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Other adverse pregnancy outcomes and future chronic disease

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ABSTRACT

Cardiovascular disease is the leading cause of morbidity and mortality in females worldwide. Pregnancy is associated with significant physiologic changes that may function as a natural stress test to detect women at future risk. It is established that women who have had a pregnancy complicated by gestational diabetes or a hypertensive disorder of pregnancy are at increased risk of cardiovascular disease later in life, and there is growing evidence that women who deliver infants preterm or growth-restricted infants have an elevated risk as well. Consideration should be given to including these outcomes as indicators of cardiovascular risk. Pregnancy represents a teachable moment when it would be ideal to identify women at risk. Improved integration of women's primary health care and an enhanced knowledge base on the part of clinicians will be necessary to fully incorporate these findings into the clinical care of women.

Introduction

There is an accumulating body of literature examining the long-term effects of adverse pregnancy outcome on future maternal chronic disease.[1] One of the most studied of these effects is that of cardiovascular disease risk. This is of particular interest because cardiovascular disease is the leading cause of mortality in women in the United States and worldwide, with a 35% overall prevalence of cardiovascular disease among women.[2] The presence of cardiovascular risk factors is highly predictive of future cardiovascular disease,[3] and cardiovascular disease is largely preventable through risk factor modification. There has been an overall trend of decreasing cardiovascular disease in the US attributable to decreased rates of smoking and control of risk factors; this reduction has been greater for men than for women.[4] Recent epidemiologic evidence suggests that the primary prevention of risk factors themselves may be more effective than treatment of existing risk factors. The concept of "primordial prevention," ie, prevention of the major cardiovascular risk factors themselves early in the life course, may be a more cost-effective approach to continue in reducing the burden of cardiovascular disease for a population.[5]

Cardiovascular disease has been historically more difficult to predict in women than men.[6] If highly predictive, pregnancy outcomes may provide a unique opportunity to identify women at greatest risk.[7] Pregnancy is associated with dramatic changes in physiology that may serve as a natural "stress test" to predict

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women at future risk of disease. The majority of women in the United States will become pregnant at least once in their lifetime, with approximately 85% having had at least one pregnancy by 45 years of age.[8] Pregnancy provides an opportune time for interventions because gravid women are often young and reliably seek health care. Pregnancy represents a "teachable moment" whereby women are likely to be highly motivated to adopt healthy behaviors.[9]

The link between adverse pregnancy outcomes and future cardiovascular disease typically focuses on hypertensive disorders and gestational diabetes, which are now considered to be cardiovascular disease risk factors by the American Heart Association.[10] In this article, we review the current evidence focusing on the association of other common adverse outcomes with future cardiovascular disease (Table). Most of the evidence comes from large historical cohorts of European populations using administrative data to identify cardiovascular outcomes. Because the cardiovascular events of interest occur decades after pregnancy, there are enormous challenges in understanding the independence of these associations and their relationship to establish cardiovascular risk factors.

Preterm birth

Preterm birth accounts for approximately 12% of births in the United States and is a major source of neonatal morbidity worldwide.[11] Evidence of the relation between preterm birth, defined as birth before 37 completed weeks of gestation, has been recently reviewed and suggests that the mothers are at increased cardiovascular disease risk in later life.[1] The examination of the association between preterm birth is complicated by the complexity of the outcome. For example, preterm birth can be indicated or spontaneous, and only some causal pathways may be associated with later cardiovascular disease. A hypertensive disorder may lead to an indicated preterm delivery, for example, but it may in fact be the preeclampsia that is driving the later outcome. The ability of investigators to examine these differences depends upon their data source. In addition, disentangling the effects of preterm delivery and growth restriction is complex, as will be discussed in the next section.

Hastie et al. were able to consider differences in outcomes between elective and spontaneous preterm birth for a cohort of 750, 350 women from Scotland who were followed up over an average of 28 years. The outcomes for this cohort were identified from a national registry using international classification of diseases (ICD) codes for ischemic heart disease. They found an association between preterm birth and ischemic heart disease,[12] driven in large part by the association with iatrogenic preterm birth. They explored the indications for preterm birth, which included intrauterine growth restriction and preeclampsia, which are both factors associated with future cardiovascular disease risk.[13]

If preterm birth is associated with later cardiovascular disease risk, one might expect to see increased risk in women with a history of recurrent preterm birth or very early preterm birth. In a cohort of 427, 765 Danish women delivering between 1973 and 1983, recurrent preterm birth (HR = 1.78) was associated with an increased risk of cardiovascular disease compared to one prior preterm birth (HR = 1.22).[14] Birth data were derived from the Danish Medical Birth Registry, which contains data on all live and still births. Cardiovascular disease outcomes were identified using ICD codes using the National Hospital Discharge Register, which includes data from all hospital admissions since 1977. This association was independent of coexistent preeclampsia, growth restriction, or diabetes. Interestingly, women experiencing early preterm birth (gestational age <32 weeks) did not have a higher risk than those with later preterm birth.

In addition to cardiovascular disease risk, women who deliver preterm are also at increased risk for type 2 diabetes and thromboembolism.[15] This was demonstrated in a large cohort of 782, 287 women delivering their first baby in Denmark between 1978 and 2007. This association was found to be independent of any coexisting pregnancy complication.

Fetal growth

Offspring birth weight predicts future mortality in the mother.[16] In a large Swedish cohort including 783,814 births between 1973 and 1980, offspring birth weight was inversely associated with cardiovascular and all-cause mortality in both parents.[17] The adjusted hazard ratio (HR) for cardiovascular mortality in mothers was 0.75 for each standard deviation increase in birth weight, and this association was stronger than that observed for fathers (HR = 0.93).[18] Low birth weight is also associated with increased mortality in parents and grandparents.[19]

Because birth weight is a product of fetal growth and length of gestation, low birth weight could result from impaired fetal growth or a normally grown fetus that was born premature. The weight of an infant at birth is determined not only by growth velocity but also by length of gestation. Studies looking specifically at fetal growth have normalized fetal weight to gestational age. Mothers who gave birth to small for gestational age infants, defined by weight less than 10th percentile for gestational age, were more likely to have

Table – Adverse pregnancy outcome and risk of future cardiovascular mortality.

Adverse pregnancy outcome	Relative risk (range)	Comments	References
Low birth weight	1.23–1.49	per 1 SD lower birth weight	27,37,38
Fetal growth	1.44–2.56	IUGR or SGA	13,22
Preterm birth	2.06–2.45	Gestational age <37 weeks	17,37

IUGR, intrauterine growth restriction; SGA, small for gestational age; SD, standard deviation.