



Review Article



Pregnancy at Late Maternal Age and Future Cardiovascular Health

Mi-Jeong Kim , MD, PhD^{1,2}

¹Department of Cardiovascular Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea

²Department of Cardiology, College of Medicine, The Catholic University of Korea, Seoul, Korea



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Correspondence to

Mi-Jeong Kim, MD, PhD

Department of Cardiovascular Medicine,
Incheon St. Mary's Hospital, College of
Medicine, The Catholic University of Korea,
56 Dongsu-ro, Bupyeong-gu, Incheon 21431,
Korea.

E-mail: mjkim@catholic.ac.kr

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ORCID iDs

Mi-Jeong Kim 
<https://orcid.org/0000-0002-7887-3309>

Conflict of Interest

The author has no financial conflicts of
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ABSTRACT

Increasing numbers of women are delivering their first child at a later age. First pregnancy at a later age is, per se, a high-risk pregnancy. Pregnancy after 35 years is traditionally considered a late maternal age. The risks of obstetric complications including fetal and maternal complications are increased. Defective placenta syndrome, including hypertensive disorders, preterm birth, and intrauterine growth retardation, shares similar pathophysiologic mechanisms with endothelial dysfunction, although their clinical presentations differ. Recent medical advances have improved the medical performance of pregnancy-related cardiovascular disease (CVD). Recent evidence has shown that women with underlying defective placental syndrome or other pregnancy-related complications have an increased risk of unfavorable cardiovascular outcomes in later life. An increasing number of women delivering their first child at a later age have epidemiological characteristics that differ from those reported previously and for which data are limited data regarding the cardiovascular prognosis. Therefore, increased attention to public health and CVD prevention is required for women with complicated pregnancies.

Keywords: Cardiovascular diseases; Pregnancy; Pregnancy complications, cardiovascular; Pregnant women; Women

INTRODUCTION

Women in modern society tend to become pregnant at a later age, with women aged ≥ 35 years accounting for up to 20% of total live births in Canada and England and 9% of first births in the United States in the 2010s.¹ Women aged above their mid-30s have decreased fertility rates and increased fetal chromosomal anomalies, miscarriage, and pregnancy complications.² Pregnancy after 35 years has traditionally been considered a late maternal age.³ Pregnancy at a late age is a significant health concern because advanced maternal age is associated with increased maternal and perinatal morbidity and mortality.^{4,5} Pregnancy-related complications have recently been associated with unfavorable cardiovascular outcomes in later life and women who experience complicated pregnancies are at high risk of future cardiovascular diseases (CVDs).⁶ This study reviewed cardiovascular issues related to pregnancy at later ages.

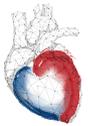


Table 1. Adverse pregnancy events⁽⁶⁾

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|--|
| Adverse fetal outcomes |
| Pre-term birth |
| Intrauterine growth retardation |
| Pregnancy loss (miscarriage, abortion, stillbirth) |
| Later life cardiovascular health risks |
| Adverse maternal outcomes during pregnancy |
| Hypertensive diseases (pre-eclampsia) |
| Peripartum cardiomyopathy |
| Later-life cardiovascular diseases |

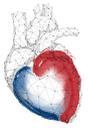
SUBOPTIMAL CARDIOVASCULAR ADAPTATION DURING PREGNANCY AND ADVERSE PREGNANCY EVENTS

Pregnancy causes dramatic cardiovascular and hemodynamic changes to ensure adequate blood flow to the placenta. Blood volume and cardiac output increase nearly 50% above baseline levels and peripheral vascular resistance decreases significantly by the end of the second trimester.⁷⁾ Significant structural alterations of the left ventricle and aorta are also observed. Both left ventricular size and mass and aortic compliance increase rapidly during a short period of time to accommodate the increased circulating blood volume.⁸⁾ Pregnancy-related hormones including estrogen, progesterone, and relaxin lead to placentation and subsequent cardiovascular adaptation. Trophoblasts invade the uterine wall and uterine spiral arteries are widened, less twisted, and less resistant. These cardiovascular system changes associated with a normal pregnancy may not be well tolerated by older women or those with hypertension or subclinical CVD. Suboptimal cardiovascular adaptation leads to a variety of adverse pregnancy events including preeclampsia, intrauterine growth restriction (IUGR), pre-term birth, stillbirth, and peripartum cardiomyopathy (Table 1).

DEFECTIVE PLACENTA SYNDROME AND THE ROLES OF ADVERSE PREGNANCY EVENTS

The pathophysiology of adverse pregnancy events is not well-known; however, defective placental formation is presumed to be the key abnormality. A well-functioning placenta is critical for adequate pregnancy outcomes as the placenta supports fetal growth. Placental insufficiency leads to adverse pregnancy outcomes including IUGR, stillbirth, and pre-eclampsia. The concept of “defective placenta syndrome” includes a series of complications and a wide spectrum of placental morphological or functional abnormalities and a variety of adverse pregnancy events.

Women with later-age pregnancy are vulnerable to suboptimal placental structure and function. A population-based study observed increased placental weight according to maternal age.⁹⁾ A larger placenta in older women appeared to indicate insufficient placental function, including both perfusion and endocrine function. The volume of the uteroplacental spiral vasculature was low¹⁰⁾ and sclerotic changes of the uterine artery and placental infarction were frequently observed in women ≥ 35 years of age compared to those in women aged < 25 years.¹¹⁾ High impedance of the uterine artery as measured by Doppler technique at 23 weeks gestational age was associated with pre-eclampsia or IUGR.¹²⁾ A cross-sectional study measured the Doppler velocity of the uterine artery of 884 normal singleton pregnant



women, reporting that the uterine artery impedance, indicated by pulsatility index, was higher in women with >35 years of age than that in women less than 35 years of age.¹³⁾

Studies have identified blood biomarkers for defective placenta syndrome. Placental growth factor (PlGF) is present in trophoblasts and represents proangiogenic activity. Low blood levels of PlGF were associated with pre-eclampsia.¹⁴⁾ Soluble fms-like tyrosine kinase-1 (sFlt-1) antagonizes angiogenic activity and high levels were also associated with pre-eclampsia.¹⁴⁾ In a recent prospective study performed in Ghana, pregnancy at age ≥ 35 years was associated with a higher rate of adverse pregnancy events and lower PlGF:sFlt-1 ratio.¹⁵⁾

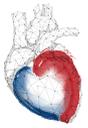
Regarding the pathophysiology of preeclampsia, a prototype of adverse pregnancy events, Roberts and Hubel¹⁶⁾ proposed a 2-stage model including a poorly-perfused defective placenta (stage 1) and the systemic alteration of maternal cardiovascular system and subsequent clinical manifestations of adverse pregnancy events (stage 2). Endothelial dysfunction is presumed to play a major role in both stages.¹⁷⁾ Failure to reduce systemic vascular resistance directly results in pre-eclampsia, placental and maternal major organ ischemia, fetal ischemia, fetal growth restriction, and poor pregnancy outcome. Endothelial dysfunction, increased inflammatory mediators, oxidative stress, and hypercoagulability result in damage to the systemic vasculature, which subsequently makes it more difficult to reduce cardiovascular resistance and worsens maladaptation to pregnancy. In its acute severe form, microvascular damage and perfusion disturbances are evident in the kidneys, liver, and central nervous system of the mother, in addition to fetal distress.

ASSOCIATION OF ADVERSE PREGNANCY EVENTS AND LATER-LIFE CVDS

Endothelial dysfunction and vascular maladaptation during pregnancy are common phenomena in adverse pregnancy events. Peripartum cardiomyopathy also shares a similar pathophysiologic mechanism.¹⁸⁾ Furthermore, these vasculopathies make affected women more vulnerable to future hypertension and a variety of CVDs.

The manifestations of CVD in later life include hypertension, ischemic heart diseases, stroke, and heart failure. A cohort study of 2,396 women with gestational hypertensive disorders during their first singleton pregnancy observed a significant association between hypertension and stroke in later life.¹⁹⁾ A retrospective cohort study in Canada analyzed 710,501 singleton live births. Women with preterm birth or small for gestational age infants had a higher rate of cardiovascular events (adjusted hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.09–2.52) after delivery than control subjects.²⁰⁾ This result was consistent with those of previous reports using the same study population of 75,380 women with defective placenta syndrome.²¹⁾ A retrospective cohort study in Scotland including 129,920 singleton first pregnancies showed that pregnancy complications were associated with the maternal risk of ischemic heart disease in later life.⁶⁾ The respective risks of lower birthweight for gestational age (adjusted HR, 1.9; 95% CI, 1.5–2.4), preterm delivery (HR, 1.8; 95% CI, 1.3–2.5), and pre-eclampsia (HR, 2.0; 95% CI, 1.5–2.5) were all significant. Moreover, the risks were additive; women with all 3 findings had a 7-fold increased risk (95% CI, 3.3–14.5) of later ischemic heart disease compared to the reference group.

It remains unknown whether defective placenta syndrome during pregnancy causes later CVD or whether subclinical CVD is unmasked in the form of defective placenta syndrome during



pregnancy. However, late pregnancy is a risk factor for both defective placenta syndrome and later CVD. Cardiovascular, antiangiogenic, and inflammatory changes might fail to completely resolve and persist after birth in women with defective placenta syndrome. In such cases, repeated pregnancies with defective placenta syndrome as a form of subclinical CVD are likely to result in cumulative cardiovascular damage. A dose-response relationship between defective placenta syndrome and later CVD has been reported. Compared to women without pre-eclampsia, women with current pre-eclampsia had an increased risk of future CVD (95% CI, 3.57–4.17) and a significantly shorter time to first cardiovascular event (10.5 years for recurrent and 12.7 years for no pre-eclampsia).²²⁾ A dose-response relationship in defective placenta syndrome may provide a plausible explanation for why traditional risk factors for adverse pregnancy outcomes include both nulliparity and multiparity. Defective placenta syndrome in a nulliparous woman may be attributed to an individual's limited cardiovascular reserve. However, a multiparous woman with defective placenta syndrome may reach a threshold of overt clinical disease resulting from repeated and accumulated subclinical CVD.

LATER CVD IN WOMEN WITH ADVERSE PREGNANCY OUTCOMES OTHER THAN CVD

Defective placenta syndrome is an established hypothesis explaining adverse pregnancy outcomes. It is primarily related to CVDs including pregnancy-related hypertension and heart failure. However, pregnancy loss can result from a variety of causes besides CVD.

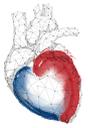
Other adverse pregnancy outcomes include miscarriage and stillbirth. Although they are less well known than CVD, they are also likely to be related to future CVD.

The national cohort of Denmark followed-up 1,243,957 women with ≥ 1 pregnancy for a median of 21.6 years.²³⁾ Among them, 261,279 women experienced pregnancy loss and 2,188 were diagnosed with dementia. Stillbirths were associated with an 86% increased risk of dementia (HR, 1.86; 95% CI, 1.28–2.71). Miscarriage was not associated with later Alzheimer's disease; however, recurrent (≥ 2) miscarriages were most strongly associated with early-onset vascular dementia (HR, 2.44; 95% CI, 1.11–5.37). Pregnancy loss and vascular diseases such as dementia suggest associations between pregnancy complications involving vascular pathology and dementia, particularly vascular dementia. Dose-response relationships have also been reported.²³⁾

The limitations of studies on adverse pregnancy outcomes are evident. The mechanisms and causes of adverse pregnancy outcomes are diverse and it is difficult to determine whether the final cause of pregnancy loss was related to CVD.

FUTURE CARDIOVASCULAR HEALTH ASSOCIATED WITH PREGNANCY AT AN ADVANCED AGE

Current knowledge indicates that pregnancy at a late age is unfavorable for most women, with a high risk of obstetric complications and an increased risk of CVD, including significant hypertensive disorders and severe heart failure. Furthermore, women who experience CVD during pregnancy are more likely to develop premature CVD in later life. However, pregnancy-related studies have many limitations. For example, many of the results are



obtained from old data. Study design and data acquisition are difficult due to the long duration between pregnancy and CVD events. Furthermore, the diagnosed causes of adverse pregnancy outcomes during pregnancy are often inaccurate.

What about women who have safely delivered their first child at a later age? An increasing number of women deliver for the first time in their late 30s and 40s. Women now commonly delay pregnancy due to social activities and professional careers. Many older pregnant women have high levels of education, economics, healthiness, and medical access. Despite their late ages women who safely deliver their first child, which indicates sufficient cardiovascular reserve, are likely to have good cardiovascular health. Such women may have an unexpectedly low CVD vulnerability. Thus, conventional study findings in women with pregnancy-related complications cannot explain these observations in this new group of older pregnant women. However, data on this topic are scarce.

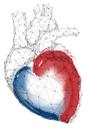
CONCLUSION

Childbirth at a late age is an important risk factor for pregnancy-related complications including defective placenta syndrome. Women with a history of pregnancy-related complications are at high risk for future CVD in later life. Women who have safely delivered for the first time, even at a late age, may not be a high-risk group for premature CVD; however, little data are available.

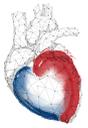
The rapidly increasing number of women delaying their first birth requires attention to public health and CVD prevention in this population. To prevent premature CVD, lifestyle therapy should be emphasized among women expecting to become pregnant at an older age. Routine pregnancy history should be included in the evaluation of women's cardiovascular health. Early systematic and continuous cardiovascular risk assessment and management are necessary for women giving birth at a later age.

REFERENCES

1. Cooke CM, Davidge ST. Advanced maternal age and the impact on maternal and offspring cardiovascular health. *Am J Physiol Heart Circ Physiol* 2019;317:H387-94.
[PUBMED](#) | [CROSSREF](#)
2. Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment. *Hum Reprod* 2004;19:1548-53.
[PUBMED](#) | [CROSSREF](#)
3. Johnson JA, Tough S. No-271-delayed child-bearing. *J Obstet Gynaecol Can* 2017;39:e500-15.
[PUBMED](#) | [CROSSREF](#)
4. Cleary-Goldman J, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, Saade GR, Eddleman KA, Klugman S, Dugoff L, Timor-Tritsch IE, Craigo SD, Carr SR, Wolfe HM, Bianchi DW, D'Alton M; FASTER Consortium. Impact of maternal age on obstetric outcome. *Obstet Gynecol* 2005;105:983-90.
[PUBMED](#) | [CROSSREF](#)
5. Blomberg M, Birch Tyrberg R, Kjølhed P. Impact of maternal age on obstetric and neonatal outcome with emphasis on primiparous adolescents and older women: a Swedish Medical Birth Register Study. *BMJ Open* 2014;4:e005840.
[PUBMED](#) | [CROSSREF](#)
6. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001;357:2002-6.
[PUBMED](#) | [CROSSREF](#)



7. Elkayam U, Goland S, Pieper PG, Silversides CK. High-risk cardiac disease in pregnancy: part I. *J Am Coll Cardiol* 2016;68:396-410.
[PUBMED](#) | [CROSSREF](#)
8. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation* 2014;130:1003-8.
[PUBMED](#) | [CROSSREF](#)
9. Haavaldsen C, Samuelsen SO, Eskild A. The association of maternal age with placental weight: a population-based study of 536,954 pregnancies. *BJOG* 2011;118:1470-6.
[PUBMED](#) | [CROSSREF](#)
10. Zalud I, Shaha S. Three-dimensional sonography of the placental and uterine spiral vasculature: influence of maternal age and parity. *J Clin Ultrasound* 2008;36:391-6.
[PUBMED](#) | [CROSSREF](#)
11. Naeye RL. Maternal age, obstetric complications, and the outcome of pregnancy. *Obstet Gynecol* 1983;61:210-6.
[PUBMED](#)
12. Papageorghiou AT, Yu CK, Bindra R, Pandis G, Nicolaidis KH; Fetal Medicine Foundation Second Trimester Screening Group. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001;18:441-9.
[PUBMED](#) | [CROSSREF](#)
13. Pirhonen J, Bergersen TK, Abdlenoor M, Dubiel M, Gudmundsson S. Effect of maternal age on uterine flow impedance. *J Clin Ultrasound* 2005;33:14-7.
[PUBMED](#) | [CROSSREF](#)
14. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003;111:649-58.
[PUBMED](#) | [CROSSREF](#)
15. Odame Anto E, Owiredu WK, Sakyi SA, Turpin CA, Ephraim RK, Fondjo LA, Obirikorang C, Adua E, Acheampong E. Adverse pregnancy outcomes and imbalance in angiogenic growth mediators and oxidative stress biomarkers is associated with advanced maternal age births: a prospective cohort study in Ghana. *PLoS One* 2018;13:e0200581.
[PUBMED](#) | [CROSSREF](#)
16. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. *Placenta* 2009;30 Suppl A:S32-7.
[PUBMED](#) | [CROSSREF](#)
17. Lane-Cordova AD, Khan SS, Grobman WA, Greenland P, Shah SJ. Long-term cardiovascular risks associated with adverse pregnancy outcomes: JACC review topic of the week. *J Am Coll Cardiol* 2019;73:2106-16.
[PUBMED](#) | [CROSSREF](#)
18. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Watkins H, Shah AJ, Seferovic PM, Elkayam U, Pankuweit S, Papp Z, Mouquet F, McMurray JJ; Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2010;12:767-78.
[PUBMED](#) | [CROSSREF](#)
19. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WC. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ* 2003;326:845.
[PUBMED](#) | [CROSSREF](#)
20. Silverberg O, Park AL, Cohen E, Fell DB, Ray JG. Premature cardiac disease and death in women whose infant was preterm and small for gestational age: a retrospective cohort study. *JAMA Cardiol* 2018;3:247-51.
[PUBMED](#) | [CROSSREF](#)
21. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet* 2005;366:1797-803.
[PUBMED](#) | [CROSSREF](#)
22. Auger N, Fraser WD, Schnitzer M, Leduc L, Healy-Profittós J, Paradis G. Recurrent pre-eclampsia and subsequent cardiovascular risk. *Heart* 2017;103:235-43.
[PUBMED](#) | [CROSSREF](#)



23. Ranthe MF, Andersen EA, Wohlfahrt J, Bundgaard H, Melbye M, Boyd HA. Pregnancy loss and later risk of atherosclerotic disease. *Circulation* 2013;127:1775-82.

[PUBMED](#) | [CROSSREF](#)