Identifying and managing younger women at high risk of cardiovascular disease

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ardiovascular disease (CVD), which is largely prevent-
able, is a leading cause of morbidity and mortality among Canadian women. For this article, we use CVD to refer to ischemic heart disease and stroke. Data for peripheral arterial disease in women are limited and are addressed elsewhere.1 Until now, risk reduction has focused largely on post-
menopausal woman with traditional risk factors: diabetes, smok-
ing, hypertension and hyperlipidemia. Consequently, CVD mortality has declined, largely driven by those aged 50 years and older.2 A recent study of 20-year temporal trends in admissions to hospital and deaths caused by atherosclerotic cardiovascular disease in Ontario reported that mortality rates for circulatory diseases in women declined 52.8% between 1994 and 2012.3 However, annual rates of decline were least evident in individ-
uals younger than 50 years of age, suggesting that CVD among younger adults remains a cause for concern.3 The lowest rate of decline in CVD-related mortality and, in some cases, an increase in CVD-related admissions to hospital and mortality have been observed in younger women.3,4

Contemporary Canadian data suggest the gap in cardiovas-
cular mortality between men and women may be closing.5 Yet young women with ST-segment elevation myocardial infarction (MI) have 15%–20% higher rates of death than men of similar age.6 Whether this is related to systematic differences in care or true biological differences, or a combination, is unclear. What is clear is that addressing cardiovascular health in women younger than 50 years of age requires thinking beyond traditional risk fac-
tors in primordial prevention.

We present a brief overview of sex differences in traditional cardiovascular risk factors and a focused review of key nontradi-
tional risk factors in younger women (i.e., ovarian dysfunction, infertility, reproductive therapies and pregnancy complications). Our approach to gathering evidence is outlined in Box 1.

What is the effect of traditional cardiovascular risk factors in young women?

A 2018 study concluded that the strongest predictor of acute cor-

ony syndrome in women under the age of 45 years is diabetes (odds ratio [OR] 6.66, 95% confidence interval [CI] 3.47–12.74), followed by hypertension (OR 4.30, 95% CI 3.42–5.38), hypercho-

lesterolemia (OR 3.45 95% CI 2.60–4.29) and smoking (OR 1.63, 95% CI 1.34–1.98).7 This study also found that smoking was more prevalent and other traditional risk factors were less prevalent among young women compared with older women with acute coronary syndrome.7 The INTERHEART study identified diabetes, metabolic syndrome and tobacco use as stronger predictors of ischemic heart disease in women under the age of 50 compared with older women.8

Findings from a 1996 cohort study suggested that, when com-
pared with men, smoking is a relatively stronger risk factor for MI in women less than 45 years of age (relative risk [RR] 7.1 in

KEY POINTS

- Pregnancy-related vascular complications, such as preeclampsia, need to be factored into risk assessment in younger women.
- Conditions such as premature ovarian dysfunction, use of reproductive therapies and infertility may increase long-term risk of cardiovascular disease.
- Early risk stratification and aggressive management of lifestyle may help mitigate future risk in premenopausal women with high-risk profiles.
- Long-term management strategies need to be defined in this population.

Box 1: Evidence used in this review

We conducted a search of PubMed for articles published in English between July 2008 and July 2018. We used the Medical Subject Heading (MESH) terms “cardiovascular disease” and “young women” for our search. We narrowed the search further by searching for articles involving humans and adults aged 19 to 64 years. This resulted in 7671 hits, which were narrowed down to 6442 by excluding articles with the term “congenital heart defect.” We reviewed the best matched first 300 articles. Relevant articles listed in the reference section of select articles were also reviewed. We discussed the highest level of evidence via randomized controlled trials when available, and where literature was limited, we used observational and case reports.
Do estrogen and hormone replacement therapy affect cardiovascular disease risk?

The incidence of CVD is lower in premenopausal women compared with men of similar age. First coronary event(s) occur, on average, 10 years later in women than men. Given that women appear to be mostly protected until mid-life, estrogen has been implicated as a protective factor. However, the cardioprotective role of estrogen is complex and not well understood. Estrogen has multiple effects on the cardiovascular system, including promotion of vasodilation, antioxidative defence and recovery from vascular injury, thereby reducing the development of atherosclerosis, and preventing cardiomyocyte and endothelial dysfunction. Despite theoretical benefits, trials examining the addition of treatment with estrogen after menopause have not shown a protective benefit for CVD. A recent analysis of data of 18-year follow-up of participants from randomized trials suggests that postmenopausal hormone replacement therapy may not be harmful in women, however.

What is the relation between ovarian dysfunction and risk of ischemic heart disease?

Younger women with ovarian dysfunction appear to have an increased risk of CVD. Women with premature ovarian failure have as much as 80% higher mortality from ischemic heart disease than those who go through menopause at the expected average age range of 49 to 55 years according to prospective research. Endothelial dysfunction, dysglycemia, abnormal lipid profile and metabolic syndrome may be potential drivers of elevated risk in this subset of younger women. Iatrogenic (i.e., surgical and chemical) menopause before the age of 50 years also confers a similar increase in risk of CVD. In a small cohort study, hormone replacement therapy in these women was shown to improve endothelial function within 6 months of treatment; however, in those with premature ovarian failure, no long-term data on CVD outcomes are available.

Polycystic ovarian syndrome is a common endocrine disorder in premenopausal women, with prevalence ranging from 6% to 15%. A review of studies involving women with polycystic ovarian syndrome found an increased risk of subclinical atherosclerotic disease, diabetes, dyslipidemia, obesity and endothelial dysfunction. Ten-year follow-up in postmenopausal women with polycystic ovarian syndrome or its characteristics did not show higher mortality or adverse cardiovascular events. However, there are methodological limitations to this study. Long-term, large-scale data for cardiovascular outcomes are lacking for this group, and this represents an area for future study.

Does reproductive therapy increase women’s risk of ischemic heart disease?

Limited and conflicting research has examined long-term risk of CVD resulting from infertility and fertility treatments. A 2017 cross-sectional analysis involving women who completed the Framingham Heart Study Third Generation and Omni Cohort Exam 2 (2008–2011) and reported infertility showed that self-reported infertility was associated with CVD risk factors such as elevated body mass index and waist circumference. However, an analysis of data from the Women’s Health Initiative Observational Study did not find a history of infertility to be associated with coronary heart disease. A 2016 observational study involving women receiving infertility therapy found that failure of therapy was associated with 19% higher annual rates of cardiovascular events. Increased thromboembolic events in this group with failure of infertility therapy may explain the elevated future risk. Another possibility is that failure of treatment unmask those with underlying endothelial dysfunction, a known risk factor for future CVD. A 2017 systematic review and meta-analysis of a small number of heterogeneous observational studies examining the association between reproductive therapies and CVD risk reported no increased rates of cardiovascular events. Further study is needed to clarify whether it is the state of infertility itself, or reproductive treatment, that is associated with future CVD. As the average age of child-bearing increases along with a rise in the number of women seeking reproductive therapy for infertility, this is a pressing question that must be addressed.
are manifestations of a “positive test.” These maternal cardiometabolic disorders have been identified as risk factors for long-term cardiovascular disease.31–39

**Hypertensive disorders of pregnancy**

Hypertensive disorders of pregnancy occur in 2%–10% of pregnancies31 and range in severity from gestational hypertension (hypertension after 20 weeks of gestation) to preeclampsia (hypertension after 20 weeks with end-organ damage with or without proteinuria), eclampsia (preeclampsia and seizure) and HELLP syndrome (hemolysis, elevated liver enzyme and low platelet count levels). Women who had maternal placental syndromes (defined as preeclampsia, gestational hypertension, placental abruption and placental infarction) in pregnancy showed a twofold increase in CVD compared with those with pregnancies without maternal placental syndrome, with a mean age of onset of 38 years in a population-based retrospective cohort study involving over 1 million women.32 Maternal placental syndromes occurred in 7% of deliveries and showed an incremental rise in risk of future CVD with an adjusted hazard ratio of 3.1 in maternal placental syndromes with poor fetal growth and 4.4 in maternal placental syndromes with intrauterine death, compared with 1.8 and 2.1 for gestational hypertension and preeclampsia, respectively.32 Findings from the GENESIS-PRAXY study showed a threefold increase in premature CVD in women with a history of preeclampsia.33

Maternal placental syndromes also predict prognosis and survival following cardiovascular disease.34 Maternal placental syndromes double the risk of death in women undergoing coronary revascularization and recurrence quadruples this risk. Mechanisms are complex; however, endothelial dysfunction is implicated in preeclampsia and may be the driver for long-term cardiovascular risk31 (Figure 1).

**Maternal dysglycemia**

Gestational diabetes occurs in 3%–4% of pregnancies31 and is associated with maternal postpartum diabetes, metabolic syndrome and CVD.35 Women with gestational diabetes had a 15-fold higher rate of subsequent type 2 diabetes over 8.5 years follow-up, with a median age at onset of 37 years.36 Long-term 30-year follow-up of these women showed higher prevalence of cardiovascular disease (15.5% v. 12.4%; adjusted OR 1.85, 95% CI 1.21–2.82), with presentation at a younger age (45.5 ± 2.2 v. 52.5 ± 11.9 years) independent of development of postpartum diabetes or metabolic syndrome.37 Another study involving women aged 29 to 49 years with live births between April 1994 and March 1997 in Ontario found a HR of 1.71 (95% CI 1.08–2.69) for CVD events in those with gestational diabetes over a median follow-up time of 11.5 years; however, this effect was less clear when adjusted for development of type 2 diabetes.38 In 2018, a Canadian retrospective cohort study involving over 1 million women showed an association between gestational diabetes and elevated ischemic heart disease (HR 1.23, 95% CI 1.12–1.36) and MI (HR 2.14, 95% CI 1.15–2.47) as much as 25 years after the index pregnancy.39

**Other complications of pregnancy and risk of cardiovascular disease**

There is increased cardiovascular risk, both in the short and long term, following maternal placental syndromes.40 In addition to preeclampsia, these syndromes include placental infarction and

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**Figure 1:** Cardiovascular disease cascade relating to nontraditional, sex-specific risk factors such as maternal placental syndromes (e.g., preeclampsia), premature ovarian failure, polycystic ovarian syndrome and infertility.
abruption, both indicators of placental microvascular dysfunction. The outcome is often miscarriage or preterm delivery. In a large retrospective cohort study ($n = 36713$), women with any manifestation of this syndrome had a 19% higher risk of CVD than pregnant women without maternal placental syndromes. Those with more than 1 manifestation of this syndrome had 40% higher risk of CVD within 4.9-year follow-up. Maternal placental syndromes in combination with preterm birth or small for gestational age increased risk of CVD by 45%. Similarly, a 2017 population-based cohort study in Denmark found a 2.7-fold increase in CVD mortality and a 1.5-fold increase in morbidity among women with a history of placental abruption over long-term follow-up (median 18 years). Repeated miscarriages were also associated with future coronary heart disease (OR 1.99, 95% CI 1.13–3.50) but not cerebrovascular disease in a systematic review and meta-analysis of 10 studies involving over 500 000 women with coronary heart disease and over 100 000 with cerebrovascular disease.

**How should premenopausal women at risk of cardiovascular disease be screened and managed?**

A challenge in risk assessment is addressing a subpopulation at elevated risk within a lower-risk group. Current risk assessment tools are largely based on age and traditional risk factors and tend to underestimate risk in certain groups of younger women who are at higher risk. The National Health and Nutrition Examination Survey reported that 82% of adults in the US (mean age 44 years) were categorized as having low short-term or 10-year risk, but two-thirds of this group were reclassified as having high lifetime risk. This disparity in short- and long-term classification was more prevalent in women. In younger adults, 30-year and lifetime CVD risk scores have shown predictive value. Whether the nontraditional risk factors we discussed in this article have independent additive predictive value in risk assessment of young women requires further study.

Young women and health care providers often lack understanding of nontraditional risk factors. This is complicated by the ambiguity in guidelines until recently. In 2011, the American Heart Association updated the guideline for the prevention of CVD in women and introduced pregnancy-related vascular complications in the CVD risk profile. Current evidence on CVD risk factors specific to women was reviewed in a 2016 American Heart Association Scientific Statement. The Canadian Cardiovascular Society guideline recently introduced the category of higher-risk younger women with hypertensive disorders of pregnancy in their screening recommendations.

Based on these data and guidelines, we suggest that premenopausal women with both traditional and nontraditional risk factors for cardiovascular disease, as identified above, undergo early screening and close follow-up. Pharmacologic preventive therapy in addition to aggressive lifestyle management are indicated in those with risk factors. Pharmacologic therapy may include anti-hypertensive therapy, diabetes management, lipid management, medications for smoking cessation and estrogen replacement therapy in young women with premature ovarian dysfunction.

**Box 2: Unanswered questions**

- What are the ideal screening protocol and risk stratification strategies in higher-risk younger women?
- Which existing risk assessment scores are validated and calibrated to identify appropriately 10-year and lifetime risk in these women?
- Which postpartum interventions are effective and, ultimately, have benefit in reducing long-term cardiovascular risk?

Possible suggestions for nonpharmacologic risk reduction include weight loss after gain in pregnancy, regular exercise and standard follow-up at 1 year postpartum to assess other cardiometabolic risks such as lipid profile and blood glucose levels. However, formal guidelines are lacking and further clarifying evidence is required to support such recommendations.

Management strategies are not all proven effective. An interdisciplinary, hospital-based postpartum clinic found no significant weight reduction or improvement in cardiometabolic risk despite improved physical activity, due, in part, to low levels of participation and dropout rates. Strategies to increase buy-in among young women, such as effective electronic health (e-health) interventions, need to be fostered. Use of e-health technologies to engage young mothers in weight-loss strategies has shown some benefit. Further study is warranted in this area.

**Conclusion**

Some younger women are at increased risk of CVD. Pregnancy complications and maternal placental syndromes present early markers of endothelial dysfunction. The postpartum period is an essential window of opportunity for risk stratification and early intervention to prevent long-term CVD. Premature ovarian dysfunction, reproductive therapies, and possibly infertility, can also be used to identify young women who may have elevated risk of future cardiovascular events. Long-term assessment and studies examining data on these women at higher risk are needed, and long-term management strategies need to be defined. Research questions to be addressed are summarized in Box 2. Increasing awareness of the interplay between both traditional and nontraditional cardiac risk factors in premenopausal women, greater focus in research on this topic and dissemination of practice guidelines with explicit screening and target measures, may help reduce the burden of CVD in young women.

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Contributors: Both authors contributed equally to relevant literature review, manuscript writing and the revision process. Both authors gave final approval of the version to be published and agreed to be accountable for all aspects of this work.

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