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REVIEW

Pregnancy complications and later life women's health

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Abstract

There has been increasing recognition of the association between various pregnancy complications and development of chronic disease in later life. Pregnancy has come to be regarded as a physiological stress test, as the strain it places on a woman's body may reveal underlying predispositions to disease that would otherwise remain hidden for many years. Despite the increasing body of data, there is a lack of awareness among healthcare providers surrounding these risks. We performed a narrative literature review and have summarized the associations between the common pregnancy complications including gestational hypertension, pre-eclampsia, gestational diabetes, placental abruption, spontaneous preterm birth, stillbirth and miscarriage and subsequent development of chronic disease. Hypertensive disorders of pregnancy, spontaneous preterm birth, gestational diabetes, pregnancy loss and placental abruption are all associated with increased risk of various forms of cardiovascular disease. Gestational diabetes, pre-eclampsia, early miscarriage and recurrent miscarriage are associated with increased risk of diabetes mellitus. Pre-eclampsia, stillbirth and recurrent miscarriage are associated with increased risk of venous thromboembolism. Pre-eclampsia, gestational diabetes and stillbirth are associated with increased risk of chronic kidney disease. Gestational diabetes is associated with postnatal depression, and also with increased risk of thyroid and stomach cancers. Stillbirth, miscarriage and recurrent miscarriage are associated with increased risk of mental health disorders including depression, anxiety and post-traumatic stress disorders. Counseling in the postnatal period following a complicated pregnancy, and advice regarding risk reduction should be available for all women. Further studies are required to establish optimal screening intervals for cardiovascular disease and diabetes following complicated pregnancy.

KEYWORDS
chronic disease, maternal health, noncommunicable disease, postnatal care, post-pregnancy health

Abbreviations: aHR, adjusted hazard ratio; aRR, adjusted risk ratio; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HR, hazard ratio; NICE, National Institute for Health and Care Excellence; OR, odds ratio; RR, relative risk; SBP, systolic blood pressure; sFLT-1, soluble fms-like tyrosine kinase-1; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism.

1 | INTRODUCTION

Pregnancy causes major changes to a woman's physiological function from the very early stages to support the growing fetus.[1] It has come to be regarded as nature's "stress test" due to the pressure put on the pregnant woman's body, and may cause predisposition to chronic disease to be revealed years earlier than it might have been.[1,2] It is accepted that pregnancy complications can negatively influence maternal and child outcomes, and there is growing evidence that pregnancy complications are also associated with maternal health problems long after the pregnancy is are over. For example, there is a well-described association between gestational diabetes (GDM) and risk of development of type 2 diabetes (T2DM), but there is much less awareness among women's healthcare providers of other long-term health risks following pregnancy complications.[3,4]

One important example of a risk marker for later life noncommunicable disease is pre-eclampsia. The relation between pre-eclampsia and later cardiovascular disease (CVD) was first described in 1927 by Corwin, and has been the subject of significant focus in the past decade as interest in prevention of CVD in women has increased.[2,5] Despite this, a survey of physicians from 2021 showed that the majority of internal medicine, family medicine and cardiology physicians did not ask about adverse pregnancy outcomes when screening for cardiovascular risk factors, and were unfamiliar with the American Heart Association and American College of Obstetricians and Gynecologists' guidelines concerning treatment and follow-up of women with pre-eclampsia.[6] Other studies have also identified knowledge gaps in risk assessment and screening following adverse pregnancy outcomes.[4,7] Valuable opportunities for postnatal counseling and risk reduction, as well as potential screening for chronic disease in the following years, are then lost.

Several recent systematic reviews have been performed around this area. To support improved awareness and action regarding pregnancy care for later life health promotion, the aim of this review is to summarize the current data regarding pregnancy complications and later life health problems.

2 | METHODS

We designed a strategy for a comprehensive narrative literature review. The PubMed and Cochrane library databases were searched for evidence investigating associations between pregnancy complications and later life health problems divided by organ system. The searches were performed between January 14 to 28, 2022. Limits were placed on the searches for papers in English. If the search returned more than 5000 titles, limits were placed on the search to reviews and systematic reviews from the past 10 years. Duplicate papers were excluded, and titles were screened for relevant meta-analyses, systematic reviews, reviews and cohort studies. Recently published systematic review and meta analyses were prioritized if available, followed by reviews and then large cohort studies if no review could be identified. The abstracts of titles considered relevant for this review were read in full and were collated into a database on Microsoft Excel. The final list of selected articles were read in full.

Please see Appendix S1 for full search strategy and terms.

Key message

Experiencing an adverse pregnancy outcome increases a woman's risk of noncommunicable disease in later life. We summarize associations between hypertensive pregnancy, gestational diabetes, placental abruption, low birthweight, stillbirth, miscarriage and later health problems.

3 | CAUSUALITY

Although the major pregnancy complications tend to be studied separately, and are regarded as different disease processes, there is evidence that there is some overlap in pathophysiology. When the increase in risk for later cardiovascular disease in these apparently diverse conditions is considered, this makes sense. The common mechanism is thought to be abnormal placentation – or abnormal development of the uteroplacental maternal-fetal interface - associated with a number of important obstetric complications, including fetal growth restriction, preterm labor, and placental abruption.[8] It remains under debate whether complications of pregnancy conditions cause, exacerbate, or simply reveal, a predisposition to CVD.[9] We further discuss this below as related to each pregnancy complication individually.

4 | PRE-ECLAMPSIA

Pre-eclampsia is a multisystem disorder of pregnancy characterized by new-onset hypertension after 20 weeks' gestation, with evidence of organ dysfunction such as proteinuria, deranged renal or liver function, coagulopathy or fetal growth restriction.[10] Although not fully established, it is thought that defective placentation prompts a generalized inflammatory response which affects endothelial function.[9] This, along with the demands of the suboptimally implanted feto-placental unit, causes hypertension. Endothelial disturbance is also a characteristic of essential hypertension and contributes to atherosclerosis.[11] A history of pre-eclampsia confers a two-fold higher risk of future ischemic heart disease (risk ratio [RR] 2.11 [95% CI: 1.60–2.77]) a 3.5-fold increased risk of heart failure (RR 3.62 [95% CI: 2.25–5.85]) and a 71% higher risk of stroke (RR 1.71 [95% CI: 1.38–2.11]) according to a systematic review by Wu et al.[12] For coronary heart disease (CHD), heart failure, stroke and CVD death, the adjusted risk ratio (aRR) was higher in the first 10 years following the affected pregnancy, compared to >10 years postpartum.[12]

TABLE 1 Risk of noncommunicable disease following pre-eclampsia.

Heart failure	RR 3.62 (95% CI: 2.25–5.85)[12]
Coronary heart disease	RR 2.11 (95% CI: 1.60–2.77)[12]
Composite cardiovascular disease	RR 1.65 (95% CI: 1.36–2.21)[12]
Cerebrovascular morbidity	OR 2.95 (95% ICI: 1.10–7.90)[14]
Vascular dementia	HR 3.46 (95% CI: 1.05–1.99)[15]
Stroke	RR 1.71 (95% CI: 1.38–2.11)[12]
Venous thromboembolism	aHR 2.3 (95% CI: 1.3–4.2)[19]
Diabetes	RR 2.37 (95% CI: 1.37–4.10)[22]
Chronic kidney disease	HR: 1.82 (95% CI: 1.27–2.62)[17]
End stage renal disease	HR 3.01 (95% CI: 1.92–4.70)[17]

Note: Statistics quoted as per reporting study.

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Hypertension in pregnancy is traditionally defined as mild (systolic blood pressure [SBP] 140–149 mmHg/diastolic blood pressure [DBP] 90–99 mmHg), moderate (SPB 150–159 mmHg/DBP 100–109 mmHg) or severe (SBP≥160 mmHg/DPD ≥110 mmHg). Moderate pre-eclampsia is defined as mild–moderate hypertension with proteinuria, and severe pre-eclampsia as severe hypertension and/or severe proteinuria and/or pre-eclampsia with evidence of end-organ dysfunction.[13] A systematic review by Grandi et al.[14] using this traditional definition revealed the risk of cardiovascular morbidity increases by two-fold for moderate pre-eclampsia (odds ratio [OR] 2.24 [1.72–2.93]), and by more than 2.5-fold for severe pre-eclampsia (OR 2.74 [2.48–3.04]). A recent cohort study with >1 million participants reported a three-fold increased probability of developing vascular dementia following pre-eclampsia (hazard ratio [HR] 3.46 [95% CI 1.05–1.99]).[15] This association was stronger for late-onset vascular dementia (≥65 years old) compared to early-onset (<65 years old).[15]

Pre-eclampsia is associated with other chronic diseases, including an increased risk of chronic kidney disease (CKD). The endothelial dysfunction of pre-eclampsia causes an imbalance in proangiogenic and antiangiogenic factors. This results in an increase in soluble fms-like tyrosine kinase-1 (sFLT-1), an antiangiogenic protein which is one of the most recognized factors in the pathophysiology of pre-eclampsia.[16] sFLT-1 causes characteristic injuries to the kidney; both podocyte lesions and glomerular endotheliosis, which is a variant of thrombotic microangiopathy.[17] The renal injury usually reverses rapidly following delivery, but still confers an increased risk for end-stage renal disease and CKD both postnatally and in the longer-term.[17] The exact mechanism requires further study.[17] A systematic review and meta-analysis by Costa Ferriera et al.[17] in 2020 found that the probability of developing CKD is 75% higher following pre-eclampsia (HR 1.82 [95% CI: 1.27–2.62]), and probability of end-stage renal disease is three-fold higher (HR 3.01 [95% CI 1.92–4.70]).

Women who have a history of pre-eclampsia also have an increased risk of future venous thromboembolism (VTE).[18] A retrospective cohort study of more than 30 000 women found a two-fold increased probability of subsequent hospitalization with VTE up to 10 years post pregnancy following severe pre-eclampsia (adjusted hazard ratio [aHR] 2.3 [95% CI: 1.3–4.2]).[19] Pregnancy itself is a prothrombotic state, and pre-eclampsia increases this risk in the short-term via deranged platelet and endothelial function and impaired endogenous anticoagulation pathways.[20] Permanent injury to the endothelium and residual dysfunction may increase risk of VTE in the longer term, or there is a common underlying predisposition to pre-eclampsia and vasculopathy.[21]

There is a two-fold increased risk of future T2DM following pre-eclampsia (RR 2.37 [95% CI: 1.37–4.10]) according to a systematic review by Wu et al.[22] in 2016, which remains after adjusting for GDM and body mass index. The mechanism for this relation is as yet unclear. Pre-eclampsia and T2DM may be related via common risk factors only, but given the fact that pre-eclampsia is a risk factor for later CVD it may be an earlier expression of an adverse metabolic phenotype.[22] Table 1.

5 | GESTATIONAL HYPERTENSION

Gestational hypertension is defined by the International Society for the Study of Hypertension in Pregnancy as new onset hypertension (SBP>/=140 mmHg or DBP>/=90 mmHg) after 20 weeks' gestation without the features of pre-eclampsia.[9] It has yet to be proven whether it is part of the disease spectrum of pre-eclampsia, or a distinct entity. Essential hypertension has a complex multifactorial pathophysiology. These include genetics, environment, sex and ethnicity, vascular, renal, hormonal and sympathetic nervous system mechanisms, as well as contributions from obesity, insulin resistance and sleep apnea if these are present as comorbidities.[11] Gestational hypertension may be a contributing factor, or the physiological demands of pregnancy may simply reveal an underlying susceptibility.

A systematic review and meta-analysis by Grandi et al.[14] pooled the results of nine cohort studies to examine 3 204 633 women with a median follow-up length of 4.9–17.9 years. They found that gestational hypertension, when analyzed separately from pre-eclampsia, is associated with a 67% higher risk of cardiovascular morbidity, including coronary artery disease, myocardial infarction, coronary revascularization, peripheral arterial disease, transient ischemic attack, and stroke (pooled OR 1.67 [95% CI: 1.28–2.19]).[14] This increased to 87% higher risk following sensitivity analysis excluding studies with composite outcomes, and reduced between-study heterogeneity (OR 1.87; 95% ICI: 1.55–2.25; I2: 60.6% vs. 83.9%).[14] There was a 41% higher risk of cerebrovascular morbidity alone (pooled OR 1.41 [95% CI: 1.31–1.52]).[14] (Table 2).

6 | PLACENTAL ABRUPTION

Placental abruption occurs when the decidual arteries rupture and cause premature separation of the placenta.[23] Some of the underlying pathological processes decribed are associated with placental abruption, pre-eclampsia, fetal growth restriction and preterm

labor.[8] Placental inflammation is caused by abnormal vascular remodeling or failure of deep placentation, thrombosis and angiogenesis and may contribute to development of one or more of these pregnancy complications.[23]

Placental abruption is associated with an overall 82% higher risk of cardiovascular morbidity and mortality (OR 1.82 [95% ICI: 1.42–2.33]).[14] It confers a 1.5-fold higher risk of ischemic heart disease (HR = 1.6 [95% CI: 1.4–1.9]) congestive heart failure (HR = 1.7 [95% CI: 1.2–2.3]) and stroke (HR = 1.4 [95% CI: 1.1–1.9]).[23] Risk of acute myocardial infarction and hypertensive heart disease is two-fold higher (HR = 1.9 [95% CI: 1.4–2.4] and HR = 2.2 [95% CI: 1.1–4.5], respectively).[23] (Table 3).

7 | PRETERM BIRTH

Preterm delivery is defined as delivery of the infant prior to 37 completed weeks' gestation. The precise mechanism of spontaneous preterm delivery is often not established in individual cases. It is thought to be a syndrome caused by multiple factors including inflammation, uteroplacental ischemia or hemorrhage, uteroplacental infection, uterine over-distension, stress and other immune mediated processes.[24] Inflammation may be the process linking spontaneous preterm birth with later CVD, or abnormal placentation may be the trigger event.[24] Iatrogenic preterm delivery may be necessitated by uncontrolled pre-eclampsia or hypertension, fetal growth restriction or placental abruption, among other causes.

Delivery of a preterm infant, whether spontaneous or iatrogenic, is associated with a 1.5-fold higher risk of composite cardiovascular morbidity (OR 1.63 [95% ICI: 1.39–1.93]),[14] CHD (RR 1.49 [95% CI: 1.38–1.60])[25] and stroke (RR 1.65 [95% CI: 1.51–1.79]).[25,26] Iatrogenic preterm delivery has a stronger association with future all-cause mortality compared to spontaneous preterm delivery, but spontaneous preterm delivery remains an independent risk factor for future maternal cardiovascular disease when cardiovascular risk factors are controlled for.[27,28] There is also some evidence that spontaneous preterm birth increases the risk for future maternal CKD, but further studies are needed.[29] (Table 4).

8 | LOW BIRTHWEIGHT

A history of delivering a low-birthweight infant (birthweight <2500 g) may also increase risk of future maternal CVD. Meta-analysis of four studies examining low birthweight infant as a risk factor showed a trend towards increased risk of CVD, but this was not statistically significant.[14] Studies examining history of small-for-gestational age infants (birthweight <10th percentile for gestational age) were not pooled due to heterogeneity of exposure definition, but also showed a trend towards increased risk of later maternal CVD.[14] Infants may be small-for-gestational age or have low birthweight due to intrauterine growth restriction (IUGR) and placental insufficiency, but a significant number are constitutionally normal.[30] Equally, IUGR and small-for-gestational age may be caused by other pathological processes such as intrauterine infection, genetic disorder or congenital anomaly.[30] Further studies examining the effect of IUGR secondary to placental insufficiency would be required to examine this further, but given the association between CVD and other manifestations of abnormal placentation, a relation is possible.

A retrospective cohort study of 982 091 women found that delivery of a very-low-birthweight infant was associated with a 18% higher risk of future all-type cancer (HR 1.18 [95% CI: 1.02–1.37]).[31] Another recently published retrospective cohort study of >2 million women demonstrated significant increased mortality from cancer in women who had a preterm delivery, which supports this finding.[27] Cosibling analysis in the Crump et al. cohort study suggested that this is not attributable to genetic factors and early life environmental exposure.[27] Common inflammatory pathways, and also vitamin D deficiency have been identified as possible mechanisms, but further studies are needed.[27]

9 | GESTATIONAL DIABETES

Insulin sensitivity changes are part of the physiological adaptation to normal pregnancy. Insulin sensitivity increases in early gestation, promoting glucose uptake to store energy for the later stages of pregnancy.[32] As pregnancy progresses, increases in local and placental hormones cause a shift towards insulin resistance.[32] Blood glucose levels become slightly elevated to promote glucose transfer to the growing fetus.[32] Glucose homeostasis is maintained by hypertrophy and hyperplasia of the pancreatic B-cells, and increased glucose-stimulated insulin secretion.[32]

Approximately 80% of GDM cases are caused by beta-cell dysfunction on a background of chronic insulin resistance, compounded by the physiological insulin resistance of pregnancy.[32] This pathophysiology is similar to that of T2DM, and there has been some debate about whether they should be considered part of the same disease spectrum. The remainder of cases are attributed to evolving autoimmune diabetes and other causes.[32] GDM is associated with an almost 10-fold higher risk of developing T2DM (RR 9.51 [95% CI: 7.14–12.67]) compared to normoglycemic pregnancy.[33]

Diabetes of any cause is a risk factor for CVD. This is due to the effects of chronic hyperglycemia on the vasculature, chronic inflammation leading to thrombosis, and the frequent presence of obesity,

TABLE 2 Risk of noncommunicable disease following gestational hypertension.

Cardiovascular-related morbidity[a]	OR 1.67 (95% ICI: 1.28–2.19)[14]
Cerebrovascular morbidity	OR 1.83 (95% ICI: 0.79–4.22)[14]

Note: Statistics quoted as per reporting study.

Abbreviation: OR, odds ratio.

[a]Including coronary artery disease, myocardial infarction, coronary revascularization, peripheral arterial disease, transient ischemic attack, and stroke.

TABLE 3 Risk of noncommunicable disease following placental abruption.

Cardiovascular-related morbidity and mortality[a]	OR 1.82 (95% CI: 1.42–2.33)[14]
Ischemic heart disease	HR = 1.6 (95% CI: 1.4–1.9)[23]
Acute myocardial infarction	HR = 1.9 (95% CI: 1.4–2.4)[23]
Hypertensive heart disease	HR = 2.2 (95% CI: 1.1–4.5)[23]
Congestive heart failure	HR = 1.7 (95% CI: 1.2–2.3)[23]
Stroke (ischemic or hemorrhagic)	HR = 1.4 (95% CI: 1.1–1.9)[23]

Note: Statistics quoted as per reporting study.

Abbreviations: HR, hazard ratio; OR, odds ratio.

[a]Including coronary artery disease, myocardial infarction, coronary revascularization, peripheral arterial disease, transient ischemic attack, and stroke.

dyslipidemia and hypertension.[34] GDM confers a 85% higher risk of composite cardiovascular morbidity and mortality (OR 1.68 [95% ICI: 1.11–2.52]),[14] a two-fold higher risk of future cardiovascular events (RR 1.98 [95% CI: 1.57–2.50])[35] and a 59% higher risk of coronary artery disease (aRR 1.59 [1.30–1.94]).[36] There is also a significantly increased risk of stroke by 25% (OR 1.25 [95% CI: 1.07–1.48]).[36]

Black women with a history of GDM have an increased risk of developing CKD (aRR 1.78 [95% CI: 1.18–2.70]),[29] although it is not possible to say whether there is an independent relation between GDM and CKD based on the current literature.[29] Black women have a higher risk for CKD compared with white women, and a higher risk for progression to end-stage renal disease. It is possible that GDM may compound this risk, but the mechanism is poorly understood.[29]

A recent systematic review has shown a significant association between GDM and thyroid cancer (RR 1.28 [95% CI: 1.16–1.42]), stomach cancer (RR 1.43 [95% CI: 1.02–2.00]) and liver cancer (RR 1.27 [95% CI: 1.03–1.55]).[37] T2DM also confers a significantly increased risk of thyroid and stomach cancer, pointing to a common underlying mechanism.[37] Longer duration of follow up and larger study cohorts could potentially expose links to other cancers.[37]

Women with a history of GDM also have a 59% higher risk of postnatal depression based on a systematic review and meta-analysis by Azami et al.[38] in 2019 (RR 1.59 [95% CI: 1.22–2.07]). Suggested mechanisms that may link the conditions are chronic inflammation, disturbance of the hypothalamic–pituitary–adrenal axis, disordered serotonin regulation, and the stress of being diagnosed with chronic disease.[38] (Table 5).

TABLE 4 Risk of noncommunicable disease after preterm birth.

Cardiovascular-related morbidity[a]	OR 1.63 (95% CI: 1.39–1.93)[14]
Coronary heart disease	RR 1.49 (95% CI: 1.38–1.60)[25]
Stroke	RR 1.65 (95% CI: 1.51–1.79)[25,26]

Note: Statistics quoted as per reporting study.

Abbreviations: OR, odds ratio; RR, relative risk.

[a]Including coronary artery disease, myocardial infarction, coronary revascularization, peripheral arterial disease, transient ischemic attack, and stroke.

TABLE 5 Risk of noncommunicable disease following gestational diabetes.

Type 2 diabetes mellitus	RR 9.51 (95% CI: 7.14–12.67)[33]
Cardiovascular-related morbidity and mortality[a]	OR 1.68 (95% CI: 1.11–2.52)[14]
Cardiovascular events in first decade postpartum	RR 2.31 (95% CI: 1.57–3.39)[35]
Coronary artery disease	OR 1.59 (95% CI: 1.30–1.94)[36]
Stroke	OR 1.25 (95% CI: 1.07–1.48)[36]
Chronic kidney disease (black women)	aRR 1.78 (95% CI: 1.18–2.70)[29]
Thyroid, stomach and liver cancer	Thyroid RR 1.28 (95% CI: 1.16–1.42)[37] Stomach RR 1.43 (95% CI: 1.02–2.00)[37] Liver RR 1.27 (95% CI: 1.03–1.55)[37]
Postnatal depression	RR 1.59 (95% CI: 1.22–2.07)[38]

Note: Statistics quoted as per reporting study.

Abbreviations: aRR, adjusted relative risk; OR, odds ratio; RR, relative risk.

[a]Including coronary artery disease, myocardial infarction, coronary revascularization, peripheral arterial disease, transient ischemic attack, and stroke.

10 | STILLBIRTH

Stillbirth has a variety of etiologies, including post-term pregnancy, maternal infection and congenital anomalies, but noncommunicable conditions such as diabetes and hypertension, diseases of abnormal placentation and maternal age over 35 make up a significant proportion of causes.[39] A history of stillbirth is associated with a 50% increased odds of composite CVD (OR 1.49 [95% ICI: 1.08–2.06]),[14] a 20% increased probability of CHD (HR 1.18 [95% CI: 1.03–1.37])[40] and 25% increased probability of CKD (aHR 1.26 [95% CI: 1.09–1.45]).[29] It confers an almost two-fold higher probability of future dementia (HR 1.86 [95% CI: 1.28–2.71])[41] and a 2.5-fold probability of future VTE (HR 2.56 [95% CI: 1.09–6.05]).[42] Whether there is a variation in risk depending on the underlying cause has not been explored. The increased risk of later CVD following a stillbirth corresponds with the significant contribution of pre-eclampsia, intrauterine growth restriction, pre-existing hypertension and diabetes to stillbirth rates. Again, it is unclear whether this is due to

TABLE 6 Risk of noncommunicable disease following stillbirth.

Cardiovascular-related morbidity[a]	OR 1.49 (95% CI: 1.08–2.06)[14]
Coronary heart disease	HR 1.18 (95% CI: 1.03–1.37)[40]
Venous thromboembolism	HR 2.561 (95% CI: 1.085–6.046)[42]
Chronic kidney disease	aHR 1.26 (95% CI: 1.09–1.45)[29]
Depression	RR 2.14 (95% CI: 1.73–2.66)[44]
Anxiety	RR 1.75 (95% CI: 1.27–2.42)[44]
Dementia	HR 1.86 (95% CI: 1.28–2.71)[41]

Note: Statistics quoted as per reporting study.

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; OR, odds ratio; RR, relative risk.

[a]Including coronary artery disease, myocardial infarction, coronary revascularization, peripheral arterial disease, transient ischemic attack, and stroke.

TABLE 7 Risk of noncommunicable disease following first trimester miscarriage.

Coronary heart disease	OR 1.45 (95% CI: 1.18–1.78)[48]
Diabetes	aIRR 1.25 (95% CI: 1.15–1.36)[71]
Anxiety	OR 1.62 (95% CI: 1.25–2.11)[47]
Depression	OR 2.38 (95% CI: 1.65–3.42)[47]
Suicide	OR 3.80 (95% CI: 2.80–5.20)[47]
Post-traumatic stress disorder	OR 4.39 (95% CI: 0.18–105.50)[47]

Note: Statistics quoted as per reporting study.

Abbreviations: aIRR, adjusted incidence rate ratio; OR, odds ratio.

an underlying predisposition, common risk factors, primary injury caused by the placental disease process or a combination of factors.

Fetal or infant loss is a traumatic life event,[43] and as such stillbirth is also associated with a two-fold increased risk of anxiety or depression (RR = 1.75 [95% CI: 1.27–2.42] and RR = 2.14 [95% CI: 1.73–2.66] respectively).[44] On top of the impact of mental illness on the person's life, including chronic symptomatology, impact on interpersonal relationships, reduced work productivity and disability,[45] mental illness itself is an independent risk factor for CVD.[46] (Table 6).

11 | FIRST TRIMESTER MISCARRIAGE

First trimester pregnancy loss is a common event, with 10%–15% of clinical pregnancies ending this way.[47] Early pregnancy loss is associated with a 50% increased risk of CHD (OR 1.45 [95% CI: 1.18–1.78]).[48] Metabolic effects contributing to miscarriage is one possible link to future CVD. Decidualisation is adversely affected by metabolic disorders, and endocrine disorders such as hypothyroidism and polycystic ovarian syndrome.[47] However, there are many other factors that may contribute to or cause miscarriage, such as demographic risk factors such as maternal age, smoking, work shift patterns, alcohol intake and high stress state.[47] There is significant overlap with risk factors for CVD, so any association may be down to common risk factors. Furthermore, 60% of miscarriages show evidence of spontaneous genetic mutations,[47] and endometrial defects may also contribute to or cause miscarriage.

A single first trimester pregnancy loss is also associated with a 1.5-fold higher risk of anxiety (OR 1.62 [95% CI: 1.25–2.11]), a two-fold higher risk of depression (OR 2.38 [95% CI: 1.65–3.42]), a four-fold higher risk of post-traumatic stress disorder (PTSD) (OR 4.39 [95% CI: 0.18–105.50]) and three-fold higher risk of suicide (aOR 3.80 [95% CI: 2.80–5.20]).[47] Collated mean/median follow-up was not reported. (Table 7).

TABLE 8 Risk of noncommunicable disease following recurrent miscarriage.

Coronary heart disease	OR 1.99 (95% CI: 1.13–3.50)[48]
Diabetes mellitus	OR: 1.82 (95% CI: 1.15–2.88)[51] aHR 1.03 for each pregnancy loss[52]
Venous thromboembolism	OR 6.13 (95% CI: 2.48–15.16)[47]
Depression	OR 3.88 (95% CI: 1.87–8.03)[47]
Anxiety	OR 4.34 (95% CI: 2.08–9.03)[47]
Post-traumatic stress disorder	OR 4.89 (95% CI: 1.57–15.27)[47]

Note: Statistics quoted as per reporting study.

Abbreviations: aHR, adjusted hazard ratio; OR, odds ratio.

12 | RECURRENT MISCARRIAGE

There is a lack of consensus surrounding the exact definition of recurrent miscarriage, whether it should be two or three pregnancies, whether they are consecutive or not, and how to diagnose the pregnancy.[49] Causes include spontaneous and inherited chromosomal abnormalities, antiphospholipid syndrome and uterine structural abnormalities.[50] In over 50% of couples investigated, no abnormalities are found. It is thought that unexplained recurrent losses are caused by implantation failure, due to underlying immunological, inflammatory and hormonal processes.[49] If underlying inflammatory processes are involved this may tie in with risk of future cardiovascular and metabolic disease. Again, there may be a risk factor overlap with stress, maternal age and demographics, and risk of mental illness as discussed above.

Recurrent miscarriage (when defined as two or more miscarriages) confers a two-fold risk of CHD (OR 1.99 [95% CI: 1.13–3.50]).[48] A prospective cohort study of 13 612 women demonstrated an 82% higher risk of future diabetes (OR: 1.82 [95% CI: 1.15–2.88]) associated with recurrent miscarriage,[51] and secondary analysis of a prospective cohort study of 273 383 women found an increasing hazard ratio for diabetes with each pregnancy loss, irrespective of the number of live births.[52] The adjusted HR was 1.03 (95% CI: 1.00–1.05) for each additional pregnancy loss.[52] A history of three or more miscarriages is associated with a six-fold increased risk of future VTE (OR 6.13 [95% CI: 2.48–15.16]).[47] Two or more miscarriages is associated with a three-fold higher risk of depression (OR 3·88 [95% CI: 1·87–8·03]), anxiety (4·34 [95% CI: 2.08–9.03]) and an almost five-fold higher risk of PTSD (4.89 [95% CI: 1.57–15.27]).[47] (Table 8).

13 | DISCUSSION

There is a large body of evidence highlighting that adverse pregnancy outcomes are potential sentinel events for future chronic disease in women. Despite the increasing evidence, pregnancy complications are often forgotten when assessing risk factors for noncommunicable diseases.[4,6,7] Obstetrician-gynecologists and family medicine practitioners are best placed to advise otherwise healthy young women about long-term risk, relevant screening recommendations and potential mitigating strategies following an adverse pregnancy event or complication, but there is some variation in guidance surrounding optimal postnatal follow up timing and what the visit should entail. The National Institute for Health and Care Excellence (NICE) recommends women who experienced hypertension in pregnancy attend their general practitioner at 6–8 weeks postpartum.[53] NICE guidance states that they be counseled about their long-term risk of CVD and advised to avoid smoking, and maintain a healthy lifestyle and weight.[53] The International Federation of Gynecology and Obstetrics (FIGO) suggests following up mothers at risk for T2DM at the same time as their child's routine checks and vaccinations.[54] The American College of Obstetricians and Gynecologists recommends discussing the implications of any pregnancy complications on future maternal health, including atherosclerotic CVD, at the routine postnatal visit.[55] Breastfeeding is recommended, due to its positive effect on blood pressure, metabolic and lipid profile, reducing future maternal risk of developing T2DM and CVD.[56–58] Cardiovascular screening for all women with a history of adverse pregnancy outcomes within 3 months postpartum is advised.[59] Some hospitals have introduced specific postnatal clinics for women who have experienced pregnancy complications in order to commence screening and counsel women about risk reducing behaviors.[60–62]

Access to postnatal care is not equal across the globe. Rates of receipt of a routine postnatal check-up for mothers may be as low as 10% and as high as 90%, with a median of just over 60% across 48 countries.[63,64] Both socioeconomic and geographical factors contribute to this inequity.[64] If a positive impact is to be made on women's future morbidity and mortality from noncommunicable disease, access to postnatal follow up and primary care must be made convenient and available to as many women as possible. For women who live in less advantaged circumstances and communities, or in remote areas, other solutions including use of mobile device based telemedicine (M-health) and community based peer education have shown potential for risk reduction, although long-term studies with hard outcomes are needed to confirm their effectiveness.[65] Using more accessible methods of follow up for educating and supporting women in lifestyle changes for risk reduction postpartum may improve engagement.[65] A collaborative approach between maternity care and primary care providers would be optimal to ensure long-term follow up of higher risk women is maximized.

Lifestyle changes such as weight control, smoking cessation, healthy diet and adequate exercise will benefit women by reducing overall risk of noncommunicable disease, and also positively impact their mental health.[66,67] The American Heart Association's Prevention of CVD in Women Guideline recommends risk stratification and lifestyle interventions for all women, although screening intervals are not defined.[2] Tailored primary prevention pharmacotherapy is recommended for women at moderate or high risk of CVD.[2] Screening for T2DM is required for women with a history of GDM, although recommended intervals vary from opportunistically to three-yearly.[54,68] Lifestyle interventions and pharmacotherapy may reduce risk of progression to T2DM in women who developed GDM.[69] Focussing on higher risk women for follow up, such as those who suffered from gestational diabetes or pre-eclampsia, would be a method of directing funding to where it could have the most impact. For example, despite the significant link with future mental health disorders, the evidence behind routine counseling for women who have experienced miscarriage is equivocal, and further studies are needed to identify useful interventions for this cohort.[70]

Future studies should be directed towards establishing optimal timing, and type, of screening for noncommunicable disease following pregnancy complications, so that healthcare providers can ensure evidence-based postnatal and long-term follow up for this higher risk population. Studies examining pharmacotherapy for primary prevention of chronic disease in this specific cohort are also required. Funding should be directed towards evidenced-based postnatal follow-up, screening and interventions. Education of care providers and women about future risks following complicated pregnancy, and about opportunities for risk reduction is paramount.

14 | CONCLUSION

Experiencing an adverse pregnancy outcome increases a woman's risk of noncommunicable disease in later life. Optimal screening windows and methods need to be defined, and evidence-based prevention strategies developed for this population. This study is a resource for women and their physicians attempting to refine individual lifetime health risk following a pregnancy complication.

AUTHOR CONTRIBUTIONS

CMN – Designed and carried out the search, reviewed the data and wrote the paper. SLK – Critically revised the manuscript for intellectual content. RKC – Critically revised the manuscript for intellectual content. FMMA – Conceived the idea for the review and revised and approved the manuscript.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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