concerns have been raised that insulin glargine, which has avidity for the insulin-like growth factor receptor-1 and which might cause fetal macrosomia, this has not been confirmed [5].

A basal-bolus regimen, adjusted to fasting and 2-hour postprandial maternal blood glucose, is typically prescribed [4]. Although Mrs. N. might require insulin therapy during pregnancy, given that she had been so treated during her previous pregnancy, her current oral hypoglycemic regimen (metformin and gliclazide) needed to be reviewed prior to conception.

The use of metformin in pregnancy has been assessed in several trials, mainly in patients with polycystic ovary syndrome and in GDM. Though metformin does cross the placenta, there is no increase in congenital abnormalities with its use. Unlike insulin, metformin curtails weight gain and does not carry a significant risk of hypoglycemia. Moreover, by reducing peripheral insulin resistance, its use may allow smaller insulin doses to achieve optimal glycemic control [2]. Limited data suggest no longer-term ill effects on offspring health, cognition, and metabolism [2, 3].

Sulfonylureas are usually avoided in pregnancy due to perceived risks of causing neonatal hypoglycemia, but second-generation agents (e.g., glibenclamide) have been found to be effective and without major adverse events in small trials and cohort studies in the pregnant diabetic population. Although gliclazide may perhaps cross the placenta more easily than glibenclamide, there does not appear to be any significant risk of teratogenesis with these drugs [2].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers should generally be ceased during pregnancy: their prolonged use in pregnancy has been associated with abnormalities associated with fetal renal shutdown and anuria, but recent data suggest they are not teratogenic [see Chapter 2 on hypertension]. They may be substituted with methyldopa, labetalol, oxprenolol, nifedipine, clonidine, or prazosin [5]. Atenolol should be ceased in the first trimester due to concerns regarding fetal growth restriction. Diuretics should be avoided unless there is evidence of left ventricular failure. Statins are contraindicated [5].

Glycemic control

Glycemia has a major impact on pregnancy outcomes [3]. It should be stabilized/established prior to conception, as the harmful effects of hyperglycemia during embryogenesis may be more detrimental than the unknown effects of some antihyperglycemic medications [4]. Mrs. N.'s management would optimally include a combination of dietary and lifestyle modifications, insulin, and possibly metformin.

Glycemic control is assessed through patient-monitored fasting and postprandial blood glucose values, together with laboratory measurement of $HbA1_c$ [4]. Mrs. N.'s $HbA1_c$ indicated poor control. Ideally, $HbA1_c$ should be <7% preconception, and preferably within normal limits (<6.1%) [2, 5]. A 1% reduction in $HbA1_c$ correlates with a 40–60% relative risk reduction for congenital malformations [2]. $HbA1_c$ should be monitored each trimester, as a reflection of control over the preceding 8–10 weeks. In pregnancy, $HbA1_c$ normally declines, due to accelerated erythrocyte turnover, particularly in the last two trimesters [5].

During pregnancy, current recommended glucose targets are fasting 4.0–5.5 mmol/L, <8.0 mmol/L at 1 hour postprandial, and <7.0 mmol/L at 2 hours postprandial [5]: it has been suggested that these values are too lax, but there are no randomized trials of treatment to establish either targets in pregnancy or timing of monitoring. Regular blood glucose monitoring is necessary to assist with titration of medication doses. The recommended control of diabetes prepregnancy may take months to achieve, and culturally appropriate education is essential.

Diabetic complications

Patients with diabetes should be screened for complications [5]. Microvascular disease manifests as retinopathy, nephropathy, and neuropathy. These conditions should receive appropriate specialist attention/referral [3].

Diabetic retinopathy (proliferative and nonproliferative) contributes to visual impairment. Pregnancy is a risk factor for acceleration of this condition [3]. Affected women should be reviewed by an ophthalmologist within 12 months before conception [2]. Evidence of proliferative retinopathy warrants treatment (e.g., laser photocoagulation) prior to or during pregnancy [5]. Given Mrs. N.'s mild retinopathy, counseling was considered appropriate regarding the potential for sight deterioration if pregnancy was pursued.

Diabetic nephropathy may also be exacerbated by pregnancy. An assessment for proteinuria and serum creatinine is necessary [2]. Microalbuminuria implies an increased risk for preeclampsia (32–65%), premature delivery (57–91%), and intrauterine growth restriction (12–45%) [3]. Mrs. N.'s proteinuria put her in a higher risk pregnancy category relative to T2DM without proteinuria [5]. Although her serum creatinine was in the upper range of normal, serum creatinine remains within normal limits until substantial deterioration of renal function occurs. A steadily rising creatinine indicates significant renal disease. Nephrology review is recommended for patients whose serum creatinine is >120 mmol/L or whose protein excretion is >2 g/24 hours. Control of glycemia and blood pressure slows disease progression [3].

Neuropathy (autonomic or peripheral) may manifest with orthostatic hypotension, hypoglycemic unawareness, and sensory neuropathy [5]. Pregnant women with these conditions should be advised to be careful when moving from a supine to an erect posture so as to minimize syncope. The risk of hypoglycemic unawareness rises in pregnancy, and these events may be more frequent, particularly in women receiving insulin [4]. Sensory neuropathy is a risk factor for neuropathic ulcers. Weight increase alters the load on the feet. Women should be advised to seek early care if they suspect skin breakdown. Podiatric input may be required.

Macrovascular complications require attention [5]. Some diabetic women will develop cardiovascular disease (e.g., acute coronary syndrome) when cardiology referral is required [2]. A screening ECG is necessary, as well as blood pressure management (particularly in the presence of microalbuminuria and renal impairment) [4]. The target blood pressure is <125/80 mmHg. Mrs. N.'s blood pressure was above that recommended, so it was possible that antihypertensive therapy would be required.

Weight management

Mrs. N. met the BMI criteria for obesity (≥30 kg/m^2). Obesity is associated with adverse pregnancy outcomes, additive to those of T2DM [2, 5]. Mrs. N. needed to attempt weight reduction (through exercise and dietary changes), and this would have additional benefit for her diabetes [4]. Any weight loss would be beneficial [2, 3]. Pregnancy weight gain in obese patients is controversial. Some experts recommend restricting weight gain in such women [2, 3].

General advice

T2DM women contemplating pregnancy should be advised to reduce or cease consumption of recreational substances (e.g., alcohol and smoking) and to engage with a management

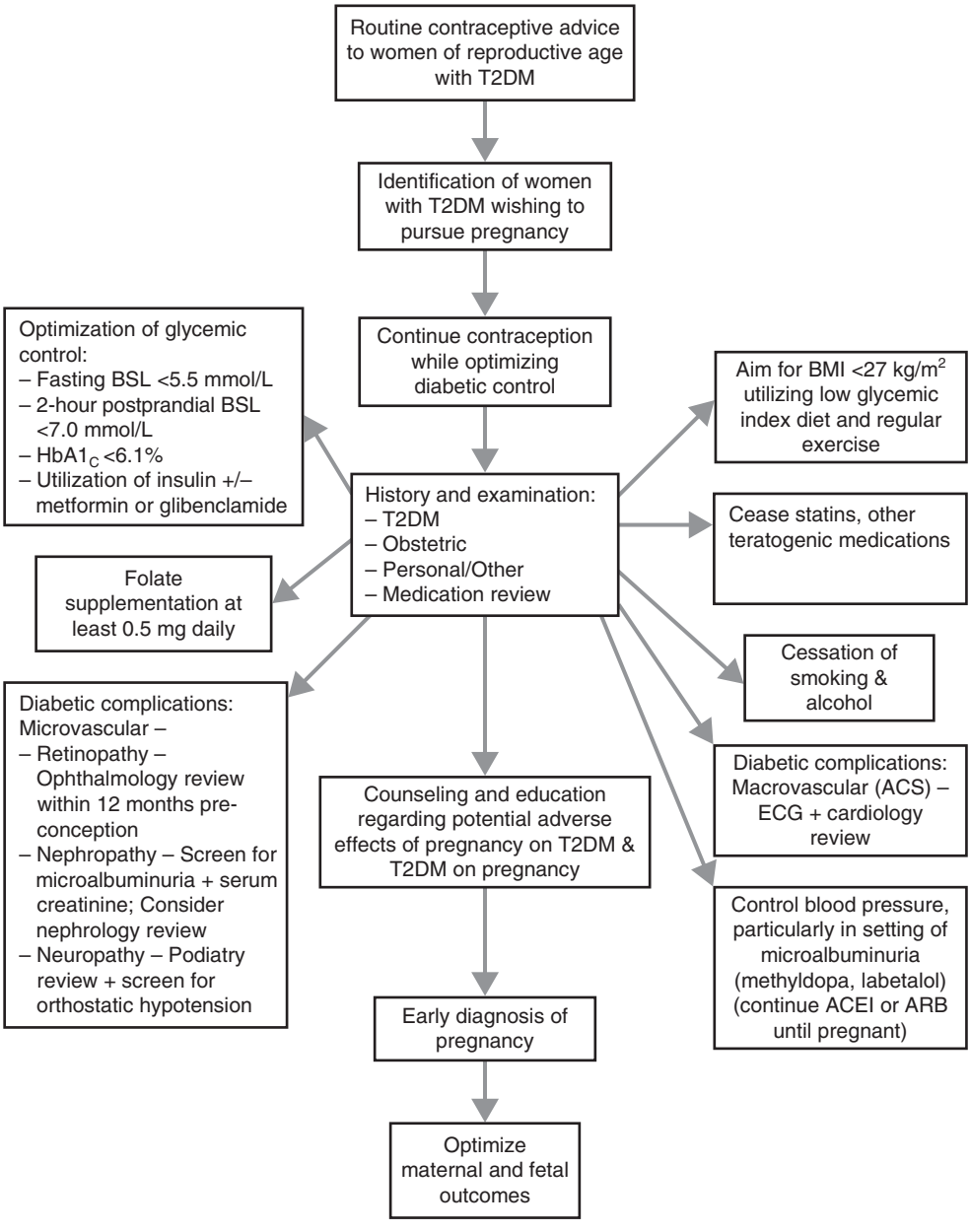

Figure 1.1 A road map for preconception care.

plan to work toward a successful outcome [3]. Preconception folate supplementation until 12 weeks gestation is recommended to prevent neural tube defects [2]. The patient's rubella status should be known and vaccination updated as necessary. Accurate dating of a pregnancy with a late first-trimester ultrasound will guide management throughout the pregnancy, and serum screening should be offered [5]. Pregnant T2DM patients should be encouraged to

watch their diet and exercise [2]. A diabetic educator/dietician can advise about the need for low glycemic index foods to stabilize diabetes in a state of flux (i.e., pregnancy) [3]. Dietary habits may be common to the members of the same household. The oligospermia in Mrs. N.'s husband might have been indicative of his personal health issues (e.g., T2DM). Lifestyle changes may well benefit the entire family and improve the fertility of the couple.

Antenatal, intrapartum, and postnatal care

The antenatal, intrapartum, and postnatal care of Mrs. N. will affirm the high-risk nature of any such pregnancy. Close monitoring and tight glycemic control should be continued during and after pregnancy [4]. Assessment for congenital abnormalities and monitoring of fetal growth should be undertaken, with collaboration between obstetricians, obstetric physicians, midwives, endocrinologists, and allied health personnel [5].

Conclusion

T2DM is a major health issue affecting increasing numbers of women of reproductive age. Optimizing glycemic control preconception improves maternal and fetal outcomes with lifelong benefits for offspring. Multidisciplinary care is required to attain positive outcomes. This should commence preconception, and continue until the puerperium. Despite Mrs. N.'s suboptimal diabetic management, alterations to therapy can improve significantly both her health and that of any offspring. Lifestyle modifications may also have benefits for the family.

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Chapter 2

A woman with hypertension

Mark R. Morton and William M. Hague

Clinical history

Ms. B. was a 28-year-old teacher from the northern suburbs of the metropolis, who had never been pregnant, despite 2 years of unprotected intercourse, regular ovulatory menses, and a 38-year-old partner with three previous paternities. She was diagnosed with hypertension while taking the combined oral contraceptive pill and remained hypertensive despite coming off the pill. Her father was hypertensive and had a stroke in his sixties. Her current treatment included irbesartan 150 mg daily. On examination, she was anxious. Blood pressure was 150/90 mmHg. Eyes were normal. Urine dipstick showed a trace of protein. Electrolytes, blood glucose, and renal function were normal.

What further investigations should be considered?

The family history of hypertension and cerebrovascular disease suggests a diagnosis of essential hypertension. However, secondary causes of hypertension should also be considered, particularly renal disease, which can also be familial. The urine dipstick result is probably not significant, but it would be worth quantifying any proteinuria with a urinary microalbumin test, which can be measured on a spot urine. The presence of significant urinary albumin would support a diagnosis of underlying renal disease or renal damage from long-standing hypertension. A renal ultrasound should be performed to assess renal size and to look for any renal scarring. Renal artery stenosis due to fibromuscular dysplasia is a rare secondary cause of renovascular hypertension, but can occur in young women. This can sometimes be diagnosed on renal artery Doppler studies, but computed tomography (CT) or magnetic resonance (MR) angiography are more sensitive investigations for renal artery stenosis.

Hypertension in a young person, especially if severe, can be due to a coarctation of the aorta, so the femoral pulses should be checked and compared to the radial pulses to see whether there is any radio-femoral delay.

Hypertension with symptoms, such as abdominal pain, palpitations, sweating, and anxiety, could indicate a pheochromocytoma. This is an epinephrine (adrenaline)- and/or norepinephrine (noradrenaline)-secreting tumor, usually of the adrenal gland. Ten percent of such tumors can be extra-adrenal and 10% are malignant. Although this is a very rare cause of secondary hypertension, if it is missed in pregnancy the consequences can be catastrophic for both the mother and fetus. A 24-hour urine collection for urinary catecholamines is an appropriate screening test for pheochromocytoma. (It is important to collect the urine into a container with added acid to minimize spontaneous degradation of any catecholamine present.)

Not infrequently, the finding of elevated blood pressure in the clinic may be related to anxiety rather than to true chronic hypertension. Ambulatory 24-hour blood pressure monitoring is increasingly being used to identify patients with "white-coat" hypertension. Women with "white-coat" hypertension do have better outcomes in pregnancy than those with true chronic hypertension, but despite the label they are still at slightly increased risk of developing hypertensive disorders of pregnancy.

Preexisting hypertension for any reason is a risk factor for the subsequent development of preeclampsia. The risk of developing preeclampsia is increased 5-fold in women with prior hypertension. Ms. B. should therefore be counseled regarding the possibility of preeclampsia and associated intrauterine growth restriction. These risks are further increased in women undergoing assisted reproduction, particularly if the woman is obese. Multifetal pregnancy also compounds the risk, and every effort should be made to ensure a singleton pregnancy in the hypertensive woman undergoing assisted reproductive technology.

Should she be given agents to prevent preeclampsia?

Many studies have been performed to identify agents that might prevent preeclampsia, particularly in high-risk women. Aspirin, calcium, and antioxidant vitamins have been the most extensively studied.

A Cochrane review found that use of antiplatelet agents, in particular aspirin at a dose of 75–150 mg/day, gives a small but significant reduction (0.83: 95% confidence interval [CI] 0.77 to 0.89) in the relative risk of developing preeclampsia, as well as a reduction in the risk of perinatal mortality (0.86: 95% CI 0.76 to 0.98). In high-risk women, only 19 need to be treated to prevent one case of preeclampsia. There is a halving of the risk when treatment is started before 16 weeks gestation. Meta-analysis of individual patient data from the Cochrane review did not show any difference in risk reduction for the presence of chronic hypertension. Current guidelines recommend that aspirin should be commenced after 12 weeks gestation and before 20 weeks gestation in women with moderate or high risk of developing preeclampsia. Low-dose aspirin is considered safe in pregnancy: it does not increase the rates of antepartum or postpartum hemorrhage or of placental abruption.

Calcium supplementation of at least 1 gram per day during pregnancy can reduce the overall risk of developing preeclampsia (RR 0.65: 95% CI 0.53 to 0.81). This relative risk reduction is greatest in populations with poor dietary calcium intake and is less marked in populations that have adequate dietary calcium. Current guidelines recommend that calcium supplements should be given to women with poor dietary calcium intake and to those at high risk of preeclampsia.

Randomized controlled trials of the antioxidants vitamin C and vitamin E have failed to show any benefit in preventing preeclampsia or improving pregnancy outcomes. Observational data suggest that continuing folic acid supplements beyond the end of the first trimester is associated with a lower risk of preeclampsia: a large international RCT is currently in progress to assess this further.

If she is planning a pregnancy, does her antihypertensive treatment need to be changed?

Use of angiotensin-converting enzyme (ACE) inhibitors in the second and third trimesters of pregnancy is contraindicated because of an increased risk of adverse fetal outcomes.

Exposed fetuses are at increased risk of oligohydramnios, intrauterine growth restriction, hypocalvaria, renal dysplasia, and death. It is thought that a functioning renin–angiotensin system is required for the development of the fetal kidney. Because of a similar mechanism of action, angiotensin II receptor antagonists, such as irbesartan, are also contraindicated in the second and third trimesters.

The use of ACE inhibitors or angiotensin II receptor antagonists in the first trimester was also previously considered to be undesirable. However, recent population-based cohort studies and a meta-analysis have challenged this view.

In 2006, a cohort study of 29 507 births reported an increase in congenital malformations in the 209 infants that had been exposed to ACE inhibitors in the first trimester. Compared with fetuses who had had no exposure to antihypertensive agents in the first trimester, those exposed to ACE inhibitors had a 2.7-fold increase in congenital malformations, mainly of the cardiovascular and central nervous systems [1]. However, a more recent and much larger cohort study of 465 754 mother–infant pairs, in which 400 infants were exposed to ACE inhibitors, found only a nonsignificant 20% increased risk of any congenital malformation [2]. Furthermore, infants exposed to any antihypertensive agent in the first trimester, as well as infants of women who had hypertension but who did not take antihypertensive medication in the first trimester, had similar increased rates of congenital malformations. The apparent increased risk of congenital malformations in women with hypertension seems likely to be associated with the hypertension itself rather than the antihypertensive drugs.

A meta-analysis performed in 2011 of five observational cohort studies of 786 exposed infants and over one million controls concluded that first-trimester exposure to ACE inhibitors and angiotensin II receptor blockers was not associated with an elevated risk of major malformations compared with exposure to other antihypertensive agents [3]. Therefore, if Ms. B. needs antihypertensive treatment, it will be reasonable to continue the angiotensin receptor blocker until a pregnancy is confirmed.

Does she need to continue her antihypertensive agent?

In women with mild hypertension controlled on a single antihypertensive agent, given the natural fall in blood pressure in the first trimester, it is reasonable once a pregnancy is confirmed to cease the antihypertensive agent and to monitor the blood pressure. The levels of blood pressure at which hypertension in pregnancy should be treated are controversial. A Cochrane review has concluded that it is unclear whether the treatment of mild to moderate hypertension in pregnancy is worthwhile [4]. Hypertension treatment in pregnancy will halve the risk of a woman having one or more episodes of severe hypertension. Between 8 and 13 pregnant women will need to be treated with an antihypertensive drug to prevent one episode of severe hypertension. There are insufficient data to determine whether this provides substantial maternal benefits or improves fetal or neonatal outcomes. Overtreatment of blood pressure in pregnancy may impair utero-placental perfusion, leading to fetal growth restriction and adverse fetal outcomes. More data are needed and it is hoped that the results from the Control of Hypertension in Pregnancy Study (CHIPS), a multicenter randomized controlled trial examining nonsevere nonproteinuric hypertension in pregnancy that has recently completed recruitment, will provide much-needed guidance on appropriate targets for blood pressure control in pregnancy [5]. Until then, the question whether "less tight" control or "tight" control of blood pressure in pregnancy increases or decreases the likelihood of pregnancy loss or high-level neonatal care remains moot.

What antihypertensive agent should be used?

A Cochrane review of antihypertensive treatment in pregnancy failed to find that any particular drug was superior to any other [4]. Consensus guidelines have been published in the United Kingdom, Canada, United States, Australia, and New Zealand. The three most commonly used antihypertensive drugs used in pregnancy are labetalol, methyldopa, and nifedipine.

Labetalol is a competitive α_1- and nonselective β-adrenoreceptor blocker. The combined α- and β-blockade contributes to the blood pressure lowering effect, while the β-blocking properties prevent the reflex tachycardia that can occur with α-blocking agents. Chronic administration results in considerable reduction in blood pressure and peripheral resistance and a less-marked reduction in heart rate and cardiac output. Labetalol is a reasonable choice for treatment of hypertension in each trimester of pregnancy. An intravenous formulation is available for treatment of hypertensive emergencies in pregnancy. Very low amounts of the drug are excreted in breast milk and it is considered safe to use while breast feeding.

Methyldopa was developed in the 1950s to block the action of the enzyme dopa-decarboxylase, thereby preventing the formation of norepinephrine (noradrenaline). However, its active metabolite α-methylnorepinephrine stimulates the central α_2 receptors in the brainstem, resulting in its blood pressure-lowering effect. It is considered safe to use in each trimester of pregnancy. Sedation and tiredness are common side effects which can limit its usefulness, particularly if larger doses are needed to control blood pressure. It is safe to use while breast-feeding but it can exacerbate depression in the postnatal period. It is one of the few drugs that have any long-term outcome data in relation to the offspring exposed during pregnancy. A study published in 1982 looking at 195 children followed up to age 7 years after exposure to methyldopa used for treatment of hypertension in pregnancy did not find any adverse effects.

Nifedipine is a dihydropyridine calcium channel blocker. Calcium channel blockers cause interference with the entry of calcium ions into cells by blocking voltage-gated calcium channels in cardiac and smooth-muscle cells. This results in arterial vasodilatation and direct effects on cardiac conduction and contractility. It is considered safe to use in each trimester of pregnancy. Slow-release formulations can be used for treatment of chronic hypertension in pregnancy, while quick-acting versions are valuable for treatment of hypertensive emergencies. Side effects include headache, flushing, ankle edema, and a reflex tachycardia. Only small amounts of drug are excreted in breast milk and it is considered safe to give to nursing mothers. Nifedipine is also used as a tocolytic agent. Interestingly, there does not appear to be a marked effect on blood pressure when used in the normotensive woman in preterm labor.

Other antihypertensive agents that have been used to manage chronic hypertension in pregnancy include hydralazine, prazosin, and clonidine. Diuretics have been employed as fourth-line agents in difficult chronic hypertension, although there are concerns about potential reductions in circulating plasma volume, which might reduce placental blood flow in preeclampsia, as well as causing hyperuricemia, making assessment of superimposed preeclampsia more difficult [6].