DOI: 10.1002/ijgo.12926

SUPPLEMENT ARTICLE

WILEY International Journal of Gynecology Obstetrics FIGO

FIGO (International Federation of Gynecology and Obstetrics) Postpregnancy Initiative: Long-term Maternal Implications of Pregnancy Complications—Follow-up Considerations

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Funding Information
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In addition to the authors, the following people provided important contributions during the creation of the document. Thanks go to the following international experts: the FIGO Pregnancy and Noncommunicable Disease (PNCD) Committee members: Moshe Hod, Hema Divakar, Mark Hanson, Anil Kapur, H. David McIntyre, Mary D'Alton, Anne B. Kihara, Ronald Ma, and Fionnuala McAuliffe. Special thanks for FIGO guidance and coordination go to President Carlos Fuchtner, Past-President CN Purandare, Past-Chair of the Safe Motherhood and Newborn Health (SMNH) Committee Gerard Visser, along with Jessica Morris and Rachel Gooden (FIGO Project Manager and Project Coordinator, respectively).

ACKNOWLEDGMENTS

Publication of this Supplement was funded by FIGO.

CONFLICTS OF INTEREST

Ravi Retnakaran's research program is supported by the Sun Life Financial Program to Prevent Diabetes in Women. All other authors have no conflicts of interest to declare.

CONTENTS

1 | EXECUTIVE SUMMARY

Pregnancy poses extreme—albeit normal and adaptive—transformations to maternal physiology. The expectant mother needs to swiftly adapt to her new status to provide appropriately for the developing fetus and its immediate postpartum requirements. All aspects of this challenge are a biological "stress test" for the mother's various organ systems, most predominantly the metabolic and cardiovascular systems. It is unclear whether common predisposing factors are implicated during pregnancy complications and postpartum morbidities, or whether the chronic morbidity is the consequence of gestational adverse events. Whatever the reason may be, pregnancy can and should be viewed as a window offering a glimpse of forthcoming adverse maternal health conditions. This may allow for heightened awareness, a priori prediction, early detection, and most importantly, an opportunity to implement appropriate preventive interventions. This Supplement reviews current data regarding the consequences for future maternal health following a complicated pregnancy, with possible implications for surveillance and interventions. The most predominant consequences are myriad noncommunicable diseases (NCDs) implicating mostly cardiovascular and metabolic health.

Data regarding the immediate pregnancy complications of gestational diabetes mellitus (GDM) are strong: (1) there is a clear and substantial risk of pregnancy complications associated with GDM; (2) these complications are reduced by detection and treatment of GDM; and (3) treatment of GDM is cost-effective in terms of reduction in pregnancy complications. An important clinical consideration in women with a history of GDM is the recognition and management of their future risk of cardiometabolic disease; most notably, women with previous GDM have a markedly elevated lifetime risk of developing future diabetes. In addition to type 2 diabetes, it should also be recognized that women who are diagnosed with GDM have elevated future risks of other major medical conditions, most importantly cardiovascular disease (CVD) with various metabolic syndrome components (obesity, hypertension, dyslipidemia), but also advanced liver disease, chronic kidney disease, ophthalmic morbidity, and even female malignancies.

Placentation is a highly complex vascular event, requiring multiple changes to allow appropriate blood flow to the baby via the evolving and rooted placenta. Defective placentation is a key insult in pre-eclampsia and is associated with other, and nearly all, the great obstetric syndromes: hypertensive disorders in pregnancy, fetal growth restriction, stillbirth or intrauterine fetal death, preterm birth, and recurrent pregnancy loss.

Hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) is a common problem, complicating almost 10% of pregnancies. Women with hypertensive disorders in pregnancy are at an increased risk of long-term morbidity, including cardiovascular disease and its subsets (hypertension, cerebrovascular accidents, coronary artery disease), type 2 diabetes, as well as renal and ophthalmic disease. Placental syndromes other than hypertensive disorders in pregnancy—fetal growth restriction, preterm birth, recurrent pregnancy loss, and placental abruption—are also associated with similar long-term maternal morbidity.

CVD is the leading cause of death for both men and women worldwide—even more so for women than for men. CVD accounts for 31.5% of all deaths, which is more than twice that caused by cancer.

Over the last decade, pregnancy has been acknowledged increasingly as an early life "stress test" for several NCDs in women, including CVD, type 2 diabetes, metabolic syndrome, and renal, ophthalmic, and cognitive morbidities. However, pregnancy outcome has hitherto been underused as a stratification tool for targeting women at increased risk for various NCDs. Such targeting of young women would enable intensified preventive strategies early in life, when interventions are likely to be most efficient, as well as providing optimal clinical follow-up to reduce the severity of the clinical disease.

We suggest that the following pregnancy-related risk factors should be acknowledged as predictors of long-term cardiovascular morbidity: hypertensive disorders in pregnancy and gestational diabetes mellitus. The following pregnancy-related risk factors should also be acknowledged as predictors of long-term cardiovascular morbidity: fetal growth restriction, preterm birth, recurrent pregnancy loss, and placental abruption.

Pre-eclampsia: long-term follow-up

We recommend that the following measures are implemented at 6–12 weeks after birth, and periodically thereafter, following a pregnancy complicated by hypertensive disorders:

- History and physical examination
- Blood pressure measurements
- Consider screening for other cardiovascular risk factors. We suggest that once acknowledged, risk-reducing measures are implemented, including lifestyle modifications (nutrition and physical activity, treating obesity and overweight, controlling hypertension, smoking cessation).

Gestational diabetes mellitus: long-term follow-up

We recommend that the following measures are implemented at 6–12 weeks after birth, and periodically thereafter, in a pregnancy complicated by gestational diabetes, regardless of the criteria used to diagnose GDM:

- History and physical examination
- Blood pressure measurements
- Screening for diabetes by either an oral glucose tolerance test (OGTT—the most recommended test), fasting glucose, or glycated hemoglobin (HbA1C, less suitable for the first months after birth). Postpartum screening using a 75 g OGTT is recommended over measurement of HbA1c for two reasons: first, in the early postpartum period, HbA1c might not accurately reflect glycemic exposure owing to the impact of either increased red blood cell turnover in pregnancy or blood loss at delivery (both of which will promote reticulocytosis and thereby lower HbA1c by virtue of less time for exposure to glycemia); second, the OGTT provides greater

sensitivity for detecting pre-diabetes, particularly impaired glucose tolerance.

Other "placental" complications—great obstetric syndromes (fetal growth restriction, stillbirth or intrauterine fetal death, preterm birth, placental abruption, and recurrent pregnancy loss: long-term follow-up

We suggest that the following measures are considered at 6–12 weeks after birth, and periodically thereafter, following other placental-associated pregnancy complications, including fetal growth restriction, preterm birth, recurrent pregnancy loss, intrauterine fetal death, and placental abruption:

- History and physical examination
- Blood pressure measurements
- Consider screening for other cardiovascular risk factors. We suggest that once acknowledged, risk-reducing measures are implemented, including lifestyle modifications (nutrition and physical activity, treating obesity and overweight, controlling hypertension, and smoking cessation).

2 | THE SIGNIFICANCE OF GESTATIONAL DIABETES MELLITUS AND PLACENTAL-ASSOCIATED PREGNANCY COMPLICATIONS FOR LONG-TERM MATERNAL HEALTH

2.1 | Introduction

Pregnancy poses extreme—albeit normal and adaptive—transformations to maternal physiology. The expectant mother needs to swiftly adapt to her new status to provide appropriately for the developing fetus and its immediate postpartum requirements. All aspects of this challenge are a biological "stress test" for the mother's various organ systems, most predominantly the metabolic and cardiovascular systems.

Presumably, maternal physiology returns to the prepregnancy state, starting immediately after birth and up to the end of the puerperium. However, growing evidence suggests that pregnancy complications are the seeds of maladaptive maternal physiology. Pregnancy comorbidities such as GDM and hypertensive disorders of pregnancy not only have an immediate impact on maternal and neonatal health, but also bear short- and long-term health consequences years and possibly decades after delivery, such as type 2 diabetes, CVD, and many other implications. In addition, and although not the scope of this Supplement, it also incurs long-term impacts on the well-being of the offspring and on maternal mental health, social conditions, quality of life, sexual satisfaction, and functioning/disability, among others.[1–4]

It is unclear whether and how much of the chronic morbidity is the direct consequence of the gestational adverse event, and what role is played by the common predisposing factors both during and after pregnancy. Whatever the reason may be, pregnancy can and should be viewed as a window offering a glimpse of forthcoming adverse maternal health conditions. This may allow for heightened awareness, a priori prediction, early detection, and most importantly, an opportunity to implement appropriate preventive interventions.

This Supplement reviews current data regarding the consequences for future maternal health following a complicated gestation, with possible implications for surveillance and interventions. The most predominant consequences are myriad NCDs, implicating mostly cardiovascular and metabolic health.

> FIGO acknowledges that various complications during pregnancy have implications for future maternal health, which may justify postpartum surveillance. **Level of evidence: Low (⊕⊕OO)**

2.2 | Target audience of the FIGO postpregnancy initiative

This Supplement is directed at multiple stakeholders with the intention of bringing attention to the important postpartum period, as a possible window of opportunity for prevention of NCDs and their long-term consequences for maternal health. The intended target audience includes:

- **Healthcare providers:** All those qualified to care for pregnant women, in particular those responsible for prenatal and postnatal follow-up (general practitioners/family physicians, midwives, community health workers, nurses, obstetricians, maternal–fetal medicine specialists, internists, pediatricians, nutritionists, pharmacists, etc.).
- **Healthcare delivery organizations and providers**: governments, federal and state legislators, healthcare management organizations, health insurance organizations, international development agencies, and nongovernmental organizations.
- **Professional organizations:** international, regional, and national professional organizations of obstetricians and gynecologists, internists, pediatricians, family practitioners, and worldwide national organizations dedicated to the care of pregnant women and children.

2.3 | Assessment of quality of evidence and grading of recommendations

In assessing the quality of evidence and grading of strength of the recommendations, this Supplement follows the terminology

TABLE 1 Interpretation of strong and conditional (weak) recommendations according to GRADE.[a]

Implications	1 = Strong recommendation phrased as "we recommend"	2 = Conditional (weak) recommendation phrased as "we suggest"
For patients	Nearly all patients in this situation would accept the recommended course of action. Formal decision aids are not needed to help patients make decisions consistent with their values and preferences	Most patients in this situation would accept the suggested course of action
For clinicians	According to the guidelines performance of the recommended action could be used as a quality criterion or performance indicator, unless the patient refuses	Decision aids may help patients make management decisions consistent with their values and preferences
For policy makers	The recommendation can be adapted as policy in most situations	Stakeholders need to discuss the suggestion

[a]Reprinted with permission of the American Thoracic Society. © 2019 American Thoracic Society. Schunemann HJ, Jaeschke R, Cook DJ, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med 2006;174:605–614. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

TABLE 2 Interpretation of quality of evidence levels according to GRADE.[a]

Level of evidence	Definition
High ⊕⊕⊕⊕	We are very confident that the true effect corresponds to that of the estimated effect
Moderate ⊕⊕⊕O	We are moderately confident in the estimated effect. The true effect is generally close to the estimated effect, but it may be slightly different
Low ⊕⊕OO	Our confidence in the estimated effect is limited. The true effect could be substantially different from the estimated effect
Very low ⊕OOO	We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect

[a]Adapted with permission from Balshem et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6. © 2011, with permission from Elsevier.

proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group.[5] We used consistent language and graphical descriptions for the strength and quality of the evidence and recommendations based on them. Strong recommendations are numbered as 1 and conditional (weak) recommendations are numbered as 2. For the quality of evidence, cross-filled circles are used: ⊕OOO denotes very low-quality evidence; ⊕⊕OO low quality; ⊕⊕⊕O moderate quality; and ⊕⊕⊕⊕ high quality of evidence (Tables 1 and 2).

Both caregivers and care recipients need to be involved in the decision-making process before adopting recommendations.

3 | HYPERGLYCEMIA IN PREGNANCY

3.1 | Insulin resistance, gestational diabetes mellitus, and metabolic syndrome

Hyperglycemia in pregnancy is a broad term that encompasses various forms of glucose dysregulation seen during pregnancy. It includes diabetes in pregnancy as well as GDM. Diabetes in pregnancy may be either pre-existing diabetes (type 1 or type 2) predating pregnancy, or overt diabetes first diagnosed during pregnancy. When hyperglycemia—first detected at routine testing anytime during the course of pregnancy in women with no previous history of known diabetes—meets the criteria for the diagnosis of diabetes in the nonpregnant state (fasting plasma glucose ≥7.0 mmol/L or 126 mg/dL and/or 2-hour 75 g OGTT value ≥11.0 mmol/L or 200 mg/dL or random plasma glucose ≥11.0 mmol/L or 200 mg/dL associated with signs and symptoms of diabetes), the condition is called diabetes in pregnancy. Hyperglycemia first detected in pregnancy during routine testing (often between 24 and 28 weeks) that does not meet the criteria for overt diabetes is called GDM. Various diagnostic criteria and glucose cut-off values have been proposed by various organizations and professional groups to diagnose GDM.

Globally, there is increasing evidence that metabolic events occurring in the earliest stages of human development influence the mother's and offspring's short- and long-term health. The two most obvious and prevalent influences—maternal overweight/obesity and maternal hyperglycemia/insulin resistance—are both core components of what is commonly termed metabolic syndrome outside of pregnancy. The other major components of metabolic syndrome across various competing definitions are hypertension and dyslipidemia. Obesity, insulin resistance, and diabetes are all major risk factors for pre-eclampsia and other pregnancy complications.[6] In the following section we explore their relationship to future postpartum maternal health.

Hyperglycemia in pregnancy currently affects around 16.8% of pregnancies worldwide, amounting to 21.4 million births per year, of which over 90% occur in low- and middle-income countries.[7] Recent predictions suggest that, by 2025, more than 21% of women globally will be obese.[7] Although there are wide variations across countries, the trends toward increasing obesity and hyperglycemia are uniform.[8,9] They pose major health challenges for the future, both in terms of immediate pregnancy complications (such as excess fetal growth, hypertensive disorders in pregnancy, preterm birth) and short- and long-term complications, as discussed in the following sections. Furthermore, in many countries, prediabetes is very common in young women, with estimates of around 14% in the USA even in adolescence,[10] and over 30% in the US population aged 20–49 years.[11] A similar trend of rising rates of overweight and obesity, and prediabetes and diabetes among young reproductive-aged women, is also emerging in low-resource countries. In the absence of systematic pre-pregnancy screening, these cases are largely unidentified,[12] and thus contribute to the high prevalence of GDM when systematic testing is undertaken in pregnancy.

Metabolic syndrome is clearly more common in women who have been diagnosed previously with GDM,[13] but lack of detailed prepregnancy documentation of key features, such as lipid profiles and waist circumference, in many studies makes it more difficult to clearly define whether a diagnosis of metabolic syndrome adds *additional* risk compared with the identification of its components in terms of immediate pregnancy complications.[14]

The physiologic increase in insulin resistance that occurs during pregnancy compounds pre-existing obesity-related insulin resistance, exacerbating mild maternal hyperglycemia and unmasking subclinical reduced beta-cell function. After the first trimester, pregnancy also produces changes in serum lipids some of which are like those seen in metabolic syndrome. Pregnancy is associated with higher levels of low-density cholesterol, free fatty acids, and triglycerides, as well as high-density cholesterol, which contrasts with the lower levels seen in metabolic syndrome.[15] These changes are variably reported as being more marked in pregnancies complicated by hyperglycemia.[15] Gestational weight gain may further compound maternal metabolic regulation, and failure to normalize weight in the postpartum period contributes to a "vicious cycle" of worsening metabolic syndrome risks in the longer term.

3.2 | Immediate and short-term consequences of gestational diabetes mellitus

Historical definitions of GDM referred to "any degree of hyperglycemia" first noted in pregnancy,[16] but more contemporary definitions clearly separate those women with hyperglycemia severe enough to be termed "diabetes" outside pregnancy. Because of their higher risk status and possible pre-existing diabetic microvascular disease,[17] these very high-risk women are best classified as having "overt diabetes"[18] or diabetes in pregnancy.[19] They require immediate medical attention as they are likely to experience higher rates of pregnancy complications, even when appropriate treatment is commenced early in pregnancy.[20] Therefore, in current terminology, the term GDM is reserved for those with lower measured glucose values, generally in the range considered "prediabetes" outside pregnancy.

Although there is still some dissent regarding the precise glucose levels recommended to define GDM, consensus currently favors the recommendations of the International Association of Diabetes in Pregnancy Study Groups (IADPSG),[18] which have been endorsed by the World Health Organization (WHO)[21] and the International Diabetes Federation (IDF).[22] These criteria are based on the risk of pregnancy complications, specifically excess fetal adiposity, large-for-gestational-age infants, and neonatal hyperinsulinemia, all of which are features of the fetal consequences of maternal hyperglycemia. The International Federation of Gynecology and Obstetrics (FIGO) has promoted the use of pragmatic guidelines for GDM diagnosis, adapted to the healthcare resources and epidemiology of hyperglycemia in individual countries or regions.[19] These recommendations are summarized in Table 3.

The range of pregnancy complications related to GDM has been demonstrated clearly in the Hyperglycemia and Adverse Pregnancy

TABLE 3 Options for the diagnosis of gestational diabetes mellitus based on resource settings (Source: Reproduced from Hod et al.[19]).

	Strategy			
Setting	**Who to test and when**	**Diagnosis test**	**Interpretation[a]**	**Grade**
Fully resourced settings	All women at booking/first trimester	Measure FPG, RBG, or HbA1C to detect diabetes in pregnancy		1I⊕⊕⊕O
	24–28 wk	If negative: perform 75 g 2-h OGTT		
Fully resourced settings serving ethic populations at high risk[b]	All women at booking/first trimester	Perform 75 g 2-h OGTT to detect diabetes in pregnancy		2I⊕OOO
	24–28 wk	If negative: perform 75 g 2-h OGTT		
Any setting (basic): particularly medium- to low-resource settings serving ethnic populations at risk	All women between 24 and 28 wk	Perform 75 g 2-h OGTT		1I⊕⊕⊕O
Alternative strategies as currently used in specified countries				
China: Medium- to low-resource settings serving populations at high risk	All women at booking/first trimester	Measure FPG to detect diabetes in pregnancy	>7.0 mmol/L or >126 mg/dL, FPG values between 5.6 and 6.9 mmol/L (100–125 mg/dL) consider as GDM[23]	2I⊕OOO
	24–28 wk	If negative: perform 75 g 2-h OGTT *Or*		1I⊕⊕⊕O
		To reduce the number of OGTTs measure FPG. Only in women with values between 4.5 mmol/L and 5.0 mmol/L (81–90 mg/dL) perform 75 g 2-h OGTT	Value >5.1 mmol/L or >92 mg/dL diagnostic of GDM	2I⊕OOO
Indian subcontinent: Medium- to low-resource settings serving rural/semiurban/urban ethnic populations at high risk	All women at booking/first trimester	Measure fasting or nonfasting 2-h value after 75 g OGTT	Reading between 7.8 and 11.0 mmol/L or 140 and 199 mg/dL indicates GDM[24,25,c]	2I⊕OOO
	24–28 wk	If negative: repeat test		
Latin America: Medium- to low-resource settings	All women at booking/first trimester	Measure FPG to detect diabetes in pregnancy	>7.0 mmol/L or >126 mg/dL. FPG values between 5.6 and 6.9 mmol/L (100–125 mg/dL) consider as GDM	2I⊕OOO
	24–28 wk	If negative: perform 75 g 2-h OGTT	75 g 2-h glucose value >7.8 mmol/L or >140 mg/dL is diagnostic of GDM[d]	
UK: all settings	Selected women at booking/as soon as possible[e]	Perform 75 g 2-h OGTT	FPG of 5.6 mmol/L or above, or 2-h plasma glucose of 7.8 mmol/L or above is diagnostic[g]	
	24–28 wk	If negative: perform 75 g 2-h OGTT		

(Continues)

TABLE 3 (Continued)

Setting	Strategy			Grade
	Who to test and when	Diagnosis test	Interpretation[a]	
	Offered also to other women with risk factors for GDM[f]			

Abbreviations: FPG, fasting plasma glucose; RBG, random blood glucose; HbA1C, glycosylated hemoglobin; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

[a]Interpret as per IADPSG/WHO/IDF guidelines unless stated otherwise.

[b]Asian women are at high risk of hyperglycemia during pregnancy, which may include previously undiagnosed diabetes. The proportion of previously undiagnosed diabetes is highest in the youngest age group particularly among women.[26] In Asian populations, FPG and HbA1c have much lower sensitivity to diagnose diabetes than the 2-h post-glucose value.[27] In a study of 11 Asian cohorts, more than half of the diabetic subjects had isolated postchallenge hyperglycemia.[28] In a study in China, 46.6% of the participants with undiagnosed diabetes (44.1% of the men and 50.2% of the women) had isolated increased 2-h plasma glucose levels after an OGTT.[29] Therefore, the need to identify postprandial hyperglycemia seems especially relevant in Asian populations.

[c]Diabetes in Pregnancy Study Group in India (DIPSI) Guideline.[18]

[d]Latin America Study Group.[30]

[e]Women with a history of GDM or women with glycosuria of 2 + or above on one occasion or of 1 + or above on two or more occasions (as detected by reagent strip testing during routine prenatal care in the current pregnancy).

[f]BMI above 30 (calculated as weight in kilograms divided by height in meters squared), previous macrosomic baby weighing 4.5 kg or above, family history of diabetes, first-degree relative with diabetes, minority ethnic family origin with a high prevalence of diabetes.

[g]National Institute for Health and Care Excellence (NICE).[31]

Outcome Study (HAPO).[32] Using IADPSG diagnostic criteria, the HAPO study clearly documented higher rates of a wide range of pregnancy complications in untreated women diagnosed post hoc with GDM.[20] The risks related to excess fetal size are doubled with a GDM diagnosis, as is the risk of pre-eclampsia. The risks of preterm delivery, primary cesarean delivery, and shoulder dystocia are increased by 40%[33] (Table 4).

In addition to the clear epidemiologic data from HAPO and other studies, two landmark randomized controlled trials from groups led by Crowther in Australia[34] and Landon in the USA[35] demonstrated that treatment of GDM reduces the frequency of excessive fetal growth and pre-eclampsia. These conclusions have been supported by systematic reviews.[36,37] Treatment of GDM has also been shown to be cost-effective based on analyses derived from these randomized trials.[38,39]

In summary, data regarding the immediate pregnancy complications of GDM are strong: (1) there is a clear and substantial risk of pregnancy complications associated with GDM; (2) these complications are reduced by detection and treatment of GDM; and (3) treatment of GDM is cost-effective in terms of reduction in pregnancy complications.

3.3 | Long-term consequences of gestational diabetes mellitus

An important clinical consideration for women with a history of GDM is the recognition and management of their future risk of cardiometabolic disease; most notably, women with previous GDM have a markedly elevated lifetime risk of developing future diabetes.

3.3.1 | Type 2 diabetes

There is a seven-fold higher incidence of type 2 diabetes in the first decade after a pregnancy complicated with GDM compared with non-GDM peers. This relationship between GDM and subsequent type 2 diabetes is a reflection of the shared pathophysiology of these two conditions.[40] Specifically, GDM arises in women in whom pancreatic beta cells are unable to sufficiently increase insulin secretion to fully compensate for the physiologic insulin resistance that characterizes the latter half of pregnancy.[41] Accordingly, the insulin resistance of late pregnancy can be seen as providing a stress test for the beta cells—one that identifies women who develop GDM to have an underlying defect in beta-cell compensation.[42]

The chronic nature of this beta-cell defect in women who develop GDM is also the pathophysiologic basis for their future risk of type 2 diabetes. Indeed, women with previous GDM have both chronic insulin resistance and beta-cell dysfunction that is readily apparent in the years after the pregnancy.[43–45] The secretory demands placed on the beta cells by chronic insulin resistance contribute to the worsening of beta-cell function over time, a deterioration that is apparent within the first year after birth, which continues in the years thereafter in the absence of preventive lifestyle measures.[43–45] Ultimately, this worsening of beta-cell function leads to rising blood glucose levels over time, resulting first in prediabetes before subsequent progression to type 2 diabetes. Accordingly, in the clinical management of women with previous GDM, postpartum screening for abnormal glucose tolerance is warranted for early detection of the clinical manifestation of their underlying risk of type 2 diabetes.

3.3.1.1 | Diabetes impacts women more severely

Although diabetes affects men and women equally, women are more severely impacted by its consequences. Premenopausal women with diabetes lose the protection against heart disease that nondiabetic women have[46] and are 50% more likely to die from heart disease than men.[47–50] A study showed that 36.9% of women with diabetes who had a heart attack died within a year, compared with 20.2% women without

TABLE 4 Immediate pregnancy outcomes from the HAPO study, comparing women classified post hoc as having gestational diabetes mellitus by IADPSG criteria versus women not identified or treated during the index pregnancy.

Perinatal outcome	IADPSG GDM, %	Non-GDM, %
Pre-eclampsia[a]	9.1	4.5
Preterm delivery (<37 wk)[a]	9.4	6.4
Primary cesarean delivery[a]	24.4	16.8
Shoulder dystocia/birth injury[b]	1.8	1.3
Birthweight >90th percentile[a]	16.2	8.3
Newborn % body fat >90th percentile[a]	16.6	8.5
Cord c peptide >90th percentile[a]	17.5	6.7
Clinical neonatal hypoglycemia[a]	2.7	1.9
Admission to newborn intensive care[b]	9.1	7.8

Abbreviations: HAPO, Hyperglycemia and Adverse Pregnancy Outcome Study; GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes in Pregnancy Study Groups.
[a]$P<0.001$ comparing IADPSG-GDM and non-GDM women.
[b]$P<0.01$ comparing IADPSG-GDM and non-GDM women.

diabetes.[51] Compared with men, women are also at a greater risk of blindness due to diabetic retinopathy.[52] Pregnancy may worsen pre-existing diabetic retinopathy and lead to significant visual impairment. Pregnancy may also worsen pre-existing kidney disease. Elderly women with type 2 diabetes and end-stage renal disease have a significantly higher risk of death than men with similar problems.[53] Women with diabetes are four times more likely to suffer a stroke than women without diabetes.[54] While the higher burden of cardiovascular and other complications in women with diabetes may be due to biological reasons, it is also true that in all countries, including high-income economies, women tend to receive less intensive care and treatment for diabetes compared with men.[55] Gender not only influences vulnerability to disease but also affects access to health services and health-seeking behavior among women, which may amplify both the short- and long-term adverse impact of diabetes.

3.3.2 | Other major medical conditions

In addition to type 2 diabetes, it should also be recognized that women who are diagnosed with GDM have elevated risks of other major medical conditions, including advanced liver disease,[56] chronic kidney disease,[57,58] ophthalmic morbidity in general and retinopathy in particular,[59] female malignancies[60] and, most importantly, CVD.[61,62] Of note, the risks of serious liver disease, end-stage kidney disease, and severe ophthalmologic outcomes appear to be dependent on the intercurrent development of type 2 diabetes in this patient population.[56,57] Accordingly, ongoing surveillance for type 2 diabetes can serve to identify those at risk for these serious outcomes. In contrast, the cardiovascular risk of women with a history of GDM is not dependent upon the development of type 2 diabetes.[57,61] Indeed, a recent meta-analysis[61] involving over 5 million women showed that women with previous GDM have a two-fold higher risk of developing CVD compared with their peers. Importantly, this increased risk was evident in women with GDM who did not develop type 2 diabetes and emerged within the first decade after birth. Moreover, the relationship between glycemia in pregnancy and future risk of CVD extends into the non-GDM range. Indeed, even among women who do not have GDM, those with higher glucose levels on the glucose challenge test (commonly administered for prepartum screening) have an elevated risk of CVD compared with their peers.[63] Thus, prepartum glucose screening provides the opportunity to identify a woman's risk of CVD at an early point in the natural history of vascular disease.[63]

While the precise pathophysiologic basis of this CVD risk remains uncertain, the cardiovascular risk factor profile of women with recent GDM may provide a relevant clue. Notably, compared with their peers, women with a history of GDM have an enhanced cardiovascular risk factor profile that becomes apparent as early as 3 months after birth, including higher rates of dyslipidemia, hypertension, and metabolic syndrome.[64,65] Thus, cardiovascular risk factor screening may be prudent in women with a history of GDM. In addition, there is a growing body of evidence indicating that pregravid cardiovascular factors can predict subsequent GDM.[66,67] Taken together, these data support the emerging concept that women who develop GDM may have a chronically enhanced cardiovascular risk factor profile that contributes to their lifetime risk of developing CVD.[68,69] Accordingly, the diagnosis of GDM identifies a population of women in whom ongoing surveillance and screening of both glucose tolerance and cardiovascular risk factors warrant consideration in practice.

Women with gestational diabetes are at an increased risk for long-term morbidity, including type 2 diabetes and cardiovascular disease with various metabolic syndrome components (obesity, hypertension, dyslipidemia). **Level of evidence: Moderate (⊕⊕⊕O)**

Women with gestational diabetes are at an increased risk for long-term morbidity, including liver, kidney, and ophthalmic disease. **Level of evidence: Low (⊕⊕OO)**

4 | PLACENTAL SYNDROMES

4.1 | Hypertensive disorders in pregnancy, pre-eclampsia, and other placental syndromes

Placentation is a highly complex vascular event that requires multiple changes to allow appropriate blood flow to the placenta and fetus. Defective placentation is a key insult in early-onset pre-eclampsia[70] and is associated with other, and nearly all, great obstetric syndromes: hypertensive disorders in pregnancy (HDP), fetal growth restriction, stillbirth or intrauterine fetal death, preterm birth, and recurrent pregnancy loss.[71] All these syndromes are associated with increased morbidity in future maternal life: chronic hypertension, cardio- and cerebrovascular disease, and all-cause mortality. These future risks can be attributed to underlying common factors, or alternatively to the hypothesis that pregnancy acts as a vascular trigger for CVD, similar to the metabolic stress test for the future development of diabetes among women with GDM. Placental syndromes, specifically HDP, induces physiologic and metabolic changes associated with CVD, such as endothelial dysfunction,[72] insulin resistance,[73] inflammatory activation, and dyslipidemia,[74] all of which may sustain in the postpartum period and eventually cause long-term morbidity, most commonly CVD.

4.2 | Immediate, short-term, and long-term consequences of hypertensive disorders in pregnancy

Hypertension (i.e. systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) is a common problem, complicating nearly 10% of pregnancies.[75] The spectrum of HDP is categorized as follows: chronic hypertension (elevated blood pressure before 20 weeks of pregnancy or persisting beyond 12 weeks after birth); gestational hypertension (new-onset hypertension at or beyond 20 weeks of pregnancy); pre-eclampsia (gestational hypertension coupled with proteinuria and/or end-organ dysfunction); superimposed pre-eclampsia with chronic hypertension.[76,77]

The immediate maternal outcome of HDP is usually benign as complete resolution normally occurs in the postpartum period, with potential maternal symptoms disappearing quickly (e.g. headache) and others possibly taking weeks or months to resolve (e.g. proteinuria). Hypertension may worsen during the first or second postpartum weeks but normalizes in most women within 4 weeks of birth.[78] Nevertheless, progression to severe disease and eclampsia may present after delivery, with approximately 11%–44% of eclampsia events occurring in the postpartum period.[79] Although most cases of postpartum eclampsia occur within the first 48 hours, some cases can develop beyond 48 hours and have been reported as late as 23 days after birth.[80]

4.2.1 | Cardiovascular disease

Even after the resolution of symptoms, an elevated risk for future cerebrovascular and cardiovascular morbidity has been consistently and repeatedly suggested and documented in multiple studies with various designs, comparing women with and without a history of HDP, most predominantly pre-eclampsia.[81] Predicting CVD in women is difficult but important, since CVD is a significant and increasing cause of death in females. Globally, one in three women dies from CVD.[81]

The short-term outcomes (up to 10 years following pregnancy) were studied in several cohorts. In a retrospective study of more than 300 000 women, Cain et al.[82] found that the risk of vascular-related morbidity (CVD, ischemic heart disease, peripheral arterial disease, or congestive heart failure) among women with prior pre-eclampsia was 42% higher, even after adjusting for pre-existing cardiovascular risk factors and behavioral and sociodemographic factors. The risk of a vascular disease was also 18% higher for women with gestational hypertension alone, but its significance was attenuated after adjustment. In a longitudinal follow-up study in which 300 women with a history of HDP and 94 women with normotensive pregnancies were followed for 2.5 years, Hermes et al.[83] demonstrated that women with a history of HDP had a significantly higher extrapolated 10- and 30-year cardiovascular event risk compared with normotensive women. Furthermore, women with prior HDP have been found to have a roughly 2.4-fold greater adjusted odds of hospitalization due to cardiovascular causes within 3 years of delivery compared with normotensive women.[84]

The long-term outcomes have been assessed in several large-scale reviews and meta-analyses, which demonstrated an association between prior HDP and future CVD (Table 5).

In a meta-analysis[85] of 25 studies and more than 3 million women, higher risk was documented for hypertension (relative risk [RR] 3.70; 95% confidence interval [CI], 2.70–5.05), ischemic heart disease (RR 2.16; 95% CI, 1.86–2.52), stroke (RR 1.81; 95% CI, 1.45–2.27), and venous thromboembolism (RR 1.79; 95% CI, 1.37–2.33), as well as for overall mortality (RR 1.49; 95% CI, 1.05–2.14).

Another meta-analysis of case-control and cohort studies[87] 1 year later found a higher odds ratio (OR) for cardiac disease (OR 2.47; 95% CI, 1.22–5.01) in the case-control studies, and higher risk in the cohort studies, not only for future cardiac morbidity (RR 2.33; 95% CI, 1.95–2.78), but also for cerebrovascular morbidity (RR 2.03; 95% CI, 1.54–2.67) and cardiovascular mortality (RR 2.29; 95% CI, 1.73–3.04). An even larger meta-analysis[86] of 43 studies similarly concluded that previous pre-eclampsia is associated with three-fold increased odds of chronic hypertension and a two-fold increase in CVD and cerebrovascular disease. Most recently, in 2017, Wu et al.[88] meta-analyzed more than 6.4 million women, including 258 000 with pre-eclampsia, adjusting for age, body mass index (BMI), and diabetes. They demonstrated that pre-eclampsia was independently associated with future heart failure (RR 4.19; 95% CI, 2.09–8.38), coronary heart disease (RR 2.50; 95% CI, 1.43–4.37), CVD mortality (RR 2.21; 95% CI, 1.83–2.66), and cerebrovascular morbidity (RR 1.81; 95% CI, 1.29–2.55).

The strength of these data has already led major health organizations to consider HDP as a major risk factor for CVD,[89] with specific follow-up recommendations.[90]

4.2.2 | Chronic hypertension

An elevated risk of subsequent hypertension within 1–10 years following a pregnancy complicated by HDP was also demonstrated in various studies.

Black et al.[91] studied approximately 6000 normotensive women who developed HDP and reported more than twice the risk for pre-hypertension or hypertension in the year after delivery compared with those without HDP. A report by Behrens et al.[92] found a 12–25-fold higher rate of hypertension 1 year after birth among women with HDP compared with normotensive parturients. Hermes et al.[93] found that 42% of women with a history of pre-eclampsia and 39% of women with gestational hypertension developed hypertension within 2.5 years following birth. Egeland et al.,[94] in a population-based Norwegian cohort, showed that pre-eclampsia and gestational hypertension were associated with a six- and seven-fold increase in the risk of hypertension, respectively, within a 10-year period after birth.

4.2.3 | Type 2 diabetes

Other than the higher magnitudes of vascular complications in women with prior HDP, studies have also found these conditions to be a risk factor for future type 2 diabetes. HDP increased the risk of future type 2 diabetes by 3.4-fold (for gestational hypertension) and 4.1-fold (for pre-eclampsia with severe features),[95] even after adjustments for age, primigravity, and GDM at a mean follow-up of 8.2 years.[96] More recently, Feig et al.[97] reported that women with pre-eclampsia were at an elevated risk for type 2 diabetes, even after controlling for pregnancy complications such as GDM, with 3.5% of the women in the study cohort developing type 2 diabetes at 8.5 years. Furthermore, approximately 25% of the women in the study with GDM and HDP had developed type 2 diabetes within 5 years following pregnancy compared with 19% of the women with only GDM.

4.2.4 | End-stage renal disease

HDP also confers a small additive risk for future end-stage renal disease (ESRD). Primiparous women with a pre-eclamptic delivery ran a four-fold risk of ESRD compared with women without pre-eclampsia, although the accumulated 20-year risk was less than 1%.[98] The risk for ESRD increased with HDP severity: 0.1% at baseline rising to 0.2% and 0.5% for mild or severe pre-eclampsia, and 1.1% following a pregnancy complicated with eclampsia.[99] As for other long-term complications, ESRD may represent the result of a subclinical renal pathology acting during pregnancy and thereafter, or it is possible that pre-eclampsia and ESRD share common risk factors predisposing these women to both conditions.

4.2.5 | Ophthalmic disease

Microangiopathic retinal lesions occurring during pre-eclampsia may represent a predisposition for future ophthalmic complications, such as diabetic retinopathy and retinal detachment.

Beharier et al.[100] found that a history of pre-eclampsia was independently associated with higher rates of ophthalmic morbidity; the risk was associated with HDP severity: 0.2%, 0.3%, 0.5%, and 2.2% for women without pre-eclampsia, mild pre-eclampsia, pre-eclampsia with severe features, and eclampsia, respectively.[100]

Women with hypertensive disorders in pregnancy are at an increased risk for long-term morbidity, including cardiovascular disease and its subsets (hypertension, cerebrovascular accidents, coronary artery disease), type 2 diabetes, and renal and ophthalmic disease. **Level of evidence: Moderate (⊕⊕⊕O)**

4.3 | Risk stratification for the long-term consequences of hypertensive disorders in pregnancy

Risks of CVD, cerebrovascular morbidity, hypertension, type 2 diabetes, and mortality are related to specific HDP parameters, which allows risk stratification in accordance with particularly poor prognostic features, such as gestational age at onset (preterm pre-eclampsia prior to 34 weeks of gestation), specific HDP spectrum and severity (normotensive, gestational hypertension, pre-eclampsia with or without severe features and eclampsia), as well as the number of disease recurrences.

4.3.1 | Gestational age at onset of hypertensive disorders in pregnancy

Importantly, early-onset pre-eclampsia is associated with poor placentation and fetal growth restriction, leading to a greater risk for short- and long-term adverse maternal outcomes. A large population-based study by Irgens et al.[101] demonstrated that a first delivery complicated by preterm pre-eclampsia indicates a much higher risk of CVD mortality than after term pre-eclampsia. Pre-eclampsia was associated with a 1.2-fold long-term risk of death compared with those without pre-eclampsia, increasing to 2.7 and 8.1 in women with preterm pre-eclampsia versus those without pre-eclampsia, for all-cause and CVD-related mortality, respectively.[101] Similar studies report even higher odds of 3.7–9.5 for CVD mortality following preterm pre-eclampsia and 1.6–2.1 following term pre-eclampsia versus normotensive controls.[102,103] In line with these epidemiological findings, Melchiorre at al.[104] demonstrated that women with preterm pre-eclampsia were at significantly greater risk of having poor cardiovascular profiles and hypertension 1–2 years after delivery compared with women with term pre-eclampsia. Veerbeek et al.[105] found that common cardiovascular risk factors, such as fasting blood glucose, insulin, triglycerides, and total cholesterol, were significantly higher among women with early-onset pre-eclampsia than in women with late-onset pre-eclampsia and gestational hypertension.

4.3.2 | Spectrum and severity of hypertensive disorders in pregnancy

Other than gestational age at onset, the nature of the hypertensive disorder also affects the severity of the risk. Women with gestational hypertension presented with higher CVD risk factors and significantly higher blood pressure than women with a history of pre-eclampsia 2–5 years after pregnancy.[105] Andersgaard et al.[106] demonstrated that women with gestational hypertension were at greater risk of developing hypertension than women with pre-eclampsia. The risk of subsequent hypertension increases 5.3-fold after gestational hypertension and 3.6–6.1-fold after pre-eclampsia, without or with severe features, respectively.[95]

Kessous et al.[99] also demonstrated a significant dose–response relationship between severity of pre-eclampsia and long-term risk of CVD: linearly from no pre-eclampsia (2.75%), mild pre-eclampsia (4.5%), pre-eclampsia with severe features (5.2%), and eclampsia (5.7%).

This also holds true for other rare long-term complications other than CVD, such as ESRD[99] and ophthalmic disease.[100]

4.3.3 | Recurrent hypertensive disorders in pregnancy

Women with two pregnancies complicated by pre-eclampsia had a six-fold increased risk of subsequent hypertension compared with women with pre-eclampsia only in their first pregnancy and women with pre-eclampsia only in their second pregnancy.[95] As for disease severity, several studies report a significant linear association between the number of previous pregnancies with pre-eclampsia and the risk for future CVD.[99]

4.4 | Long-term consequences of other placental syndromes

As previously discussed, pregnancy has been suggested as a window of opportunity to predict CVD-related mortality and morbidity, mainly in the setting following a pregnancy complicated by HDP. Other than a response to hypertension, a woman's response under gestational demands—be it a physiological or pathological response—could unmask the underlying elevated risk of microvascular disease leading to the development of several placenta-related complications. Besides early-onset pre-eclampsia, other pregnancy complications that result from impaired placentation have also been associated with an increased risk of future maternal morbidity and mortality and, therefore, these complications—fetal growth restriction, preterm birth, recurrent pregnancy loss, intrauterine fetal death, and placental abruption—have been proposed as potential predictors.

4.4.1 | Fetal growth restriction

One of the first studies reporting an association between the birthweight of the offspring and subsequent maternal morbidity was published in 1997. Davey Smith et al.[107] reported in their cohort of 794 married couples that maternal mortality, from all causes and CVD, was inversely related to the offspring's birthweight. Although the analysis was adjusted for age, diastolic blood pressure, cholesterol level, BMI, height, social class, smoking, angina, and electrocardiographic evidence of ischemia, a major limitation of the study was that it did not account for relevant pregnancy comorbidities, such as pre-eclampsia and preterm birth. Although the causal pathway is not clear, considerable evidence on the association between birthweight and maternal CVD has been accumulated.[108–111]

Maternal CVD risk is highest with smaller babies and this risk declines by 25% with each standard deviation increase (approximately 500 g) in the birthweight of the first child.[112] Other than mortality, studies have also reported an increased risk of CVD-related morbidities in women who have delivered a small-for-gestational-age neonate. Coronary heart disease, cerebrovascular events, heart failure, hypertensive renal disease, chronic renal failure, and need for renal transplantation are more prevalent in these women.[113–116] It is probable that the association between neonatal birthweight and maternal cardiovascular risk reflects both environmental and genetic influences.

4.4.2 | Preterm birth

One-third of preterm deliveries are medically indicated, often as a result of placental syndromes. In the remaining two-thirds, the onset of labor is spontaneous and impaired placentation has also been implicated as the underlying pathophysiology. A growing body of evidence, synthesized in systematic reviews, has demonstrated that women who deliver preterm, spontaneously or medically-indicated, are at a greater risk of developing CVD.[117–123]

A review of 10 studies assessing the association between pre-term birth and subsequent CVD morbidity or mortality demonstrated that women with a history of pre-term birth had a higher risk of ischemic heart disease (adjusted hazard ratio [aHR] 1.3–2.1), atherosclerosis (aHR 4.1), and stroke (aHR 1.7). The risk of cardiovascular morbidity and mortality (variously defined) was higher among women with two or more affected pregnancies, compared with women who had at least two births but only one episode of preterm delivery.[118] A subsequent review also reported that spontaneous preterm birth was an independent risk factor for ischemic heart disease, stroke, and overall CVD.[122]

The latest systematic review and meta-analysis of 21 studies including over 5.8 million women (out of whom more than 338 000 women had a history of preterm birth) demonstrated that preterm birth was associated with an increased adjusted risk of future CVD (RR 1.43; 95% CI, 1.18–1.72), CVD mortality (RR 1.78; 95% CI, 1.42–2.21), coronary heart disease (RR 1.49; 95% CI, 1.38–1.60), coronary heart disease mortality (RR 2.10; 95% CI, 1.87–2.36), and stroke (RR 1.65; 95% CI, 1.51–1.79).[123] Most importantly, the highest risk occurred when preterm birth occurred before 32 weeks of pregnancy or was medically indicated.

Interestingly, in a recent population-based cohort study of 711 726 singleton births in Norway from 1967–2002, a strong

link between maternal CVD mortality, neonatal birthweight, and preterm birth was observed. Adjusting birthweight for gestational age uncovered an unexpected strong association between large birthweight (z-score >2.5) and maternal CVD mortality (HR 3.0; 95% CI, 2.0–4.6) and this risk was apparently restricted to preterm births. In stratified analyses, the hazard ratio for maternal cardiovascular mortality was 1.5 (95% CI, 1.03–2.20) for large preterm babies and 0.9 (95% CI, 0.7–1.2) for large term babies (interaction $P = 0.02$), using normal weight preterm and term, respectively, as references.[124] This study has confirmed the strong association between preterm delivery and maternal cardiovascular mortality and that this effect is not mediated only through small babies but is also important for larger preterm babies.

4.4.3 | Recurrent pregnancy loss and intrauterine fetal death

Stillbirth is closely related to other placental complications such as pre-eclampsia, fetal growth restriction, and placental abruption.[125]

A prospective, population-based, cohort study reported a dose–dependent effect from a history of spontaneous abortion on the age-adjusted risk of myocardial infarction. The risk increased by 40% with each spontaneous abortion (aHR 1.42; 95% CI, 1.14–1.78) and recurrent spontaneous abortions (>3) were associated with an approximately nine-fold (aHR 8.90; 95% CI, 3.18–24.90) increased risk of myocardial infarction.[126] In a more recent study of 93 676 postmenopausal women, using an age-adjusted Cox proportional hazards analysis, the risk of coronary heart disease was shown to be greater in women with a single spontaneous abortion (HR 1.13; 95% CI, 1.05–1.22), 2–4 spontaneous abortions (HR 1.28; 95% CI, 1.16–1.41), and more than five spontaneous abortions (HR 1.55; 95% CI, 1.15–2.09) compared with women without a history of spontaneous abortion.[127]

Similarly, the risk of myocardial infarction was more than 3.4-times higher (95% CI, 1.53–7.72) in women with a history of stillbirth, after adjusting for smoking, alcohol consumption, BMI, waist-to-hip ratio, physical activity, education, number of pregnancies, hypertension, hyperlipidemia, and diabetes mellitus.[126] Women with a history of one stillbirth had an increased risk of coronary heart disease with the age-adjusted Cox proportional hazard of 1.24 (95% CI, 1.07–1.44).[127] Pariente et al.[128] demonstrated that after stillbirth, women had a significantly higher cumulative incidence of cardiovascular and renal morbidity with a significant stepwise increase between the number of stillbirths and future risk for CVD.

4.4.4 | Placental abruption

Placental abruption is an uncommon but potentially serious pregnancy complication involving premature detachment of the placental lining from the uterus before delivery. Placental abruption is a strong indicator of placental microvascular disturbance and therefore it has been postulated that it is likely to be associated with an increased risk of maternal cardiovascular morbidity and mortality. However, this placental complication often occurs with other comorbidities, such as pre-eclampsia or fetal growth restriction. As such, most studies could not suggest an independent association between placental abruption and long-term maternal cardiovascular risk.[110] Ray et al.[129] examined the risk of early CVD in women with a history of assorted placental complications (HDP, abruption, and infarction) and were able to demonstrate that in women with isolated placental abruption or infarction, the risk of CVD was increased (HR 1.7; 95% CI, 1.3–2.2).

Pariente et al.[130] demonstrated that in women who experienced isolated placental abruption in one of their pregnancies, the long-term cardiovascular mortality risk was increased (OR 6.6; 95% CI, 2.3–18.3), with a 13% CVD-related fatality rate in their cohort after placental abruption versus 2.5% in the comparison group.

Similar results were found in more recent studies. DeRoo et al.[131] explored the mortality risk associated with placental abruption using linked Medical Birth Registry and Death Registry data among over 2 million women with a first singleton birth in Sweden and Norway, and found that women with placental abruption in any pregnancy had a 1.8-fold increased risk (95% CI, 1.5–2.2) of CVD mortality, compared with those who had never experienced the complication. Results were essentially unchanged by excluding women with diabetes, chronic hypertension, or pre-eclampsia. A Danish population-based study of over 1 million women found an increased risk for ischemic heart disease (HR 1.6; 95% CI, 1.4–1.9), acute myocardial infarction (HR 1.9; 95% CI, 1.4–2.4), hypertensive heart disease (HR 2.2; 95% CI, 1.1–4.5), congestive heart failure (HR 1.7; 95% CI, 1.2–2.3), and cardiovascular mortality (HR 2.7; 95% CI, 1.5–5.0), up to 18 years after pregnancies complicated by placental abruption in the first birth, adjusted for year of delivery, parity, and maternal education.[132]

4.4.5 | Comorbid placental syndromes

It is important to emphasize that when more than one comorbidity of the above-mentioned placental complications is experienced, the risk for future maternal CVD is greatly affected. Ray et al.[129] reported that the future risk of CVD remained significant irrespective of the types of maternal placental syndrome (gestational hypertension, pre-eclampsia, placental abruption, or infarction), and found that the risk was highest in women who had a placental syndrome in combination with fetal growth restriction or intrauterine fetal death, relative to women with neither complication (aHR 2.0 vs 3.3 vs 4.4, respectively). A recent study also demonstrated that having more than one placental complication carries the highest risk for future CVD, especially if preterm birth or fetal growth restriction is present.[82]

Other placental syndromes other than hypertensive disorders in pregnancy (fetal growth restriction, preterm birth, recurrent pregnancy loss, and placental abruption) are also associated with similar long-term maternal morbidity. **Level of evidence: Low (⊕⊕OO)**

4.4.6 | Possible mechanisms for pregnancy complications linked to future maternal cardiovascular disease

It is unclear whether the link between HDP, CVD, and type 2 diabetes is correlational or causal. Two major theories link maternal CVD with placental syndromes. Firstly, there are shared risk factors for systemic inflammation and endothelial dysfunction, such as obesity, dyslipidemia, diabetes, insulin resistance, and hypertension. Although shared genetic risk factors are likely to contribute to the association, a simple underlying genetic predisposition to essential hypertension is an unlikely pathway for the complex syndrome of pre-eclampsia.[133] Alternatively, a second possible mechanism that does not exclude the contribution of common risk factors is that the pregnancy, and especially HDP or other placental dysfunction complications, may cause long-lasting effects on the maternal cardiovascular system, including accelerated arterial wall inflammation and myocardial dysfunction[104] that fail to resolve after delivery, thereby mediating increased long-term CVD risk[134]—the so-called *legacy effect*. In pre-eclampsia, a higher systemic vascular resistance and substantial cardiac changes in structure and function are observed, especially with early-onset pre-eclampsia, both in pregnancy and the postpartum period,[104] with possible contribution by inflammatory stress, dyslipidemia of pre-eclampsia, and angiogenic changes—all of which could accelerate progression toward hypertension and CVD.[135]

A degree of placental dysfunction is implicated, either as a biomarker or as a mediator of the risk for future maternal CVD. In pre-eclampsia, malperfusion of the placenta remains a common pathophysiological feature for both early- and late-onset pre-eclampsia.[136,137]

The compromised placental perfusion induces inflammatory and antiangiogenic stress response factors into the maternal circulation, leading to endothelial dysfunction and possible cardiovascular damage, more so in early-onset than late-onset pre-eclampsia.[136,138] Such differences in type and degree of placental stress and placental factors could potentially explain the differences in CVD risk observed between the early- and late-onset pre-eclampsia subtypes. For example, pre-eclampsia with severe features is associated with a significantly higher prevalence of asymptomatic global left ventricular dysfunction and myocardial impairment than a normotensive pregnancy,[104] likely progressing later in life to symptomatic CVD.[139] Moreover, the impaired recovery of the maternal cardiovascular system after pre-eclampsia seems to affect both arterial and venous systems, as asymptomatic left ventricle systolic and diastolic dysfunction can persist up to a year after birth.[80] Melchiorre et al.,[104] in a longitudinal prospective study, found that women with moderate to severe left ventricular abnormalities at 1 year after birth were more likely to develop hypertension at 2 years after birth compared with those with normal or mild left ventricular pathology. However, studies have also indicated that women who develop HDP have risk factors that predispose them not only to HDP but to future cardiovascular complications.

A large Norwegian population-based study proposed that pre-pregnancy risk factors (i.e. obesity, dyslipidemia, and elevated blood pressure) were more important for future CVD than actual HDP, but they also showed that most CVD risk factors remained significantly elevated after pre-eclampsia despite adjustment for prepregnancy values.[140,141] Recent epidemiological data from Norway demonstrated that pre-existing classical CVD risk factors cannot fully explain the association between pregnancy hypertensive disease and premature hypertension within 10 years after pregnancy,[94] in line with pregnancy stress such as pre-eclampsia independently increasing the remote maternal cardiovascular risk.[134]

TABLE 5 Summary of meta-analysis of long-term cardiovascular morbidity following a pregnancy complicated by hypertensive disorders in pregnancy.

Outcomes	References	Studies	HDP(+)	Controls	Risk/odds
Hypertension	Bellamy[85]	13	3658	16 086	3.70
	Brown[86]	30	40 544	782 011	3.13
Cardiovascular disease[a]	Bellamy[85]	8	121 487	2 187 112	2.16
	McDonald[87]	14	118 990	2 259 576	2.47–2.33
	Brown[86]	15	99 782	1 910 874	2.24–2.57
	Wu[88]	17	6 004 621		2.11–3.62
Cerebrovascular accident	Bellamy[85]	4	64 551	1 568 629	1.81
	McDonald[87]	7	86 858	1 780 344	2.03–2.60
	Brown[86]	7	62 235	1 364 253	1.60–2.46
	Wu[88]	9	4 906 182		1.71
Mortality	Bellamy[85]	4	49 049	745 413	1.49
	McDonald[87]	5	44 943	731 598	2.29
	Wu[88]	8	3 291 558		2.10

[a]Variously defined across studies, generally including ischemic/coronary heart disease, myocardial infarction, and congestive heart failure.

5 | LONG-TERM FOLLOW-UP OF INCREASED MATERNAL CARDIOVASCULAR RISK AFTER PREGNANCY COMPLICATIONS

CVD is the leading cause of death for both men and women worldwide,[142] but even more so for women.[143] The 2013 Global Burden of Disease study estimated that CVD accounts for 31.5% of all deaths, more than twice that caused by cancer. CVD also takes away the most years of life compared with any other NCD.[144,145] The preclinical stages of atherosclerotic CVD begin early in life, progress with advancing age, and are influenced by potentially modifiable risk factors.[146] Although both short- and long-term survival after myocardial infarction have remarkably improved over the last decades,[147] the total burden of CVD has increased globally. As deaths from infectious diseases have decreased, the world's population is increasing in age and size. As such, higher rates and more people will develop NCDs, of which CVD represents a major issue. Prevention of CVD is therefore an increasing global challenge; not only does it cause personal and family suffering, but the costs of CVD to society are expected to increase dramatically over the next decades.[148] The Global Action Plan (WHO 2013–2020) reflects the need to increase prevention and control of the increasing NCD epidemic.[149]

5.1 | Identifying young women at increased risk of future cardiovascular disease

Over the last decade, pregnancy has been acknowledged increasingly as an early life "stress test" for several NCDs in women, including CVD, type 2 diabetes and metabolic syndrome, and renal, ophthalmic, and cognitive morbidities.[134,150–152] However, pregnancy outcome has hitherto been underused as a stratification tool to target women with increased risk of various NCDs. Such targeting of young women would enable intensified preventive strategies early in life, when interventions are likely to be most efficient, as well as providing optimal clinical follow-up to reduce the severity of the clinical disease. The US Framingham Heart Studies identified risk factors that were causally associated with CVD, including hyperlipidemia, smoking, obesity, physical inactivity, hypertension, and diabetes.[153,154] Mental stress and lack of consumption of fresh fruits and vegetables have also been proposed as additional risk factors.[50] These risk factors may be prevalent in young women, but the clinical disease often starts later in life and in perimenopausal ages it is rapidly progressive.[155] As risk factors for CVD are modifiable, and prevention of CVD is most likely to be effective when introduced in the early stages of atherosclerosis, there is a need to improve risk stratification at a younger age to improve cardiovascular health in middle-aged and elderly women.

Pregnancy complications and other peripregnancy characteristics may also impact future maternal CVD risk. In 2011, the American Heart Association added pre-eclampsia, gestational hypertension, and GDM as sex-specific risk factors for CVD.[89]

- Pre-eclampsia and gestational diabetes mellitus: As detailed in previous sections of this Supplement, it is well established that women with previous placental and metabolic syndromes are at increased risk of future CVD.
- As previously emphasized, there is a dose–response association between HDP and increased risk of CVD; the risk increasing by severity of or repeated pre-eclampsia, premature delivery, and with coexistent fetal growth restriction.
- Preterm birth (either spontaneous or indicated, with or without HDP), recurrent pregnancy loss, fetal growth restriction, intrauterine fetal death, and placental abruption, all previously discussed, have similar associations with increased CVD risk.
- The impact of breastfeeding on long-term maternal CVD risk seems to be protective.[156]
- An increased number of pregnancies has been found to increase the risk of future maternal CVD in some studies,[157–160] but this association was absent in another study.[161] A J-shaped trend between the number of births and maternal cardiovascular mortality, after adjusting for confounding factors, has been found in Sweden[162] and Norway,[163] but for the Norwegian population this was only in women with fewer than 10 years of education. Number of offspring does not seem to increase the CVD risk for male partners, after correcting for obesity and metabolic risks,[159] suggesting a pathophysiologic effect from pregnancy.

We suggest that the following pregnancy-related risk factors should be acknowledged as predictors of long-term cardiovascular morbidity: hypertensive pregnancy disorders, gestational diabetes mellitus. **Level of evidence: Moderate (⊕⊕⊕O). Strength of recommendations: Conditional (2|2)**

The following pregnancy-related risk factors should be also acknowledged as predictors of long-term cardiovascular morbidity: fetal growth restriction, preterm birth, recurrent pregnancy loss, and placental abruption. **Level of evidence: Low (⊕OOO). Strength of recommendations: Conditional (2|2)**

5.2 | Female cardiovascular disease differs from male cardiovascular disease

Significant epidemiological differences have been demonstrated between female and male CVD. Women develop clinical CVD 10–15 years later than men. They often present with "atypical" symptoms, which could cause delayed diagnosis, with poorer outcomes and less survival.[164,165] Women less often have angina before myocardial infarction, and women are more likely to die of their first infarction than men,[89] especially after an ST-elevation myocardial infarction.[147]

Women are also more prone to microvascular dysfunction than men, a lower incidence of plaque rupture, and a higher incidence of plaque erosion, especially when young women present with myocardial infarction.[166] Asymptomatic diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) are also more common in women than men.[167] HFpEF is associated with high rates of

microvascular inflammation and vasculopathy as well as with particularly high morbidity and mortality.[168,169]

The pathophysiological mechanisms underlying sex-based differences in CVD remain incompletely understood. The lower incidence of CVD prior to menopause suggests that female sex hormones may play a role.[166] Women and men respond differently to cardiovascular stressors and smoking may play a larger role in the pathogenesis of female CVD.[166] There are also sex differences in how cardiovascular hemodynamics affect cardiac remodeling[170] and arterial stiffness.[171]

5.3 | Follow-up of cardiovascular disease after pregnancy complications

Currently, systematic and population-based follow-up after pregnancy complications for the prevention of future CVD is lacking, even in high-income countries that focus on population-based preventive medicine. There are some local exceptions, where a 6-month postpartum check-up is offered to women with pregnancy complications such as gestational hypertension, pre-eclampsia, GDM, fetal growth restriction, low birthweight baby, preterm birth, or abruption.[172] As such, more research is needed to discriminate between the specific effects of pregnancy and prepregnancy factors, as well as their interaction, on future maternal CVD. To facilitate progress, we suggest methods of harmonizing study designs, long-term follow-up of pregnancy cohorts and biobanks, and pooling of the world's data in ways that can enhance the power of current and future research.[134]

At present, it is not clear when follow-ups should be initiated after pregnancy complications, how often follow-ups should be undertaken, or which strategies would be the most cost-effective at a population level. Presumably, postponing the first follow-up after pregnancy complications to menopause is not optimal, as prevention success is more likely when started at a younger age. High-quality research is needed to ascertain whether a specifically targeted group of women with pregnancy complications would benefit from specific CVD-prevention strategies, such as oral statins, metformin, or low-dose aspirin, and thereby improve their long-term maternal health.[134]

A first step toward implementing our knowledge of pregnancy as a stress test would include that care givers, as well as women themselves, are aware of the associations and the opportunities to modulate CVD risk. Simple measures, such as treating existing risk factors for CVD, should be encouraged. Ideally, prepregnancy counseling could be offered to all women with risk factors, such as obesity and hypertension, with the aim to reduce pregnancy complication rates as well as improve long-term maternal health. The global challenge is whether avoidable and severe pregnancy complications occur at very high and unacceptable rates in low-income countries due to poor obstetric care. In this setting of poor health resources for the total or part of the population, focusing on improving pregnancy outcomes would be the priority, and thereafter prevention of future NCDs.

Short-term follow-up: In most pre-eclamptic women, blood pressure normalizes within days to weeks after delivery.

- Women with prepregnancy cardiovascular or renal disease are recommended to continue attending check-ups irrespective of whether the pregnancy was complicated by pre-eclampsia.
- Previously healthy women who have had pre-eclampsia and who still have elevated blood pressure at postpartum discharge should receive regular follow-up by health services until their blood pressure has normalized.
- Secondary causes of hypertension should be investigated if hypertension sustains for many weeks.
- Women who continue to have proteinuria after delivery should be checked for renal disease.

Long-term follow-up: Currently, there are no quality-assured guidelines on how women should be followed-up after HDP to prevent and detect future CVD at an early stage.

- Annual follow-up by a general practitioner even in women who seem clinically healthy starting at 3 months postpartum follow-up, is advised by several clinicians,[134] especially for women with previous severe pre-eclampsia.
- Women should discuss their history at routine check-ups in the healthcare system, for instance at follow-up 6–12 weeks after birth.
- A general practitioner can schedule a customized follow-up program, taking into account the woman's general health and cardiovascular risk factors.

We recommend that the following measures are implemented at 6–12 weeks after birth, and periodically thereafter, following a pregnancy complicated by hypertensive disorders:

- History and physical examination
- Blood pressure measurements
- Consider screening for other cardiovascular risk factors.

Level of evidence: Moderate (⊕⊕⊕O). Strength of recommendations: Strong (1|2).

We recommend that the following measures are considered at 6–12 weeks after birth, and periodically thereafter, following other placental-associated pregnancy complications including fetal growth restriction, preterm birth, recurrent pregnancy loss, intrauterine fetal death, and placental abruption:

- History and physical examination
- Blood pressure measurements
- Consider screening for other cardiovascular risk factors.

Level of evidence: Low (⊕⊕OO). Strength of recommendations: Conditional (2|2).

These adverse pregnancy outcomes should serve as a screening tool for a first postpartum cardiovascular evaluation at 6–12 weeks, when many women seek a routine postpartum check-up anyway.

We suggest that a simple cardiovascular screening is indicated in these women, such as blood pressure and proteinuria assessment, evaluation of BMI and lifestyle, smoking, and family history of CVD. Diabetes screening with HbA1c or fasting glucose or the oral glucose tolerance test is recommended after GDM, as outlined in other sections, but we suggest it is extended to women with previous pre-eclampsia as well. Patient education and minimizing risk factors would be an important goal of this first screening visit and repeated at each screening visit. Following this initial screening 3 months after birth, these women would be triaged to a specialist or community follow-up within 1 year and thereafter individual timing of follow-up according to total risk. This follow-up could also be implemented in other national screening programs that are offered to the female population in some countries (e.g. breast cancer and cervical cancer screening), providing added value without much extra cost.

Extended and resource-demanding cardiovascular phenotyping would likely be clinically indicated only for a restricted group among these women at risk for CVD. This could include investigation of macrovascular function (e.g. reactive hyperemia index, pulse-wave velocity, augmentation index) structure (e.g. carotid intima thickness), microvessel structure, or cardiac echocardiography. Whether some of these tools can also provide a cost-benefit screening option for routine follow-up of the larger group of women with pregnancy complications at high risk for remote CVD is not known yet. In addition, biomarkers during pregnancy that reflect placental dysfunction (such as low levels of placenta-derived placental growth factor) or after birth (reflecting cardiovascular stress) could be explored as risk markers for future CVD, further individualizing and intensifying follow-up of the group at highest risk.

Possible preventive measures: Based on the evidence currently available:

- A healthy lifestyle is recommended for all women with previous pre-eclampsia to prevent CVD. This recommendation includes healthy physical activity and food intake, smoking avoidance, and healthy normal body weight (BMI 19–25).
- There is no evidence available on efficient preventive medications for CVD in women with only previous pre-eclampsia as a risk factor, such as statins, metformin, and aspirin (such initiatives should be tested as part of clinical trials).

We suggest that, once acknowledged, risk-reducing measures are implemented, including lifestyle modification (nutrition and physical activity, treating obesity and overweight, controlling hypertension, and smoking cessation). **Level of evidence: Low (⊕⊕OO). Strength of recommendations: Conditional (2|2).**

6 | MANAGEMENT OF MATERNAL HISTORY OF GESTATIONAL DIABETES MELLITUS

6.1 | Screening for altered carbohydrate metabolism and type 2 diabetes

It is widely recommended that women with recent GDM undergo glucose screening within the first 6 months after delivery.[173,174] Whereas the incidence of overt diabetes in the early postpartum period is generally not high (ostensibly reflecting pre-existing type 2 diabetes that was first identified in pregnancy and hence diagnosed as GDM), the prevalence of prediabetes in this population is considerable, with approximately 30% of women with GDM exhibiting impaired glucose tolerance at 3 months after delivery.[45] For this initial postpartum screening, a 75 g OGTT is recommended over measurement of HbA1c for two reasons: (1) in the early postpartum period, HbA1c might not accurately reflect glycemic exposure owing to the impact of either increased red blood cell turnover in pregnancy or blood loss at delivery (both of which will promote reticulocytosis and thereby lower HbA1c by virtue of less time for exposure to glycemia); and (2) the OGTT provides greater sensitivity for detecting prediabetes, particularly impaired glucose tolerance. Unfortunately, despite its wide recommendation by authoritative bodies, the rates of performance of this initial postpartum OGTT generally remain suboptimal in clinical practice, representing a gap in care and a missed opportunity for early identification of a patient population at high risk for developing diabetes.[175,176]

If the OGTT reveals the presence of prediabetes, then both lifestyle intervention and metformin have been shown to reduce the risk of progression to type 2 diabetes in women with a history of GDM.[177,178] Prolonged breastfeeding also reduces this risk.[179,180]

Importantly, even if the initial OGTT is normal, women with recent GDM remain at risk of progression to prediabetes and type 2 diabetes because of worsening of beta-cell function.[44,181] Accordingly, ongoing surveillance for abnormal glucose tolerance in the years thereafter is warranted in women with previous GDM. While it is recognized that an evidence base for the optimal approach to this surveillance is not yet available, the clinical immediacy for managing the recognized diabetic risk of this patient population dictates a need for guidance in the interim. As such, the American Diabetes Association (ADA) recommends that these women should be tested every 1–3 years thereafter, with the frequency of testing determined based on risk factors for diabetes (such as family history, BMI, and the need for antidiabetic therapy during the pregnancy). The ADA suggests that this ongoing testing may be performed with any glycemic test (i.e. HbA1c, fasting glucose, or OGTT).[173] Screening with the OGTT is preferable for early detection of prediabetes. Research to provide an evidence base to inform optimal surveillance of this high-risk population remains ongoing. FIGO has also provided guidance on immediate and long-term follow-up for women manifesting hyperglycemia in pregnancy.[19]

7 | THE HEALTH ECONOMIC ARGUMENT FOR FOCUSING ON POSTPREGNANCY CARE

Identifying "at risk" mothers and offspring during pregnancy creates the opportunity for targeted early preventive action. Interventions to address NCDs in pregnancy have beneficial effects for both the mother and offspring in the short term as well as in the long term, particularly when accompanied by additional low-cost preventive actions following pregnancy.

Overweight, obesity, hyperglycemia, and hypertensive disorders often occur in various combinations during pregnancy and their combined occurrence has a greater adverse impact on the health of the mother and her offspring in both the short and long term compared with their occurrence individually. In addition, since preventive actions to address obesity, hypertension, type 2 diabetes, and cardiovascular diseases have a common lifestyle approach, identifying any one of these problems in pregnancy provides an opportunity to address long-term prevention for all of them.

Health economic analysis that only focuses on the short term does not capture the full value of downstream long-term benefits. Comprehensive screening and integrated care cost-effectiveness models must, on the cost side, consider the costs of identifying the condition, the intervention during pregnancy, and preventive actions after pregnancy; on the benefits side, models must consider the cost savings from reduced complications in the short term and discounted cost savings from deferring or preventing the disease and reducing its complications in the long term.

While there are some health economics studies looking at long-term prevention of type 2 diabetes in women with GDM, the additional economic benefits of preventing potential cardiovascular diseases in these women have not been considered in most of these modelling studies and, therefore, the economic benefits are likely to be underestimated.

The additional economic benefits of early postpartum testing and long-term follow-up and preventive action for preventing type 2 diabetes and CVD in women with HPD, pre-eclampsia, and other placental syndromes, is not adequately documented. There is a need for more comprehensive health economic studies to support the case for structured postpartum follow-up and care for women with NCD-related pregnancy complications.

7.1 | Overweight and obesity

Given the additional risks of pregnancy complications associated with overweight and obesity, it can safely be assumed that these pregnancies require additional tests, clinic visits, and a higher level of care resulting in additional costs. Very few studies have assessed the economic costs of overweight and obesity associated with pregnancy. A study from the UK estimated that considering only the additional maternity-care needs, costs for women who were overweight, obese, or severely obese (mean [95% CI], adjusted analyses) were: £59.89 (£41.61–£78.17), £202.46 (£178.61–£226.31), and £350.75 (£284.82–£416.69), respectively.[182] It has been estimated that the total costs for overweight and obese pregnant women with GDM during pregnancy and up to 2 months following delivery increase by 23% and 37%, respectively, compared with women with normal BMI.[182,183] Not only are the maternity costs higher in overweight and obese women, but there is a strong association between infant healthcare usage cost and maternal BMI. This is attributed to a significantly greater number and duration of inpatient visits and a higher number of general practitioner visits. Total mean additional resource cost in a study from within the UK's national health service was estimated at £65.13 for infants born to overweight mothers and £1138.11 for infants born to obese mothers compared with infants of healthy weight mothers.[184]

7.2 | Hypertensive disorders in pregnancy

Compared with an uncomplicated pregnancy, costs associated with pre-eclampsia are significantly higher—for both the mother and neonate—in any given regional setting. This is because of its severity and life-threatening nature, requiring advanced intensive care. The cost of an uncomplicated vaginal delivery in California, in 2011, was estimated to be about US $4500[185] and the average incremental cost for a pregnancy complicated by hypertensive disease was estimated to be US $8200, amounting to an additional cost of US $200 million for all Californian births. Costs were highest for women who had severe disease requiring early delivery (<34 weeks of pregnancy). In this cohort, the incremental cost was US $70 100 per pregnancy.[185]

The annual financial burden of pre-eclampsia, including the care of mother and child for the first 12 months after delivery in the USA, in 2012, was US $2.18 billion: US $1.03 billion for mothers and US $1.15 billion for infants. The cost burden per infant is dependent on gestational age, ranging from US $150 000 at 26 weeks gestational age to US $1311 at 36 weeks gestational age.[186]

Use of novel biomarkers for pre-eclampsia diagnosis has been shown to be cost-effective.[187] Using a decision analysis model, the clinical and economic benefits of a first-trimester screening program based on the Fetal Medicine Foundation algorithm for prediction of early-onset pre-eclampsia coupled with early (<16 weeks) use of low-dose aspirin in those at high risk was simulated and tested with current practice in Canada.[188] Among the theoretical 387 516 births per year in Canada, the estimated prevalence of early-onset pre-eclampsia based on first-trimester screening and aspirin use declined 1.5-fold to 705 cases compared with 1801 cases based on current practice. This resulted in an estimated saving of Can $13 130 per case averted (Can $14.39 million annually). Universal implementation of a first-trimester screening program for pre-eclampsia and early intervention with aspirin in women at high risk for early-onset pre-eclampsia has the potential to prevent a significant number of early-onset pre-eclampsia cases with a substantial cost savings to the healthcare system in Canada.[188]

A study from Nepal[189] showed the cost-effectiveness of a pilot project to provide calcium supplementation through the public sector

to pregnant women during prenatal care, in addition to the existing practice for pre-eclampsia/eclampsia prevention.

A cost-effectiveness study using a decision analysis model assessed a screening strategy for early-onset pre-eclampsia relative to no screening in Israel.[190] The cost per case of pre-eclampsia averted was US $67 000, which was equivalent to US $19 000 per quality-adjusted life-year—generally considered to be cost-effective.

The 2008 National Institute for Health Research Health Technology Assessment provided a detailed consideration of the evidence relating to screening for pre-eclampsia.[191] Unlike other modelling exercises, it systematically considered all possible tests and management interventions available at that time in a variety of different strategies rather than a single intervention. It considered strategies in which treatments were applied without any previous testing ("No test/Treat all"). The results led to the conclusion that the most cost-effective approach to reducing pre-eclampsia was the provision of an effective, affordable, and safe intervention (such as low-dose aspirin) applied to all mothers without previous testing. From a short-term perspective, the "No test/Treat all" strategy will always be most effective when the cost of the intervention is less than the cost of the test, and when there is an assumption that all women who could benefit from the intervention will receive and take it. The "Test/Treat if positive" strategy can only match this if its sensitivity is 100%. The key provisos are that there are no adverse events from the intervention and pregnant women are willing to have treatment (however safe and low cost) without being confirmed that they are at risk. The best available evidence suggests that only 70% of high-risk women are compliant with low-dose aspirin therapy.[192] Moreover, despite its general safety, use of aspirin for any indication (and not necessarily low dose) has been shown to be associated with a small increase in the prevalence of cerebral palsy[193]; therefore, its use for pre-eclampsia may be better restricted to pregnancies at true risk of preterm delivery. Most importantly, if the long-term implications of pre-eclampsia (such as future risk of CVD and type 2 diabetes) are taken into account, the "No test/Treat all" strategy will probably be deemed much inferior as it would fail to identify women at risk who would benefit from intensive postpartum follow-up and lifestyle interventions.

7.3 | Hyperglycemia in pregnancy

Only a few studies that have evaluated the cost-effectiveness of an integrated approach to GDM screening and care also include the postpartum prevention component. Most studies have evaluated the cost-effectiveness of one screening strategy over another; for example, selective screening versus universal screening, or the IADPSG criteria versus the WHO 2009 criteria or the American Diabetes Association/American College of Obstetrics and Gynecology criteria. Some of these studies are summarized below.

Using a decision analysis tool, GeDiForCE (Novo Nordisk, Bagsværd, Denmark) that assesses the full range of costs and benefits of GDM screening and intervention in specified populations, Marseille et al.[194] reported data from India and Israel to demonstrate that the intervention is highly cost-effective in both countries. The program cost in international dollars per 1000 pregnant women was $259 139 in India and $259 929 in Israel. Net costs for India and Israel, adjusted for averted disease, were $194 358 and $76 102, respectively. The costs per disability-adjusted life year (DALY) averted were $1626 in India and $1830 in Israel, considered cost-effective and cost-saving, respectively.

Another decision analysis modelling study reported by Werner et al.[195] from the USA compared the cost–utility of three strategies to identify GDM: (1) no screening; (2) current screening practice (1-hour 50 g glucose challenge test performed between 24 and 28 weeks followed by a 3-hour 100-g glucose tolerance test when indicated); or (3) screening practice proposed by the IADPSG. Assumptions in the study included that: (1) women diagnosed with GDM received additional prenatal monitoring, mitigating the risks of pre-eclampsia, shoulder dystocia, and birth injury; and (2) GDM women had the opportunity for intensive postdelivery counseling and behavior modification to reduce future diabetes risks. The primary outcome measure was the incremental cost-effectiveness ratio (ICER). For every 100 000 women screened, 6178 quality-adjusted life-years (QALYs) are gained, at a cost of US $125 633 826. The ICER for the IADPSG strategy compared with the current standard was US $20 336 per QALY gained. When postdelivery care was not accomplished, the IADPSG strategy was no longer cost-effective. These results were robust in sensitivity analyses.

Mission et al.,[196] in the USA, used a decision analysis model to compare the cost-effectiveness of treating patients with GDM versus not treating them. They considered patients in HAPO category 5 (top 3%–12% of fasting glucose levels), which is consistent with the diagnosis of marginal patients according to the IADPSG recommendations. Pre-eclampsia, mode of delivery, maternal death, macrosomia, shoulder dystocia, brachial plexus injury (permanent and transient), hypoglycemia, hyperbilirubinemia, and neonatal death were included as maternal and neonatal outcomes. Treating patients was found to be cost-effective at a cost of US $44 203 per QALY. A one-way sensitivity analysis suggested that treatment remained cost-effective when it met 64% of its reported efficacy.

Ohno et al.[39] compared treating versus not treating mild gestational diabetes from a societal perspective. Maternal outcomes included pre-eclampsia, shoulder dystocia, cesarean versus vaginal delivery, and maternal death; neonatal outcomes included macrosomia (more than 4000 g), brachial plexus injury (permanent or transient), hypoglycemia, admission to a neonatal intensive care unit, hyperbilirubinemia, and neonatal death. In the base-case analysis, treatment was found to be cost-effective at US $20 412 per QALY below the willingness to pay threshold of US $100 000). Sensitivity analyses showed that treatment remained cost-effective when the incremental cost to treat was less than US $3555 or when the reported efficacy was at least 49% (at baseline cost).

An Australian study by Moss et al.[38] compared the treatment of women with mild gestational diabetes by dietary advice, blood glucose monitoring and, when required, insulin therapy with routine pregnancy care from a health system perspective. Based on data from the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial, the incremental cost per additional serious perinatal

complication (defined as one or more of the following: death, shoulder dystocia, bone fracture, nerve palsy) prevented was estimated at A$27 503. The incremental cost per perinatal death prevented was calculated as A$60 506 and A$2988 per life-year saved.

A study from China[197] using the GeDiForCE (Novo Nordisk) model assessed the cost-effectiveness of GDM screening versus no GDM screening, comparing costs and DALYs averted. Modeling inputs such as costs of GDM screening and prenatal care, GDM prevalence, and cost of perinatal adverse effects as a consequence of GDM were based on actual assessment in six tertiary hospitals from different cities in China. Cost for postpartum care was calculated based on published literature adjusted for China or published studies from China. Perinatal adverse effects-DALYs, lifetime cost for postpartum type 2 diabetes, and effectiveness of interventions were based on published literature. An annual discount rate of 3.0% was used for long-term benefit assessment. One-way sensitivity analyses were conducted on some key indicators. The total costs of GDM screening, intervention, and life-time preventive care per 1000 pregnant women was US $7 092 398 in the GDM screening group, saving US $1 329 671 in costs compared with the no screening group. A total of 277.4 DALYs were averted in the screening group, mainly resulting from postpartum care for type 2 diabetes prevention. Sensitivity analyses demonstrated the robustness of the results. GDM screening by IADPSG protocol and intervention is cost-saving in an urban Chinese setting. The authors concluded that, because DALYs averted mainly come from prevention of type 2 diabetes, China should pay more attention to providing postpartum care for GDM women in the future.[197]

Another study from China[198] reported that the average cost of a pregnancy with GDM in China in 2015 was ¥6677.37 (international $1929.87), which was 95% higher compared with a pregnancy without GDM owing to additional expenses during pregnancy and at delivery: ¥4421.49 for GDM diagnosis and treatment, ¥1340.94 (+26%) for maternal complications, and ¥914.94 (+52%) for neonatal complications. In China, 16.5 million babies were born in 2015.[198] With a GDM prevalence rate of 17.5%, an estimated 2.90 million pregnancies were affected by GDM in 2015. Therefore, the annual direct short-term cost due to GDM was estimated to be ¥19.36 billion (international $5.59 billion).[198] Sensitivity analyses confirmed the robustness of the results.

Estimation of the direct health economic burden of maternal overweight, GDM, and related macrosomia indicates that associated healthcare expenditures are substantial. The calculation of the budgetary impact of GDM, based on a conservative approach, using the USA costing data in the model, indicates an annual cost of more than US $1.8 billion without considering the long-term consequences.[199]

A recent US study reported that each case of GDM was associated with US $5800 in higher medical expenditures. GDM only slightly raised medical costs for newborns (average US $40/newborn) but substantially raised the mother's costs related to the pregnancy and birth (average US $5760/mother). The breakdown for higher costs includes inpatient care (US $3140), prescription medicine (US $1200), ambulatory visits (US $1140), and emergency care (US $280).[200] The overall health and economic costs associated with unrecognized and untreated GDM will undoubtedly be several-fold higher underscoring the importance of screening for and management of GDM.

A study to evaluate the preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the USA reported that 2.2% of US births are to women with pregestational diabetes. Among women with diagnosed diabetes, universal preconception care might avert 8397 (90% prediction interval [PI], 5252–11 449) preterm deliveries, 3725 (90% PI, 3259–4126) birth defects, and 1872 (90% PI, 1239–2415) perinatal deaths annually.[201] Associated discounted lifetime costs averted for the affected cohort of children could be as high as US $4.3 billion (90% PI, 3.4–5.1 billion) (2012 US dollars). Preconception care (including screening for diabetes) among women with undiagnosed diabetes could yield an additional US $1.2 billion (90% PI, 951 million to 1.4 billion) in averted costs.[201]

Evidence from prospective studies demonstrates that lifestyle and pharmacological interventions for prevention of diabetes are as effective in women with GDM as in non-GDM women with impaired glucose tolerance and men with impaired glucose tolerance.[177,178,202]

A recent study showed that not only does metformin treatment continue to exert its diabetes prevention effect even 15 years after randomization in the Diabetes Prevention Program (DPP) and the Diabetes Prevention Program Outcomes Study (DPPOS), but that its effect was significantly better in women with a history of prior GDM (HR 0.59; rate difference [RD] 24.57 cases/100 person-years) compared with parous women with impaired glucose tolerance without previous GDM (HR 0.94; RD 20.38 cases/100 person-years.[203]

Breastfeeding for more than 10 months has also been reported to decrease the risk of diabetes mellitus at 2 years after delivery by 57% in women with a history of GDM.[179]

Given that lifestyle interventions or use of medications for prevention of diabetes in people at risk in various settings are regarded as highly cost-effective,[204–209] and that treatment of GDM is cost-effective in preventing perinatal complications,[38,39,196] it seems intuitive that screening and comprehensive care for GDM should be highly cost-effective overall.[199]

8 | ADDRESSING THE DETERMINANTS OF AND BARRIERS TO IMPLEMENTING POSTPREGNANCY FOLLOW-UP AND PREVENTIVE CARE

The ability to track and follow up women with an NCD-related pregnancy complication after delivery and to continuously engage and empower the "at risk" mother–child pair to adopt a healthy lifestyle is a critical issue.[208] Focusing only on the short-term survival in terms of lowered maternal and perinatal morbidity and mortality does not capture the outcomes that have longer-term implications for adult health, life expectancy, quality of life, and accumulation of human capital.[209]

Pregnancy offers a window of opportunity to provide maternal care services, not only to reduce the traditionally known maternal and perinatal morbidity and mortality indicators, but also for intergenerational prevention of several chronic diseases. Multiple barriers stand in the way of these objectives.[210] The barriers operate at different levels: cultural and societal, health system resources, and healthcare provider and client characteristics. Lack of knowledge and understanding of the severity of the issue among policy makers, healthcare providers, and affected women and their families is perhaps the biggest hurdle.

Compartmentalization of care and lack of communication/collaboration between healthcare providers are important barriers resulting in postpartum women slipping through the net and being lost to follow-up. Following delivery, women with GDM, HDP, pre-eclampsia, preterm birth, or other pregnancy complications that are markers for future long-term maternal health risks no longer have the condition and are asymptomatic (and no longer pregnant); they are therefore unlikely to visit either the physician or the obstetrician for check-ups and may then be lost to follow-up. However, these women do visit health services that are focused on the well-being of their babies, for instance for the child's vaccination program and regular check-ups, and are likely to do so at regular intervals for at least 5 years. Can this opportunity be used to provide these women follow-up advice and conduct necessary tests? Can the health system tag the mother's pregnancy complication status to the child's history to ensure maternal follow-up for the benefit of both the mother and child?[208]

There is an urgent need to study and understand the determinants of and barriers to postpartum follow-up and care, and to find regional, health-system specific, and culturally relevant local solutions to mitigate these barriers. Improving follow-up and preventive care could improve the long-term health of mothers and achieve the long-term objective of reducing the risks of NCDs in women.

FIGO encourages obstetricians to establish connections with family physicians, internists, and pediatricians to support postpartum follow-up of mothers linked to their children's vaccination programs to ensure continued follow-up and engagement of the high-risk mother–child pair.

9 | SUMMARY

Pregnancy occurs relatively early in a woman's lifespan. Experiencing a complicated pregnancy with either placental syndromes or GDM can uniquely serve as an early indicator of future maternal NCDs, and therefore can offer an opportunity to initiate meaningful risk-reduction strategies. Although only scarce evidence exists on the long-term effectiveness of risk-reduction interventions, the postpartum period should still be the focus for actions such as lifestyle modification (optimal weight goals, exercise, smoking cessation) and controlling for cardiometabolic risk factors (blood pressure, glucose, lipids, and weight gain) that may help abate the development of future NCDs as early as their preclinical stage, thereby interrupting a vicious cycle of intergenerational transfer of disease.

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