Brief Review

Pregnancy and Long-Term Maternal Cardiovascular Health
Progress Through Harmonization of Research Cohorts and Biobanks

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● **Online Data Supplement**

Background: Why We Need to Better Understand the Associations Between Pregnancy and Future Cardiovascular Health

In 2011, the American Heart Association added preeclampsia, gestational diabetes mellitus (GDM), and delivery of a growth-restricted child as pregnancy-related risk factors for cardiovascular disease (CVD).[1] This move was applauded by the obstetric research community, which for some years had emphasized the importance of pregnancy as a stress test for detecting women at excessive risk for premature CVD.[2–4]

CVD is the leading cause of death for men and women in high-income and most low-to-middle–income countries.[5] Globally, coronary artery disease kills more women than men,[6] although women develop CVD 10 to 15 years later than men. Women frequently present with unrecognized CVD symptoms and are twice as likely as men to die of a first acute myocardial infarction if <50 years old.[7] The preclinical stages of CVD are evident from a young age and are modifiable through control of classic risk factors (insulin resistance/diabetes mellitus, obesity, lack of exercise, tobacco smoking, hypertension, and hyperlipidemia).[8,9] In this regard, pregnancy is a window of opportunity for identifying those women with perinatal complications who may benefit from early risk detection and early CVD prevention.

In this article, we summarize the associations between pregnancy, placenta-related pregnancy complications, and future maternal CVD. We present established as well as more novel hypotheses, which may explain these epidemiological associations. The interventions that potentially could reduce risks of future CVD are enumerated. To facilitate progress, we suggest methods of harmonizing study designs, long-term follow-ups of pregnancy cohorts and biobanks, and pooling of the world's data in ways that can enhance the power of current and future research.

Associations Between Pregnancy Complications and Future CVD Risk

Preeclampsia and Fetal Growth Restriction and Future CVD Risk

Preeclampsia is a pregnancy-specific multisystem disorder defined by new-onset hypertension and proteinuria after gestational week 20, or new onset preeclampsia-associated signs in the absence of proteinuria.[8] Preeclampsia requires the presence of a placenta or residual placental components (postpartum preeclampsia), but the relative contributions of maternal predisposing factors versus placental factors to its pathophysiology are not well delineated.[9] Women with essential hypertension, obesity, pregestational diabetes mellitus, and renal disease are at elevated risk for developing preeclampsia. Several large-population–based studies demonstrate that women who have had preeclampsia are at increased risk for later CVD and premature death compared with women with healthy pregnancies.[10–14] Women who have experienced either preeclampsia or fetal growth restriction have a 2-fold increased risk compared with pregnancies with a normal outcome. When a woman has both preeclampsia and fetal growth restriction, the likelihood of CVD may be as much as 8-fold higher.[15,16] Recurrent,[12,14,17] more severe, and early-onset preeclampsia, as well as preeclampsia with concurrent neonatal morbidity, increases the risk of later life CVD,[14,16,18,19] much more than gestational hypertension (without proteinuria

or other preeclampsia-associated features) or late-onset preeclampsia.[13,20–22]

Prematurity, Miscarriage, and Future CVD Risk

Women with a history of preterm birth (<37 weeks gestation), even without pregnancy-induced hypertension[23] or preeclampsia,[10,11,24] are twice as likely to die from CVD compared with women who delivered at term. Spontaneous preterm labor is caused by multiple pathological processes[25]; nonetheless, delivery of a preterm or small for gestational age infant overall, independent of smoking and other risk factors, has been shown to increase the risk of CVD death and hospitalization later in life.[26] Although less frequently investigated, recurrent miscarriages have also been linked to future CVD[27] and to endothelial dysfunction.[28] Additionally, recurrent pregnancy loss is associated with pregnancy complications, such as placental abruption and hypertensive pregnancy disorders, which are independently associated with markers of cardiovascular dysfunction, at least in the short term.[29,30]

Diabetes Mellitus in Pregnancy and Future CVD Risk

Women who develop GDM have a 70% higher risk for future CVD than those with no history of the disorder, mostly attributed to an increased risk for developing type 2 diabetes mellitus.[31] As many as half of women with a pregnancy complicated by GDM develop type 2 diabetes mellitus within 5 years,[32] and the diabetes mellitus risk is reported as 7-fold when compared with normoglycemic pregnancies.[33] Whether pregnancy per se exacerbates the increased risk for later life CVD associated with pre-existing diabetes mellitus is not known. Women with type 1 diabetes mellitus seem, however, to be more at risk for developing retinopathy and nephropathy later in life if they had preeclampsia.[34] Chronic kidney disease is considered an independent CVD risk factor,[35] and nephropathy may, therefore, add to the overall CVD risk after a preeclamptic pregnancy in women with pregestational diabetes mellitus.

Normal Pregnancy and Future Risk for CVD

Several studies report an association between the number of a woman's pregnancies, even without adverse outcomes and maternal CVD risk,[36–40] whereas others fail to find such an association.[41,42] For men, a high number of children does not associate with increased CVD risk.[43] In a large Swedish population-based registry study, parity was independently associated with future maternal CVD in a J-shaped fashion (where 2 births represented the lowest risk) after adjustment for socioeconomic factors and pregnancy-related complications. The highest risk was among women with >5 births.[40] The same J-shaped trend between number of births and maternal cardiovascular mortality was found in a recent study from the Norwegian Birth Registry, but only in women with <10 years of education.[44] The number of offspring does not seem to increase the CVD risk for the male partners, after correcting for obesity and metabolic risks,[38] suggesting a pathophysiologic effect from pregnancy, but this finding requires replication. Not only nulliparity per se has been associated with increased CVD risk[40] but also subfertile women who eventually conceive and have a child are at

increased risk for CVD, even after adjusting for CVD risk factors and adverse pregnancy outcomes, suggesting shared risk factors for CVD and infertility.[45]

Women who deliver either large or small birth weight for gestational age infants have been identified as being at increased risk for future CVD.[46] However, study results are inconsistent,[46] and the association may be influenced by the population prevalence of gestational and pregestational diabetes mellitus, as these conditions lead to large gestational age babies. The association of both large gestational age and small gestational age with preeclampsia[47] further confounds the birth weight and CVD relationship. Perhaps, because placental weight and newborn weight are highly correlated, low placental weight also seems to increase maternal risk for future CVD.[48] The impact of breast feeding on long-term maternal CVD seems also to be protective.[49]

Pregnancy: Mechanistic Associations to Future CVD

During pregnancy, the maternal cardiovascular system undergoes substantial physiological adaptive changes,[50] which may also differ according to fetal sex and pregnancy outcome.[51] Repetitive cardiac stress could underlie a report of an association between the number of live births with a small, but significant, increase in left ventricular mass and a small reduction in left ventricular ejection fraction from middle age.[52] In addition, the metabolic consequences of uncomplicated pregnancies could be potentially atherogenic,[53] which could be exaggerated in those with pre-existing dyslipidemia, for example, in obese women or diabetics.

Preeclampsia/Placental Dysfunction and Mechanisms for Increased Maternal CVD Risk

The most widely held hypothesis to explain the link between preeclampsia and CVD focuses on common risk factors.[54] Preeclampsia and CVD may share common genetic risk factors,[55,56] although specific genetic origins of preeclampsia and placental dysfunction remain ill defined. Both preeclampsia[57] and atherosclerosis[58,59] arise from vascular inflammation with its associated endothelial dysfunction. Common risks include obesity, diabetes mellitus, insulin resistance and hyperglycemia, dyslipidemia (including hypertriglyceridemia and small, dense low-density lipoprotein particles),[60–64] hypertension, a family history of CVD,[65] and the metabolic syndrome.[18,66] Paradoxically, cigarette smoking, which augments the risk for atherosclerosis and CVD, reduces the risk for preeclampsia in women who smoke in middle and late pregnancy.[67] The latter may be mediated by a modulatory effect of carbon monoxide on placental production of angiogenic and antiangiogenic factors.[68] The antiangiogenic factor soluble fms-like tyrosine kinase 1 (sFlt1; reviewed below as an important biomarker for early-onset preeclampsia) is lower in smokers than in nonsmokers during pregnancy.[69]

An alternative hypothesis suggests that pregnancy in general, and preeclampsia (and other placental disorders) in particular, worsen pre-existing, subclinical CVD risk factors or even induce de novo risk as reviewed above. A large Norwegian population-based study, while proposing that prepregnancy risk factors are more important,[70–72] also showed

that most CVD risk factors remained significantly higher after preeclampsia following adjustment for prepregnancy values. Possibly, the dyslipidemia of preeclampsia could accelerate progression toward clinical and more advanced atherosclerotic lesions and hypertension.[73]

It is possible that products of the dysfunctional placenta in preeclampsia could permanently compromise the maternal cardiovasculature.[73,74] These could include inflammatory molecules in general as well as factors that perturb maternal angiogenic balance: increased circulating sFlt1 and soluble endoglin and reduced placental growth factor (PlGF), as well as unmeasurable low levels of free vascular endothelial growth factor during pregnancy.[75] Although sFlt1 falls rapidly after delivery, a modest dysregulation several months and years after a preeclamptic pregnancy has been described.[76–78] Increased angiotensin II sensitivity and sFlt1 response to angiotensin II infusion in women with previous preeclampsia has been reported, supporting lasting dysfunctional angiogenic responses.[79] Interestingly, agonistic autoantibodies against the angiotensin II type 1 receptor are present in many preeclamptic pregnancies and may also persist postpartum in some cases and seem to correlate with dysregulated angiogenic biomarkers,[80] suggesting another potential molecular link between pregnancy and future CVD that merits further research. Studies before conception are needed to determine whether these pregnancy and postpartum findings reflect a pre-existing profile or placental dysfunction. Of relevance, a precipitating role for preeclampsia per se has been implicated in the study of the serum proteome of an experimental mouse model in which preeclampsia was induced by adenovirus delivery of sFlt1. At 6 months postpartum, increased expressions of proteins related to CVD were found in comparison with the postpartum profile of normally pregnant mice.[81]

Stem cells, either maternal mesenchymal stem cells or endothelial progenitor cells (EPCs), offer intriguing potential as mediators of persistent cardiovascular dysregulation caused by a dysfunctional placenta. Circulating EPCs are reportedly reduced in preeclampsia,[82] but prepregnancy studies of EPC are lacking. EPCs, markers of endothelial health, are similarly reduced in patients with essential hypertension, in whom EPC senescence is accelerated. It is possible, although not established, that the extremely low free vascular endothelial growth factor concentrations associated with any pregnancy, and possibly even lower in early-onset preeclampsia or fetal growth restriction, could reduce EPCs. Both vascular endothelial growth factor and PlGF increase EPC recruitment, mobilization, and survival outside of pregnancy.[83,84] A reduction in EPC in pregnancy, such as observed in preeclampsia, could potentially affect long-term endothelial function.

The influence of pregnancy on the maternal heart,[52] and effects of preeclamptic pregnancies in particular, has recently been strongly implicated in long-term cardiovascular risk.[85] Eighty percent of women with preeclampsia show an adaptive response to the increased afterload of preeclampsia by left ventricular remodeling. One year postpartum, even in the absence of hypertension, one third of previously preeclamptic women presented global diastolic and regional longitudinal systolic dysfunction with septal bulging, indicative of myocardial

damage, possibly as a consequence of ischemia or fibrosis. These changes were more severe and more frequent when associated with preterm, rather than term preeclampsia.[85] The long-term CVD outcome remains unknown,[74] but as diastolic dysfunction is recognized to predate heart failure and increased mortality,[86,87] poor long-term cardiovascular health is likely.

Important Research Questions

One of the most important questions is whether pregnancy causes or reveals an increased risk for CVD problems. The primary issues are of prepregnancy predisposition, the effect of pregnancy itself, and exaggeration of risk by pregnancy complications. These can only be resolved by new and necessarily expensive prospective longitudinal cohort studies of women prepregnancy and postpregnancy. Medical management will be much better targeted and evidence based once these issues have been clarified.

Optimal Long-Term Medical Supervision of Women After Pregnancies Associated With Increased CVD Risk

In general, it is recommended that after pregnancy, women with pre-existing renal or cardiac complications or who had diabetes mellitus should be offered appropriate specialist follow-up to assess CVD risk and reduce ultimate CVD morbidity. The advice for clinical follow-up of an otherwise healthy woman after complication in pregnancy associated with higher CVD risk is, however, fragmentary, and there is no global consensus (Table S1 in the online-only Data Supplement). Furthermore, many of the recommendations recognize the inadequacy of informative data,[88] and in the case of the American College of Obstetricians and Gynecologists, the recommendations are presented only as suggestions.[8] For women with GDM, several guidelines (Table S1) recommend routine oral glucose tolerance testing postpartum, or measurements of fasting glucose and hemoglobin A1c (HbA1c).[32] Adherence to these postpartum recommendations is generally unknown, and long-term follow-up recommendations after GDM are lacking in most guidelines. Currently, there are no recommendations for maternal follow-up after premature delivery, fetal growth restriction, small gestational age, or recurrent pregnancy loss in relation to future CVD.

A much better understanding of the natural history and time course of progression toward CVD after at-risk pregnancies is needed if evidence-based strategies for follow-up are to be more widely adopted. Demonstration of cost benefit is essential to convince policy makers and payers. We also need to know if early intervention would be more effective than current ad hoc and unsystematic follow-up. An established risk score for CVD, the Framingham score, calculates the 10-year sex-specific risk for cardiovascular events. A young population is in general unlikely to have CVD in the next 10 years. Framingham risk score is, therefore, low for young women, even for those with classical and sex-independent risk factors for CVD, such as diabetes mellitus and obesity.[89] This present risk score, therefore, seems inapplicable for young women, especially because the CVD risk associated with pregnancy disorders is not included. Indeed, the American

Heart Association emphasizes that a low Framingham risk score is not sufficiently exclusive of risk for CVD in young women[5] and have implemented lifestyle advice independent of this scoring system for women whose pregnancies were complicated by preeclampsia, fetal growth restriction, GDM, or a premature delivery (Table S1).

Pregnancy Biomarkers and Improved Risk Stratification for CVD and Targeted Intervention

Preeclampsia and preterm birth are associated with increased insulin resistance, dyslipidemia, and inflammatory activation all relevant in the nonpregnant setting to CVD. It is possible that the degree of abnormality could be relevant to later life CVD. Specific to pregnancy, maternal circulating angiogenic and antiangiogenic biomarkers are dysregulated in placenta-related pregnancy disorders.[76] Elevated circulating sFlt1 and low PlGF in pregnancy may have potential as predictors also of long-term CVD many years after pregnancy; a high sFlt1:PlGF ratio might direct postpartum interventions to those with greatest need. This hypothesis is readily testable in cohorts with postpartum clinical cardiovascular follow-up data.

Outside pregnancy, a high circulating PlGF (assumed to be endothelial derived) is related to an increase in CVD events but has only been investigated in elderly women with a previous CVD event.[90] There is little data on the associations between pregnancy and postpartum sFlt1 or PlGF levels and not known if they play a role as potential biomarkers of future CVD risk. A continuing search for guidance of stratification by preeclampsia biomarkers is an important target for future research.

Therapeutic Strategies to Reduce Long-Term Risk for CVD

Both the American College of Obstetricians and Gynecologists[8] and the UK National Institute for Health and Clinical Excellence[91] guidelines include advice for women after pregnancy complications associated with increased CVD risk to keep a healthy weight, engage in increased physical activity, and refrain from smoking (Table S1). The impact of short-term prolongation of a severely preeclamptic pregnancy, or of more aggressive antihypertensive therapy during pregnancy, on the risk for future maternal CVD is uncertain. Also, the independent effect of a further pregnancy is not known, either if it is normal or complicated by recurrent preeclampsia. Because the early stages of atherosclerosis are reversible, it is possible that prompt postpartum intervention (eg, with statins, metformin, platelet inhibitors/anti-inflammatory drugs, such as low-dose aspirin, angiotensin-converting–enzyme inhibitors, or angiotensin receptor blockers) could reduce CVD risk. But, currently, there is no evidence in favor of any intervention whether reserved for the highest risk groups or more widely applied.

Use of Existing Pregnancy Cohorts and Research Biobanks

Collaboration between researchers who have existing pregnancy cohorts and biobanks across the world is a necessary prerequisite to solving the problems identified. By prolonging follow-up, using standardized protocols and combining data, it should be possible to establish if pregnancy or postpartum biomarker measurement can help stratify risk in seemingly healthy parous women whose pregnancy outcomes identify them as at risk for CVD. Angiogenic factors measured in pregnancy and postpartum[78] and related factors should be evaluated as CVD risk assessment tools, and -omics strategies could be used to identify new candidate risk or pathophysiological factors. Such large data sets, with data collected in a unified way across multiple institutions and nations, could be a powerful guide to future intervention trials aimed at reducing the global burden of CVD.

Potential Pregnancy Biobanks for Long-Term Cardiovascular Follow-Up

The Global Pregnancy Collaboration (CoLab) (https://preempt.cfri.ca/colaboratory) includes 30 international member centers, with data from >300000 pregnancies and biological materials from 20000 pregnancies. The goal is to provide conclusive and globally generalizable insight into disorders of pregnancy. The CoLab initiative has published recommendations for standardizing clinical data and sample collection in studies of preeclampsia.[92,93] It is also undertaking a pooling of individual measurements of placentally associated biomarkers analyzed in 28 different cohorts worldwide.[94]

Several of the contributing pregnancy registries and biobanks within the CoLab network are undertaking or planning long-term follow-up of maternal disease remote from pregnancy. Data and samples have been usually acquired during pregnancy, and only rarely before pregnancy. The Dutch Generation R study has followed a large population-based cohort of women and their offspring after pregnancy.[95–97] Another, the Norwegian MoBa study[98,99] including >70000 women and 100000 pregnancies also has a long-term follow-up goal. One longitudinal United Kingdom study, OxWatch,[100] is studying women from before pregnancy, during pregnancy, and beyond. The Preeclampsia Registry, developed and managed by the Preeclampsia Foundation and associated with CoLab, is accepting participants worldwide and has currently enrolled 2000 women, most of whom have had preeclampsia. The database also includes nulliparous and parous sisters, other family members, and controls.

Harmonization of Databases

The ability to merge the data or samples from different studies is limited by the heterogeneity in how and which data are collected, as well as in the frequencies and intervals of clinical follow-up. CoLab is developing an online clinical database, originally for prospective studies of preeclampsia, which will standardize collection of appropriate data for pregnancy research and will be available for general use in 2016. It follows up on previously recommended minimal and optimal data sets for preeclampsia research[92] and will facilitate pooling of data from such new prospective studies. The principle of harmonization of study data can be extended to all other long-term health outcomes after pregnancy, uncomplicated or complicated. Any research study related to human pregnancy information (both within and outside the CoLab organization) is encouraged to register their pregnancy and long-term follow-up research study at an open web platform (www.linkregistry.org), to promote research collaboration across studies.

Table.   Harmonization of Research Studies for Future CVD Follow-Up in Low-Risk Young Women

Visit	Clinical Information	Biological Samples for Research Biobanking	CV Risk Phenotyping
Pregestational	Family history of CVD: CVD/CVD death in firstst-degree relative, type of CVD, age at time of diagnosis or death*	Blood (plasma and serum) and urine sampling†	BP, measured and reported according to accepted guidelines*
	Basics (physical, anthropological and ethnographic data): age, height, and weight (body mass index) and waist/hip ratio*		Blood screen for dyslipidemia (total cholesterol, LDL cholesterol, and HDL cholesterol) and diabetes mellitus (fasting blood glucose or HbA1c)*
	Smoking history (never, irregularly, regularly use, current use): cigarette/cigar or snuff or chews tobacco/nicotine*		Urine screen: protein (and hematuria/glucosuria)*
	Medical history: hypertension, cardiac disease, stroke, renal disease, pregestational diabetes mellitus (type and treatment), collagen vascular disease, systemic lupus erythematosus, obstructive sleep apnea*		
	Obstetric history (gravidity, parity: indicate numbers and gestational age at deliveries): miscarriage, stillbirth, abortions (induced/spontaneous); pregnancy-induced hypertension, preeclampsia, eclampsia, HELLP, small for gestational age/fetal growth restriction, GDM (treatment type), preterm delivery (<37 wk), neonatal death, placental weights*		
	Self-described ethnicity (white, black, Asian, Hispanic, unknown, or other [mixed])*		Cardiovascular phenotyping 1: Macrovasculature function (endothelial function and arterial stiffness) and structure (carotid imaging)†
	Years of schooling/other socioeconomic indicator†		Cardiovascular phenotyping 2: microvasculature (rarefaction)†
	Maternal/paternal (and grandparent) country of birth†		Cardiovascular phenotyping 3: echocardiography†
	Physical activity (IPAQ) and diet questionnaires†		Oral glucose tolerance test (OGT)/HOMA score†
	Breast feeding history (duration and after how many pregnancies?)†		
Pregnancies (all trimesters preferably)	Updated family history of CVD, basics, smoking, medical/obstetric history (as in pregestational visit above)*:	Longitudinal blood (plasma and serum) and urine sampling, according to Myatt et al[92]†	BP, measured and reported according to accepted guidelines (Supplemental references in the online-only Data Supplement for pregnancy BP)*
	Pregnancy clinical information, including maternal/fetal outcome and placenta variables[92]*	Placental sampling, according to Burton et al[93]†	Urine screen: protein (and hematuria/glucosuria and UTI screen). Albumin/creatinine ratio (longitudinal, until positive diagnosis of proteniuria/preeclampsia)*
			OGT/HOMA score*
	US registrations from pregnancy: uteroplacental Doppler blood flow findings and fetal growth measurements†		Cardiovascular phenotyping:1–3 (as above)†
Postpartum (6–12 wk, 6 mo, and 1 y after index pregnancy, then every 5th year)	Update of family history of CVD, basics, smoking, medical/obstetric history (as in pregestational visit above)*	Blood (plasma and serum) and urine sampling†	BP, measured and reported according to accepted guidelines*
	Physical activity (IPAQ) and diet questionnaires†		Urine screen: protein (and hematuria/glucosuria)*
	Breast feeding history (duration)†		Blood screen for dyslipidemia (total cholesterol, LDL cholesterol, HDL cholesterol), and diabetes mellitus (fasting blood glucose or HbA1c)*
			Oral glucose tolerance test (3–6 mo postpartum after GDM is recommended clinically)†
			Cardiovascular phenotyping: 1–3 (as above)†

BP indicates blood pressure; CVD, cardiovascular disease, GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HELLP, hemolysis, elevated liver enzymes, low platelets; HOMA, homeostasis model assessment; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein; and UTI, urinary tract infection.

*Minimal data set.

†Extended data set.

Ideal Cohort to Study Remote CVD After Pregnancies

An option, although costly, is to construct a new international, prospective, longitudinal, research cohort, which would commence before pregnancy, and follow women longitudinally over many years to include the hard end points of CVD (eg, death, stroke, and myocardial infarct). Such a cohort should be global in every sense. This International Longitudinal Women's Health Cohort will be challenging to fund and administer. Even without such a large formal cohort, we encourage that our recommendations of data storage harmonization are adopted for smaller individual studies to facilitate study linkages at a later date.

Minimal and Extended Follow-Up Research Data Set for Future CVD After Pregnancy

The Table summarizes our suggestions for a minimal and extended research data set for studying long-term cardiovascular health after pregnancy, including suggestions for cardiovascular phenotyping, collection of general health assessments, and pregnancy information. Recruitment should not only be limited to women at elevated risk for CVD but also to uncomplicated pregnancies. Ideally, recruitment should be population based. The suggested follow-up in the Table focuses specifically on CVD but could be modified to meet the needs of different health outcomes after pregnancy, such as renal, thyroid, neurodegenerative, or psychiatric disease. Such studies could hopefully identify suitable time points for cost-efficient analyses of the follow-up of (apparently) healthy parous women after pregnancy complications.

In contrast, women in high-income countries who have clinical evidence of CVD, either prepregnancy, during pregnancy, or postpartum, would be followed up by a specialist (eg, a cardiologist), with clinical strategies that need individualization and may differ from the suggested research oriented suggestion of the Table. Women with prepregnancy diabetes mellitus or renal disease should be offered appropriate specialist follow-up postpartum, whatever pregnancy complications, to reduce the risk for end-stage organ damage.

It is important that the data collected and the timing of collection in follow-up studies are similar across different studies (Table). We suggest that follow-up research studies after pregnancy obtain a clinical history, including data on smoking, hypertension and diabetes mellitus, obstetric history and length of breast feeding from all pregnancies,[92] and family history of CVD risk factors. In addition, we suggest a minimal clinical assessment including blood pressure measurement and testing for insulin resistance (with fasting blood glucose as a first screening[1] or HbA1c or the more labor extensive oral glucose testing or homeostasis model assessment score for the extended data set). Our suggested testing for other risk factors for CVD, such as renal disease (urine dipstick for proteinuria as a first screening or albumin/creatinine ratio), body mass index, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein -cholesterol, is consistent with CVD risk screening recommended by the American Heart Association.[1] The Table presents a minimal data set and an extended data set for research follow-up. The minimal data set is chosen as information that can be collected also in low-resource setting, in recognition of the necessity of information specific to settings with the highest rates of pregnancy complications and deaths from these conditions.

An extended follow-up research plan for CVD includes more detailed cardiovascular phenotyping as well as blood sampling for research purposes. Currently, there is no biomarker that is known to precisely predict future CVD in young and symptom-free women, who have normal kidney function, blood sugar, lipids, and blood pressure, and therefore, adequate samples for various analytic options should be collected. Sampling and storage of biological material (blood, placenta, possibly urine and feces, and other material) would cover a broad range of analytic options and biomarker discovery, including options for -omics (metabolomics, etc.). [1]H nuclear magnetic resonance metabonomics (a form of metabolomics related to nutrition) could, for example, explore atherosclerotic and CVD pathophysiology.[101] Supplemental Data S2 in the online-only Data Supplement details the current most sensible options for extended cardiovascular phenotyping in a long-term follow-up clinical research setting, provided the necessary skill base is available. Linking imaging and physiological phenotypes with later health outcomes, similar to approaches being used in large-scale longitudinal cohorts, such as UK Biobank,[102] may also identify novel vascular or cardiac risk markers that predict which women are at greatest risk for later CVD.[5] Such studies typically use a comprehensive approach that captures data on a broad range of cardiovascular parameters and often include assessment of other related systems through metabolic, bone, cerebral, or renal imaging and assessment. We recognize that many pregnancy-associated research centers may have specialist experience or equipment for evaluation of only one, or a few, of these different areas but, through a collaborative approach, centers with similar data could be linked to generate combined data sets. In addition, there are some noninvasive techniques that do not require major infrastructure and so are widely available across multiple sites. Supplemental File S2 considers these common noninvasive techniques that could be incorporated into an extended follow-up data set for research purpose and would allow comprehensive assessment across the woman's macrovasculature (both functional and structural investigations), microvasculature, and heart.

Time Points for Measurement and Frequency of Postpartum Research Follow-Up Visits

The optimal time points for measurements of cardiovascular variables in longitudinal follow-up cohorts are unknown. Prepregnancy measures will be invaluable to discriminate those cardiovascular changes that predispose to pregnancy outcomes as opposed to those developing or aggravated by pregnancy itself. However, the challenges of a prepregnancy cohort include that women do not always plan their pregnancies, nor do pregnancies necessarily occur when planned. Thus, the time between prepregnancy testing and the subsequent pregnancy will vary. Because vascular measures change with age, the gap between the time of measurement and the index pregnancy may reduce the value of the prepregnancy measure. It is not known whether or when in pregnancy vascular phenotyping would be most relevant for unmasking the

most reliable risk for long-term CVD. Until this question is resolved, testing could ideally be done in early, mid, and late pregnancy and, if possible, in the case of preeclampsia, when the woman manifests the clinical signs.

The frequency of the suggested clinical research follow-up after pregnancy should be standardized to allow determination of the natural history of the progression to CVD. Potential clinical findings at the follow-up will likely vary between premenopausal and postmenopausal women. Postmenopausal women have a higher short-time CVD risk, with greater disease prevalence. However, identifying increased risk in younger women would be optimal to prevent CVD, favoring more frequent and regular examinations of younger and clinically healthy women. For harmonizing purposes, we suggest a first 6 to 12 weeks postpartum follow-up after pregnancy, as this timing is used clinically today as a routine check-up after pregnancy in many countries. Thereafter, we suggest a 6-month and 1-year follow-up, with subsequent follow-up at least every 5 years for the clinically healthy women. If evidence of clinical CVD is found in this research setting, appropriate clinical and specialist follow-up is, of course, recommended. Importantly, even if the resources are not available for such work-intensive follow-up, we strongly recommend studies be designed to allow coupling of pregnancy data from the recruited women to other potential registries or patient databases documenting clinical (including hard) CVD end points.

Several countries currently offer population-based health screening programs, such as screening for cervical and breast cancer, which are assumed to be cost-effective. However, CVD is the greatest cause of death and years of life lost in the world,[103] yet no screening is offered due to lack of evidence for its efficiency. To increase patient compliance and to secure a cost-efficient follow-up of CVD screening, our suggested minimal data set follow-up could be adapted to such pre-existing screening programs, providing added value without much extra cost. This may be a payer issue in countries without government-provided health care, which needs to be taken on by professional and consumer organizations as an advocacy initiative.

Women's Involvement in Long-Term Follow-Up for CVD

The involvement of women with relevant pregnancy experience in the development of these research programs is underappreciated, but important and enlightening.[104] We, therefore, recommend that this research initiative is developed with continuing discussion with appropriate patient groups to ensure that their views are fully expressed and incorporated into research planning. Patient-run organizations, such as in the United States (www.preeclampsia.org), United Kingdom (www.action-on-pre.eclampsia.org.uk), and Australia (www.aapec.org.au), actively support preeclampsia research and long-term follow-up for CVD. These organizations have a key role in updating women about the evidence for risks of CVD in relation to their pregnancy histories, even though women cannot expect routine follow-up without sound evidence that this is beneficial. But women can strengthen the call for more and better research to gain the evidence. They can also help to update health personnel

who are still relatively unfamiliar with the association of future CVD with pregnancy complications.[105] They can demand that hospitals provide more and better patient-oriented information regarding long-term CVD risk after pregnancy complications (eg, www.themothersprogram.ca).

Supporting patient involvement should increase compliance with current (well-meant but often ignored) advice on weight control, smoking cessation, and management of additional CVD risk factors (eg, diabetes mellitus and hyperlipidemia). The current United States[8] and United Kingdom[106] advice on patient-oriented recommendations is general. More CVD follow-up research is needed to enable better and more specific recommendations.

Translation into Clinical Practice

We hope that, in the future, the longitudinal research studies, described here, will be translated into widely practiced, evidence-based routines of clinical follow-up, for selected women who have had complicated pregnancies. A suggested template is given in Figure S1 in the online-only Data Supplement. Resolution of the outstanding research issues that have been identified in this article could identify which biomarkers would help to refine recommendations for, and timing of, the follow-ups and maximize health outcomes cost effectively. This or a similar template could be adapted to differing health systems and even linked to other established screening programs, for example, those for cervical and breast cancer.

Perspectives

Despite a clearly documented increased risk for CVD after pregnancy complicated by placental dysfunction or GDM, our understanding of the underlying mechanisms is poor. It is also not clear how to appropriately target preventive strategies to the women at highest risk and what interventions are likely to confer benefit. More long-term research programs are needed particularly to discriminate between the specific effects of pregnancy and prepregnancy risk factors on future maternal CVD.

The need for adequately powered, large, longitudinal studies is identified as a critical issue. These are expensive and difficult to achieve in isolation. Progress will be faster if data and samples are collected in such a way that separate studies can be combined to achieve collaboratively determined goals that are otherwise unattainable. This would be powerfully facilitated by preagreed harmonization of research protocols to ensure that important data and samples can be readily pooled. We suggest a provisional format for such harmonization and encourage discussion, between those involved, to refine its design. In addition, to address the crucial question of the role of prepregnancy risk factors, we promote the concept of a new International Longitudinal Women's Health Cohort. It should then become possible to validate markers of long-term CVD in young women and identify new therapeutic targets for intervention, in collaboration with clinical experts on CVD. Better surrogate markers, singly or in combination, for long-term CVD in young women will enable targeted testing of primary prophylactic agents many decades before the first, and possibly lethal, evidence of atherosclerosis and CVD.

Appendix

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None.

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PREGNANCY AND LONG-TERM MATERNAL CARDIOVASCULAR HEALTH: PROGRESS THROUGH HARMONIZATION OF RESEARCH COHORTS AND BIOBANKS

By

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S1. Examples of current guidelines on clinical follow-up for future cardiovascular disease (CVD) after a pregnancy outcome associated with increased CVD risk .

BP: blood pressure; FGR: fetal growth restriction; GDM: gestational diabetes mellitus; OGTT: Oral glucose tolerance test; PE: preeclampsia

Pregnancy outcome	Preeclampsia, FGR, GDM and Premature Delivery	Hypertensive Disorder of Pregnancy	Gestational Diabetes Mellitus
AHA[1]	**Assessments:** BP, Lipids, Fasting blood glucose, BMI **Lifestyle advice:** BMI<25kg/m^2 Healthy diet Physical activity No smoking		
ACOG[2]		**Assessments** (yearly if preterm PE/recurrent PE)**:** BP, Lipids, Fasting blood glucose, BMI **Lifestyle advice:** Maintain maternal weight Physical activity No smoking	**Assessments:** OGTT (6 weeks postpartum)
ADA[3]			**Assessments:** Screen for diabetes (6-12 weeks postpartum and every 1-3 years)
NICE[4;5]		**Information:** Increased risk of gestational hypertension/PE in future pregnancy Increased risk of hypertension and its complications later in life **Lifestyle advice:** Maintain maternal weight (BMI 18.5-24.9 kg/m^2). Healthy diet	**Information:** GDM risk next pregnancy Symptoms of hyperglycemia **Assessments:** Fasting plasma glucose before hospital discharge and 6-13 weeks postpartum Test for diabetes when planning next pregnancy **Lifestyle advice:** Maintain maternal weight Healthy diet Physical activity
SOMANZ[6]		**Assessments:** BP (yearly) Lipids (every 5 years) Glucose (every 5 years) **Lifestyle advice:** Maintain maternal weight Healthy diet Physical activity No smoking	
ADIPS[7]			**Assessments:** OGTT (6-12 weeks postpartum) Fasting plasma glucose/HbA1C (at least every 1-2 years)

S2.

A suggestion of current most sensible options for extended cardiovascular phenotyping in a long-term follow-up clinical research setting after pregnancy complications (also including women with uncomplicated pregnancies), provided local available necessary skills and resources.

Macrovasculature (Function - Endothelial). A plethora of studies have shown that impaired endothelial function is associated with increased risk of CVD,[8-10] representing an important factor in the pathogenesis of atherosclerosis, hypertension and heart failure. Furthermore, endothelial function is known to be significantly altered during pregnancy in preeclampsia and in other hypertensive pregnancy disorders as well as for several years after pregnancy. However, studies that have addressed this question are still relatively small and often lack pre-pregnancy testing data. Therefore, we believe there remains a need to assess endothelial function in larger linked datasets to gather definitive information.

Non-invasive endothelial testing methods typically involve measurement of a change in a vascular parameter that is endothelial-dependent, e.g. brachial artery diameter or microvascular blood flow, in response to a reactive hyperemic stimulus. Reported methods include flow-mediated vasodilation (FMD), peripheral artery tonometry (PAT) and other reactive hyperemic index devices.[11] All have been validated as being endothelial-dependent and choice should be based on the local expertise of the center in measurement of endothelial function.
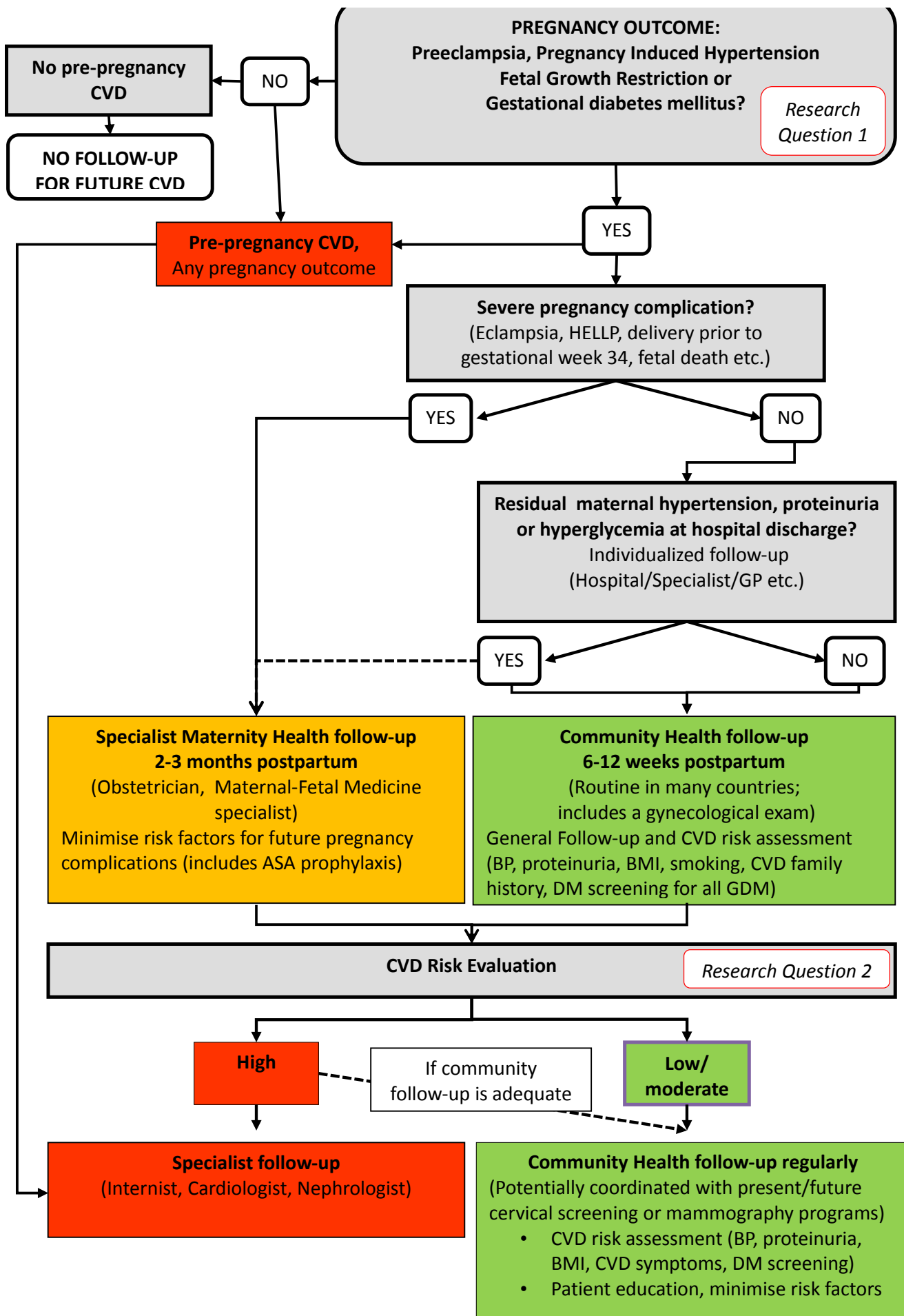
Macrovasculature (Function – Arterial Stiffness). Measurement of arterial stiffness provides additional information on large artery structure and function. It is also closely linked to CVD endpoints[12] and is recommended in the evaluation of hypertension, according to European guidelines.[13] Typically arterial stiffness is measured as carotid-femoral pulse wave velocity (PWV) by applanation tonometry and extensive guidelines for measuring PWV have been published by van Bortel et al.[14] Most techniques for assessment of arterial stiffness based on applanation tonometry also apply pulse wave analysis (PWA) techniques to generate the augmentation index (AIx) which is related to how the reflected pulse wave alters the pulse profile.[15] This measure is reproducible[16] and predicts cardiovascular disease in hypertensive patients[17] and those undergoing percutaneous coronary intervention (PCI).[18] However, the measure does not exclusively characterize central arterial stiffness being altered by heart rate and the peripheral vasculature. Therefore we suggest this measure should not be collected as the only measure of vascular stiffness, but rather as an adjunct to pulse wave velocity.

Macrovasculature (Structure). Information on structural changes of potential relevance to atherosclerotic or hypertensive heart disease can be gathered by measuring carotid vessel changes with ultrasound. These measures include carotid intima-media thickness (CIMT), which is highly reproducible,[19] and also presence of plaque. CIMT alone may not predict CVD beyond traditional risk factors for CVD,[20;21] but the presence of plaque does appear to allow better risk stratification. Therefore, we suggest carotid imaging should be considered in an extended vascular phenotyping dataset.

Microvasculature. Assessment of capillary rarefaction or microvessel structure[22] involves analysis of the microcirculation in the tongue, retina or dorsal finger. Each of these microvascular beds are under different physiological control and also have different embryological origins. However, altered microvascular rarefaction is observed early in the onset of preeclampsia and changes in the microcirculation are seen during the development of several vascular conditions such as hypertension. Therefore analysis of the microcirculation may be of interest to understand the pathway between hypertensive pregnancy disorders and cardiovascular disease. Current techniques based on capillaroscopy of the skin or subungual microvasculature are time-consuming although

retinal imaging is relatively rapid. We suggest, where there is appropriate expertise, microvascular measures in an "extended" dataset follow-up after pregnancy to study how women after a history of pregnancy complications associated with future CVD differ from those without these pregnancy complications.

Cardiac. There is particular interest in the impact of pregnancy on cardiac function and therefore, in centers with appropriate expertise, we suggest to include cardiac echocardiography in longitudinal studies to characterize cardiac structure and function,[23] ideally also including pre-pregnancy evaluations.

PREGNANCY OUTCOME:
Preeclampsia, Pregnancy Induced Hypertension
Fetal Growth Restriction or
Gestational diabetes mellitus?

Research Question 1

No pre-pregnancy CVD

NO

NO FOLLOW-UP FOR FUTURE CVD

YES

Pre-pregnancy CVD, Any pregnancy outcome

Severe pregnancy complication?
(Eclampsia, HELLP, delivery prior to gestational week 34, fetal death etc.)

YES

NO

Residual maternal hypertension, proteinuria or hyperglycemia at hospital discharge?
Individualized follow-up
(Hospital/Specialist/GP etc.)

YES

NO

Specialist Maternity Health follow-up 2-3 months postpartum
(Obstetrician, Maternal-Fetal Medicine specialist)
Minimise risk factors for future pregnancy complications (includes ASA prophylaxis)

Community Health follow-up 6-12 weeks postpartum
(Routine in many countries; includes a gynecological exam)
General Follow-up and CVD risk assessment (BP, proteinuria, BMI, smoking, CVD family history, DM screening for all GDM)

CVD Risk Evaluation

Research Question 2

High

If community follow-up is adequate

Low/ moderate

Specialist follow-up
(Internist, Cardiologist, Nephrologist)

Community Health follow-up regularly
(Potentially coordinated with present/future cervical screening or mammography programs)
- CVD risk assessment (BP, proteinuria, BMI, CVD symptoms, DM screening)
- Patient education, minimise risk factors

Supplemental Figure S1. An example of follow-up flow chart after 3 categories of complicated pregnancies associated with increased risk for future cardiovascular disease (CVD).
ASA: Acetylic Salicylic Acid (low-dose). HELLP: Hemolysis, elevated liver enzymes, low platelets syndrome.

Italic Text- Remaining Research Questions:
1. *Which biomarkers (before or during pregnancy) can best predict CVD risk in young women?*
2. *Which biomarkers (postpartum or any time point after pregnancy) can best predict CVD risk in young women?*

Green colour: Community Health Level (e.g. General Practitioner: GP)
Orange colour: Specialist Maternity Health Care (e.g. Obstetrician)
Red colour: Specialist Medical Care (e.g. Internist, Cardiologist, Nephrologist)