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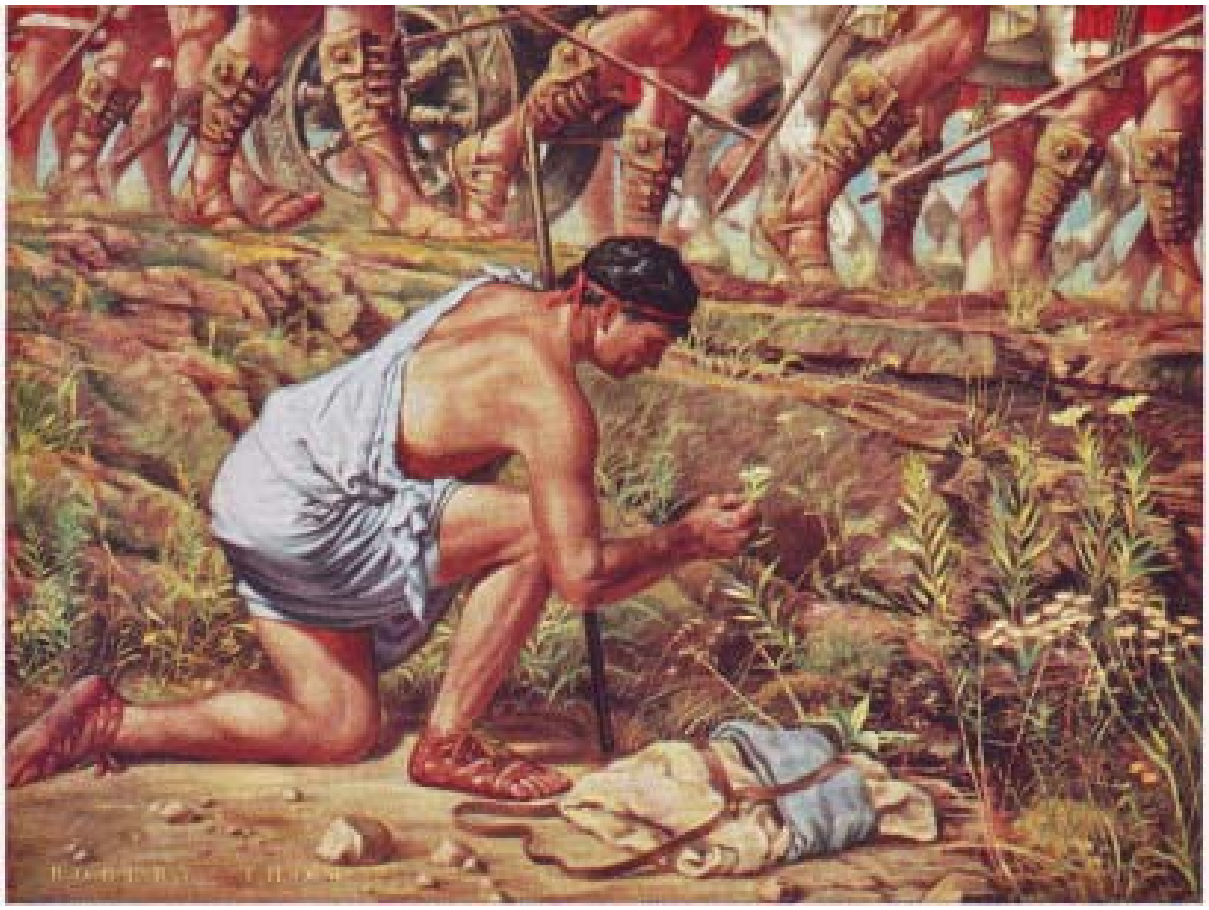

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Cover picture

PEDANIOS DIOSCORIDES (50-100 A.D.)

To study the materia medica of his time, Dioscorides accompanied the Roman legions over much of the known world. His rules for drug collection and preparation were scientifically sound.

One of a series: *A History of Pharmacy in Pictures,* presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Antiplatelet medications in treatment

Introduction

Atherothrombosis is a systemic process that affects the cardiovascular, cerebrovascular and peripheral arterial systems. Acute arterial thrombosis results in myocardial infarction and stroke.Atherosclerosis is a chronic inflammatory process that provides the underlying substrate for occlusive thrombus formation. The platelet, a mediator of endothelial, thrombotic, immune, and inflammatory responses, is pivotal in the pathogenesis of atherothrombosis. It is also a key player in the initiation and progression of atherosclerosis. Antiplatelet medications are effective in the management of cardiovascular and cerebrovascular disease, and their efficacy is backed by evidence from randomised clinical trials. When these drugs are used in combination, they are more likely to increase risk of bleeding.

Antiplatelet medications

Medicines targeting pathways in the cascade of events involved in platelet activation have been developed for use as antiplatelet medications. They include medicines aimed at inhibiting thromboxane A2, thrombin, collagen, and von Willebrand factor. Complex interactions may occur between receptors, limiting effectiveness of treatment. Presently the most widely used antiplatelet medications are aspirin and clopidogrel. Dipyridamole and glycoprotein IIb/IIIa (GpIIb/IIIa) receptor blockers are of limited use. It is tantalising to use combination therapy, as theoretically these drugs work synergistically and result in greater platelet inhibition than when a single agent is used. However, the combination increases risk of bleeding and must be used with caution in selected situations where the benefits outweigh risks.

Use in cardiovascular disease

Antiplatelet medications are used for primary and secondary prevention of cardiovascular disease. Aspirin is the most commonly used and clopidogrel is effective as an alternative when aspirin is contraindicated. The antiplatelet medication (either aspirin or clopidogrel) is given for life. Aspirin is effective in primary prevention of myocardial infarction in apparently healthy people with a 10-year cardiovascular (CV) risk >10%. The risk should be calculated based on the Framingham score. For patients with diabetes and a 10-year CV risk >10%, aspirin 75-150 mg/day is given. There is insufficient evidence to recommend aspirin for primary prevention in lower risk individuals. If aspirin is contraindicated or not tolerated, clopidogrel is given, but there is **no** place for combination therapy even in high risk patients, as benefits have not been shown, whereas the risk of bleeding increases.

Secondary prevention is indicated for patients with stable coronary artery disease (CAD), acute coronary syndrome (ACS), and ST elevation myocardial infarction (STEMI), with the objective of preventing a new or a subsequent myocardial infarction. All patients with stable CAD should receive aspirin 75 mg/day for life or clopidogrel as an alternative antiplatelet medicine in patients with aspirin intolerance. Combination of aspirin and clopidogrel is **not** recommended for patients with stable CAD, as there is no additional benefit. All patients with acute coronary syndromes (ACS) (unstable angina and non ST-elevation myocardial infarction (NSTEMI) should receive loading doses of both aspirin and clopidogrel at presentation, as non-enteric coated aspirin 300mg and clopidogrel 300 mg. These drugs are continued for a minimum of one month but preferably for one year, with maintenance doses of 75 mg/day for each drug. Combination therapy reduces the risk of reinfarction and death. The benefits are seen across all risk groups and subsets of patients such as the elderly, diabetics, and patients with ST deviation with normal or elevated cardiac biomarkers. Combination therapy increases risk of bleeding, especially in patients undergoing an urgent coronary artery by-pass graft (CABG) within five days of treatment discontinuation.

The role of the Gp IIb/IIIa antagonists in ACS is less well defined. They may be beneficial in high-risk patients with NSTEMI and elevated cardiac troponin levels who are scheduled to undergo percutaneous coronary intervention (PCI). There is insufficient data to support use of triple therapy in those who are managed medically.

The beneficial effect of aspirin in reducing mortality when used alone or with thrombolytics in STEMI is well established. Loading doses of aspirin and clopidogrel are given at presentation followed by low dose aspirin 75-100 mg/day for life if there is no contraindication and clopidogrel 75 mg daily for 12 months. In patients with contraindications to aspirin, clopidogrel can be given for a longer period.

In patients undergoing CABG, aspirin 75-300 mg/day is associated with a significant reduction in venous graft occlusion rates and mortality. Preoperative therapy with aspirin and clopidogrel increases risk of bleeding, and should be discontinued at least five days before surgery. No advantage was shown with combination therapy after surgery. If no stents are used during percutaneous intervention (PCI), aspirin alone is adequate. Combination therapy with aspirin and clopidogrel is indicated after PCI when stents have been inserted.

Use in cerebrovascular disease

The place of antiplatelet therapy for primary prevention of ischaemic stroke in people with cardiovascular risk factors is poorly defined. Low dose aspirin 75 mg/day is known to reduce ischaemic strokes in women having risk factors but not in men. Using aspirin and clopidogrel in combination has no benefit in primary stroke prevention. In high risk patients with non-valvular atrial fibrillation, warfarin is the best medication for stroke prevention. Combination antiplatelet therapy with aspirin and clopidogrel is an alternative if oral anticoagulation therapy (OAT) is contraindicated. For patients at low risk aspirin 75-150 mg/day is effective and for those with a moderate risk, either OAT or aspirin can be prescribed, depending on comorbid conditions.

Treatment of acute ischaemic stroke and transient ischaemic attacks (TIA) with antiplatelet medication prevents early recurrent stroke, and long term treatment is indicated for secondary prevention of stroke. Aspirin 75-150 mg/day given within the first week, ideally within first 48 hours of acute ischaemic stroke and TIA, significantly reduces recurrence of stroke or death in the first few weeks.

The combination of aspirin 25 mg plus extended release dipyridamole 200 mg given twice a day is more effective than aspirin alone. However, the combination is associated with severe headache, and expensive. Clopidogrel 75 mg/day is as effective as aspirin alone in preventing ischaemic stroke. Aspirin plus clopidogrel offers no advantage, increases risk of bleeding, and is not recommended in secondary prevention of ischaemic stroke.

Problems associated with use

Bleeding is the major problem with all antiplatelet medicines. Risk of bleeding with aspirin is dose dependent. The lowest possible dose (75 mg/day) can be prescribed, unless there is a need for a higher dose. The risk of bleeding increases with combination therapy. The benefits of antiplatelet therapy in primary and secondary prevention of cardiovascular and cerebrovascular events far outweigh the increased risk of bleeding. The risk can be further reduced by careful attention to comorbid conditions.

Summary

- Aspirin remains the key pharmacological intervention in all atherothrombotic cardiovascular diseases. It is affordable, widely available, effective and reasonably safe.
- Use of other antiplatelet medications will depend on the clinical picture and risk: benefit ratio.
- High risk patients may benefit from intensive antiplatelet therapy but this increases cost and risk of bleeding.
- The optimal regimen for a particular individual will depend on the specific disease and patient characteristics.
- The place of combination antiplatelet medicines is limited, and careful patient selection for combination therapy is vital to maximise benefit and minimise harm.

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Varicella vaccine – an update

Chickenpox: clinical features and complications in children

Chickenpox is popularly considered to be a benign childhood illness, characterized by fever and pruritic vesicular rash of generalised distribution. Prodomal symptoms such as headache, malaise and fever usually occur 24 to 48 hours before the onset of the rash. In a minority, serious complications such as skin and soft tissue infections, pneumonitis, otitis media, endocarditis, cerebellar ataxia, and encephalitis are known to occur. Skin and soft tissue infections are more common in children, whereas in adults pneumonitis is the commonest.

In hospitalised children, neurological complications occurred in 11.5% to 38%. Acute cerebellar ataxia is reported in about 1 in 4000 with *Varicella zoster* virus (VZV) infection. Ataxia occurred about a week after onset of rash and has a good prognosis. Encephalitis, the most serious neurological complication, is reported in about 4 per 10 000 cases and may have a fatal outcome.

Chickenpox in adults

The epidemiology of chickenpox in Sri Lanka is markedly different to that in other countries. Only 50% of people living in rural areas had had chickenpox at the age of 60 years. In addition, 56.2% of women of childbearing age were not immune to chickenpox. Mortality rates are *25 times greater in adults* than in children. VZV infection associated viral pneumonia has an incidence of 0.3% to 50% and a reported mortality of 2.15% to 20% in adults. Primary varicella infection during pregnancy may cause serious complications in mother and baby. Pregnant women who contract chickenpox during pregnancy are also at a higher risk of developing VZV associated pneumonia, which is associated with a higher mortality rate than in non-pregnant women. Infection in first or second trimesters may cause congenital varicella.

Need for the chickenpox vaccine

The introduction of live attenuated VZV vaccine has had a significant effect on epidemiology of primary VZV infections.

The vaccine has an efficacy of up to 85% against any form of the disease and is about 92 to 100% effective against moderate to severe disease. It is immunogenic and relatively safe, and has been shown to induce virus specific memory T cell responses similar to those following natural infection. Immune responses are influenced by the number of doses given, immune status, and age of receiving vaccine. Adults generally have lower seroconversion rates and lower vaccine specific T cell responses when compared to children. Seroconversion rates are also lower in children with malignancies.

Administration of vaccine

Before year 2006, only one dose was recommended for children <13 years of age and 2 doses for individuals >13 years of age. However, it was shown that with one dose, protective immunity decreased over time in children, especially five years after vaccination. Hence in year 2006, a second dose was recommended. Guidelines recommended for administration are the same for all chickenpox vaccines.

Two doses of the vaccine are effective in preventing any form of clinical disease in 98% of recipients and 100% effective against severe disease 10 years after vaccination. The two dose schedule significantly reduced occurrence of breakthrough chickenpox.

Difference between two dose schedule in adults and children

The two dose schedule is different for adults and children. Those aged 13 years or more should receive two 0.5 ml doses of the vaccine, 4 to 8 weeks apart. In countries which practice universal varicella vaccination, children aged 12 months to 12 years are given the first dose at 12 to 15 months of age and the second dose at 4-6 years of age (a booster dose). If the first dose was not given 12-15 months of age, it can be given any time later, but the second dose should not be administered within 3 months of the first dose in children less than 12 years.

Safety of the vaccine

The vaccine has a good safety profile. It may cause mild pain, redness at the site of administration, and rarely, a vesicular rash. However, the number of vesicles is far less than with the wild type virus and infectivity of vesicles is lower. As the vaccine is live attenuated, the virus is still able to establish latent infection in the vaccinated host.

Absolute contraindications

The vaccine is absolutely contraindicated in people suffering from cellular immune deficiencies and any malignant condition, have a family history of congenital or hereditary immunodeficiency in first-degree relatives, and people receiving high-dose systemic immunosuppressive therapy, including persons on oral steroids ≥2 mg/kg of body weight. Patients with Human Immunodeficiency Virus (HIV) infection can receive the vaccine if CD4> 200 cells/μL, or if CD4 counts >25% of the total lymphocyte count. Although pregnancy is an absolute contraindication, no adverse effects have been reported in instances where the vaccine has been accidentally administered.

The vaccine may be administered with caution in individuals with impaired humoral immunity. However, in such cases clinical judgement should be used. It can also be used with patients on steriods <2 mg/kg of body weight per day or in those with leukemia, lymphoma, or other malignancies whose disease is in remission, and whose chemotherapy has been terminated for at least 3 months.

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Food allergy

The immune response is meant to be protective. However, under certain circumstances it can be harmful due either to excessive immune response (hypersensitivity) or inappropriate immune response (autoimmunity). When an immunologically mediated adverse clinical reaction results from a food protein it is known as food allergy. Immune problems occurring with food are either IgE mediated or non-IgE mediated.

IgE mediated food allergy

People who produce IgE instead of IgG, are know as atopic individuals, and they are prone to develop allergy. The main mediator of the allergic reaction is histamine produced by mast cells. In addition to IgE, activation of mast cells slowly produces thromboxane and leukotrine from cell wall phospholipids. These substances together contribute to allergic manifestations involving almost all the organs of the body.

Clinical manifestations vary from mild to fatal anaphylactic reactions. Common clinical features include itching, flushing and hives (urticaria) of the skin and difficulty in breathing due to bronchospasm. It is important to exclude non-allergic manifestions resembling food allergy due to food intolerance which could result from food additives such as sodium ciromoglicate.

Non-IgE mediated food allergy

The protein causing allergy is taken up by antigen presenting cells, and this produces cell mediated immunity with more delayed and prolonged clinical manifestations, including enterocolitis, proctocolitis and enteropathy.

Mixed mechanisms

Both IgE- mediated and cell-mediated immunity collectively may lead to harmful effects in certain patients with gastro-oesophageal reflux and atopic dermatitis (see panel 1).

Panel 1. Clinical spectrum of food allergy

IgE mediated conditions

- Anaphylaxis
- Urticaria and angio-oedema
- Immediate gastrointestinal reaction eg. diarrhoea
- Immediate respiratory reaction eg. bronchospasm

Non-IgE mediated conditions

- Food protein induced enterocolitis syndrome
- Allergic proctocolitis
- Allergic enteropathy

Conditions resulting from mixed mechanism

- Atopic dermatitis
- Allergic eosinophilic gastroenterocolitis
- Gastro-oesophageal reflux
- Unexplained abdominal symptoms

Food items causing allergy

The types of food causing allergy vary in different age groups and different geographical locations.

In children, classical allergy may start with respiratory manifestations followed by gastrointestinal conditions and end up with skin allergies. However, throughout the life certain food items may cause allergic manifestations.

Common allergens among children in western countries include cow's milk, egg and peanuts, whereas in adults they include shellfish, peanut, tree nuts, wheat, fish and eggs. Sri Lanka being a tropical country, we encounter a variety of fruits and it is common to find allergy at any age to fruits, in particular to unripe fruits such as mango. Seventy-five percent of children who have allergy to a milk product are able to tolerate baked-in milk products such as cookies and cakes.

Wide geographical variation has been found on red meat allergy even within developed countries. Although reliable data are not available regarding the prevalence in Sri Lanka, it is observed that we see more red meat allergy than in the west.

Natural history of food allergy

In the United States, food allergy affects as many as 5% of children less than 3 years of age and 3 to 4% of adults. About 50% of children with allergy to milk, egg, soy and wheat will outgrow their allergy by the age of 6 years. Those who are still allergic by the age of 12, have less than an 8% chance of outgrowing allergy. Only 20% of peanut and 9% of tree nut allergy adults outgrow the allergy as they get old.

The true prevalence of food allergy in Asia is uncertain. Estimates from Chinese studies range from 4.9 % to 16.4%. The latter percentage represented people diagnosed by skin prick tests and reflect sensitisation rather than true clinical allergy.

Diagnostic testing

For IgE mediated food allergy

1. History

IgE mediated allergic manifestations usually occur within two hours of taking an offending food item. A carefully taken history and a food diary play a crucial role in finding out the responsible allergen.

2. Food challenge

Introduction and elimination of food items help in identification of the offending allergen. However, introduction of a food item may sometimes induce a severe reaction. So the test requires careful monitoring in a place with facilities for rescucitation.

3. Serum food-specific IgE antibody

This has over 95% positive predictive value and is useful in eliminating the offending food, but it is important to note that measurement of total IgE plays a very minor role in the diagnosis, because it only indicates the tendency to develop allergy. It is also important to note that the commercially available kits developed for allergens in western countries are not directly applicable in our setting.

4. Toral serum IgE estimation

The measurement of total serum IgE has only a minor role to play in the diagnosis of allergic diseases except in difficult cases of distinguishing food intolerance from food allergy. Moreover, the total IgE is higher in Sri Lanka compared to the west probably due to higher prevalence of helminthic infestations.

5. Skin prick test

Each allergen from a panel is placed over the volar aspect of the forearm and a prick is made with a lancet. 0.9% NaCl and histamine are used as negative and positive controls. The diameter of the wheal is read in 15 minutes and the test is considered to be positive if the difference in the diameter between the test and the negative control is more than 3 mm. The patient is advised to refrain from taking an antihistamine for a period of 3 days before to the test. If the positive control is negative the result of the test is considered invalid.

6. Allergen epitope recognition

Peptide microarray technology is used to detect exact epitope of the allergen, which is useful in deciding appropriate immunotherapy for essential food items.

7. Challenge with recombinant allergen

The risk of food challenge is greatly reduced by challenging with recombinant allergens. Although the specificity of the challenge increases, the sensitivity declines with this procedure.

For non-IgE mediated food allergy

1. Patch testing

A panel of allergens is placed over the upper back and observed for skin reaction in 72 hours. It is important to note that patch test is not done for the detection of allergens responsible for type 1 hypersensitivity.

2. **Measurement of cytokine production by T lymphocytes following stimulation with food allergens**

   Pro-allergic cytokines are targeted using in vitro testing such as ELISA and RT/PCR.

3. **Measurement of eosinophilic markers and cytokines in stools**

   The presence of eosinophilic markers in stool points to allergy and IL-5 acts as a chemotactic cytokine for eosinophils.

4. **Endoscopy and biopsy**

   In addition to the detection of infiltration by cells such as mast cells, basophils, eosinophils and Th_2 lymphocytes, mucosal biopsy helps in the exclusion of inflammatory bowel disease and neoplastic disease.

Treatment

The mainstay of the treatment is avoidance of foods that have been identified as allergens. For people who are extremely sensitive, this may involve the total avoidance of any exposure with the allergen, including touching or inhaling the particular food.

With accidental exposure of the food, the treatment has to be decided depending on the severity of the symptoms. Mild reactions such as itching or hives could be managed with either local or systemic antihistamine preparations. Short-acting antihistamines such as chlorphenamine would be sufficient. If drowsiness is a problem, a non-sedative longer acting antihistamine such as loratadine, cetirizine or fexofenadine is preferred. However, in the case of severe reactions such as anaphylactic reaction or people not responding to initial antihistamine therapy may need urgent treatment with adrenaline and hydrocortisone at the closest medical institution. It is advisable to carry self-injectable adrenaline pens (Epipen) by people who are liable to get anaphylactic reactions. However, it is not practical in Sri Lankan settings due to social and economic reasons. Moreover, it is not economical as Epipen expires within one year.

Panel 2. Commonly used drugs in allergy

Antihistamines

Chlorphenamine (chlorpheniramine) 4 mg twice a day
Cetirizine 10 mg daily
Loratadine 10 mg daily
Desloratadine 5 mg dailty
Fexafenadeine 180 or 120 mg daily

Mast cell stabilizers

Ketotifen 1 mg daily

H_2 receptor blockers

Ranitidine 150 mg twice a day

Steroids

Dexamethasone 0.5 mg daily

Prevention

There is evidence that breast-feeding for at least 4 months, compared with feeding infant formulae made with cow's protein, prevents or delays the occurrence of atopic dermatitis, cow's milk allergy, and wheezing in early childhood. To avoid an allergic reaction, a strict diet can be followed. It is difficult to determine the amount of allergenic food required to elicit a reaction, so complete avoidance should be tried unless otherwise suggested by a clinician. In some cases hypersensitive reactions can be triggered through skin contact and inhalation.

When avoiding certain foods to lessen the risk of reaction, it is important to note that children may develop nutritional deficiencies and appropriate precautions should be taken.

Desensitisation is widely practiced for aeroallergens such as pollen and house-dust mite in the case of asthma, and the same principle can be used in the cure of food allergy in precisely identified food allergies.

Education of health care professionals and the public on the range of food allergic disorders, together with proper preventive and management strategies, reduces morbidity and mortality linked to food allergy.

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Drugs for gestational diabetes

Summary

The prevalence of gestational diabetes is increasing in Australia. Non-pharmacological intervention with dietary measures and exercise is the mainstay of therapy in most cases, but insulin is increasingly necessary to achieve adequate glycaemic control in some women. Basal-bolus insulin is the optimal management strategy, but therapy needs to be individualised. Although there is mounting evidence for the efficacy and safety of metformin, the lack of long-term follow-up data has prevented it from being recommended by most experts in the field. Women with gestational diabetes need long-term follow-up because of their increased risk of type 2 diabetes.

Key words: hypoglycaemic drugs, insulin, metformin, pregnancy.

(Aust Prescr 2010;33:141-4)

Introduction

Gestational diabetes is defined as an intolerance to glucose that is first diagnosed or has its onset during pregnancy. It is estimated to affect almost 5% of pregnancies in Australia and between 3% and 9% worldwide. Its prevalence increases with age, from 1% in women aged 15-19 years to 13% in those aged 44-49 years.[1] Other risk factors for developing gestational diabetes include being overweight or obese, having a family history of type 2 diabetes or a personal or family history of gestational diabetes or glucose intolerance, being from an Aboriginal or Torres Strait Islander background or belonging to certain ethnic groups (for example Polynesian, Middle Eastern, Indian or other Asian origin).[2] Although gestational diabetes does not affect perinatal mortality, it does increase morbidity, including the risk of shoulder dystocia, nerve palsies and neonatal hypoglycaemia. Maternal outcomes are also affected, with a higher incidence of pre-eclampsia and caesarean section (particularly with poor glycaemic control) in mothers who develop gestational diabetes.[3]

Diagnosis

Universal screening for gestational diabetes has been recommended in Australia since 1998. A fasting glucose challenge test should be performed at 26-28 weeks gestation. If abnormal, this is followed by a formal two-hour 75 g oral glucose tolerance test. Criteria for diagnosis are presented in Table 1. For women at risk of gestational diabetes, a glucose tolerance test can be performed at any stage during pregnancy. However, as placental production of diabetogenic hormones tends to increase throughout the second and third trimesters, a normal glucose tolerance test in the early part of pregnancy does not exclude the development of gestational diabetes later on. A second oral glucose tolerance test should therefore be performed at the standard 26-28 weeks of gestation even if an earlier test was normal.

New recommendations for screening and diagnosis are currently under consideration, but have yet to be adopted or approved by expert groups in gestational diabetes. It is likely, however, that the glucose challenge test will be removed from the screening process, so that a diagnosis of gestational diabetes will be made if the blood glucose is abnormal when fasting, or one or two hours after a 75 g glucose load (see Table 1).

Table 1

Current and possible future diagnostic criteria for gestational diabetes

	Test	Venous plasma glucose – for diagnosis
Current practices	screen: non-fasting 50 g glucose challenge	1 hour ≥ 7.8 mmol/L (requires confirmatory testing)
	confirmatory testing: fasting 75 g glucose tolerance	one of either: ▪ fasting ≥ 5.5 mmol/L or ▪ 2 hour ≥ 8.0 mmol/L
Potential new criteria[13]	fasting 75 g oral glucose tolerance	any one of three: ▪ fasting ≥ 5.1 mmol/L ▪ 1 hour ≥ 10.5 mmol/L ▪ 2 hour ≥ 8.5 mmol/L

Blood glucose targets

Once diagnosed, all women need to be educated about the possible implications of gestational diabetes (both fetal and maternal) and be taught how to perform home blood glucose monitoring. Finger-prick testing should be performed four times a day (before breakfast and two hours after each meal. Target blood glucose concentrations, shown in Table 2, need to be explained. The results of the Hyperglycemia and Adverse Pregnancy Outcomes trial have demonstrated that the risks associated with maternal hyperglycaemia are on a continuum above the normal blood glucose concentration and treatment targets might be lowered in the future to reflect this.[4] As yet, a consensus on where these targets will be set has not been established.

Non-pharmacological interventions

All women with gestational diabetes should receive advice from a dietitian with specific knowledge in the area and dietary intervention should be initial therapy for most women. Dietary advice needs to be individualised, taking into account factors such as the patient's body mass index (BMI) and overall nutritional requirements.[2] Care should be taken to avoid excessive caloric restriction, as this can result in ketonuria and adverse pregnancy outcomes.[5] Moderate intensity exercise, such as a brisk walk for 30 minutes each day, can decrease insulin resistance and should be encouraged.[6]

Insulin

Insulin therapy remains the mainstay of pharmacotherapy and its use is becoming increasingly prevalent. In 2005-06, about 30% of confinements with gestational diabetes were treated with insulin, with women in older age groups requiring it in about 40% of cases.[1] Insulin should be considered when blood glucose concentrations (Table 2) exceed recommended targets on two or more occasions within one week. The indication for starting insulin is stronger if there is evidence of macrosomia or increased fetal abdominal circumference.[2]

All women started on insulin need education regarding storage of insulin, correct injection technique as well as recognition and treatment of hypoglycaemia. The assistance of a diabetes educator with this can be invaluable.

Insulin therapy needs to be individualised and is dependent, upon the patient's blood glucose concentrations, her weight and her wishes. The regimen is determined by whether the blood glucose is elevated when fasting, after a meal, or both.

Elevated fasting glucose

If the fasting glucose is elevated, but postprandial levels are within the recommended target range, a single bedtime injection of intermediate-acting insulin (for example insulin isophane) will often suffice. A starting dose of 4-12 units is reasonable. If postprandial hyperglycaemia occurs later in the pregnancy, mealtime injections of rapid-acting insulin may need to be introduced.

Postprandial hyperglycaemia

Occasionally, women may have elevated postprandial blood glucose with normal fasting levels. Dietary intervention can be useful in this situation. However, should this prove inadequate, mealtime injections of rapid-acting insulin (for example insulin aspart, insulin lispro) can be introduced. Starting doses of 4-8 units with each meal are reasonable. Soluble human insulin is an alternative, but has the disadvantage of needing to be injected 30 minutes before eating.

Table 2

Target blood glucose concentrations in gestational diabetes

	Blood glucose (mmol/L)
Fasting capillary	< 5.5
Postprandial capillary	< 7.0 (2 hours) < 8.0 (1 hour)

Fasting and postprandial hyperglycaemia

A basal-bolus insulin regimen (mealtime rapid-acting insulin and bedtime intermediate-acting insulin) is generally preferred as it provides the patient with greater flexibility in diet and exercise. Twice-daily mixed insulin (for example insulin aspart/protamine or lispro/protamine) is an alternative, particularly if the patient is reluctant to inject four times per day or might find it too difficult.

Dosing

Larger doses of insulin are reserved for those with higher BMI or blood glucose readings significantly above target. Smaller doses might be appropriate for women with a slighter build. The dose can be titrated every two to three days as required, with increments of 2-4 units (no greater than 20% dose increase) until targets are met or the patient develops excessive hypoglycaemia (more than two to three times per week or any episode of severe hypoglycaemia).

It remains unclear if maternal hypoglycaemia adversely affects the fetus. If there are concerns, it tends to be in women with pre-existing diabetes in the first trimester of pregnancy (during organogenesis)[7] and not in those with gestational diabetes.

Insulin doses may be anticipated to rise throughout the third trimester as a result of increasing maternal insulin resistance. This tends to reach a plateau at 36-38 weeks.

Insulin analogues

There is currently little evidence to support the use of other insulin analogues (for example insulin glargine, insulin detemir) in pregnancy, although their use is increasing.

Metformin

There is increasing evidence for the use of metformin in pregnancy. The Metformin in Gestational Diabetes (MiG) trial, an open-label randomised controlled trial comparing metformin with insulin, was conducted throughout Australia and New Zealand.[8] It showed the efficacy and safety of metformin in the second and third trimesters with no difference in perinatal complications between treatments. Not surprisingly, patients preferred oral metformin to insulin injections. Almost half of the patients taking metformin also required insulin to achieve treatment targets. There does not appear to be an increase in the risk of congenital malformations, even when the fetus is exposed to metformin in the first trimester.

Although this is promising, there is no long-term follow-up of children born to mothers who took metformin during pregnancy. The use of metformin in pregnancy is therefore not currently endorsed by regulatory authorities or professional bodies, including the Australian Diabetes in Pregnancy Society. Although no adverse effects have been demonstrated, metformin does cross the placenta, leading authorities to be very cautious in their recommendations. Nonetheless, metformin is used for the treatment of gestational diabetes in many centres around Australia and New Zealand, but has found much less favour in Europe and the USA.

Metformin could be considered for use in patients who have failed non-drug therapies and who either refuse or are unable to take insulin. The mother should be educated about the potential risks, benefits and areas of uncertainty so that an informed decision can be made.

Sulfonylureas

Glibenclamide has the most evidence for use in pregnancy. Unlike the older sulfonylureas, glibenclamide does not appear to cross the placenta to a significant degree. There does not appear to be an increase in fetal complications, but, like metformin, it is currently not recommended for widespread use in pregnancy because of a lack of long-term follow-up of children exposed to glibenclamide *in utero.*

There is little evidence for the safety or efficacy of other sulfonylureas in pregnancy and their use is not recommended.

Other drugs

There are few data about the safety or efficacy of acarbose, thiazolidinediones or incretin mimetics and enhancers in pregnancy. Currently these drugs are not recommended and their use in pregnancy should be considered experimental.

Follow-up and prognosis

Gestational diabetes resolves postpartum in more than 90% of women. In general, all insulin and oral hypoglycaemic drugs are ceased immediately post-partum with ongoing blood glucose monitoring until discharge from hospital. If concentrations return to normal, which occurs in the overwhelming majority of cases, a repeat glucose tolerance test should be performed 6-8 weeks postpartum to ensure that the patient does not have overt type 2 diabetes.

The long-term risk for developing type 2 diabetes is increased over sevenfold in women who develop gestational diabetes compared with those who have a normoglycaemic pregnancy.[9] Women with a pre-pregnancy BMI of more than 27 kg/m^2, those of advancing maternal age and those who required insulin for glycaemic control in pregnancy are at particularly increased risk.[10] It is important to counsel women about these issues and the need to continue with dietary measures, regular exercise and attempts at achieving and maintaining a normal body weight long into the future. Both intensive lifestyle intervention and drug therapy (metformin) may be useful to decrease the risk of these patients developing type 2 diabetes.[11]

There are no evidence-based guidelines for long-term follow-up of mothers with gestational diabetes. Australian guidelines recommend a glucose tolerance test at least every two years,[2] while others believe that a fasting glucose test one to two yearly is sufficient. A more intensive follow-up regimen would be rational if the patient has evidence of impaired glucose tolerance or impaired fasting glucose on early postnatal testing, a strong family history of type 2 diabetes, or if there are other major risk factors such as marked obesity or polycystic ovary syndrome.

Children and adolescents whose mothers had gestational diabetes seem to be at higher risk of developing features of metabolic syndrome compared with mothers who do not have diabetes. Although unproven, it is likely that these children will also have a higher risk of developing type 2 diabetes as adults.[12]

Conclusion

Gestational diabetes is increasing in Australia. Appropriate screening, diagnosis and management is important, not only to improve perinatal and maternal outcomes, but also because it may help to decrease the incidence of type 2 diabetes in the future. Insulin remains the mainstay of pharmacotherapy, but there is increasing use of oral hypoglycaemic drugs (particularly metformin) in Australia and New Zealand.

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Further reading

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Conflict of interest: none declared

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Current information about drug registration

New chemical entities registered

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class / use(s)
Tocilizumab	Actemra	Injection, 20 mg/mL	Chugai, Japan	Baurs	Rheumatoid arthritis
Liraglutide	Victoza	Injection in pre-filled pen, 18 mg in 3 mL	Novo Nordisk, Denmark	Swiss Biogenics	Type 2 diabetes
Ivabradine	Coralan	Tablet, 5 mg 7.5 mg	Servier, France	Hemas	Angina

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