MARCH 2019

# GP Connect

CARDIOVASCULAR CLINICAL UPDATE

## Women and Cardiovascular Disease

### Cardiovascular Risk Factors in Women

### Gestational Diabetes Management and the Role of Primary Care

Sydney Cardiology

# WELCOME

## From the editor – Dr Andrew Terluk

Welcome to the first edition of GP Connect for 2019. In this issue Dr Fiona Foo (interventional Cardiologist) and Dr Shan Jiang (Endocrinologist) have offered a state of the art review regarding a range of pregnancy related health issues. Gestational health aside from its immediate impacts to mother and child have emerged important indicators of future health risks, including cardiovascular risk.

We hope you enjoy reading.

# MEET OUR TEAM

We have experienced cardiologists in all major sub specialities to provide the highest quality of patient care. Within our Sydney Cardiology team are:

**Dr James Wong**

Specialising in general cardiology, prevention of coronary artery disease and hypertension.

**Dr Fiona Foo**

Specialising in general and interventional cardiology with a strong interest in sports cardiology and women and heart disease.

**Dr Abhinav Luhach**

Specialising in general adult cardiology, Cardiac CT and preventive cardiology.

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Specialising in general and interventional cardiology, including cardiac haemodynamic studies and complex coronary intervention.

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Specialising in general adult cardiology and electrophysiology, including atrial fibrillation and device implantation.

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Specialising in general adult cardiology and non-invasive cardiac imaging, particularly echocardiography and cardiac CT.

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Specialising in advance heart failure, pulmonary hypertension and transplant cardiology.

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Specialising in general cardiology with an interest in cardiomyopathy in the setting of cancer.

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# WOMEN AND CARDIOVASCULAR DISEASE

**Dr Fiona Foo**

Heart disease is the leading cause of death in Australian women[1] 22 Australian women die from heart disease every day.[2] 10 australian women die from a myocardial infarction (MI) every day,[3] one woman dies every two hours.[4]

This review aims to describe the unique/different characteristics of ischaemic heart disease (IHD) in women; the gender disparities in acute coronary syndromes (ACS); and the heart conditions that have a predisposition to affect females.

## ISCHAEMIC HEART DISEASE IN WOMEN

IHD is ischaemic disease originating in the coronary arteries, the microcirculation, or from an imbalance of myocardial oxygen supply and demand. In women this is not only obstructive coronary artery disease (CAD) - vascular disease limited to the epicardial arteries; but also includes coronary microvascular dysfunction (CMD), spontaneous coronary artery dissection (SCAD) and stress-induced cardiomyopathy.[5]

### PATHOPHYSIOLOGY

The pathophysiology of IHD in women extends beyond anatomic epicardial coronary artery stenosis. In the Women's Ischemia Syndrome Evaluation (WISE) study, nearly 60% of women with chest pain did not have a significant (>50%) lesion on coronary angiography.[6]

The WISE and other studies have implicated abnormal coronary reactivity, microvascular/endothelial dysfunction and plaque erosion/distal embolization as the pathophysiology behind female specific IHD.[7,8]

The characteristics of IHD in women are: more angina, more NON obstructive CAD on angiography, and a poorer prognosis in comparison to men[9] with greater rates of myocardial ischaemia and mortality.[10,11,12,13,14]

### OBSTRUCTIVE VS NON OBSTRUCTIVE CAD

Women have more non-obstructive CAD, however this is still associated with a rate of major adverse cardiovascular events (MACE) similar to obstructive CAD.[15] Recently reported 10year mortality of the WISE study found a cardiac mortality rate of 12%; 31% of these cardiovascular deaths occurred in women without obstructive CAD.[16]

About 10% of MI patients have non-obstructive CAD[17] These patients have better 12month mortality than those with MI with obstructive CAD, but still have a threefold higher rate of cardiovascular events compared with asymptomatic women.

Thus, when evaluating women with ischaemic symptoms and non-obstructive epicardial CAD, alternate mechanisms for ischaemia such as microvascular dysfunction should be considered.

## CLINICAL PRESENTATION

Women have more atypical presentation such as shortness of breath, jaw/neck/shoulder or back pain weakness, fatigue, nausea, sweating, lightheadedness/ fainting,; however, chest pain is still the most common presenting symptom of ACS in both men and women.[18] At the time of presentation women are generally older and have more risk factors than men.[19]

## GENDER DISPARITIES IN ACS

ACS includes ST elevation MI (STEMI), non ST elevation MI (NSTEMI), and unstable angina. Women with ACS have less obstructive CAD but are more likely to have thrombus formation, plaque erosion and diffuse atherosclerosis. Women are older at presentation[20], have more comorbidities, more atypical symptoms and are more likely to assume these symptoms are non cardiac, leading to delays in seeking and receiving treatment.

Physicians may not evaluate symptoms of myocardial ischaemia as early in women, due to atypical symptoms, comorbidities and underestimation of risk factors[21] Women have a worse prognosis, a higher mortality post ACS (in hospital and at one year) and more frequent serious complications of ACS such as cardiogenic shock/heart failure. Young women (<55yo) with MI, have greater morbidity and mortality compared with both young men and older women with acute MI.[22]

Women with ACS receive less evidence based pharmacotherapies such as aspirin, betablockers and statins; and clopidogrel.[23,24,25] and less intense treatment.[26] They have less invasive/revascularisation procedures such as percutaneous coronary intervention (PCI)[27,28] and more delays to PCI (in STEMI)[29] Women with ACS have fewer bypass surgeries compared to men.[30]

Women have higher complications such as bleeding with ACS treatment[31] but this can be reduced by dose adjusting anticoagulation. Females also have higher vascular access site complications, but radial access can help reduce this risk.[32] Despite the evidence and recommendations, women are less likely to be referred for Cardiac rehabilitation than men.[33]

Recently reported Australian Evidence found that Women with STEMI are less likely to receive invasive management such as angiography, revascularisation, and timely revascularisation. STEMI women were older at presentation and had higher GRACE scores. Six months after admission, the rates of major adverse cardiovascular events and mortality were higher for women. At discharge, significantly fewer women than men received b-blockers, statins, and referrals to cardiac rehabilitation.[34]

## CORONARY MICROVASCULAR DYSFUNCTION (CMD)

CMD is coronary endothelial dysfunction and limited coronary flow reserve.[35]

CMD has been implicated as causative to female specific IHD pathophysiology. It is not benign, is associated with increased rate of cardiac death, stroke, or heart failure.[36,37] The annual rate of MACE is 2.5% in women with CMD;[38] and the prognosis is worse in women.[39]

The microcirculation is not seen in a coronary angiogram, and requires functional assessment of coronary flow; the gold standard is an invasive coronary reactivity test. PET and cardiac MRI are emerging noninvasive modalities to detect subendocardial ischaemia, but are not readily available.

Treatment of CMD includes risk factor/lifestyle modification. Exercise training and cardiac rehabilitation is recommended. Statins improve endothelial dysfunction with their anti-inflammatory effects. Traditional anti-ischaemic medications such as nitrates, betablockers, ACE-I and calcium channel blockers are first line; ranolozine/aminophylline has also been evaluated with variable results. Tricyclic antidepressants may be helpful for altered cardiac pain perception.[40]

## SPONTANEOUS CORONARY ARTERY DISSECTION (SCAD)

SCAD, although rare, is increasingly identified as a cause of ACS. It classically occurs in a young healthy woman without cardiovascular risk factors.[41] In SCAD there is a sudden separation between the layers of a coronary artery wall, creating an intimal flap and intramural haematoma which obstructs intraluminal blood flow distally and results in myocardial ischaemia.[42]

In an Australian study, 23% of ACS events in women <60yo were attributed to SCAD.[43] 80% of SCAD patients are female, average age 42yo, 20-25% of cases occurring in in the peripartum period.[44] ~50% of patients there is associated fibromuscular dysplasia, thus patients are routinely screened with

CT angiography from base of skull to pelvis and brains MRI (cerebral aneurysms).

Diagnosis of SCAD requires careful angiographic study and high degree of suspicion. Treatment differs from atherosclerotic ACS. PCI is technically less successful in SCAD compared with atherosclerotic ACS[34] A conservative management is favoured due to the high rate of spontaneous vascular healing.[34,44] Patients should be monitored as inpatients for 4-5 days because of a small early threat of dissection progression warranting acute intervention.

SCAD carries a <20% recurrence rate.[34] Statins are associated with recurrent SCAD and thus are discouraged unless there is hyperlipidaemia[45,34] Aspirin and cardiac rehabilitation is recommended.[46]

## STRESS CARDIOMYOPATHY (TAKOTSUBO/ BROKEN HEART SYNDROME)

This is a cardiomyopathy characterised by transient left ventricular dysfunction with regional wall motion abnormalities - classically mid to apical akinesis and basal hyperdynamic function, similar to an octopus trapping pot (hence the name takotsubo, first described in japan).[47] This condition mainly affects postmenopausal women, is often preceded by extreme physical or emotional stress and presents similar to an ACS. However there is no obstructive CAD on angiography.[48] The cause remains unknown, but is thought to be related to a disproportionate distribution and activation of myocardial sympathetic receptors. The ventricular dysfunction generally resolves within a few weeks, (of supportive therapy) however patients may be at risk for recurrence years after the first event.[49]

## PREGNANCY AND CAD

CAD occurs 3-4 times more often in pregnant women than age matched non-pregnant women. The incidence of ACS in pregnancy is 1 in 10000, but increases to 3 per 10000 deliveries in women >40yo.[50] Antepartum, the cause is coronary atherosclerosis, postpartum SCAD is the dominant etiology.

## MANAGEMENT OF IHD

Lifestyle changes such as daily exercise, weight loss and reducing intake of saturated fats/cholesterol should be recommended.Patients should be on medical therapies for ischaemia - aspirin, ACE-I/A2RBs, betablockers, aldosterone antagonists, statins. Statins should be used in intermediate to high risk women.

Statins have pleiotropic effects that improve endothelial dysfunction[51] and are of benefit in the coronary microcirculation.[52] ACEIs also improve coronary flow reserve (CFR) in women with low CFR.[53] Betablockers are first line for relief of symptoms in stable IHD. Calcium channel blockers, long acting nitrates and ranolazine can be used when beta blockers cause side effects/contraindicated or if persistent symptoms.

Hormone replacement therapy (HRT) is not recommended for reducing cardiovascular risk. In a metaanalysis, Combined HRT increased the risk of a coronary event, venous thromboembolism and stroke; estrogen only therapy increased the risk of venous thromboembolism and stroke but not of coronary events.[54]

Lastly, revascularization with PCI or coronary artery bypass graft is recommended if maximal medical therapy fails.

## HEART FAILURE IN WOMEN

### HEART FAILURE WITH PRESERVED EJECTION FRACTION. (HFPEF)

Women are ~twice as likely then men to develop HFpEF. This is caused mainly by diastolic dysfunction, but other factors contribute.[55] Common risk factors for HFpEF include aging, adiposity, hypertension, and metabolic stress.

No treatment has been shown to be effective in HFpEF (as compared with HF with reduced ejection fraction). Management includes: BP control, diuretics to reduce volume overload symptoms, coronary revascularisation for those with CAD and ischaemia, and management of atrial fibrillation. Women have a worse quality of life after diagnosis of heart failure and more frequently exhibit depression.[56]

### PERIPARTUM CARDIOMYOPATHY (PPCM)

Is an idiopathic form of left ventricular systolic dysfunction that develops during pregnancy or postpartum in a woman with no history of heart disease.[57] Females >30, a history of gestational hypertension, and those with multifetal pregnancies have a higher incidence.[58] Most women have partial or complete recovery within 2-6months after diagnosis, however, there is the risk of recurrence in subsequent pregnancies, even if LV function returns to normal.

Management in advanced heart failure with hemodynamic instability is urgent delivery (irrespective of gestation).[59] Management of acute heart failure is similar to management of acute heart failure due to other causes.

## CONCLUSION

Heart disease is the leading killer of Australian women. IHD in women includes obstructive CAD, CMD, SCAD and stress induced cardiomyopathy. The pathophysiology of IHD in women includes epicardial coronary artery obstruction, endothelial dysfunction, coronary vasospasm, plaque erosion and SCAD. Female specific IHD is characterised by non-obstructive CAD, more symptoms and a worse prognosis than men. Physicians may not recognise that even with non-obstructive CAD, females with IHD have a poor prognosis, leading to less aggressive lifestyle and medical treatment, which in turn has contributed to the observed sex mortality gap.

Women with ACS have more atypical symptoms, delayed treatment, less intense treatment and revascularisation procedures and more complication and a higher mortality. HFpEF disproportionately affects women and PPCM is unique to females.

There is still much research to be done however, as gaps in knowledge exist, and females are often underrepresented in cardiovascular trials. However we are gradually increasing awareness that CVD and its optimal management differs between men and women. Efforts should also be directed to improving delivery of current gender neutral guidelines in women just as men.

### FOR MORE INFORMATION

For More Information – please see Australian Doctor Therapy Update Article – https://www.howtotreat.com.au/therapy-update/gps-guide-heart-disease-women (please note the site requires registration and log on).

**Endnotes**


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# CARDIOVASCULAR RISK FACTORS IN WOMEN

**Dr Fiona Foo**


Some worrying facts about women and heart disease:

- Heart disease is the leading killer of Australian women[1]
- Heart disease kills almost three times as many women as breast cancer[2]
- Twenty-two Australian women die from heart disease every day (8,207 deaths in 2016)[3]
- 10 Australian women die from a heart attack every day[4]
- An Australian woman dies from a heart attack every two hours[5]
- In 2016, almost half (46.8 %) of all deaths from heart attacks were women[5]
- Although women are more likely to experience atypical symptoms (jaw, shoulder, neck and back pain) when having a heart attack, only one in five women are aware of at least one of the symptoms.[6]

There are a number of traditional and emerging non-traditional Cardiovascular Disease (CVD) risk factors specific to women, (particularly pregnancy related complications) that doctors should aware of. Management involves identifying the risk factors and a combination of lifestyle modifications and medications. This review will summarise these risk factors and how we can manage them to reduce the burden of CVD in women.

## TRADITIONAL CARDIOVASCULAR RISK FACTORS IN WOMEN

- 90% of Australian females will have 1 risk factor for CVD
- 50% will have 2 or more risk factors.

**Table1. Traditional risk factors for women**

| Traditional CVD Risk Factors |
|---|
| Diabetes |
| Smoking |
| Obesity and overweight |
| Physical inactivity |
| Hypertension |
| Dyslipidaemia |
| Family history of premature CAD |

**Diabetes Mellitus (DM)** - In Australia the prevalence of diabetes in women is ~5%, (self reported data),[7] the prevalence increases with age. Diabetes is a potent risk factor for CVD. Diabetic women have a 3fold excess risk of fatal Coronary artery disease (CAD) compared with nondiabetic women.[8]

**Hypertension** – One in four (28.3 %, 1.8 million) Australian women aged 35 years and over have high blood pressure (BP) (≥ 140/90 mmHg).[9]

**Smoking** – One in seven (1.2 million) Australian women smoke. Women in the 18 to 24 age group have the highest rate of smoking (more than one in six).[5] Women who smoke, have a 300% greater risk of CAD, compared to non smoking women.

**Obesity and Being Overweight** - More than one in four Australian adult women are obese (27.4 %, 2.5 million) or overweight. (28.8 %, 2.6 million), and this has been increasing. The average BMI of adult woman is 27.1, placing her in the overweight category.[5]

**Physical Inactivity** – 76% of Australian women are physically inactive.[10]

**Dyslipideamia** – One in three (33.2%, 2.9 million) Australian adult women have high cholesterol (≥ 5.5 mmol/L) in 2011-12.[11]

**Family history of premature CAD** - women whose parents have had a MI under the age of 60 have a 5x greater CAD mortality. Premature CAD in a first degree female relative is a relatively MORE potent risk factor than is premature CAD in male relatives.

**The Heart Foundation Recommend a "Heart Health Check" in all women >45 years old**

**Table 2. Traditional Risk Factors and Management**

| Risk Factor | Management |
|---|---|
| Diabetes Mellitus | Aggressive management of CVD Risk Factors.<br>Women may require greater frequency/intensity of physical activity than men to reduce CVD events. |
| Hypertension | Encourage lifestyle modifications for optimal BP control (diet, exercise, avoidance of excess alcohol and sodium).<br>Pharmacotherapy is indicated in those with high cardiovascular risk and Stage 2 hypertension (BP >140/90mmHg); or who have concomitant diabetes, chronic kidney disease, ischaemic heart disease, or heart failure. |
| Dyslipidaemia | Lifestyle modification - diet and exercise.<br>Statins in secondary prevention and moderate to high CVD risk. |
| Obesity | Women should lose weight through physical activity and diet. For weight loss or sustaining weight loss, women should exercise a minimum of 60-90min of at least moderate intensity on most and preferably all days of the week. |
| Physical inactivity | Encourage 150minutes/week of moderate exercise or 75min/week of vigorous exercise, or an equivalent combination. Incorporate muscle strengthening training at least 2x/week |
| Smoking | Women should be advised not to smoke and to avoid second hand smoke. Counselling, nicotine replacement, and medical +/-behavioural therapy should be advised. |

## NON TRADITIONAL CVD RISK FACTORS IN WOMEN

**Table 3. Non traditional CVD Risk Factors**

| Non traditional CVD Risk Factors |
|---|
| **PREGNANCY COMPLICATIONS**<br>Hypertensive disorders in pregnancy (including preeclampsia)<br>Gestational Diabetes<br>Preterm Delivery<br>Small for Gestational Age |
| **POLYCYSTIC OVARIAN SYNDROME**<br>**ENDOMETRIOSIS** |
| **AUTOIMMUNE DISEASES** |
| **BREAST CANCER TREATMENT** |
| **DEPRESSION** |
| **EARLY ONSET MENOPAUSE/SURGICAL MENOPAUSE** |

## PREGNANCY COMPLICATIONS

The physiologic and metabolic demands of pregnancy serve as a "stress test."

**Hypertensive Pregnancy Disorders** – include gestational hypertension, chronic hypertension and preeclampsia.

Women with a history of pre-eclampsia or gestational hypertension are at increased risk of hypertension and heart disease later in life (2-4times).[12] Up to 30,000 Australian women each year can develop high blood pressure in pregnancy.[13]

**Gestational hypertension** - Gestational hypertension is new onset hypertension >140/90mmHg after 20 weeks gestation, in a woman who was originally normotensive. Though not as high as preeclampsia, is associated with increased CVD and future arterial hypertension. Women with gestational hypertension have increased risk of Ischaemic heart disease (IHD) MI, MI deaths, Heart failure, kidney disease and diabetes.[14] The rate of hypertension is 3 to 10fold higher in the first 1-10 years post pregnancy and remains twice as high 20 years later in those with gestational hypertension. It is also higher for first time older mothers.[15]

**Preeclampsia** is new onset hypertension (>140/90mmHg) after 20 weeks gestation, proteinuria (0.3g/24h) and end organ dysfunction. Women with preeclampsia have a 3.7fold RR for developing

hypertension, 2.16RR for IHD, 1.81fold RR of stroke, and a 1.79fold RR for VTE.[16]

The largest meta-analysis, (>64million women with 34 years of follow up), found women with a history of preeclampsia have a 71% increased risk of CVD mortality, a 2.5 fold increase in risk of CAD and a 4 fold increase in heart failure when compared to women without preeclampsia.[17]

Earlier preeclampsia is associated with poorer outcomes; the more severe the preeclampsia the greater severity of future CVD. Recurrent preeclampsia is associated with twice the risk of atherosclerosis compared to women with non recurrent preeclampsia.[18]

In addition, women with preeclampsia and an additional complication such as preterm delivery (PTD) or a small for gestational age (SGA) infant, are at an even greater cardiovascular risk. Preeclampsia with PTD or SGA were 4times more likely to have a major coronary event as women with uncomplicated pregnancies (compared to twice the risk with preeclampsia alone).[19]

**Gestational diabetes mellitus (GDM)** - newly diagnosed DM beyond the first trimester of pregnancy.

Almost 10% to 13% of pregnant women in Australia will develop gestational diabetes, which is associated with an increased risk of Type 2 Diabetes (T2DM) and CVD later in life.[20] GDM increases the risk of developing Type2DM - 1/3of women develop T2DM in the 3-5 years following delivery, and nearly 70% of women develop T2DM >10y postpartum.[21]

In one study GDM was associated with a 71% greater risk of future CVD events.[22] Other studies have found those with GDM had a 43% higher risk of developing CVD (MI or stroke). Those who developed T2DM had a fourfold elevation in risk, those without interim T2DM still had a 30% increased risk for cardiovascular events.[23,24]

GDM increases risk of future hypertension.[25] Having GDM and high blood pressure in the same pregnancy, increases a woman's future risk of diabetes by 37fold, and a 6x higher risk of future hypertension. There is also an increased CVD mortality with having both compared to either GDM or hypertension.[26]

**Preterm delivery (PTD)** - Preterm delivery (birth <37 weeks gestation) is independently associated with a 42% greater risk of CVD[27] and a meta-analysis found PTD was associated with a 38% increased risk of IHD, 71% increased risk of stroke, and 2-fold increased risk of overall CVD.[28] The risk for CVD is further increased with a history of early PTD (<32weeks gestation), and recurrent PTD.[29]

**Low birthweight/ Small for Gestational Age (SGA)** - smaller in size than normal for the gestational age and fetal sex; weight below the 10th percentile for the gestational age at delivery. A number of cohort studies have found women with SGA infants are about twice as likely to experience future CVD.[30,31] This association increases with severity of SGA. The combination of PTD and SGA are at even higher risk of CVD.[32]

Women with SGA infants also have increased mortality, a Denmark registry found a 2.5fold increase in death from cardiovascular causes and a 1.9 fold increase in all-cause mortality associated with birth of an SGA infant.[33] A meta-analysis also demonstrated a 33% increase in maternal cardiovascular mortality associated with every approx. 500gdecrease in infant birth weight.[34]

**Miscarriage** – females with >1 miscarriage compared with women with no miscarriage have an increased rate of MI (1.13times), for cerebrovascular infarction, (1.16x) renovascular hypertension (1.2x) the rates for all 3 outcomes increases with the number of miscarriages.[35] A UK biobank study found adjusted HR for CVD, were 1.04 for each miscarriage, and 1.14 for each still birth.[36]

## MANAGEMENT OF PREGNANCY RELATED COMPLICATIONS THAT INCREASE CVD RISK

In general:

1. Identify those at risk: take a pregnancy history - Table 3
2. Counsel patients about their increased cardiovascular risk and advise on risk reduction
3. Measure BP, lipids, BSL, insulin regularly
4. Advise Lifestyle modification (see below)
5. Pharmacological treatment – antihypertensives, statins, diabetic meds if required. Some evidence for metformin and pioglitazone in reducing diabetes incidence in those with GDM.

**Table 3. Pregnancy History**

| Suggested Pregnancy History Questions | Target adverse pregnancy outcomes |
|---|---|
| How many pregnancies have you had? | |
| How many miscarriages have you had? | |
| Any babies delivered early (>3weeks before your due date)<br>• How many?<br>• Were they delivered early because you were ill or did you go into labour early? | PTD, Preeclampsia |
| Hypertension in any pregnancy?<br>• Protein in your urine during pregnancy? | Gestational hypertension, Preeclampsia |
| Preclampsia in any pregnancy?<br>• Which pregnancy?<br>• How many times?<br>• Early delivery because of preeclampsia?<br>• How many weeks before due date was delivery? | Preeclampsia |
| Family history of preeclampsia? | Preeclampsia |
| Gestational diabetes during any of your pregnancies?<br>• Which pregnancy?<br>• How many times?<br>• Did you require insulin or oral medication to reduce blood glucose? | GDM |
| Birth weight of each baby?<br>• How many weeks before due date were they delivered? | SGA<br>SGA, PTD |
| Number of pregnancies you breastfed?<br>• Number of months in each pregnancy? | |

Adapted from Roberts and Catov[37]

## LIFESTYLE MODIFICATIONS

- Diet modification and regular exercise. The Mediterranean diet reduces stroke/MI or cardiovascular mortality in patients with high cardiovascular risk. Dietary interventions reduces the risk of GDM, gestational hypertension and preterm birth
- Physical activity before and in early pregnancy is significantly associated with lower GDM risk
- Maintain smoking cessation
- Avoid weight gain/maintain a healthy weight - Interpregnancy weight gain is associated with a 2fold increased risk of gestational diabetes and preeclampsia with a subsequent pregnancy

**Breast feeding** >12m decreased CVD (by 72%), decreased the occurrence of hypertension, diabetes, and hyperlipideamia. The longer the lactation the lower the cardiovascular risk. Even >3months of breastfeeding is associated with a lower risk of T2DM progression, breastfeeding >5months is linked to a 50% reduced incidence of T2DM in women who have had GDM. In a large study in china, women who breastfed were 12% less likely to have CVD, 9% less likely to have CAD, and 8% less likely to have a stroke compared to women who had children but never breastfed.[38]

Management of specific pregnancy complications is summarised in table 4.

**Table 4. Management of Specific Pregnancy Complications**

| Adverse Pregnancy Outcome | Recommendations |
|---|---|
| Gestational hypertension or preeclampsia | • Educate patient about the increased risk of hypertension and CVD later in life<br>• Follow up regularly with BP, (aim <120/80), lipids, fasting glucose and BMI<br>• Encourage a healthy lifestyle with weight loss, physical activity, smoking cessation<br>• Maintain a BMI <25kg/m2 (obesity increases hypertension)[39]<br>• DASH diet, low sodium and minimal alcohol<br>• Aspirin prophylaxis in future pregnancies in those with preeclampsia[40]<br>• Encourage Breastfeeding if possible |
| Gestational Diabetes | • Screen for persistent diabetes 6-12 weeks postpartum and every 1-3 years depending on other risk factors (family history, prepregnancy BMI, need for medication during pregnancy)<br>• Advise women that they have an increased risk of developing type 2 diabetes and increased CVD risk, and that lifestyle modifications can reduce their risk*<br>• Encourage healthy eating patterns,** and lifestyle intervention to support weight loss<br>• Regular exercise<br>• Annual check of BP, lipids and blood glucose<br>• Earlier screening for GDM (prior to 28weeks) – in those at higher risk of the condition eg obesity, previous GDM, PCOS, metabolic syndrome, first degree relative with diabetes or those with high BP/abnormal cholesterol profile<br>• Encourage Breastfeeding if possible |
| PTD/SGA | • No real consensus or guideline as to when to screen<br>• Increase the patient's awareness of their increased CV risk and follow up their risk factors |

*IN the Harvard Nurses' Health Study II, the GDM women who followed healthy lifestyle practices (such as maintaining a healthy weight, regular physical activity, not smoking and following a heart healthy diet) had no significant increased risk of developing cardiovascular disease. Women who did not follow these lifestyle practices, or who followed only one or two of them, had a substantial increase in risk.

**Having a healthy diet (DASH diet, mediteranean diet, and alternative healthy eating index) reduces the risk of developing hypertension in GDM patients by 20-30%-[41]

## NON PREGNANCY RELATED CVD RISK FACTORS

**Polycystic Ovarian Syndrome/Insulin resistance:** increases risk for future development of CVD, and probably increases risk of developing hypertension. Women with PCOS have a higher risk of developing diabetes (RR 2 – 4), and have increased prevalence of impaired glucose tolerance and metabolic syndrome.[42] A large Taiwanese study found for PCOS, the RR of CAD was 1.44 and increases to 21.2 for women with PCOS, diabetes, hypertension and hyperlipidaemia.[43]

Management recommendation: screen regularly for diabetes, check lipids and BP, encourage a healthy diet and regular exercise.

**Endometriosis:** increases the risk for coronary heart disease (MI, angina, cabg/angioplasty/stent) by 62% overall and by 200% in women aged 40 or younger. CHD risk was not increased in women older than 55y.[44] Compared to women without endometriosis, women with endometriosis were 1.52times more likely to have an MI, 1.91times more likely to develop angiographically confirmed angina, and 1.35times more likely to need CABG surgery, a coronary angioplasty or a stent. However, 42% of the association between CHD and endometriosis could be explained by greater frequency of hysterectomy/oophorectomy and earlier age at surgery.

Recommendation: Young women with endometriosis should have their risk factors evaluated and aggressively managed, with consideration of referral to a cardiologist. Women who have surgical menopause should be aware that this confers a higher cardiovascular risk.

**Autoimmune Diseases:** Both male and female patients with inflammatory diseases such as Rheumatoid arthritis (RA) and Systemic Lupus Erythematosus (SLE) have increased mortality, mainly as a consequence of CVD.[45] There is a female predisposition in the prevalence of these disorders, making it a common risk factor in women – female to male ratio for RA is 2.5:1; and for SLE is 9:1. Patients with RA have a 2-3fold higher risk of MI and a 50% higher risk of stroke.[46] The higher the RA disease activity, the higher the risk of MI. For SLE, the risk of MI is increased 9-50fold over that in the general population.[47]

Recommendation: Aggressive treatment of cardiovascular risk factors.

**Radiation and Chemotherapy for Breast Cancer:** Radiotherapy for breast cancer often involves exposure to the heart to ionizing radiation, which increases the risk of subsequent IHD. The risk is proportional to the mean dose to the heart, beginning within a few years after exposure, and continuing for at least 20years.[48] This is greater in those irradiated on the left than on the right, and with pre-existing cardiac risk factors. Radiation heart disease can also manifest as valvular disease and cardiomyopathy. Chemotherapy for breast cancer has been associated with dose dependent acute, subacute and late cardiotoxicity including LV dysfunction/heart failure, hypertension, arrhythmias, thromboembolic disease and pericarditis. This is particularly with anthracyclines and transtuzumab like agents.

Recommendation: Recognise that for older women, CVD poses a greater mortality threat that the breast cancer itself. Guidelines recommend echo evaluation (looking at LV function/strain) based on signs and symptoms; echo surveillance 5 years after treatment in high risk (eg. anthracycline chemo) patients and 10years in all other patients; high risk patients should also receive a functional non invasive stress test within 5-10years of completion of chest radiation therapy. Adhering to 7 heart healthy behaviours, is associated with a trend toward a lower incidence of breast cancer, and a significantly lower risk of CVD. These include being physically active, achieving and maintaining a healthy body weight, eating a healthy diet, avoiding tobacco and maintaining healthy levels of BP, cholesterol and blood sugar.

**Depression:** is an increasingly prevalent and recognised risk factor for development of CAD and portends an unfavourable outcome after a CAD event.[49] It is a powerful risk factor especially in younger women.[50] Younger women have higher rates of depression[51]and also higher mortality rates after acute MI compared with men.[52]

Management: recognise and treat depression. Regularly evaluate risk factors and encourage lifestyle modifications.

## MENOPAUSE AND CVD

Premenopausal women are relatively protected against CVD compared with age-matched men. After menopause, the risk increases to equal that of men. Thus hormone replacement therapy (HRT) was hypothesized to be cardioprotective. This has subsequently been refuted by many randomized clinical trials.[53,54] Further review of trials have found that estrogen only HRT, may have favourable CAD outcomes in younger women,[55] reduces CAD risk in women <60yo but not in older women.[56] Current guidelines recommend that HRT at the lowest effective dose is appropriate for treatment for menopausal symptoms in early (within 5 years) of menopause, but should not be prescribed for the sole purpose of preventing CVD.[57]

**Early-Onset Menopause** – women who experience early onset menopause – (younger than 45) carry an increased cardiovascular risk; with a RR of 1.50 for overall CAD, 1.19 for CVD mortality and 1.12 for all cause mortality.[58]

Another study found those who had menopause before age 47 were 33% more likely to develop cardiovascular disease and 42% more likely to have a stroke than women who went through menopause later.[45]

**Surgical Menopause:** surgical menopause in young women is associated with increased risk for development of premature CVD.[59] Those who had a hysterectomy were 12% more likely to get cardiovascular disease, and the increased risk is even higher for women who had an oophorectomy as well. In the UK Biobank study, the HR for incident cardiovascular disease in women with hysterectomy without oophorectomy was 1.16 (1.06-1.28), and 2.30 (1.2-4.43) for women with hysterectomy with previous oophorectomy.[36] The age at hysterectomy or oophorectomy were inversely related to risk.

Management: those who experience early menopause or surgical menopause, consider control for hypertension, dyslipidaemia, insulin resistance earlier, as they are considered higher risk for CVD.

## CONCLUSION

Heart disease is the number one killer of Australian women. Most of us are aware of the traditional risk factors for CVD, however there are many emerging non traditional risk factors specific to women, particularly pregnancy related complications, and others that affect younger women. Thus a heart health check should be performed in women >45yo and a pregnancy history should also be incorporated in assessing a woman's cardiovascular risk. Identifying these women at risk allows us to start intervention with the aim to reduce the burden of cardiovascular disease in women.

## FOR MORE INFORMATION

For further information, please see an article and quiz written for Australian Doctor. To read the original and do the RACGP and ACRRM accredited quiz: www.australiandoctor.com.au/how-treat/women-and-heart-disease (site requires registration and log on).

**Watch these videos:**
https://www.houseofwellness.com.au/health/conditions/heart-disease-women

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**Visit:**
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https://www.heartfoundation.org.au/campaigns/making-the-invisible-visible

# CARDIOVASCULAR RISK FACTORS IN WOMEN (CONTINUED)

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# GESTATIONAL DIABETES MANAGEMENT AND THE ROLE OF PRIMARY CARE


## Dr Shan Jiang (Endocrinologist)


Gestational diabetes (GDM) is a state of carbohydrate intolerance arising during pregnancy. Adverse pregnancy outcomes associated with poorly controlled GDM include increased risk of pre-eclampsia, fetal macrosomia and neonatal hypoglycaemia, whereas treatment has been shown to be effective in decreasing these risks. This article will outline the latest recommendations regarding the diagnosis and management of gestational diabetes, as well as the important roles GPs have in the management of these conditions.

## DIAGNOSIS

The International Association of Diabetes and Pregnancy Study Group (IADPSG) in 2010[1] updated its recommendation for universal screening of GDM via 75g Oral Glucose Tolerance Test (OGTT). The diagnostic criteria for gestational diabetes was also updated whereby the glucose thresholds were set at which confers a 1.75 odds ratio of developing four major pregnancy adverse outcomes of neonatal large for gestational age, neonatal hypoglycaemia, primary caesarean section and high cord c-peptide compared to women without GDM, based on the landmark Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study[2]. The Australasian Diabetes in Pregnancy Society (ADIPS) in Australia has also adopted these recommendations[3]:

- **Standard Timing of Screening –** 24 – 28 weeks gestation to all pregnant women
- **Diagnostic Test –** 75g oral glucose tolerance test measuring fasting, 1 hour post load and 2 hours post load glucose levels
- **Diagnostic Criteria –**
  Fasting  Fasting ≥5.1 mmol/L
  1 hour≥10.0 mmol/L
  2 hour ≥8.5 mmol/L

## MANAGEMENT

### TREATMENT TARGETS

Following the diagnosis of GDM, women are commenced on glucose monitoring 4 times a day for the duration of the rest of pregnancy. The timing of these glucose testing occurs at fasting, and 2hours post each main meal. There is no inferiority in management based on the 1hour versus the 2 hour post prandial glucose reading in correlation with adverse pregnancy outcome,[4] hence in women who are diagnostic of GDM exclusively on the 1hour reading on the OGTT may be monitored via fasting and 1 hour post prandial glucose levels.

**Treatment Targets**[3]

- Fasting≤5.0mmol/L
- 1hour post prandial≤7.4mmol/L
- 2hour post prandial ≤6.7mmol/L

These targets are derived from extrapolations of the HAPO study, epidemiology data, as well as interventional trials which have demonstrated benefits in the intervention arm.

# GESTATIONAL DIABETES MANAGEMENT AND THE ROLE OF PRIMARY CARE (CONTINUED)


## LIFESTYLE MODIFICATION

### Diet

A balance between sufficient nutritional requirement to maintain pregnancy whilst preventing hyperglycaemia is the principle for dietary management in GDM. This is achieved via a healthy diet consisting of 9 – 12 carbohydrate exchanges (135 – 180g) of low glycaemic index carbohydrates per day, divided into 2 – 3 carbohydrate exchanges per main meal, with 1 carbohydrate exchange each for morning tea, afternoon tea and supper. Often this is achieved via a review with a dietitian or diabetes educator in which the women are given education regarding carbohydrate counting and commencement of a food diary. It is important to ensure the woman does not calorie restrict, as this can increase the risk of small for gestational age and other nutritional deficits. A ketogenic/carbohydrate-free diet is contraindicated in pregnancy due to risk of maternal ketosis and fetal intrauterine growth retardation.

### Exercise

At least 30 minutes of moderate intensity exercise per day is recommended for women with uncomplicated pregnancy. This can be divided into 3 intervals of 10minutes duration. Moderate intensity exercise entails the heart rate be increased to 50 – 90% of maximum heart rate for age (which can be calculated by 220 – age). This has the benefit of not only decreasing hyperglycaemia but also prevents excess gestational weight gain in pregnancy.

### Medications

Medications are added as adjunct to lifestyle management should these be unable to achieve adequate glycaemic control. Insulin has the longest safety data in the use for gestational diabetes and does not cross the placenta to affect the foetus. The type of insulin used is tailored to the timing of hyperglycaemia experienced by the woman whilst frequent reviews of glycaemic control every 2 – 4 weeks are necessary for titration of insulin dose, due to the increase in insulin resistance occurring with advancing gestation from pregnancy related hormones such as human placental lactogen, cortisol, progesterone. On the other hand, detection of a sudden decrease in insulin requirement >30% in late pregnancy may be an early sign of placental insufficiency warranting an urgent assessment of fetal welfare.[5]

Metformin has been shown to be safe in pregnancy without teratogenicity. It is effective in managing mild hyperglycaemia from GDM and decrease risk of fetal macrosomia. However Metformin does cross the placenta and there is a lack of long term safety data in terms on any effect to childhood development later on.[6] Hence use of Metformin has not been uniformly adopted by treating physicians.

# ROLE OF PRIMARY CARE

## PRE-PREGNANCY PLANNNG

There is some evidence that initiation of a healthy lifestyle consisting of diet and exercise can decrease the risk of developing gestational diabetes.[7] Often women seek the advice of GPs in the pre-pregnancy planning period in which such advice can be provided, especially in those with risk factors for development of GDM.

## EARLY PREGNANCY SCREENING IN THOSE AT RISK

Early pregnancy screening of GDM via OGTT starting from 16 weeks gestation is recommended for women with high risks of developing gestational diabetes. Some of the risk factors for consideration of early screening[3] include:

- Previous hyperglycaemia in pregnancy
- Previously elevated blood glucose level
- Maternal age ≥40 years
- Ethnicity: Asian, Indian subcontinent, Aboriginal, Torres Strait Islander, Pacific Islander, Maori, Middle Eastern, non-white African
- Family history of diabetes (1st degree relative with diabetes or a sister with hyperglycaemia in pregnancy)
- Pre-pregnancy BMI > 30
- Previous fetal macrosomia
- Polycystic ovarian syndrome
- Medication use of corticosteroids, antipsychotics

This also enables detection of women who may have undiagnosed pre-diabetes or type 2 diabetes requiring earlier treatment. For many of these women in early pregnancy and have not yet had a specialist obstetrics review, a GP is often the first doctor they have seen in pregnancy where the risk factors are identified and early OGTT screening can be initiated. In those women who are not found to have GDM on early screening, repeat screening via OGTT at the standard 24 – 28 weeks gestation is still required. There is currently no evidence for OGTT screening in the 1st trimester as no interventional data is available on the benefit of treatment.

## POST PARTUM OGTT AND ONGOING SCREENING

A diagnosis of GDM also indicates an increased maternal risk of developing pre-diabetes and type 2 diabetes. The detection of this occurs mostly in the primary care setting as patients have been discharged from obstetrics care, and the diagnosis can occur several years after pregnancy. In the latest HAPO Follow Up Study,[8] 52.2% of women with GDM developed type 2 diabetes or pre-diabetes state in the median 11.4 years of follow up. There is currently no universal evidence based guideline for schedule of follow up in women with GDM, however a reasonable plan of approach would be:

- Repeat OGTT 6 – 8 weeks post partum
- If planning further pregnancy in immediate future then yearly OGTT
- If not planning further pregnancy, then OGTT every 2 – 3 years with fasting BSL and HbA1c in the alternating years
- Should a pre-diabetes state be detected, frequency of OGTT be increased to yearly.


**Endnotes**

1 Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes care. 2010;33(3):676-82

2 The HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcomes. New England Journal of Medicine. 2008;358(19):1991-2002

3 Nankervis, A., et al. "ADIPS consensus guidelines for the testing and diagnosis of hyperglycaemia in pregnancy in Australia and New Zealand." Australasian Diabetes in Pregnancy Society (2014): 1-8

4 Ozgu-Erdinc, A. Seval, et al. "One-hour versus two-hour postprandial blood glucose measurement in women with gestational diabetes mellitus: which is more predictive?." Endocrine 52.3 (2016): 561-570

5 Padmanabhan, Suja, Mark McLean, and N. Wah Cheung. "Falling insulin requirements are associated with adverse obstetric outcomes in women with preexisting diabetes." Diabetes Care 37.10 (2014): 2685-2692.

6 Lindsay, Robert S., and Mary R. Loeken. "Metformin use in pregnancy: promises and uncertainties." Diabetologia 60.9 (2017): 1612-1619.

7 Shepherd E, Gomersall JC, Tieu J, Han S, Crowther CA, Middleton P. Combined diet and exercise interventions for preventing gestational diabetes mellitus. Cochrane Database of Systematic Reviews 2017, Issue 11.

8 Lowe, William L., et al. "Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity." JAMA 320.10 (2018): 1005-1016

# CARDIOLOGY UPDATES 2019

Sydney Cardiology

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## SATURDAY APRIL 6

## Novotel Sydney Norwest

www.sydneycardiology.com.au

As part of our ongoing commitment to providing quality education, Sydney Cardiology Group is pleased to inform you of our next GP Education event.

**WHEN** **Saturday 6th April 2019 –** 12:00pm – 6:00pm

**WHERE** **Novotel Sydney Norwest –** 1 Columbia Court, Baulkham Hills NSW 2153

**NO REGISTRATION FEE**

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Hypertension – What's New?

**Dr Abhinav Luhach**
Heart Failure

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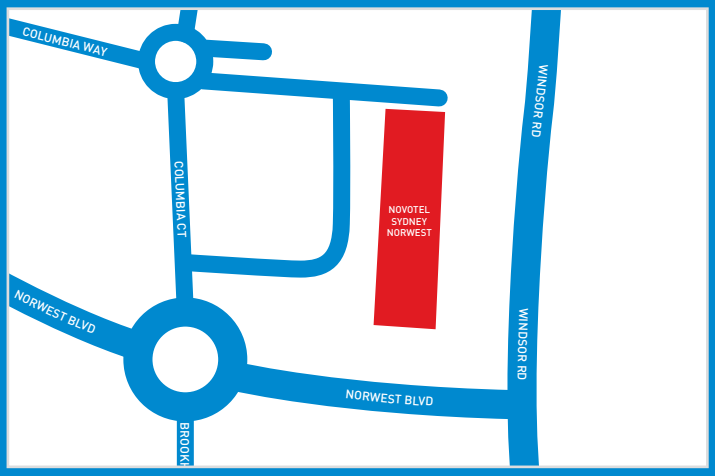
Lessons in Echo

**Dr Gunjan Aggarwal**
CTCA and Calcium Scoring

**Dr Fiona Foo**
ECG Fun-time




Ample onsite parking is available at the venue.

## Registration

**Please complete and email to: events@sydneycardiology.com.au or Fax: 9411 1904 by the 22nd of March 2019**

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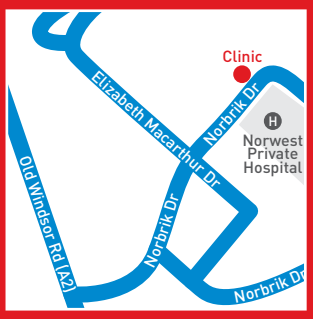


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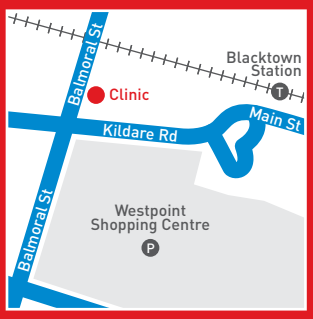


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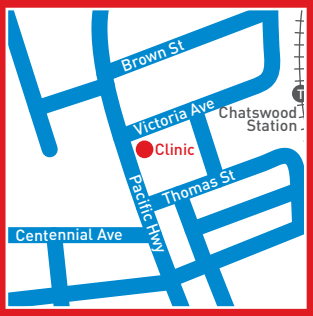


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