Long-Term Cardiovascular Effects of Pregnancy-Related Disorders

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Abstract

Usually, pregnancy-elated effects and changes in the different organs terminate after delivery or maybe within 6 months. Long-term effect of complicated pregnancies leading to long-term cardiovascular and other diseases was recognized long back. With the accumulating evidence with many landmark studies, it became mandatory to have pregnancy heart team approach not only to manage during pregnancy and peripartum period but also to monitor future events and educate the pregnant women about the modification of cardiovascular risks for prevention of anticipated events. In this review, more importance is given to risk-stratify these women with complicated pregnancy and recommendation to prevent the long-term effects.

Keywords
- cardiovascular effects
- gestational diabetes
- preeclampsia
- pregnancy

Introduction

The changes that occur during pregnancy are expected to terminate their effect after delivery, which sometimes may extend up to 6 weeks after delivery, for example preeclampsia, gestational diabetics, etc. Much was discussed on recurrence of some diseases such as preterm labor or preeclampsia that have greater chances of recurrence in subsequent pregnancies. However, in the recent past, it was realized that the events that occurred during pregnancy predicted the development of future events in the life.[1]

Similarly, it is well known that obstetric complications are related to long-term complications of the newborn. However, Pariente et al and Almasi et al showed that the small for gestational baby birth was the predictor for maternal cardiovascular disease (CVD) later in the life.[2,3] In the mother, the cause of the long-term effects of the pregnancy was debated by many researchers. Some authors suggest that the long-term effects may not be due to the pregnancy as such, but it may be due to the expression of already existing predisposing factors during pregnancy. In addition, some authors say that pregnancy acts as a long term stress (9 months) that may have effects on the long-term maternal health.[4]

In this review article, the authors discussed the different pregnancy-related problems with their pathophysiology, which may be responsible for long-term effect on the cardiovascular system of the mother with evidence of previous studies.

Gestational Diabetes

Glucose tolerance test was performed on the patients who had the previous history of gestational diabetes by giving 75 g of glucose 6 to 12 weeks after delivery. Approximately 2 to 16% patients were detected to be type 2 diabetic, and 36% of patients had an intolerance to carbohydrates. Therefore, nearly 36 to 70% of GDM (gestational diabetes mellitus) women were prone to type 2 diabetes in the long run[1] (►**Fig. 1**) and GDM itself can be precursor of future events (►**Fig. 2**).

Studies that concentrated on the subsequent development of type 2 diabetes mellitus (DM) and another cardiovascular morbidity in GDM women are mentioned in ►**Table 1.**[5–11]

As prevention is better than cure, the American College of Obstetricians and Gynaecologists (ACOG) joined a program "Call for Action" that is an initiative of the National Diabetes Education to provide better health outcomes of women with prior GDM and their children[12] (►**Fig. 3**).

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Preeclampsia

Preeclampsia induces micro-angiopathy that affects both the mother and fetus (►**Fig. 4**). These changes of micro-angiopathy on the different organs do not dissolve after index pregnancy, which may be responsible for future maternal cardiovascular events (►**Fig. 5**). The severity of development of long-term cardiovascular morbidity in the mother depends not only on having preeclampsia during pregnancy but also on how early it appears, birth weight of the baby, etc. (►**Fig. 6**). The relative risk of future events in eclampsia and preeclamptic mothers is represented in ►**Fig. 7.**[13,14] In fact, gestational hypertension in the other futures of preeclampsia can also give rise in myocardial ischemia later in the life.

The long-term effects of preeclampsia in a mother are not only for the risk of hypertension but also for stroke, ischemic heart disease, venous thromboembolism, and overall mortality in the future (►**Fig. 8**).

The fact that eclampsia can lead to late cardiovascular events are substantiated by multiple studies (►**Table 2**).[15–23]

Few authors suggested that as early preeclampsia is associated with subsequent development of significant events, it is worth starting the preventive measures immediately after delivery. Few studies have concentrated on another cardiovascular risk (CVR) in preeclamptic women, which are mentioned in ►**Table 3.**[24–27]

Studies mentioned in ►**Table 4** proved that preeclampsia increases not only CVR but other organ system disorders also.[28–31]

Pathophysiology of Preeclampsia Leading to Cardiovascular Risk

There are a few common factors for both preeclampsia and CVD. Because of this common association, these preeclamptic patients develop CVD subsequently (►**Fig. 9**).[32]

The main mechanism of preeclampsia leading to CVR later in the life is due to the endothelial dysfunction induced during pregnancy (►**Fig. 10**).[23]

Preterm Deliveries

Preterm births were categorized as late (35–36 weeks), moderate (33–34 weeks), or extreme (≤ 32 weeks), and as spontaneous or indicated. In the previous section of preeclampsia, the effect of preterm delivery and of low-birth-weight baby was discussed. Preterm delivery with preeclampsia also has the risk of having a cardiac event later in the life. Studies supporting this are mentioned in ►**Table 5.**[2,33–36]

Placental Abruption

Placental abruption is a condition with microvascular disturbance and leads to long-term effects on the mother's health. The type of future cardiac diseases predisposed by placental abruption is mentioned in ►**Fig. 11**. In ►**Table 6**,[37–40] studies on placental abruption are mentioned.

Stillbirth and Recurrent Miscarriages

A recurrent miscarriage in the mother is an indication to check for collagen vascular disorders. However, Pariente et al and Kessous et al have shown that recurrent miscarriages and stillbirths in women will predict the future cardiovascular events[41,42] (►**Table 7**).

Maternal Obesity during Pregnancy

Maternal obesity during pregnancy will lead to obesity and related complications later in life. Reduction of even a few kilograms in weight, even for a shorter duration, has good long-term effects. Sasson et al concluded that obesity during pregnancy is an independent risk factor for long-term ophthalmic complications such as diabetic retinopathy.[43] According to the 2016 Action for Health in Diabetes Study Group reports, weight loss in the overweight/obese individuals with type 2 diabetes had significant improvements in hemoglobin A_{1C} (HbA_{1C}), systolic blood pressure, high-density lipoprotein (HDL) cholesterol, and triglycerides ($p \leq 0.02$).[44]

Women with Small for Gestational Age Neonate

Delivery of a small for gestational age (SGA) infant was one of the risk factors for the future maternal health. Parient et al[45] and Almasi et al[3] state that the delivery of an SGA neonate may lead to long-term complex cardiovascular events, including congestive heart failure, hypertensive heart and kidney disease, and acute cor pulmonale (odds ratio [OR] = 2.3; 95% confidence interval [CI]: 1.3–4.4; p = 0.006), and also long-term cardiovascular mortality (OR = 3.4; 95% CI: 1.5–7.6; p = 0.006).

Miscellaneous

1. Transient hypothyroidism in pregnancy can antedate CVD in later age.
2. Peripartum cardiomyopathy—the detailed discussion was given in a separate review (See Heart Failure in Pregnancy, p. 161 this issue).

►**Table 8** shows the diseases during pregnancy and their later development of cardiovascular and other organ involvements.[46,47]

Preventive Measures

As many women come to regular checkup during pregnancy, it is an ideal time to detect the women who are at risk for the future CVD and implement at the same time the primary

preventive strategies early such as health monitoring, lifestyle modifications, and other interventions, that will help reduce the burden of CVD (►**Fig. 12**).[48]

Even though many obstetricians and gynecologists are aware of the fact that the risk of CVDs after preeclampsia is high, during the follow-up these women are not counseled and informed for preventive measures. By the implementation of the current guidelines both by obstetrician and cardiologists, these deficiencies can be overcome.[49]

Conclusion

In women with a moderate or high risk of complications during pregnancy (modified World Health Organization [mWHO] II–III, III, and IV), prepregnancy counseling and management during and around delivery should be performed in an expert center by a multidisciplinary tea the pregnancy heart team.[50] Follow them subsequently annually along with modification of CVR.

Tables and Figures

Table 1 Studies showing the increase in latter development of DM and CV morbidity in GDM women

Study author	Year	Inclusion no.	Results
Lauenborg et al	2005	9.8-y follow–up—481 Danish women; prior diet–treated GDM after pregnancy	Metabolic syndrome: 1. Prior diet–treated GDM 3-fold > age-matched control patients ($p < 0.0005$). 2. Obese women (BMI > 30) with previous GDM 7-fold > normal-weight prior GDM women (BMI < 25) 3. Prevalence—glucose tolerant GDM group > 2 times control group
Bellamy et al	2009	Comprehensive systematic review and meta-analysis	Gestational diabetes ↔ risk of type 2 diabetes
Göbl et al	2011	10-y study	Glucose tolerance—impaired in GD predictors of DM after GDM, HDL cholesterol < 50 mg/dL and age (> 35 y)
Lee et al	2012	15 prospective studies—760,925 participants	Prediabetes—↑ stroke—impairment of glucose tolerance/combination of impaired fasting glucose and glucose tolerance
Kessous et al	2013	47,909 10-y follow–up	4,928 (10.3%) GDM—↑ rate of CV morbidity—noninvasive cardiac diagnostic procedures (OR = 1.8; 95% CI: 1.4–2.2), simple CV events (OR = 2.7; 95% CI: 2.4–3.1), and total CV hospitalizations (OR = 2.3; 95% CI: 2.0–2.5)
Valizadeh et al	2015	110 women—abnormal glucose levels and metabolic syndrome; 1–6 y prior GD	36 (32.7%)—type2 DM, 11 (10%)—impaired fasting glucose or impaired glucose tolerance, and 22 (20%)—metabolic syndrome
Huang et al	2016	Meta-analysis and prospective cohort	Prediabetes—↑ CVD/CHD and mortality: impairment—glucose tolerance, fasting glucose < 5.6 mmol/L/HbA_{1C} (39 mmol/mol) and ↑ HbA_{1C} (39–7 mmol/mol)

Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; CHD, coronary heart disease; DM, diabetes mellitus; GD, gestational diabetes; GDM, gestational diabetes mellitus; HbA_{1C}, hemoglobin A_{1C}; HDL, high–density lipoprotein; OR, odds ratio.

Table 2 Studies showing the increase in late CV morbidity in preeclamptic women

Study author	Year	Results
McDonald et al	2013	Women with a history of severe preeclampsia had higher rates of previous CVD than women with nonsevere preeclampsia or women without preeclampsia (87, 72, and 72%, $p = 0.0019$). Even after accounting for CV risk factors including albuminuria, a history of severe preeclampsia was independently associated with a 3-fold higher risk of CVD.
Brown et al GENOA study	2013	A history of hypertension in pregnancy is associated with elevated CRP levels later in life, independent of traditional CVD risk factors and BMI.
Brown et al	2013	Women diagnosed with history of preeclampsia were at increased risk of future CV or cerebrovascular events, with an estimated doubling of odds compared with unaffected women.
Melchiorre et al	2014	The relative risk of developing hypertension within 2 y of birth, even after adjusting for confounding risk factors, was increased 15-fold if LV abnormalities persisted. The higher prevalence of stage B heart failure in preterm than in term preeclampsia had a higher risk of subsequent congestive heart failure and ischemic cardiac diseases compared with women with term preeclampsia or normal pregnancy
Veerbeek et al	2015	Compared with women with late-onset preeclampsia and pregnancy-induced hypertension, women with previous early-onset preeclampsia had significantly higher fasting blood glucose (5.29 vs. 4.80 and 4.83 mmol/L), insulin (9.12 vs. 6.31 and 6.7 IU/L), triglycerides (1.32 vs. 1.02 and 0.97 mmol/L), and total cholesterol (5.14 vs. 4.73 and 4.73 mmol/L). Almost one-half of women with early-onset preeclampsia developed hypertension, as opposed to 39% and 25% of women in the pregnancy-induced hypertension and late-onset preeclampsia groups, respectively.
Weissgerber et al	2016	A sibling history of hypertension in pregnancy was also associated with an increased risk of hypertension in brothers and unaffected sisters, whereas an increased risk of CV events was observed in brothers only. These results suggested that familial factors contribute to the increased risk of future hypertension in women who had hypertension in pregnancy.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; GENOA, Genetic Epidemiology Network of Arteriopathy; LV, left ventricular.

Table 3 Studies showing the increase in cardiovascular risk in preeclamptic women

Study	Year	Results
Stekkinger et al	2009	The metabolic syndrome was present in 15–25% of women after early-onset vascular-complicated pregnancy and in 10–14% of women after late–onset disease.
Kessous et al	2015	Patients with preeclampsia had significantly higher cumulative incidence of atherosclerotic–related hospitalizations and had an increased risk of cardiomyopathy during the peripartum period
Behrens et al	2016	Women with a history of hypertensive disorders of pregnancy had significantly increased rates of cardiomyopathy. These increases persisted > 5 y after the latest pregnancy.
Black et al	2016	2.36 and 2.48 times as likely, respectively, to develop pre-HTN/HTN (hypertension) in the year after delivery as those without pregnancy-related HTN. History of preeclampsia is also associated with an increased risk of future metabolic syndrome.

Table 4 Studies showing the increase in late other organ system disorders morbidity in preeclamptic women

Study	Year	Results
Aukes et al	2012	History of preeclampsia was a risk marker for early cerebrovascular damage. They noted that formerly eclamptic women demonstrate cerebral white matter lesions (WMLs) several years following the index pregnancy.
Weigman et al	2012	Vision-related quality of life (QOL): Composite scores were significantly lower in formerly eclamptic women than in control participants ($p < 0.01$ for composite scores).
Beharier et al	2016	Women who had preeclampsia had a significantly higher incidence of long-term ophthalmic morbidity such as diabetic retinopathy and retinal detachment. In addition, a positive linear correlation was found between the severity of preeclampsia and the prevalence of future ophthalmic morbidities (0.3 vs. 0.5 vs. 2.2%, respectively).
Postma et al	2016	Formerly preeclamptic women reported cognitive dysfunction but did not exhibit overt cognitive impairment when objectively tested on average 6 y following their pregnancy. The presence of WML was not related to objective or to subjective cognitive impairment, anxiety, and depressive symptoms.

Table 5 Studies showing the increase in late cardiovascular morbidity in premature deliveries in women

Study author	Year	Results
Kessous et al	2013	A linear association was found between the number of previous preterm delivery (PTD) and future risk of cardiovascular hospitalizations (5.5% for ≥ 2 PTDs; 5% for 1 PTD vs. 3.5% in the control group; $p < 0.001$). The association remained significant for spontaneous vs. induced PTD and for early (< 34 wk) and late (34 wk to 36 wk 6 days' gestation) PTD.
Robbins et al	2014	Compared with women who had term deliveries, women with any history of PTB had increased risk of cardiovascular disease (CVD) morbidity (variously defined; adjusted hazard ratio [aHR] ranged from 1.2–2.9), ischemic heart disease (aHR, 1.3–2.1), stroke (aHR, 1.7), and atherosclerosis (aHR, 4.1).
Ngo et al	2015	aHR of CVD among women who ever had a preterm birth was 1.78 (1.61–1.96). Associations were greater for extreme (aHR = 1.98 [1.63–2.42]) and moderate (aHR = 2.06 [1.69–2.51]) than late preterm birth (aHR = 1.63 [1.44–1.85]), for indicated (aHR = 2.04 [1.75–2.38]) than spontaneous preterm birth (aHR = 1.65 [1.47–1.86]), and for having ≥ 2 (aHR = 2.29 [1.75–2.99]) than having 1 preterm birth (aHR = 1.73 [1.57–1.92]).
Catov et al	2016	The relative hazard (95% confidence interval [CI]) for metabolic syndrome was 1.52 (1.22–1.88) for women with preterm compared with term births.
Almasi et al	2016	Women with either spontaneous or indicated PTD had higher rates of renal-related hospitalizations (0.2% vs. 0.1%; odds ratio [OR] = 2.6; 95% CI: 1.7–3.9; $p < 0.001$ and 0.5% vs. 0.2%; OR = 3.41; 95% CI: 1.7–6.5; $p < 0.001$, respectively).

Table 6 Studies showing the increase in late cardiovascular morbidity in placental abruption in women

Study author	Year	Results
Pariente et al	2014	Compared with 46,932 women who delivered during the same period, the cardiovascular case fatality rate for the placental abruption group was 13.0% vs. 2.5% ($p < 0.001$). Placental abruption remained an independent risk factor for long-term maternal cardiovascular mortality (adjusted hazard ratio (HR) = 4.3; 95% confidence interval [CI]: 1.1, 18.6).
Arazi et al	2015	Placental abruption, even though considered a part of the "placental syndrome" with possible vascular etiology, was not found to be a risk factor for long–term maternal renal complications.
DeRoo et al	2016	Women with placental abruption in first pregnancy had an increased risk of cardiovascular death CVD death (HR ratio 1.8; 95% CI: 1.3, 2.4). Results were essentially unchanged by excluding women with pregestational hypertension, preeclampsia, or diabetes. Women with placental abruption in any pregnancy also had a 1.8–fold increased risk of CVD mortality (95% CI: 1.5, 2.2) compared with women who never experienced the condition.
Ananth et al	2017	CVD mortality rates in women with and without abruption were 0.9 and 0.3 per 10,000 person-years, respectively (adjusted HR 2.7, 95% CI: 1.5, 5.0). The corresponding CVD morbidity complication rates were 16.7 and 10.0 per 10,000 person-years, respectively (HR 1.5, 95% CI: 1.4, 1.8).

Table 7 Studies showing the increase in late cardiovascular morbidity in still birth and recurrent miscarriages in women

Study author	Year	Results
Pariente et al	2014	After stillbirth, women had a significantly higher cumulative incidence of cardiovascular and renal morbidity and cardiovascular and renal hospitalizations, and had higher rates of simple and complex cardiovascular events. A significant stepwise increase was found between the number of stillbirths and future risk for cardiovascular morbidity.
Kessous et al	2014	Women with a history of recurrent pregnancy loss (RPL) had higher rates of renal and cardiovascular morbidity. Using a Cox proportional hazards model, adjusted for confounders such as preeclampsia, diabetes mellitus, obesity, and smoking, a history of RPL remained independently associated with cardiovascular hospitalizations.

Table 8 Long-term risks for mother following complicated pregnancy

Type of abnormality	Cardiac (HF + CAD - microvascular dysfunction, obstructive lesions, AMI, coronary calcification)	Thromboembolic	Ophthalmology	Renal	Stroke	Cor pulmonale	Others (cancer)
GDM	Yes	No	No	No	Yes	No	No
Preeclampsia	Yes	Yes	No	No	Yes	No	No
Preterm deliveries	Yes	No	No	Yes	Yes	No	No
Abruption placenta	Yes	No	No	No	No	No	No
Maternal obesity	No	No	Yes	No	No	No	No
Women with SGA neonates	Yes	No	No	Yes	No	Yes	No
Preeclampsia and eclampsia	Yes	Yes	No	Yes	Yes	No	No

Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; GDM, gestational diabetes mellitus; HF, heart failure; SGA, small for gestational age.

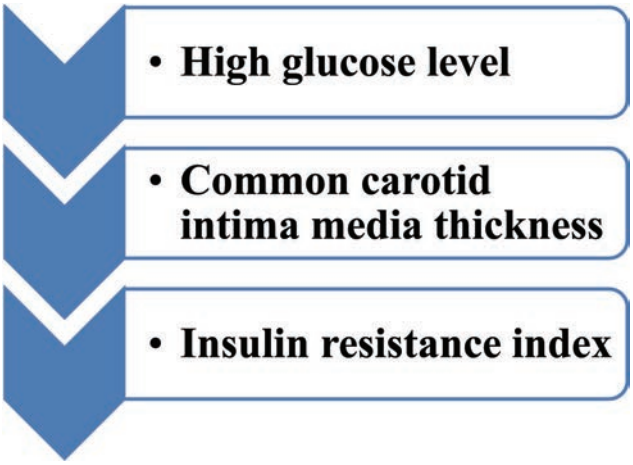

Fig. 1 Markers in GDM patients to detect the CVD subsequently.

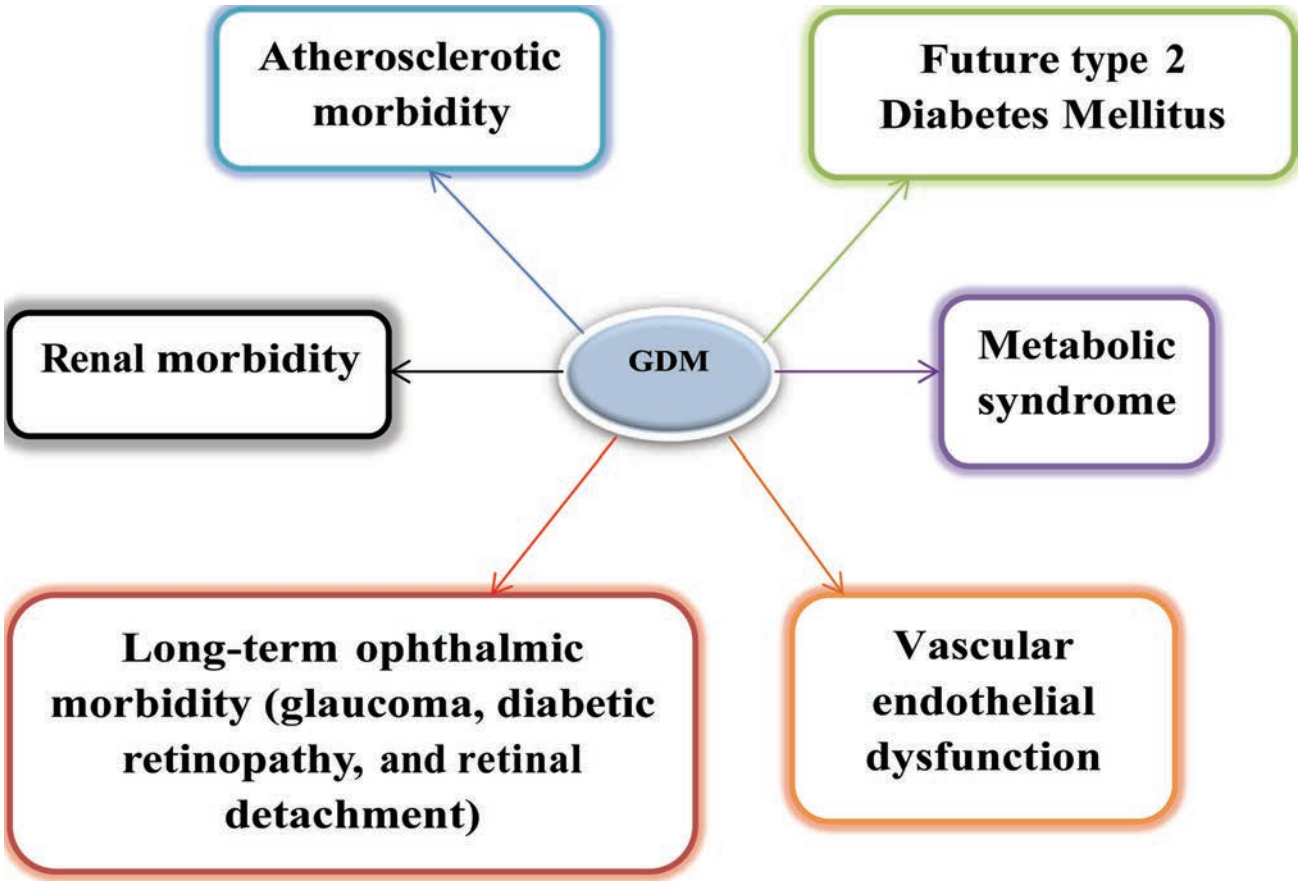

Fig. 2 GDM—future events.

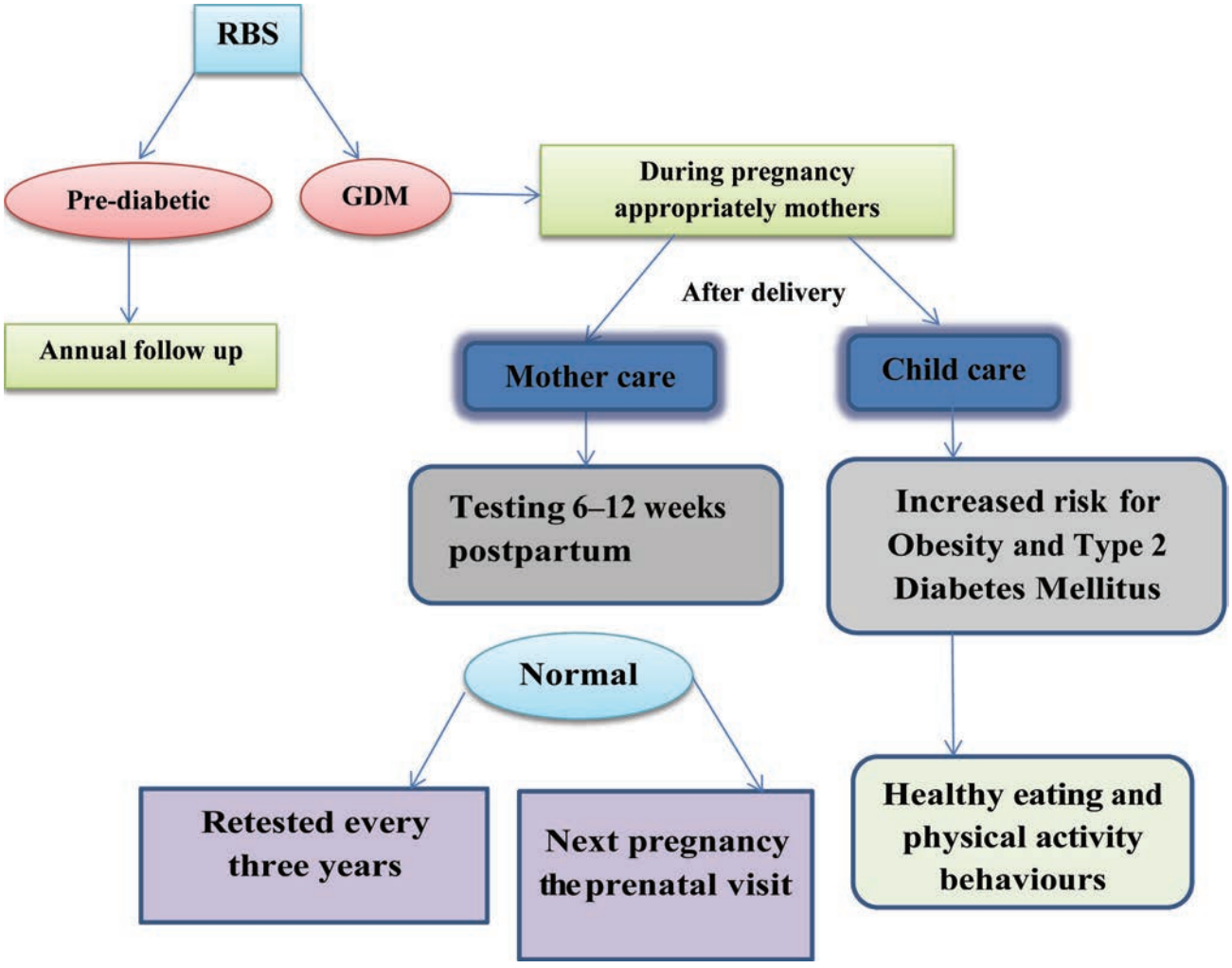

Fig. 3 Follow-up of GDM patient (ACOG and the American Diabetes Association recommend testing women recommendation).

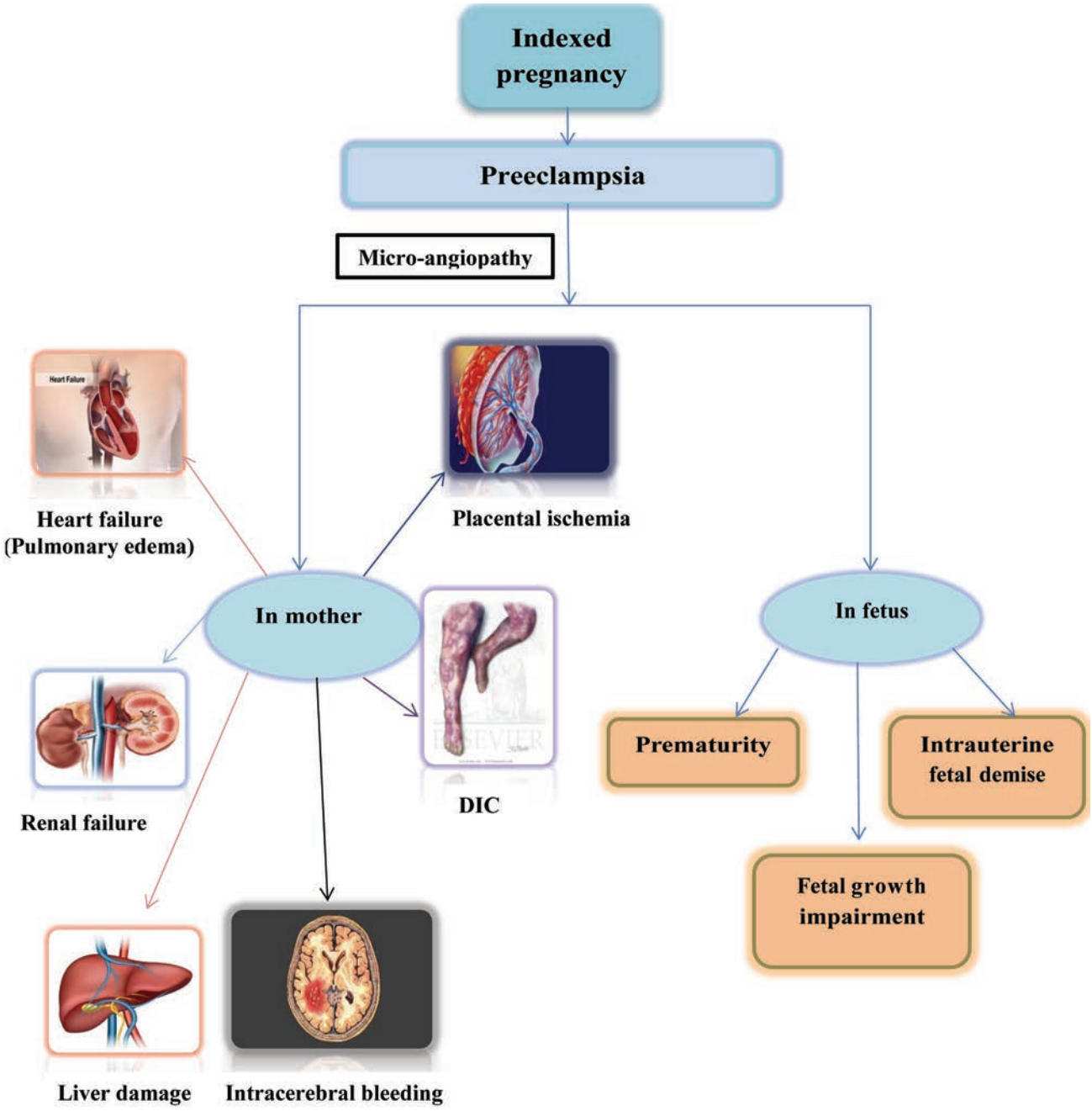

Fig. 4 Effects of preeclampsia during indexed pregnancy.

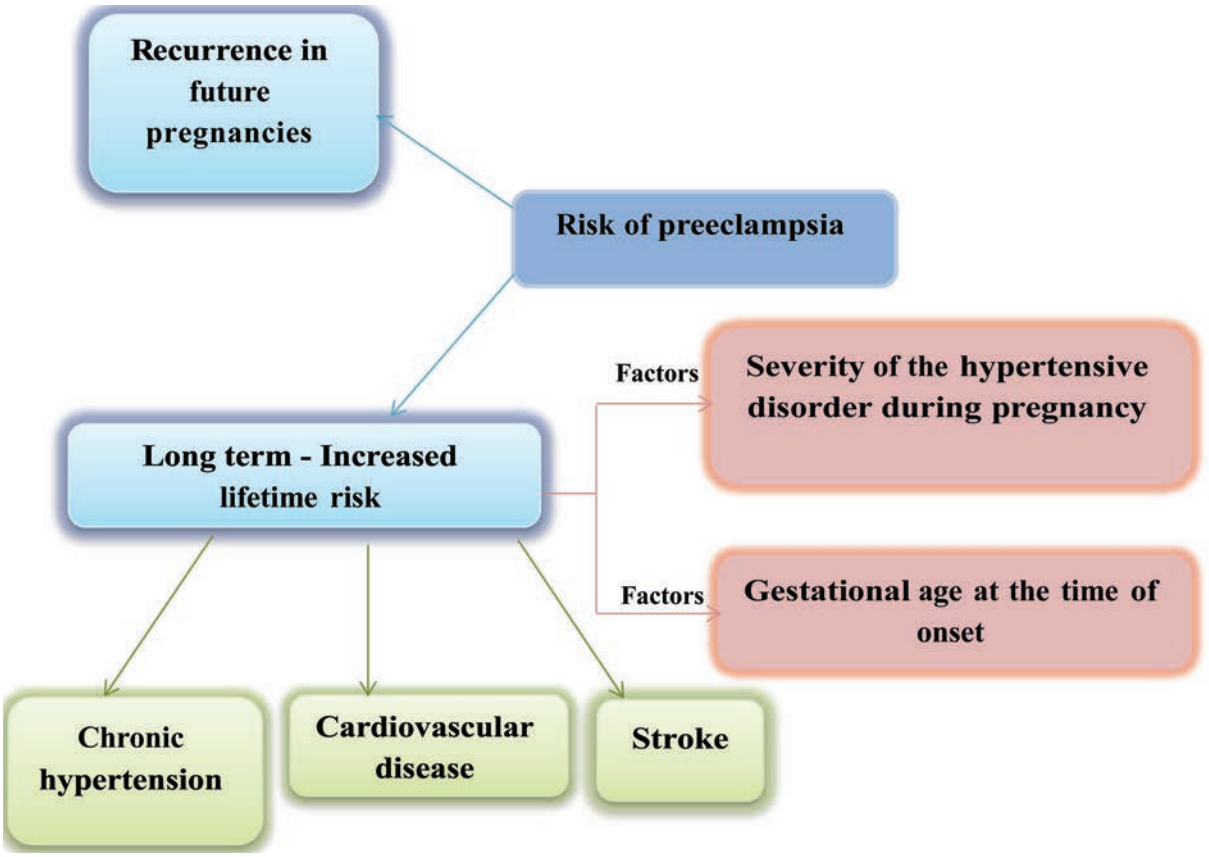

Fig. 5 Risk of preeclampsia.

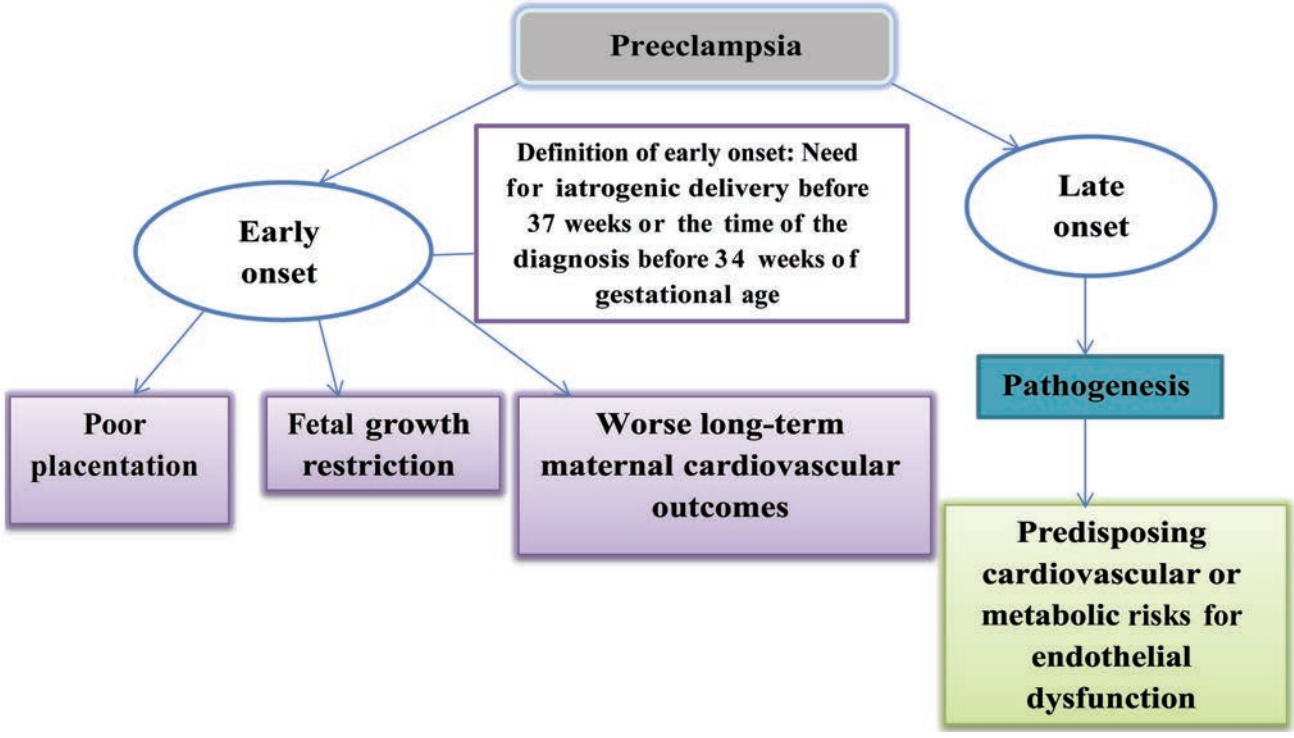

Fig. 6 Gestational age at the time of occurrence of preeclampsia.

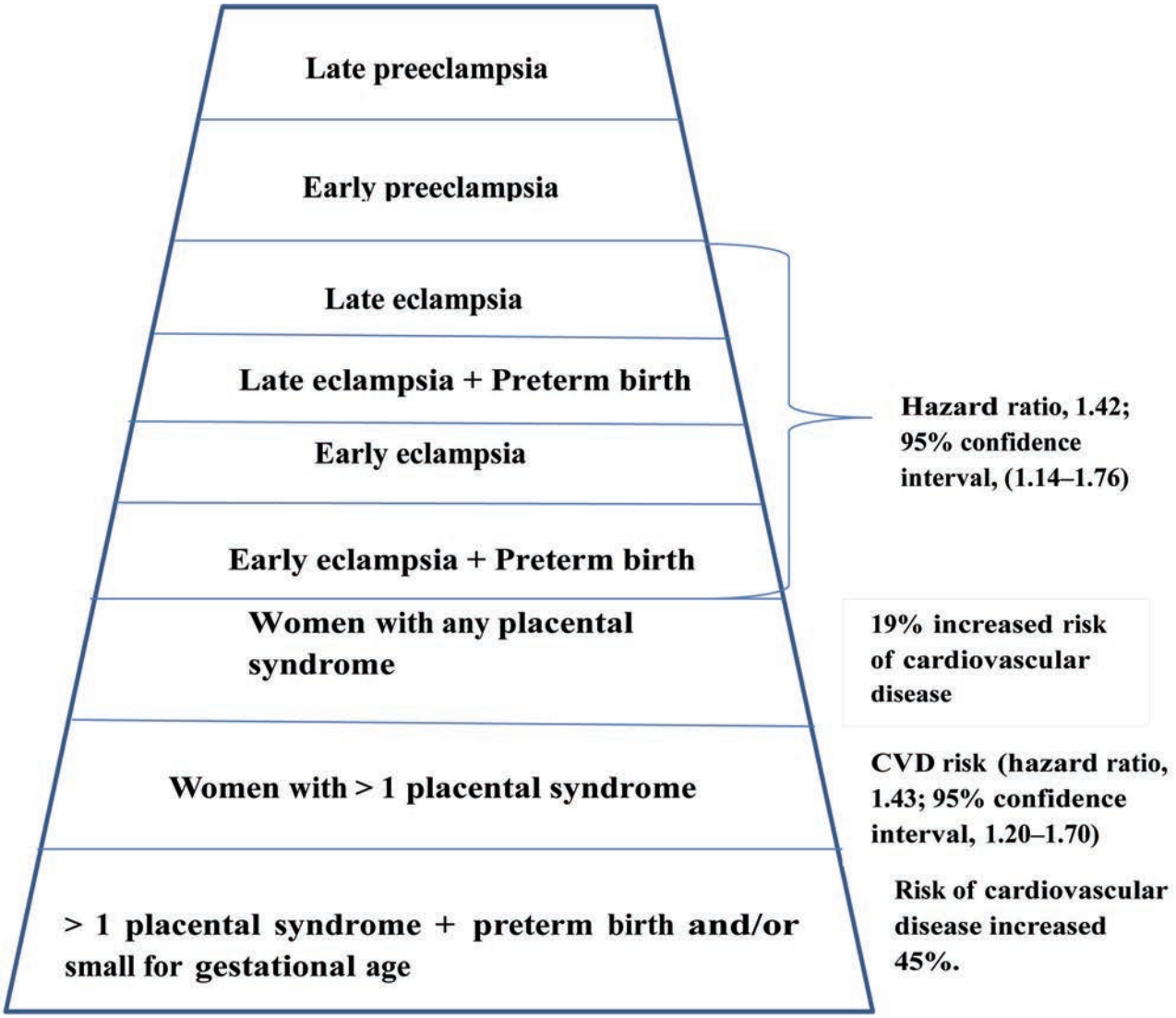

Fig. 7 Pyramid of relative risk of different stages of eclampsia for future cardiovascular disease.

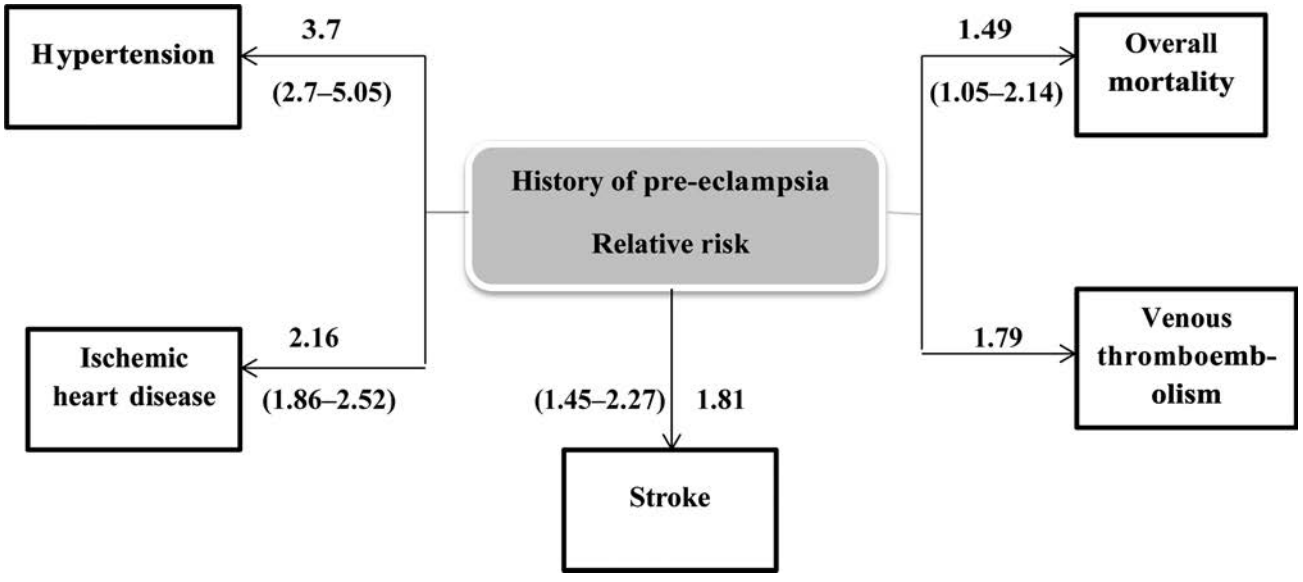

Fig. 8 Preeclampsia—subsequent cardiovascular disease.

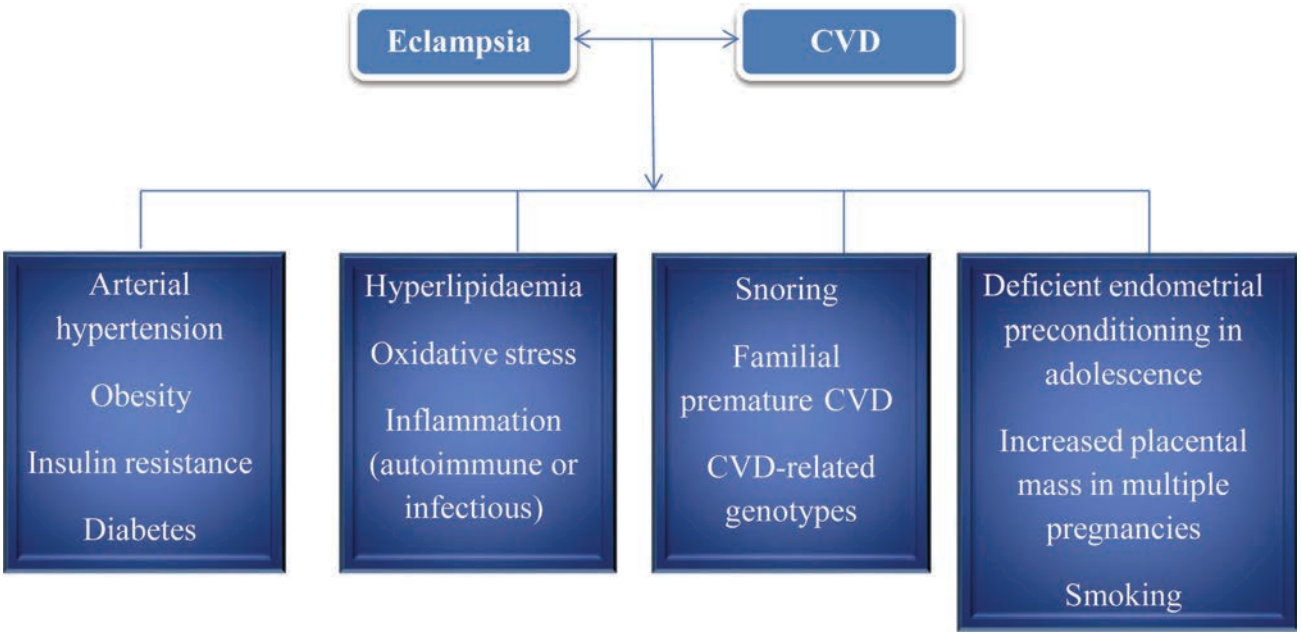

Fig. 9 Common factors for eclampsia and CVD.

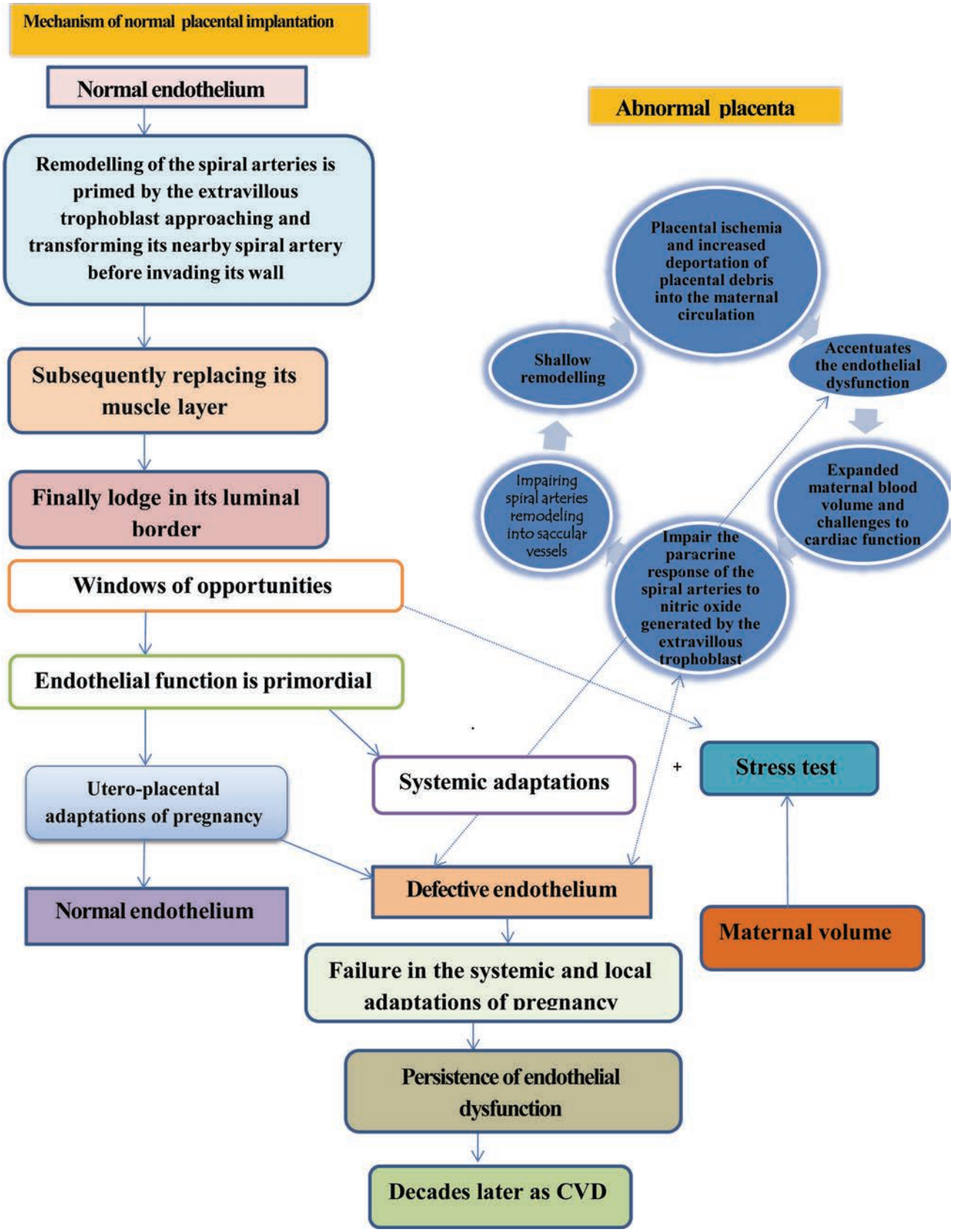

Fig. 10 Pathophysiology of complicated pregnancy leading to long-term maternal effects.

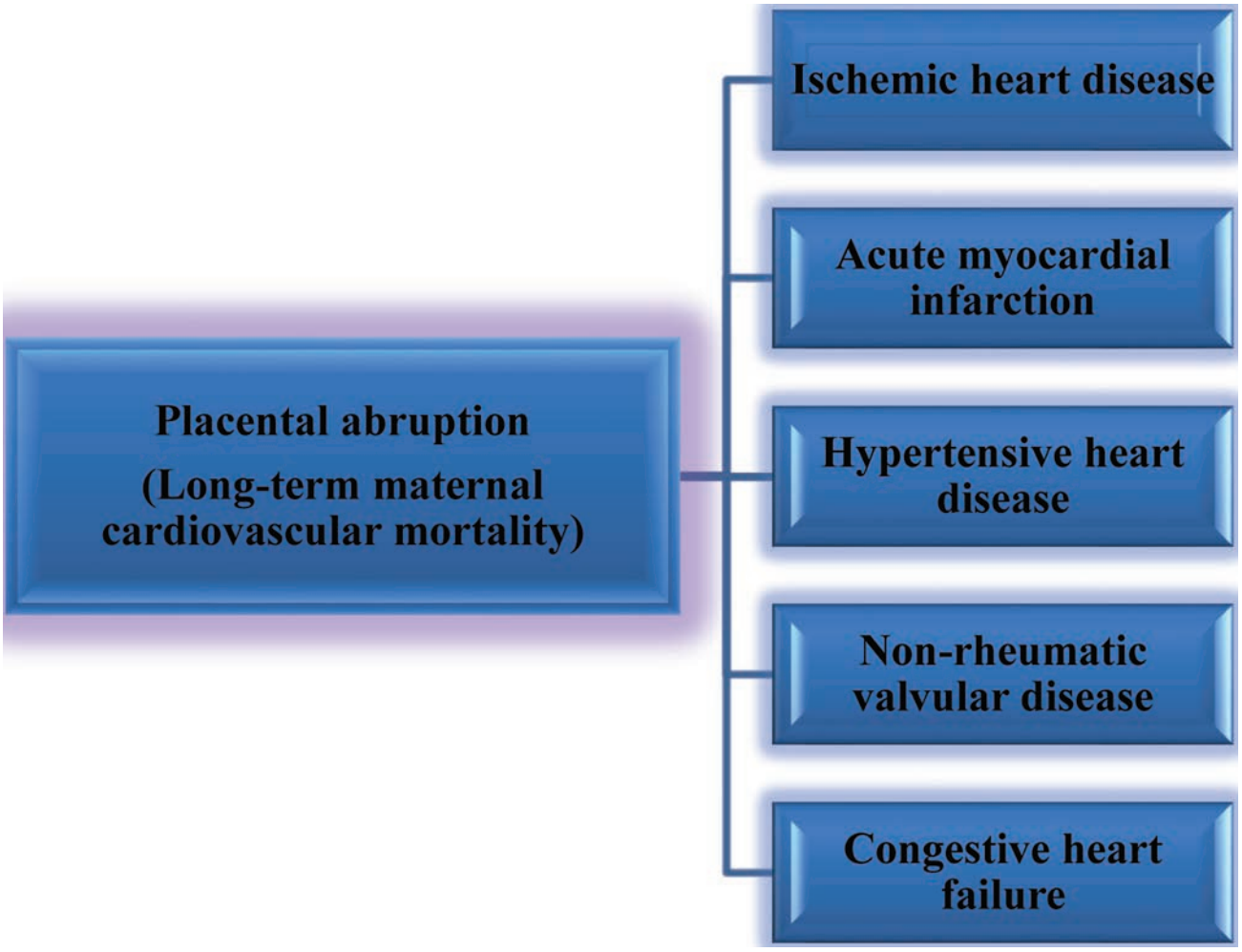

Fig. 11 Placental abruption—subsequent cardiovascular disease.

Fig. 12 Recommendations for prevention of long-term risk for mother.

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