Is it All Determined at Menarche?

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Gender differences in cardiovascular disease (CVD) risk are well-established and have entered risk prediction tools and recommendations for sex-specific interventions. Menstrual and reproductive factors may help to understand the female advantage in common cardiovascular lifetime diseases with an obvious protection during the reproductive period. Important developmental and hormonal transitions during a woman’s life are menarche and menopause. Menarche occurs late in pubertal development as an indicator of the beginning of the reproductive period.

Whereas menopause has been in the focus of an abundance of investigations over decades, menarche has received increasing attention only over the last years. From recent publications and first meta-analyses it appears that age at menstrual onset is related to cardiovascular risk factors in later life and CVD outcomes across ethnicities. Pubertal changes leading to menarche are determined by a fine-tuned interplay of endogenous hormonal regulations and complex modifying factors. In particular, nutritional status and childhood adiposity with the consecutive hormonal and metabolic changes have been shown to be related to accelerated pubertal timing and menstrual onset. Early menarche predicts higher body mass index (BMI) and adiposity in adult life. Furthermore, early menarche has been associated with hypertension, metabolic syndrome, impaired glucose tolerance and type 2 diabetes that mediate CVD. Thus, a direct or indirect association with CVD in later life must be assumed. However, former studies and meta-analyses across ethnicities have remained inconsistent regarding the associations between menarche timing and CVD outcomes. The studies were characterized by heterogeneity between cohorts, differences in adjustment for confounders and endpoint definitions.

In this context, the article by Canoy and colleagues in this issue of Circulation provides
robust novel data on over 1 million middle-aged UK women invited for routine breast cancer screening. They were followed for coronary heart disease, stroke, hypertension, and coronary heart disease mortality for an average of 11.6 years. Outcomes were available from linkage with national and hospital databases with almost complete follow-up.

Sufficient numbers allowed the calculation of solid estimates in the early and late periods of menstrual onset for single years of age. Usually <12 years of age is defined as early menarche. In their article the authors were able to examine the risk at ≤10 and 11 years at menstrual onset with good power. They showed that the younger age groups where associated with higher relative risk of coronary heart disease than at 13 years. Similarly, for the age groups 14 years and higher, a rather exponential increase in coronary heart disease risk became apparent. Stroke and incident hypertension showed highest relative risks for very early and late menarche.

Prior data suggested a U-shaped association for all-cause mortality and coronary heart disease deaths.7-9 The current study now demonstrates a similar pattern for two major cardiovascular diseases and their risk factor, hypertension. Such findings appear biologically plausible. As often seen in nature, extremes are detrimental.

Findings were consistent across categories of possible modifiers and confounders, i.e. BMI, smoking or socioeconomic status. Recent reports suggested an association between timing of menarche and CVD in non-smoking women or a study population where the prevalence of smoking was low.2,10 The present study, however, could not support these results. It needs to be considered that associations with smoking habits underlie considerable confounding that may account for discrepant findings.

Similar to earlier studies,9 the paper by Canoy et al. showed a significant association between coronary heart disease mortality and early menarche but statistical significance was not
reached for late menarche. A comparatively small number of events limited these analyses.

Furthermore, the study examined women in their fifties between 1996 and 2001. Ongoing trends in menarcheal age towards earlier onset have been observed\(^{11}\) which could mean shifts in the results in more contemporary populations. However, expected differences probably would be minor and might even be more pronounced with an increasing proportion of individuals with earlier age at menstrual onset.

The exposure age at menarche was recorded by questionnaire in middle age and may have led to recall error. However, no significant differences were demonstrated in a subgroup of a sample constituted of a birth cohort where age at menarche was registered two times, at puberty and in middle age. Most likely, misclassification would have been non-differential anyhow.

Observations presented in the article certainly need validation in independent cohorts and across ethnicities. These efforts will be facilitated by the existence of large-scale consortia that have been formed to investigate the pathophysiology and genetics of pubertal timing and menarche. Overall, Canoy and colleagues performed one of the largest studies on menarche and CVD risk. They provide substantial evidence on the importance of menarcheal timing and CVD outcomes in later life at the population level.

In the light of the findings by Canoy and colleagues, the next obvious steps are to better characterize the determinants of menarche. As outlined, menarche is the result of the sum of diverse factors. It will be a challenge to dissect the components of pubertal timing and their relation to CVD risk due to the substantial overlap of risk factors and unclear direction of potential causality. For example, it has been shown that childhood overweight and adiposity are related to earlier menarche and that earlier menarche is associated with higher BMI in later
life.\textsuperscript{3,12} Childhood BMI correlates highly with adult BMI.\textsuperscript{13} Therefore, the relationship between menarche and CVD risk may be confounded by childhood BMI. Although no measures of childhood obesity were available, the data by Canoy and colleagues and prior publications\textsuperscript{2,3} indicate that associations of menarche with CVD risk are not fully explained by BMI.

Efforts to describe the mechanisms of menarche and their role in the causal pathway of CVD will be supported by the workup of novel genetic findings and pathway analyses. About half of the variance in age at menstrual onset is explained by genetic variation.\textsuperscript{14} Recent genome-wide association studies underscore the multifactorial regulation of menarche including distinct pathophysiological pathways.\textsuperscript{15} More than hundred genomic loci with minor effect sizes have been identified for age at menarche. The overlap with common polymorphisms related to energy homeostasis and adult BMI is striking. It suggests a shared genetic etiology that needs further examination in relation to CVD risk.

In the meantime, several clinical implications can be derived: We need to learn that female specific risk indicators may be a valuable source of refining a woman’s individual CVD risk assessment. For a general cardiologist, a seemingly distant event such as puberty and age at menarche, may provide valuable information. Besides pregnancy associated complications and menopausal characteristics, pubertal development and menarche may become a routine part when taking a female’s medical history not only for the general practitioner but also for the cardiologist. Menstrual onset is a critical event in a woman’s maturation and fairly accurately recalled. Thus, it constitutes an easily assessed marker for pubertal processes and timing.

Early CVD risk assessment around menarche, with the major part of the lifespan still to come, offers opportunities. In many countries, interactions with the medical system are frequent around menarche and may offer CVD risk evaluation, counseling and early interventions long
before the cardiologist enters the stage. Gynecologists and general practitioners will need to take
over this responsibility. Closer cooperation and uniform recommendations among disciplines
need to be established.

At present, we are only at the beginning of understanding the complex associations of
puberty, reproductive factors and CVD risk and still far from defining effective screening
programs and interventions. The long story of hormone replacement therapy for CVD prevention
has proven that a simple concept may not be generally effective. With the interactions of
genetics, adiposity, hypertension, socioeconomic status, family environment, among others, as
triggers of menarche a multilevel intervention and lifestyle changes are most likely targets for
preventive efforts.

CVD risk, certainly, is not fully explained and determined at the time of menarche.

However, knowing puberty associated risk indicators may help to identify individuals at
increased risk of CVD and tailor diagnostic and preventive strategies over a lifetime. Successful
efforts would have profound public health implications eventually affecting half of our
population.

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