Adverse Pregnancy Outcomes: The Missing Link in Discovering the Role of Lactation in Cardiovascular Disease Prevention

Enthusiasm for improved understanding of how modifiable behaviors across the life course, including the reproductive period, influence cardiovascular disease (CVD) risk is gaining traction. Along these lines, the January 2022 issue of the Journal of the American Heart Association (JAHA) included the article by Tschiderer and colleagues titled, “Breastfeeding Is Associated With a Reduced Maternal Cardiovascular Risk: Systematic Review and Meta-Analysis Involving Data from 8 Studies and 1 192 700 Parous Women.”¹

The compilation and synthesis of data from over 1 million women is a valuable contribution to the literature. The primary findings were that a history of any duration of breastfeeding was associated with 11% to 17% reduction in the relative risks of later life adverse cardiovascular outcomes (hazard ratio [HR], 0.89 [95% CI, 0.83–0.95] for CVD; HR, 0.85 [95% CI, 0.78–0.95] for coronary heart disease; HR, 0.88 [95% CI, 0.79–0.99] for stroke; and HR, 0.83 [95% CI, 0.76–0.92] for fatal CVD),¹ after accounting for reproductive and sociodemographic factors. However, important caveats regarding the study limitations and interpretation of the results, as well as persistent research gaps, warrant further discussion.

First, the authors mentioned that a strength of their analysis was inclusion of “reproductive factors” as covariates in the published studies. Although the 8 included studies (all of which employed retrospective designs) adjusted their model estimates for important attributes such as parity, stillbirth, miscarriage, ages at menarche and menopause, and treatment with sex hormones,¹ none of these studies accounted for a history of adverse pregnancy outcomes (APOs), such as hypertensive disorders of pregnancy, preterm birth, or gestational diabetes, considered established risk factors for future CVD in women after pregnancy that may interfere with successful lactation.² Thus, the modest protective association for lactation and later life CVD may be overestimated as women with a history of APOs, or prior chronic hypertension, may be less likely to initiate lactation.¹,² Prepregnancy obesity, chronic conditions, and certain APOs, especially preeclampsia and preterm delivery, can interfere with breastfeeding initiation and lead to delayed onset of lactogenesis and earlier cessation,³ as well as increased CVD risk in later life.⁴

APOs affect about 20% of US pregnancies annually,⁵ with preeclampsia being the leading cause of severe maternal morbidity outcomes, with health disparities by race and ethnic groups.⁵ Details regarding the impact of lactation, according to APO type and severity, on CVD outcomes remain undefined. Maternal and neonate medical complications related to clinical outcomes (ie, prematurity) and physiologic effects (ie,
delayed onset of lactogenesis) of APOs are recognized barriers to lactation success. In severe APOs, the related perinatal complications may diminish the likelihood of initiating or successfully maintaining lactation. Women who experienced APOs may be overrepresented in the lower lactation duration categories in the recent meta-analysis. Thus, the findings of a consistent protective association between lactation and adverse CVD outcomes based on the summary risk estimates from Tschiderer and colleagues leave open the question of reverse causation, effect modification, or confounding.

Future research is needed to evaluate the lactation-CVD outcome associations among women with a history of APOs, (Figure). Limited evidence suggests that a history of hypertensive disorders of pregnancy may nullify the lactation-lower CVD risk association. Among 681 pregnant women followed up to 7–15 years post-delivery (24.6% Black, 75.4% White, or Other race [Asian or Native American]), Countouris et al. found that 6 months of lactation was associated with thinner carotid intima-media thickness and more favorable subclinical CVD risk factors in women with uncomplicated pregnancies (n=607) but not among women with hypertensive disorders of pregnancy (n=71). As the number of participants with hypertensive disorders of pregnancy was small, SDs and CIs were large, and a bigger sample is needed for more precise estimates. A second prospective study by Kirkegaard et al. of 63,260 Danish women showed that full or partial breastfeeding were each independently associated with 10% to 25% lower risk of hypertension and CVD outcomes up to 7 years postdelivery adjusted for maternal lifestyle, diabetes, preeclampsia, and preterm birth during the index pregnancy. However, subgroup analyses were not performed by APO history or specific types of APOs.

In a 30-year prospective follow up study, Gunderson and colleagues found a strong graded protective association (up to 50% lower) between longer lactation duration and subsequent incidence of diabetes in women with gestational diabetes and without gestational diabetes independent of prepregnancy body mass index, metabolic profiles before pregnancy, lifestyle behaviors, family history of diabetes, and sociodemographic factors. A 2-year prospective follow-up of 1000 women with recent gestational diabetes delivery found that greater lactation intensity and longer duration were associated with up to 50% relative reduction in the incidence of overt diabetes in a racially and ethnically diverse cohort independent of risk factors above, perinatal outcomes, and severity of gestational diabetes (ie, metabolic profile from diagnosis with 3-hour 100 g oral glucose tolerance test sum of 4 serum glucose Z-scores). Consideration of graded associations, defined by lactation duration and intensity, and cumulative lifetime lactation, are important for determining threshold and optimal lactation levels that may provide protection against CVD and chronic disease for mothers with and without a history of APO. The associations may differ substantially, by the specific APO type, and consideration of variations in diagnostic criteria over time and by country, that warrant evaluation in research studies.

A major reason for the gap is the paucity of evidence characterizing both history and severity of APOs from research studies with primarily retrospective designs. Prospective evidence showing that lactation

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may substantially lower incident cardiometabolic disease (ie, metabolic syndrome, type 2 diabetes) and CVD-related outcomes (carotid intima-media thickness, pericardial fat) is available from studies in women of childbearing age.\textsuperscript{9-13} These prospective studies are unique: they include preconception or gestational measurement of metabolic risk factors before lactation initiation; consist of repeated, research-quality measurements of cardiometabolic disease risk factors and outcomes later in life; they can take into account APOs, changes in lifestyle behaviors,\textsuperscript{14} racial identity, and social factors.\textsuperscript{1,13} Prospective study designs allowed investigators to differentiate the effects of pregnancy and lactation from the differential risk profiles preceding reproductive exposures and preserved the temporality of lactation and future cardiometabolic disease outcomes to reduce reverse causation.

These strengths contrast with the limitations of retrospective cohort studies of older women that did not assess certain APOs (such as gestational diabetes) and diabetes outcomes at all or soon after index pregnancies and births. In fact, many studies on lactation and future CVD involve large cohorts that enrolled middle-aged or elderly women. These studies found more modest risk reductions of 10% to 20% associated with 12 months lifetime lactation, but no graded protective associations. The longer latency period for emergence of overt CVD in women (generally age >60 years) compared with earlier diagnoses of metabolic disorders after pregnancy and during the reproductive years through midlife makes the link between reproductive outcomes and future CVD events more arduous to define and less clear. Longer term prospective studies including biochemical and CVD risk factor measurements before pregnancy and early postdelivery to track risk status independent of lactation, and the subsequent progression to hypertension, diabetes, and CVD outcomes in women during later life, are needed. The size of the recent meta-analysis of lactation history and CVD outcomes in older women was impressive,\textsuperscript{1} but it did not provide the important data on APOs and prelactation risk factors such as elevated blood pressure, obesity, hyperlipidemia, and metabolic dysfunction that would help elucidate the relationship of lactation itself with longer term cardiometabolic health outcomes in women. Thus, prospective studies that assess predisposing risk factors preceding lactation during the childbearing years are needed to identify and stratify risk groups to better elucidate the true associations of lactation with longer term maternal cardiovascular health outcomes (Figure).

Finally, the idea that weight loss could contribute to the protective effects of lactation is often discussed. Work from multiple sources challenge the idea that benefits of lactation depend on weight loss postdelivery or lower body weight. For example, in the prospective CARDIA (Coronary Artery Risk Development in Young Adults) Study, an analysis of 1238 women (50% Black and White participants) followed for 30 years, there was a strong graded, inverse association between increasing lifetime lactation duration and lower relative risk of incident diabetes, but the associations between weight gain and lactation duration categories did not differ between the incident diabetes and no diabetes groups.\textsuperscript{5} Overall, findings on the role of lactation on changes in maternal body weight have been equivocal. A meta-analysis from Neville et al. concluded that few studies found any moderate or strong association between lactation and weight change or body composition in the years soon after delivery.\textsuperscript{15} Four out of 5 high-quality studies included in the Neville analysis found a positive association between lactation and weight change, that is weight gain with greater lactation.\textsuperscript{15} In another systematic review and meta-analysis, there was no appreciable difference in postpartum weight retention associated with breastfeeding after adjusting for confounders.\textsuperscript{16} More rigorous studies are needed to capture variations in postpartum weight changes associated with lactation.

Preservation of maternal fat stores may be an early adaptation for species survival in times of food scarcity. Gunderson et al. showed suppression of maternal circulating adiponectin with higher lactation intensity, which may limit maternal weight loss.\textsuperscript{17} Like physical activity, another health-promoting and low-cost behavior, lactation potentially influences other facets of cardiometabolic function by improving the lipid profiles, promoting glucose disposal via insulin-independent pathways, mobilizing fat depots, and influencing systemic hormone levels.\textsuperscript{18} Benefits of lactation and physical activity may be additive. We found that Black and White women who achieved ≥3 months of lifetime lactation and above average levels of physical activity had lower cardiometabolic risk scores versus those who did not reach those benchmarks.\textsuperscript{18} The combination of behaviors was linked to lower risk versus either behavior alone.\textsuperscript{18} Some recent evidence has shown that lifetime breastfeeding is associated not only with more favorable maternal metabolic profiles but also with lower maternal fat depots in the heart, liver, and abdomen many years postdelivery that may potentially exert long-term cardiovascular health benefits through metabolic pathways.\textsuperscript{8,11,18} There is evidence that lactation may clear metabolic substrates accrued during pregnancy without substantial alterations in total body weight,\textsuperscript{20,21} that may reduce end-organ lipid depots,\textsuperscript{19} and thereby could signify lasting important protective metabolic advantages that affect future CVD risk in women.

It is noteworthy that the strong protective associations of both physical activity and lactation with future metabolic and CVD risk were not necessarily tied to
weight changes and raise the possibility that benefits involve alternative metabolic factors and other pathways, such as improved mental health.22,23 We are concerned that focusing primarily on weight loss as a motivation for lactation during the postpartum period may overburden women recovering from APOs and lead to feelings of discouragement that deter women from achieving optimal or any levels of these health behaviors. As life with a newborn presents a host of new challenges and demands, solid policies and health care practices are needed to specifically promote lactation as a key postpartum behavior, along with adequate sleep, mental health screening and care, and appropriate physical activity and healthy eating during the early years postdelivery. These factors are important for improved maternal and child health outcomes and early CVD prevention when risk profiles may progress without surveillance, especially since Medicaid health coverage may expire 60 days after delivery. Paid maternity leave can help support maternal–child health but is often limited and short lived for many women, particularly those in lower wage jobs, and members of specific racial or ethnic groups with higher APO and CVD risks.5,24

The role of lactation is a critical missing link in CVD prevention, especially for women with a history of APOs, a high-risk group for whom no clear intervention strategy has been defined. Future research is needed to generate empirical data that could support policy changes, increase awareness, and reveal lactation-specific biologic processes that may lead to new pharmacologic interventions for CVD risk reduction in women with a history of APOs, and others for whom the barriers to lactation are insurmountable. Future research must elucidate how lactation itself, or in conjunction other health behaviors, influences cardiometabolic health to equitably promote health for all families.

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