

## Lost in Menopausal Transition: the Timing of Atherosclerosis Prevention in Women

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### Summary

Advanced atherosclerotic changes can often resist even to very aggressive treatment. Although basic mechanisms of its origin and development are known, some important steps in this process are still waiting for more detailed explanation. Therefore, in addition to already proved aggressive lowering of LDL cholesterol, appropriate timing of atherosclerosis treatment is of the essence. Revealing different stages of atherosclerotic process, less or more sensitive to treatment is of primary importance; however, its detection is complicated by several facts including not exactly identifiable periods of quiescence and progression of atherosclerotic process. One of populations, study of which could add valuable information regarding this problem, are women in menopausal transition. Previously unsuccessful therapy with hormone replacement therapy is restudied with focus on the time of/after menopause. Now, it is supposed to be favorable in women soon, approximately less than 8 years, after menopause. In addition, the same principle – optimal timing of the intervention of traditional cardiovascular risk factors, especially lipids, could be also of importance. Therefore, menopausal transition could be optimal period for the intervention in women at risk. However, this approach is to be proved by evidence from controlled prospective studies focused on lifestyle and/or pharmacological intervention.

### Key words

Atherosclerosis • Timing of management • Perimenopausal women

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### Evolution of atherosclerosis – timing hypothesis

Atherosclerotic process can begin already after the birth, and is detectable at an early age (Newman *et al.* 1986). Subsequently, atherosclerosis manifests often as serious clinical events including acute and chronic forms of coronary artery disease, ischemic stroke, peripheral arterial disease, and abdominal aortic aneurysm at middle and older age. More importantly, substantial proportion of first atherosclerotic events is often fatal and not preceded by any warning signs (Chambless *et al.* 1997, Kannel and Schatzkin 1985). Therefore, intensive research is also focused on detection of persons at high risk yet before clinical manifestation of atherosclerosis. In addition to already described fatal consequences for persons with atherosclerotic disease, another important reason is that advanced stages of atherosclerosis could be less responsive to prevention measures including favorable modification of the content of circulating blood, mainly its lipoprotein composition. Therefore, in addition to already proved aggressive lowering of mainly LDL cholesterol, but also control of other cardiovascular risk factors, appropriate timing of these interventions could be of the essence.

Although the main risk factors for atherosclerotic cardiovascular events and basic mechanisms of its origin and development are known (Ganz *et al.* 1996, Goldstein and Brown 2015, Libby 2012), number of steps in this process is still waiting for a more detailed explanation. Evaluation of different stages of atherosclerotic process, which are more or less

sensitive to prevention measures and treatment, is complicated by the fact that damage to the vascular wall caused by atherosclerotic process is not a continuous process, but it is rather characterized by periods of quiescence and acceleration. The latter fact makes also difficult to evaluate atherosclerotic process in long term in experimental settings in which shorter periods and only selected stages of atherosclerotic process are studied. It is extremely difficult to define optimal time for treatment even in human studies. On one hand, in patients with already established presence of cardiovascular disease caused by atherosclerosis the positive effect of aggressive treatment of LDL cholesterol was definitely proved. On the other hand, with the exception of extremely severe disorders of lipoprotein metabolism it is still not clear how aggressively should be treated patients at intermediate risk. The latter group if labeled as diseased subject and/or subjects for increased risk for cardiovascular event could be seriously psychically traumatized and quality of their life could be substantially impaired. In contrast, waiting too long with more aggressive therapy could expose some subjects to be at avoidable risk of dying suddenly as a consequence of unrecognized atherosclerosis. One of the examples of this dilemma is the timing of treatment by powerful hypolipemic drugs, statins, in patients with end stage renal disease. If this treatment is started before dialysis it seems to be very effective. On the contrary, in patients already undergoing hemodialysis, extensive atherosclerotic changes associated with other parallel damage of the artery wall could cause treatment with statins virtually ineffective. These findings are reflected in quite recent guidelines (Schneider *et al.* 2015). In addition to timing, as already published in older studies, different cardiovascular risk factors could be associated with less or more advanced stages of atherosclerosis (Kiechl and Willeit 1999, Willeit *et al.* 2000).

Regarding these facts and needs, there is one population group, in which timing of preventive measures could be reliably and rather easily studied and the effect of this approach established. This group are women in menopausal transition.

### **Cardiovascular disease in women and changes of reproductive status**

Cardiovascular disease (CVD) occur in women approximately 10 years later than in men but CVD risk steeply increases after the menopause. This is very

probably caused by decrease of the protective effects of estrogens on vasculature at the menopause (Matthews *et al.* 1989, Woodard *et al.* 2011). Rapid changes, mainly decline in estrogen levels and possibly also very rapid, “roller coaster”, changes of other sex hormones associated with the menopausal transition may play an important role in steep increase of CVD risk factors and in their augmented effect on vasculature. In another words, in addition to increase of CVD risk factors in menopausal transition, their untoward effects on the vessel wall seem to be much greater than those observed during the pre- or post- menopausal period. Therefore, the rate of estrogen withdrawal, or rate of changes of various factors during the menopausal transition may substantially modulate the change of CVD risk. However, interventional studies with hormone replacement therapy failed to prove protective effect on CVD (Hodis *et al.* 2003). One of explanations for this failure could be non-selected population of women with high representation of older women long time after menopause on one hand insensitive to atheroprotective effects of hormone replacement therapy, but on the other hand highly sensitive to thrombotic effects of estrogens. Therefore, these women were at increased risk for atherothrombotic events caused by the presence of more advanced stages of atherosclerosis associated with older age and, logically, with longer time after menopause. The latter is considered to be critical factor for treatment of hormone replacement therapy (Hodis *et al.* 2016).

Recently, we have rather reliable tools how to select the most sensitive population of women not only for hormone replacement therapy but possibly also to modification of traditional cardiovascular risk factors. The estimate of hormonal status and the level of protective sex hormones in women are based primarily on a relatively easily obtainable data: presence or absence of menstrual bleeding and time from last menstrual bleeding. In addition to that, more precise definition of menopause and transitional periods are based on blood level of follicle stimulating hormone (FSH). One of the most widely used classification to determine the reproductive status of women combining both approaches, was published in SWAN study (Study of Women's Health Across the Nation) (Harlow *et al.* 2012, Santoro and Sutton-Tyrrel 2011). Based on these guidelines menopause could be rather reliably defined as a history of the last menstrual period more than 365 days before the time of examination; this approach could be improved also by measurements of FSH levels, which are

defined as higher than 40 IU/l. The most interesting period – menopausal transition – is then defined as the last menstrual period reported in less than 365 days but in more than 60 days before the time of examination.

However, it should be noted, that two traditional cardiovascular risk factors could cause confusion in the interpretation of the effect of menopause on the cardiovascular system. The first factor is smoking, which moves the time of menopause toward younger age. The second factor is overweight/obesity, which moves the time of menopause toward older age, therefore seems to be protective. In addition, if menopause and hormone changes are the real cause of increased cardiovascular risk is still matter of debate (Vaidya *et al.* 2011).

### **CVD risk factors and atherosclerosis in menopausal transition**

The most important factor for atherosclerosis is dyslipidemia, mainly elevated LDL cholesterol, reflecting increased number of atherogenic LDL particles. In women, unique risk factor could be also moderately elevated concentration of triglycerides, reflecting increased number of highly atherogenic remnant lipoproteins (McNamara *et al.* 2001). Therefore, the interest is focused also in this direction. However, despite already described deleterious changes of lipids after menopause (Matthews *et al.* 2009, Bittner 2009), if these unfavorable changes of circulating lipid parameters have adverse effects on vasculature has not been yet reliably established. To prove this associations and more importantly, causation is of extreme importance, because, in general, menopause as a such is still not definitely considered as an independent risk factor (Vaidya *et al.* 2011, van der Meer *et al.* 2016). In our population based study in middle aged women around the menopause, the rise in blood pressure after the menopause appeared to be due rather to increased body mass index rather than to the ovarian failure *per se* (Cifkova *et al.* 2008). However, lipid factors could be different story and detailed study of their changes and effects of vasculature could be of extreme importance. The information in this field is increasing because menopausal transition now becoming more extensively studied period regarding also CVD (Johnson *et al.* 2010, Wild 2012).

We studied the effect of cardiovascular risk factors on atherosclerosis in menopausal transition, in Prague Pre and Post Menopausal Females study (3PMFs). In the cross-sectional study we have found, that in the

representative population sample of middle-aged women subclinical atherosclerosis expressed as intima media thickness of carotid arteries was significantly associated with age, weight and systolic blood pressure. In addition, there was strong evidence that the atherogenic effect of the most robust cardiovascular risk factor – smoking – was strongest throughout the late menopausal transition (Pitha *et al.* 2013). In this study we also described several mechanisms potentially responsible for these findings including impaired vascular protection represented by changes of stem cells and endothelial progenitor cells, impaired reverse cholesterol transport, and impaired balance of sex hormones, mainly male sex hormone – (free) testosterone. In addition, we observed, that women changing their reproductive status from premenopause to menopause could be exposed to different risk factors compared to men but also compared to women who were already menopausal (Pitha *et al.* 2015). In the longitudinal part of 3PMFs, in women who became menopausal, the most robust increase was observed in the case of body mass index, waist circumference, blood pressure, fasting glycemia and plasma triglycerides in 6 year period (Pitha *et al.* 2014).

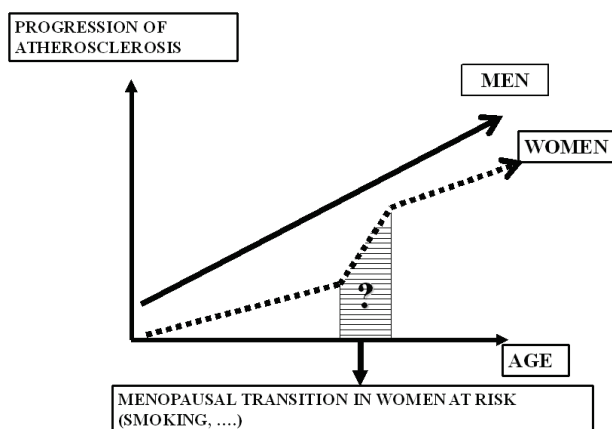
Based on available data including our studies, menopausal transition could be really critical period for the progression of atherosclerosis especially in the presence of smoking. However, in addition to such robust cardiovascular risk factor as smoking, women in menopausal transition could be more vulnerable also to other environmental insults including lipid risk factors. In addition, according to our data one of lipid risk factors associated with smoking in women could be remnant lipoprotein particles (unpublished data), lipid risk factor, recently intensively discussed (Varbo and Nordestgaard 2014).

In summary, based on recently available data, rapid progression of atherosclerosis during menopausal transition could be mediated through several mechanisms including impaired vascular protection, impaired reverse cholesterol transport, and impaired balance of sex hormones. This period could be therefore critical also for the effective intervention of cardiovascular risk factors. Detection of the molecular mechanisms responsible for this unfavorable changes and evaluation of potential effect of their modification could provide important information to personalized management of cardiovascular disease in women. However, these facts are still at the level of hypothesis.

## Future directions

The validated IMPACT mortality model using combined mortality data and the determination of risk factors in the Czech study MONICA (Multinational MONIToring of trends and determinants in Cardiovascular disease) and post-MONICA have shown that crucial role for decrease of cardiovascular events in last two decades was played by the changes in lifestyle on the population level, mainly change of diet and other habits including physical activity leading to a decrease in cholesterol level and reduction in blood pressure (Bruthans *et al.* 2012). Therefore, lifestyle measures including cessation of smoking and focused on the critical period like menopausal transition could exert even stronger impact on the health of the population.

However, until recently the population of women with these characteristics was not intensively studied and lots of interesting and important data are not available or lost in menopausal transition. One of the main reasons is fast and mostly unpredictable "roller coaster" fluctuations of sex hormones and factors associated with them during menopausal transition. This complicates substantially the possibility of interpret reliably the actual impact of hormonal status on the progression of atherosclerosis.



**Fig. 1.** Hypothetical progression of atherosclerosis men vs. women.

If hypothesis of high sensitivity to atherosclerosis during menopausal transition is correct (Fig. 1), there could be immediate possibility how to exploit these findings in everyday praxis. The transition into menopause is characterized by irregular menstrual cycles often accompanied by significant subjective

complaints like headaches, sweating and others. Therefore, in this particular period women often seek a health care professionals and are also more receptive to recommendations of lifestyle change. However, to definitely confirm this effect, the mechanisms through which lifestyle measures, or even pharmacological therapy, could attenuate atherosclerosis need to be more clearly defined. Changes of the traditional cardiovascular risk factors could only partly explain this effect and there are other important mechanisms operating in this field. One of those could be epigenetic factors including miRNA and methylation processes of DNA (Udali *et al.* 2013). These processes are also under control of sex hormones (Sharma and Eghbali 2014). In particular, to study differences in the impact of intensive lifestyle intervention on the complex cardiovascular risk profile between women in menopausal transition and premenopausal, menopausal women and men, with focus on smoking behavior could be of interest. The timing hypothesis is to be tested on the group of women in menopausal transition, well-defined by age and by cardiovascular risk profile using intensive and standardized lifestyle intervention. In addition to clinical data including measurements of pulse wave velocity and novel measurements of microcirculation and traditional laboratory factors, more detailed analyses on molecular level including sex hormones, microRNAs and methylation of DNA are to be used to test the impact of standardized intervention on the cell and molecular level. However, the selection of control group is the most important for reliable comparisons. It is not easy but very important to include as controls women after menopause or before menopause of similar age. Another solution could be to include menopausal women of higher age but to follow up this population in parallel with women undergoing menopausal transition.

## Conclusions

Research of more exact timing of preventive measures against atherosclerotic process could have important consequences on the population level. Given demographic trends in developed and also developing countries, including the Czech Republic, there is a significant increase in the age of the population. Because women are reaching higher age than men, it is obvious that the proportion of women with cardiovascular disease will continue to increase and the total population burden of these diseases will also increase. Although the

study of cardiovascular diseases among women attracted increased attention in recent years, the majority of guidelines are based largely on data from the male population. As a result, it is still not clear if both traditional and newly observed cardiovascular risk factors have different effects on the vascular system in men and women; classic example is the greater impact of smoking on the incidence of coronary and cardiovascular disease in women (Grundtvig *et al.* 2011, Huxley and Woodward 2011). Promotion of deep healthy lifestyle changes apart from obvious smoking cessation in women in menopausal transition on population level must be, however, based on sound scientific data. In particular, the impact of hormonal and metabolic changes observed during menopausal transition and shortly after menopause on the vascular health and vascular events should be reliably established in prospective observational studies. These studies should be followed by interventional controlled studies focused on predefined and robust lifestyle changes, again focused on surrogate endpoints of vascular diseases, followed by analysis of clinical events in longer time periods. However, few studies have

investigated the relationship between the menopausal transition and the development of multiple CVD risk factors over longer time and their effect on vascular system.

In addition to the health of women population, data regarding atherosclerosis from women in menopausal transition could substantially contribute to research of the processes of atherosclerotic changes in the whole population and add valuable data to still intensely debated theory of optimal timing of therapy of atherosclerosis not only in women.

### Conflict of Interest

There is no conflict of interest.

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