

ONLINE SUPPLEMENT

CARDIOVASCULAR RISK MANAGEMENT AFTER REPRODUCTIVE AND PREGNANCY RELATED DISORDERS: A DUTCH MULTIDISCIPLINARY EVIDENCE-BASED GUIDELINE

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Section 1. Methods

Five gynecologists, one cardiologist, one vascular internist, one radiologist, one general practitioner and two epidemiologists participated in the guideline development group. All were authorized by their scientific professional association (the Dutch Society of Obstetrics and Gynecology, The Netherlands Society of Cardiology, The Netherlands Society of Internal Medicine, the Radiological Society of The Netherlands and the Dutch College of General Practitioners, respectively).

The guideline was developed consistent with the “Appraisal of Guidelines for Research and Evaluation” instrument,¹ an approach that is currently used in the development of guidelines in The Netherlands by the Dutch Institute for Healthcare improvement (Centraal BegeleidingsOrgaan, CBO, <http://www.cbo.nl/en>). Initially, the development group performed a problem analysis to define the scope and relevant topics for this guideline. An invitational conference was organized with different stakeholders involved in the care of patients with reproductive and pregnancy related disorders, such as health insurers, the Health Care Inspectorate (Inspectie voor de Gezondheidszorg, IGZ, <http://www.igz.nl/english/>), patients associations (Stichting HELLP-syndroom, <http://www.hellp.nl>) and the National Health Care Institute (Zorginstituut Nederland, <https://www.zorginstituutnederland.nl>). Furthermore, three focus groups were organized to allow women with either a reproductive disorder or a history of pregnancy related disorder to inform the development group about their experiences with the provided care, as well as their needs and desires to improve current healthcare.

These obtained problem topics were translated into the following clinical key question: what is the relative risk of a cardiovascular event and what is the relative risk of having or developing a cardiovascular risk factor after a reproductive or pregnancy related

disorder? The scientific literature was systematically searched for answering these questions using the electronic databases MEDLINE and EMBASE. Separate search strategies were developed for each reproductive or pregnancy related disorder, however the same outcome measures were used in all searches, for details see Section S2. Systematic searches were conducted in collaboration with an information specialist. Studies were limited to English language. Members of the development group were allocated to clinical topics. To select relevant literature two members of the development group reviewed results of the search for each clinical topic. Discrepancies were discussed with inclusion of a third reviewer if necessary. Furthermore, the bibliographies references of relevant literature were hand-searched for other valuable references. The characteristics and methodological quality of the studies were assessed using the checklists from the Dutch Cochrane Center.² The evidence was summarized in evidence tables and in the guideline text. The relation between the reproductive or pregnancy related disorders and CVD risk and risk factors was defined and assessed by meta-analysis. If multiple published reports from the same study were available, we included the one with the largest cohort and most detailed information for both exposure and outcome. Relative risks (RR), odds ratios (OR) and hazard ratios (HR) with their 95% confidence intervals (CI) were extracted from the selected publications. When available, the results of the most complete multivariate models with adjustment for potential confounders was used. The inverse variance weighted method was used to combine the most adjusted ratios to produce a pooled RR and 95% CI. The pooled RR was estimate using a random effect's model. All statistical analysis were performed using Review Manager 5.2.

In the guideline, each pregnancy or reproductive disorder has its own section that comprises background, a summary of the literature, meta-analysis with the level of

evidence, considerations and recommendations. The grading tool of the Dutch Institute for Healthcare improvement (CBO) was used to level the evidence, see Table S1.

Conclusions and recommendations were based predominantly on the result of cohort studies, since these provide the best information about the causation of disease and are less prone to bias. The recommendations are the practical answer to the key question: what is the relative risk of a cardiovascular event and what is the relative risk of having or developing a cardiovascular risk factor after a reproductive or pregnancy related disorder? They were based on the evidence and balanced with the knowledge and experience of the development group members. The guideline ends with a general discussion. The identified knowledge gaps can be found in Section S4. The guideline was reviewed by all participating scientific societies in order to achieve consensus on statements including issues concerning organization of care.

Section 2. Search strategies for the reproductive or pregnancy related disorders and the risk of developing a cardiovascular event or risk factor.

Hypertensive disorders of pregnancy

Medline (OVID) – 1966 to 23 January 2013

- 5 exp Hypertension, Pregnancy-Induced/ (25741)
- 6 ((pregnancy-induced or gestational or maternal) adj3 hypertension*).ti. (1547)
- 7 ((transient adj3 hypertension) and pregnan*).ti. (10)
- 8 ("hemolysis, elevated liver enzymes, and low platelet*" or hellp or eclampsia or pre-eclampsia or preeclampsia or (pregnancy adj3 toxemia)).ti. (11855)
- 9 or/5-8 (27132)
- 10 exp Cardiovascular Diseases/ep, et [Epidemiology, Etiology] (439592)
- 11 (exp Renal Insufficiency/ or calcinosis/ or exp vascular calcification/ or Hypercholesterolemia/ or exp Obesity/ or exp Electrocardiography/ or exp Hypertension/ or exp Diabetes Mellitus/ or Metabolic Syndrome X/) and (epidemiology or etiology).fs. (276102)
- 12 (stroke or CVA or cerebrovascular or cardiovascul* or (myocard* adj2 infarct*) or atheroscleros* or "vascular calcification*" or ((renal or kidney) adj3 (insufficienc* or failure*)) or "ischaemic attack*" or TIA or "angina pectoris" or electrocardiogra* or ecg or hypercholesterolemia or hypertension or diabet* or ((endothelial or vascular) adj2

dysfunction*) or (("left ventricular" or myocardial) adj3 hypertroph*) or (metabol* adj2 syndrome*).ti. (630214)

13 10 or 11 or 12 (1048086)

14 9 and 13 (5425)

15 limit 14 to english language (4061) -

16 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy\$).tw. or (systematic* adj review\$1).tw. or (systematic adj overview\$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psychlit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (117463)

18 15 and 16 (57) – (SR) – keyword in reference manager: Medline-Cardio-Hypertensie-SR-23-01-2013

19 15 not 18 (3994)

Embase (Elsevier) - 1980 to 23 January 2013

('maternal hypertension'/exp/mj OR ((transient NEAR/3 hypertension):ti AND pregnan*:ab,ti) OR (('pregnancy induced' OR gestational OR maternal) NEAR/3 hypertension*):ti OR hellp:ti OR eclampsia:ti OR 'pre eclampsia':ti OR preeclampsia:ti OR (pregnancy NEAR/3 toxemia):ti OR 'haemolysis, elevated liver enzymes, and low platelet':ti OR 'haemolysis, elevated liver enzymes, and low platelets':ti OR 'hemolysis,

elevated liver enzymes, and low platelet':ti OR 'hemolysis, elevated liver enzymes, and low platelets':ti)

AND ('cardiovascular disease'/exp/mj OR 'kidney failure'/exp/mj OR 'diabetes mellitus'/exp/mj OR 'electrocardiography'/exp/mj OR 'hypercholesterolemia'/exp/mj OR 'hypertension'/exp/mj OR 'obesity'/exp/mj OR 'blood vessel calcification'/exp/mj OR 'metabolic syndrome x'/exp/mj OR stroke:ab,ti OR cva:ab,ti OR cerebrovascular:ab,ti OR cardiovascul*:ab,ti OR (myocard* NEAR/2 infarct*):ab,ti OR atheroscleros*:ab,ti OR (vascular NEAR/2 calcification):ab,ti OR ((renal OR kidney) NEAR/3 (insufficienc* OR failure*)):ab,ti OR (ischaemic NEAR/2 attack*):ab,ti OR tia:ab,ti OR 'angina pectoris':ab,ti OR electrocardiogra*:ab,ti OR ecg:ab,ti OR hypercholesterolemia:ab,ti OR obesity:ab,ti OR hypertension:ab,ti OR diabet*:ab,ti OR ((endothelial OR vascular) NEAR/2 dysfunction*):ab,ti OR (('left ventricular' OR myocardial) NEAR/3 hypertroph*):ab,ti OR (metabol* NEAR/2 syndrome*):ab,ti)

NOT 'conference abstract':it AND [english]/lim AND [embase]/lim

Preterm delivery

Medline (OVID) – 1966 to 17 July 2014

- 1 Obstetric Labor, Premature
- 2 ((preterm or premature) adj3 (birth* or deliver*)):ti,ab.
- 3 1 or 2
- 4 exp Cardiovascular Diseases

5 exp Renal Insufficiency/ or calcinosis/ or exp vascular calcification/ or
Hypercholesterolemia/ or exp Obesity/ or exp Electrocardiography/ or exp
Hypertension/ or exp Proteinuria/ or exp Diabetes Mellitus/ or Metabolic Syndrome X

6 (stroke or CVA or cerebrovascular or cardiovascul* or (myocard* adj2 infarct*) or
atheroscleros* or "vascular calcification*" or ((renal or kidney) adj3 (insufficienc* or
failure*)) or "ischaemic attack*" or TIA or "angina pectoris" or electrocardiogra* or ecg
or hypercholesterolemia or obesity or hypertension or proteinuria or diabet* or
((endothelial or vascular) adj2 dysfunction*) or (("left ventricular" or myocardial) adj3
hypertroph*) or (metabol* adj2 syndrome*)).ti,ab.

7 4 or 5 or 6

8 3 and 7

13 limit 8 to english language

16 mothers/ or (maternal adj6 (cardiovascular or risk*)).ti,ab.

17 13 and 16

22 (preterm and cardiovascular).ti.

23 8 and 22

24 17 or 23 (337)

Embase (Elsevier) - 1980 to 17 July 2014

('premature labor'/exp/mj OR ((preterm OR premature) NEAR/3 (birth* OR deliver*)):ab,ti) AND ((maternal NEAR/6 (cardiovascular OR risk*)):ab,ti OR 'mother'/exp)

AND ('cardiovascular disease'/exp/mj OR 'kidney failure'/exp/mj OR 'diabetes mellitus'/exp/mj OR 'electrocardiography'/exp/mj OR 'hypercholesterolemia'/exp/mj OR 'hypertension'/exp/mj OR 'obesity'/exp/mj OR 'proteinuria'/exp/mj OR 'blood vessel calcification'/exp/mj OR 'metabolic syndrome x'/exp/mj OR stroke:ab,ti OR cva:ab,ti OR cerebrovascular:ab,ti OR cardiovascul*:ab,ti OR (myocard* NEAR/2 infarct*):ab,ti OR atheroscleros*:ab,ti OR (vascular NEAR/2 calcification):ab,ti OR ((renal OR kidney) NEAR/3 (insufficienc* OR failure*)):ab,ti OR (ischaemic NEAR/2 attack*):ab,ti OR tia:ab,ti OR 'angina pectoris':ab,ti OR electrocardiogra*:ab,ti OR ecg:ab,ti OR hypercholesterolemia:ab,ti OR obesity:ab,ti OR hypertension:ab,ti OR proteinuria:ab,ti OR diabet*:ab,ti OR ((endothelial OR vascular) NEAR/2 dysfunction*):ab,ti OR (('left ventricular' OR myocardial) NEAR/3 hypertroph*):ab,ti OR (metabol* NEAR/2 syndrome*):ab,ti)

AND [english]/lim AND [embase]/lim NOT 'conference abstract':it

Small for gestational age infant

Medline (OVID) – 1966 to 19 December 2012

- 1 ("small for gestational age" or SGA or ("intrauterine growth" adj3 (restriction or retardation)) or ("fetal growth" adj3 (restriction or retardation)) or IUGR).ti,ab. or Fetal Growth Retardation/ or infant, small for gestational age/ (23549)
- 2 exp Cardiovascular Diseases/ (1781176)
- 3 exp Renal Insufficiency/ or calcinosis/ or exp vascular calcification/ or Hypercholesterolemia/ or exp Obesity/ or exp Electrocardiography/ or exp Hypertension/ or exp Proteinuria/ or exp Diabetes Mellitus/ or Metabolic Syndrome X/ (908008)
- 4 (stroke or CVA or cerebrovascular or cardiovascul* or (myocard* adj2 infarct*) or atheroscleros* or "vascular calcification*" or ((renal or kidney) adj3 (insufficienc* or failure*)) or "ischaemic attack*" or TIA or "angina pectoris" or electrocardiogra* or ecg or hypercholesterolemia or obesity or hypertension or proteinuria or diabet* or ((endothelial or vascular) adj2 dysfunction*) or (("left ventricular" or myocardial) adj3 hypertroph*) or (metabol* adj2 syndrome*)).ti,ab. (1292793)
- 5 2 or 3 or 4 (2620184)
- 6 1 and 5 (6023)
- 7 (Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth).m_titl. (1)
- 8 "Maternal cardiovascular disease risk in relation to the number of offspring born small for gestational age: national, multi-generational study of 2.7 million births".m_titl. (1)
- 9 7 or 8 (2)

- 10 6 and 9 (2)
- 11 limit 10 to english language (2)
- 12 limit 6 to english language (5277)
- 13 mothers/ or maternal.ti. or (maternal adj6 risk*).ti,ab. (74353)
- 14 12 and 13 (714)
- 17 mothers/ or (maternal adj6 (cardiovascular or risk*)).ti,ab. (32045)
- 18 12 and 17 (295)

Embase (Elsevier) - 1980 to 19 December 2012

('intrauterine growth retardation'/exp/mj OR 'small for date infant'/exp/mj) AND ('small for gestational age':ab,ti OR sga:ab,ti OR ('intrauterine growth' NEAR/3 (restriction OR retardation)):ab,ti OR ('fetal growth' NEAR/3 (restriction OR retardation)):ab,ti OR iugr:ab,ti) AND ('mother'/exp OR (maternal NEAR/6 (cardiovascular OR risk*)):ab,ti)

AND ('cardiovascular disease'/exp/mj OR 'kidney failure'/exp/mj OR 'diabetes mellitus'/exp/mj OR 'electrocardiography'/exp/mj OR 'hypercholesterolemia'/exp/mj OR 'hypertension'/exp/mj OR 'obesity'/exp/mj OR 'proteinuria'/exp/mj OR 'blood vessel calcification'/exp/mj OR 'metabolic syndrome x'/exp/mj OR stroke:ab,ti OR cva:ab,ti OR cerebrovascular:ab,ti OR cardiovascul*:ab,ti OR (myocard* NEAR/2 infarct*):ab,ti OR atheroscleros*:ab,ti OR (vascular NEAR/2 calcification):ab,ti OR ((renal OR kidney) NEAR/3 (insufficienc* OR failure*)):ab,ti OR (ischaemic NEAR/2

attack*):ab,ti OR tia:ab,ti OR 'angina pectoris':ab,ti OR electrocardiogra*:ab,ti OR
ecg:ab,ti OR hypercholesterolemia:ab,ti OR obesity:ab,ti OR hypertension:ab,ti OR
proteinuria:ab,ti OR diabet*:ab,ti OR ((endothelial OR vascular) NEAR/2
dysfunction*):ab,ti OR (('left ventricular' OR myocardial) NEAR/3 hypertroph*):ab,ti OR
(metabol* NEAR/2 syndrome*):ab,ti)

AND [english]/lim AND [embase]/lim,

Recurrent miscarriage

Medline (OVID) – 1966 to 19 December 2012

- 1 exp abortion, habitual/ (6296)
- 2 ((recurren* or habitual) adj3 (miscarriage* or abortion* or "pregnancy loss*")).ti,ab.
(4616)
- 3 Abortion, Spontaneous/ (13738)
- 4 Recurrence/ (151907)
- 5 3 and 4 (204)
- 6 1 or 2 or 5 (7921)
- 7 exp Cardiovascular Diseases/ (1780857)
- 8 exp Renal Insufficiency/ or calcinosis/ or exp vascular calcification/ or
Hypercholesterolemia/ or exp Obesity/ or exp Electrocardiography/ or exp
Hypertension/ or exp Proteinuria/ or exp Diabetes Mellitus/ or Metabolic Syndrome X/
(907743)

9 (stroke or CVA or cerebrovascular or cardiovascul* or (myocard* adj2 infarct*) or atheroscleros* or "vascular calcification*" or ((renal or kidney) adj3 (insufficienc* or failure*)) or "ischaemic attack*" or TIA or "angina pectoris" or electrocardiogra* or ecg or hypercholesterolemia or obesity or hypertension or proteinuria or diabet* or ((endothelial or vascular) adj2 dysfunction*) or (("left ventricular" or myocardial) adj3 hypertroph*) or (metabol* adj2 syndrome*)).ti,ab. (1292223)

10 7 or 8 or 9 (2619398)

11 6 and 10 (846)

12 limit 11 to english language (674)

17 12 not (animals/ not humans/) (670)

18 (mouse or mice or cat? or rat? or dog? or cow or horse?).ti. (1325374)

19 17 not 18 (667)

20 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy\$).tw. or (systematic* adj review\$1).tw. or (systematic adj overview\$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (121431)

21 19 and 20 (14)

22 17 not 21 (656)

Embase (Elsevier) - 1980 to 19 December 2012

('recurrent abortion'/exp/mj OR ((recurren* OR habitual) NEAR/3 (miscarriage* OR abortion* OR 'pregnancy loss' OR 'pregnancy losses')):ab,ti OR ('spontaneous abortion'/exp/mj AND 'recurrent disease'/exp))

AND (cardiovascular disease'/exp/mj OR 'kidney failure'/exp/mj OR 'diabetes mellitus'/exp/mj OR 'electrocardiography'/exp/mj OR 'hypercholesterolemia'/exp/mj OR 'hypertension'/exp/mj OR 'obesity'/exp/mj OR 'proteinuria'/exp/mj OR 'blood vessel calcification'/exp/mj OR 'metabolic syndrome x'/exp/mj OR stroke:ab,ti OR cva:ab,ti OR cerebrovascular:ab,ti OR cardiovascul*:ab,ti OR (myocard* NEAR/2 infarct*):ab,ti OR atheroscleros*:ab,ti OR (vascular NEAR/2 calcification):ab,ti OR ((renal OR kidney) NEAR/3 (insufficienc* OR failure*)):ab,ti OR (ischaemic NEAR/2 attack*):ab,ti OR tia:ab,ti OR 'angina pectoris':ab,ti OR electrocardiogra*:ab,ti OR ecg:ab,ti OR hypercholesterolemia:ab,ti OR obesity:ab,ti OR hypertension:ab,ti OR proteinuria:ab,ti OR diabet*:ab,ti OR ((endothelial OR vascular) NEAR/2 dysfunction*):ab,ti OR (('left ventricular' OR myocardial) NEAR/3 hypertroph*):ab,ti OR (metabol* NEAR/2 syndrome*):ab,ti)

AND [english]/lim AND [embase]/lim ' not conference abstract':it

Polycystic ovary syndrome

Medline (OVID) - 1966 to 23 December 2012

1 Polycystic Ovary Syndrome/ (9485)

- 2 ((("stein-leventhal syndrome" or "Polycystic Ovar*") adj3 (Syndrome* or disease*)) or PCOS).ti,ab. (9318)
- 3 1 or 2 (11469)
- 9 exp Cardiovascular Diseases/ (1774139)
- 10 exp Renal Insufficiency/ or calcinosis/ or exp vascular calcification/ or Hypercholesterolemia/ or exp Obesity/ or exp Electrocardiography/ or exp Hypertension/ or exp Proteinuria/ or exp Diabetes Mellitus/ or Metabolic Syndrome X/ (904001)
- 11 (stroke or CVA or cerebrovascular or cardiovascul* or (myocard* adj2 infarct*) or atheroscleros* or "vascular calcification*" or ((renal or kidney) adj3 (insufficienc* or failure*)) or "ischaemic attack*" or TIA or "angina pectoris" or electrocardiogra* or ecg or hypercholesterolemia or hypertension or proteinuria or diabet* or ((endothelial or vascular) adj2 dysfunction*) or (("left ventricular" or myocardial) adj3 hypertroph*) or (metabol* adj2 syndrome*)).ti. (642987)
- 12 9 or 10 or 11 (2334775)
- 13 3 and 12 (2488)
- 14 limit 13 to english language (2213)
- 15 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy).tw. or (systematic* adj review\$1).tw. or (systematic adj overview1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data

extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (120628)

16 14 and 15 (53)

Embase (Elsevier) - 1980 to 23 December 2012

('ovary polycystic disease'/exp/mj OR 'stein-leventhal syndrome':ab,ti OR ('polycystic ovary' NEAR/3 (syndrome* OR disease*)):ab,ti OR pcos:ab,ti OR 'stein-leventhal syndromes':ab,ti OR ('polycystic ovarian' NEAR/3 (syndrome* OR disease*)):ab,ti)

AND ('cardiovascular disease'/exp/mj OR 'kidney failure'/exp/mj OR 'diabetes mellitus'/exp/mj OR 'electrocardiography'/exp/mj OR 'hypercholesterolemia'/exp/mj OR 'hypertension'/exp/mj OR 'obesity'/exp/mj OR 'proteinuria'/exp/mj OR 'blood vessel calcification'/exp/mj OR 'metabolic syndrome x'/exp/mj OR stroke:ab,ti OR cva:ab,ti OR cerebrovascular:ab,ti OR cardiovascul*:ab,ti OR (myocard* NEAR/2 infarct*):ab,ti OR atheroscleros*:ab,ti OR (vascular NEAR/2 calcification):ab,ti OR ((renal OR kidney) NEAR/3 (insufficienc* OR failure*)):ab,ti OR (ischaemic NEAR/2 attack*):ab,ti OR tia:ab,ti OR 'angina pectoris':ab,ti OR electrocardiogra*:ab,ti OR ecg:ab,ti OR hypercholesterolemia:ab,ti OR hypertension:ab,ti OR proteinuria:ab,ti OR diabet*:ab,ti OR ((endothelial OR vascular) NEAR/2 dysfunction*):ab,ti OR (('left ventricular' OR myocardial) NEAR/3 hypertroph*):ab,ti OR (metabol* NEAR/2 syndrome*):ab,ti)

AND [english]/lim AND [embase]/lim

Premature ovarian insufficiency

Medline (OVID) – 1966 to 9 November 2012

1 Primary Ovarian Insufficiency/ or Menopause, Premature/ or ((premature or primary) adj2 ovarian adj2 (failure or insufficiency)).ti,ab. or ((premature or early) adj3 menopause).ti,ab.

2 exp Cardiovascular Diseases/

3 exp Renal Insufficiency/ or calcinosis/ or exp vascular calcification/ or Hypercholesterolemia/ or exp Obesity/ or exp Electrocardiography/ or exp Hypertension/ or exp Proteinuria/ or exp Diabetes Mellitus/ or Metabolic Syndrome X/

4 (stroke or CVA or cerebrovascular or cardiovascul* or (myocard* adj2 infarct*) or atheroscleros* or "vascular calcification*" or ((renal or kidney) adj3 (insufficienc* or failure*)) or "ischaemic attack*" or TIA or "angina pectoris" or electrocardiogra* or ecg or hypercholesterolemia or obesity or hypertension or proteinuria or diabet* or ((endothelial or vascular) adj2 dysfunction*) or (("left ventricular" or myocardial) adj3 hypertroph*) or (metabol* adj2 syndrome*)).ti,ab.

5 2 or 3 or 4

6 1 and 5

7 limit 6 to english language – (437)

Embase (Elsevier) - 1980 to 9 November 2012

('early menopause'/exp/mj OR 'premature ovarian failure'/exp/mj OR ((premature OR primary) NEAR/2 ('ovarian failure' OR 'ovarian insufficiency')):ab,ti OR ((premature OR early) NEAR/3 menopause):ab,ti)

AND ('cardiovascular disease'/exp/mj OR 'kidney failure'/exp/mj OR 'diabetes mellitus'/exp/mj OR 'electrocardiography'/exp/mj OR 'hypercholesterolemia'/exp/mj OR 'hypertension'/exp/mj OR 'obesity'/exp/mj OR 'proteinuria'/exp/mj OR 'blood vessel calcification'/exp/mj OR 'metabolic syndrome x'/exp/mj OR stroke:ab,ti OR cva:ab,ti OR cerebrovascular:ab,ti OR cardiovascul*:ab,ti OR (myocard* NEAR/2 infarct*):ab,ti OR atheroscleros*:ab,ti OR (vascular NEAR/2 calcification):ab,ti OR ((renal OR kidney) NEAR/3 (insufficienc* OR failure*)):ab,ti OR (ischaemic NEAR/2 attack*):ab,ti OR tia:ab,ti OR 'angina pectoris':ab,ti OR electrocardiogra*:ab,ti OR ecg:ab,ti OR hypercholesterolemia:ab,ti OR obesity:ab,ti OR hypertension:ab,ti OR proteinuria:ab,ti OR diabet*:ab,ti OR ((endothelial OR vascular) NEAR/2 dysfunction*):ab,ti OR (('left ventricular' OR myocardial) NEAR/3 hypertroph*):ab,ti OR (metabol* NEAR/2 syndrome*):ab,ti AND ('early menopause'/exp/mj OR 'premature ovarian failure'/exp/mj OR ((premature OR primary) NEAR/2 ('ovarian failure' OR 'ovarian insufficiency')):ab,ti OR ((premature OR early) NEAR/3 menopause):ab,ti)

AND [english]/lim AND [embase]/lim

Table S1. Grading system for level of evidence used at the Dutch Institute for Healthcare Improvement CBO

Level	Studies on therapy/prevention	Studies on diagnostic accuracy	Studies on harm, etiology or prognosis
A1	Systematic review/meta-analysis of at least two independent studies of A2 level with consistent results		
A2	Double-blind randomized controlled trial of good quality and sufficient power	Study with respect to a reference test (gold standard) with pre-defined cut-off values, among large series consecutive persons that received both the index and the reference test and adequate blinding of interpretation of test results	Prospective cohort study of sufficient power and follow-up, adequate control for confounding and selective follow up
B	Randomized controlled trial of modest quality or insufficient power, or other analytic study (e.g., case-control	A comparison with a reference standard that does not meet the criteria required for level A2 evidence	Prospective cohort study that does not meet the criteria required for level A2 evidence. Or

study, cohort study)

retrospective cohort
study or case-control
study

C Non-analytic study

D Expert opinion

Level Conclusion based on

1 One systematic review (A1) or at least two independent randomized controlled trials of level A2

2 One study of level A2 or at least 2 independent studies of level B

3 One study of level B or C

4 Expert opinion

Table S2. Results from meta-analysis of studies assessing the relation between preeclampsia and cardiovascular disease and risk factors

Outcome	Number of studies	RR (95% CI)	I²	Level of evidence	References
Overall CVD	8	2.15 (1.76-2.61)*	78%	2	3-10
IHD	7	2.06 (1.68-2.52)*	78%	2	3, 6, 11-15
Stroke	4	1.53 (1.21-1.92)*	33%	2	3, 5, 7, 9
Hypertension	3	2.76 (1.63-4.69)*	92%	2	11, 13, 16
	16	4.46 (3.14-6.33)**	63%	2	17-32
Diabetes	6	2.27 (1.55-3.32)*	94%	2	13, 16, 33-36
Dyslipidemia	4	1.07 (0.74-1.54)**,#	24%	2	20, 23, 27, 37

* Based on cohort studies (Level B studies)

** Based on case-control studies (Level B studies)

Combination of studies reporting on preeclampsia and pregnancy induced hypertension

CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; RR, relative risk

Table S3. Results from meta-analysis of studies assessing the relation between gestational hypertension and cardiovascular disease and risk factors

Outcome	Number of studies	RR (95% CI)	I²	Level of evidence	References
Overall CVD	4	1.89 (1.31-2.72)*	88%	2	3, 5, 7, 9
IHD	4	1.44 (1.30-1.60)*	0%	2	3, 11, 13, 15
Stroke	2	1.41 (1.20-1.65)*	22%	2	3, 13
Hypertension	3	2.40 (0.97-5.93)*	100%	2	3, 11, 13
	5	4.35 (2.18-8.70)**	79%	2	17, 23, 24, 31, 32
Diabetes	8	2.10 (1.45-3.04)*,#	96%	2	13, 16, 33-36, 38, 39
Dyslipidemia	4	1.07 (0.74-1.54)**,#	24%	2	20, 23, 27, 37

* Based on cohort studies (Level B studies)

** Based on case-control studies (Level B studies)

Combination of studies reporting on preeclampsia and pregnancy induced hypertension

CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; RR, relative risk

Section S3. Summary of the Dutch guideline for cardiovascular management

For optimal implementation in clinical practice in the Netherlands, this guideline aims to comply with the current Dutch guideline for cardiovascular risk management in the general population, published in 2011.⁴⁰ The latter guideline was developed to establish optimal and cost-effective primary and secondary CVD prevention. A short summary is given below.

Identification of high-risk patients

All patients with manifest CVD are considered as high-risk patients. In patients without previous CVD, it is recommended to obtain a CVD risk profile if one of the following is present:

- 1) Diabetes mellitus, rheumatoid arthritis or chronic kidney disease,
- 2) Family history of premature CVD (<65 year),
- 3) Systolic blood pressure (SBP) > 140 mmHg or antihypertensive therapy,
- 4) Total cholesterol (TC) > 6.5 mmol/L (>250 mg/dL) or statin therapy,
- 5) Smoking and ≥ 50 years of age.

A complete risk profile involves collection of information on:

- 1) Medical history (first-degree relative with CVD <65 years, smoking, nutrition, alcohol intake and physical activity);

2) Physical examination (body mass index (BMI), waist circumference and blood pressure);

3) Laboratory (fasting glucose, TC/ high-density lipoprotein (HDL)-ratio, serum creatinine).

Risk assessment

For individuals free of CVD, the ten-year risk of developing fatal or nonfatal CVD (in percentage) is assessed using the SCORE risk table, based on absolute risks and calibrated for Dutch CVD data.⁴¹

- Individuals at low risk for fatal or nonfatal CVD (<10%) receive recommendations for lifestyle modifications when necessary. They rarely receive antihypertensive or statin therapy.
- Individuals at intermediate risk (10 to 20%) receive recommendations for lifestyle modifications and antihypertensive (if systolic blood pressure (SBP) > 140 mmHg) and/or statin therapy (when low-density lipoprotein cholesterol (LDL-c) > 2,5 mmol/L) (>97 mg/dL) when at least one additional risk factor is present. Additional risk factors are: 1) family history of premature CVD; 2) obesity (BMI \geq 30 kg/m²); 3) physical inactivity (<30 min/day, \leq 5 day/wk or sedentary living); and 4) impaired renal function (<65 year: 30-60 ml/min/1,73m²; \geq 60 year: 30-45 ml/min/1,73m² or <30 ml/min/1,73m²).

- Individuals at high risk ($\geq 20\%$) receive recommendations for lifestyle modifications and if necessary antihypertensive (when SBP > 140 mmHg) and statin therapy (when LDL-c > 2.5 mmol/L).

The Dutch guideline for cardiovascular risk management diverges from the recommendations given in the guidelines of both the American College of Cardiology (ACC)/AHA and European Society of Cardiology (ESC). The ACC/AHA guideline on the assessment of cardiovascular risk uses race- and specific Pooled Cohort Equations to predict 10-year risk of a first hard atherosclerotic cardiovascular event.⁴² The variables that are included in this risk assessment are: age, TC, high-density lipoprotein cholesterol (HDL-c), SBP (including treated or untreated status), diabetes mellitus, and current smoking status. If an elevated 10-year risk ($\geq 7.5\%$) is found, patients are treated in accordance with the guidelines on blood cholesterol, obesity and lifestyle management.⁴² If a low 10-year risk ($< 7.5\%$) is found, it is recommended to assess 30-year lifetime risk in those 20-59 year of age and to refer to the AHA/ACC lifestyle guideline. On the other hand, the ESC guideline on cardiovascular disease prevention in clinical practice uses another SCORE system, which estimates the 10-year risk of a first fatal atherosclerotic event.⁴³ In general, those with a risk of CVD death of $\geq 5\%$ qualify for intensive advice, and may benefit from drug treatment. At risk levels $> 10\%$, drug treatment is more frequently required. In conclusion, these guidelines use a lower threshold to start treatment among women with an increased risk of CVD. The Dutch Guideline Development Group has adopted a higher threshold for treatment for two main reasons. Firstly, the number of individuals needing treatment would have increased excessively which would have substantial impact on the workload and national health care budget. Secondly, a lower threshold would cause an undesirable large-scale medicalization of a relatively healthy population without symptoms.⁴⁴

Nonpharmacological treatment

Recommendations for lifestyle interventions should be given to all individuals with modifiable risk factors, and comprise of: 1) smoking cessation; 2) increase in physical activity; 3) increase in fruit and vegetable intake, decrease in saturated and total fat intake and reduction of salt intake; 4) moderation of alcohol consumption; 5) weight reduction in the overweight (optimal weight for those aged under 70: $\text{BMI} \leq 25 \text{ kg/m}^2$; above the age of 70 years: $\text{BMI} \leq 30 \text{ kg/m}^2$).⁴⁵

Pharmacological treatment

Antihypertensive therapy

For individuals free of CVD treatment recommendations are based on the estimated ten-year risk of fatal and nonfatal CVD as described above. Individuals with a SBP > 180 mmHg on repeated measurements, and SBP > 160 mmHg below 50 years of age, should be treated with antihypertensive treatment in addition to lifestyle modification, regardless of their ten-year risk of CVD. Despite absence of evidence on the benefits of antihypertensive treatment in young individuals, it is expected that long-term exposure to a high blood pressure is harmful. Although the European Society of Hypertension (ESH), ESC and AHA currently recommends the treatment of a blood pressure $\geq 140/90$ mmHg in young adults,^{46,47} we decided to comply with the current Dutch guideline for cardiovascular risk management to establish uniformity and acceptance in the Netherlands.

Lipid lowering therapy

For individuals free of CVD treatment recommendations for lipid lowering therapy are based on the estimated ten-year risk of fatal and nonfatal CVD as described above.

Regardless of the risk of developing CVD, lipid-lowering drugs are recommended when TC/HDL-ratio > 8. By contrast, the ACC/AHA and ESC recommend treatment with lipid-lowering drugs if LDL-c \geq 4.9 mmol/l (190 mg/dl), but they recommend lower thresholds for treatment in individuals with an increased 10-year risk of CVD^{48, 49}

Oppositely, the Dutch guideline uses TC/HDL-ratio instead of TC levels, as the ratio of TC to HDL-c levels is the best lipid-screening test to identify those at high risk for IHD mortality.⁵⁰

Table S4. Results from meta-analysis of studies assessing the relation between spontaneous preterm delivery and cardiovascular disease and risk factors

Outcome	Number of studies	RR (95% CI)	I²	Level of evidence	References
Overall CVD	5	2.06 (1.58-2.68)*	72%	2	51-55
IHD	3	1.38 (1.22-1.57)*	74%	2	56-58
Stroke	3	1.71 (1.53-1.91)*	0%	2	53, 59, 60
Hypertension	2	1.29 (1.24-1.35)*	90%	2	57, 59
Diabetes	2	1.77 (1.46-2.15)*	7%	2	57, 59
Dyslipidemia	0	-	-	-	

* Based on cohort studies (Level B studies)

CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; RR, relative risk

Table S5. Results from meta-analysis of studies assessing the relation between a history of a small-for-gestational-age infant and cardiovascular disease and risk factors

Outcome	Number of studies	RR (95% CI)	I²	Level of evidence	References
Overall CVD	4	1.66 (1.26-2.18)*	93%	2	54, 61-63
IHD	3	1.68 (1.31-2.14)*	91%	2	63-65
Stroke	2	1.62 (1.51-1.74)*	0%	2	65, 66
Hypertension	1	1.23 (1.16-1.30)*	-	3	65
Diabetes	1	0.96 (0.86-1.06)*	-	3	65
Dyslipidemia	0	-	-	-	

* Based on cohort studies (Level B studies)

CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; RR, relative risk

Table S6. Results from meta-analysis of studies assessing the relation between a history of recurrent miscarriage and cardiovascular disease and risk factors

Outcome	Number of studies	RR (95% CI)	I²	Level of evidence	References
Overall CVD	0	-	-	-	
IHD	3	1.99 (0.94-4.19)*	54%	2	67-69
	2	3.20 (0.24-42.51)**	85%	2	70, 71
Stroke	2	0.98 (0.80-1.21)*	0%	2	67, 68
Hypertension	0	-	-	-	
Diabetes	0	-	-	-	
Dyslipidemia	0	-	-	-	

* Based on cohort studies (Level B studies)

** Based on case-control studies (Level B studies)

CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; RR, relative risk

Table S7. Results from meta-analysis of studies assessing the relation between polycystic ovary syndrome and cardiovascular disease and risk factors

Outcome	Number of studies	RR (95% CI)	I²	Level of evidence	References
Overall CVD	4	1.38 (1.04-1.83)*	30%	2	72-75
IHD	4	1.11 (1.09-1.81)*	0%	2	72, 74, 76, 77
Stroke	4	1.79 (0.92-3.48)*	14%	2	72, 74, 76, 77
Hypertension	10	1.26 (1.10-1.43)*, **	24%	2	72, 74-82
Diabetes	7	2.53 (1.91-3.35)*, **	86%	2	72-74, 77, 78, 81, 83
Dyslipidemia	7	1.75 (1.12-2.72)*, **	70%	2	74, 75, 77, 78, 81, 82, 84

* Based on cohort studies (Level B studies); ** Based on case-control studies (level B studies)

CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; RR, relative risk

Table S8. Results from meta-analysis of studies assessing the relation between premature ovarian insufficiency and cardiovascular disease and risk factors

Outcome	Number of studies	RR (95% CI)	I²	Level of evidence	References
Overall CVD	2	1.61 (1.22-2.12)*	0%	2	85, 86
IHD	7	1.69 (1.29-2.21)*	22%	1	85-91
Stroke	7	1.03 (0.88-1.19)*	0%	1	85, 87-89, 92-94
Hypertension	1	1.16 (0.68-1.98)*	-	2	93
Diabetes	1	1.32 (0.70-2.49)*	-	2	93
Dyslipidemia	0	-	-	-	

* Based on cohort studies (Level B studies)

CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; RR, relative risk

Section S4. Identified knowledge gaps

The guideline development group acknowledges that more research is needed to support and enhance our recommendations on cardiovascular risk management after reproductive and pregnancy related disorders. Unanswered questions are:

- Accurate estimates of absolute risk of CVD after a reproductive or pregnancy related disorder.
- Studies of the role of PE/PIH as added value in cardiovascular risk prediction models (IPD).
- Cohort studies assessing the relation between the other reproductive and pregnancy related disorders and CVD with adequate measurements of exposure, confounders and events.
- Pathways explaining the relation of reproductive or pregnancy related disorders with CVD.
- Intervention studies aiming to postpone the development of CVD events or risk factor, including cost effectiveness.

Table S9. Summary of guidelines addressing postpartum CVD prevention after reproductive and pregnancy related disorders

Guideline	Reproductive or pregnancy related disorder	Recommendation
ESC Guidelines on the management of cardiovascular diseases during pregnancy ⁹⁵	Hypertensive disorders of pregnancy	Lifestyle modifications, regular blood pressure control, and control of metabolic factors are recommended after delivery.
ESH/ESC Guidelines for the management of arterial hypertension ⁴⁶	Hypertensive disorders of pregnancy	Lifestyle modifications and regular check-ups of blood pressure and metabolic factors are recommended after delivery.
AHA Guidelines for the Prevention of Stroke in Women ⁹⁶	Preeclampsia	Consider evaluating all women starting 6 months to 1 year post partum, as well as those who are past childbearing age, and document their history of preeclampsia/eclampsia as a risk factor. Evaluate and treat for cardiovascular

risk factors including hypertension, obesity, smoking, and dyslipidemia.

AHA Effectiveness- Based Guidelines for the Prevention of Cardiovascular Disease in Women ⁹⁷	Preeclampsia, gestational diabetes, and pregnancy-induced hypertension.	Appropriate referral postpartum by the obstetrician to a primary care physician or cardiologist should occur so that in the years after pregnancy, risk factors can be carefully monitored and controlled.
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Healthcare professionals who meet women for the first time later in their lives should take a careful and detailed history of pregnancy complications with focused questions about a history of gestational diabetes mellitus, preeclampsia, preterm birth, or birth of an infant small for gestational age.

Evaluation of CVD risk factors, and provide lifestyle recommendations; blood pressure control and LDL-C lowering therapy if LDL-C \geq 190 mg/dl

AHA, American Heart Association; CVD, cardiovascular disease; ESC, European Society of Cardiology; ESH, European Society of Hypertension; LDL-C, low-density-lipoprotein cholesterol

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