remodelling in univariate as well as in multivariate analyses.2 Finally, although we agree that it would be interesting to determine the optimal cut-off value for risk prediction, an important cause of heterogeneity among studies is that some investigators restricted their analyses to non-diabetic patients, whereas others included all patients irrespective of diabetic status.

References

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Non-optimal maturation of the oocyte, maternal MTHFR polymorphisms, periconceptional folate, and decrease of congenital heart defects

The protective effect of periconceptional folate on congenital heart defects (CHDs) presented by Van Beynum et al. (2006) contributes to the governing folate paradigm. The researchers showed a quantitative trait effect between MTHFR 677 > CT heterozygosity and homoyzogosity (TT) and a modification by periconceptional folate supplementation. In addition, using the family-based transmission disequilibrium test (TDT), they identified this polymorphism in the mother as risk factor for CHDs in their progeny, independent of its presence in the foetus. Similar results were found in relation with cleft lip with or without cleft palate.2 Studies on the relation between MTHFR 677 > T polymorphism and congenital anomalies as a consequence of mildly elevated plasma homocysteine (Hcy) – presume an extensive reduction of migrating cardiac neural crest cells during early development.

The connection of a very broad spectrum of chromosomal aberrations,3 congenital anomalies, and constitutional diseases with MTHFR polymorphisms support the concept of non-optimal maturation of the oocyte as causal pathway into adverse progeny as suggested by Wynn and Wynn (1993), who moved the attention away from teratological disturbances during the early months of pregnancy into the maturation of the oocyte.4 In fact, deficiency of folate in rhesus monkeys is known to depress the concentration of oestradiol and progestagen and to slow down the replication of granulosa cells, being the principal cells in the ovarian follicle. This deficiency results in a reduction of the growth of the follicle and in delayed ovulation, as markers for retardation of embryonic growth and malformations. Therefore, they presume that folic acid is the prerequisite for optimum maturation of the oocyte and inherent favourable outcome.

Heterozygous and homozygous carriership of these polymorphisms implies increased plasma of total Hcy and, thus lower folate concentration threatening optimal maturation of the oocyte and embryonic development. Non-optimal maturation of the oocyte or over-riperseness of the egg in animal experiments and observations has been shown to be associated with a wide spectrum of chromosomal and developmental anomalies. It has also been presumed in a range of conditions in which the maturation of the oocyte is at stake, such as very premature and advanced reproductive age, postpartum restoration of the ovariatory pattern, seasonally bound transitional stages of it, etc. This is in line with the association between follicular fluid Hcy levels and detrimental effect on embryo quality in couples undergoing assisted reproductive techniques (ART), as well as with the greater risk for miscarriage, particularly when foetal chromosomal anomalies are present.5

Low folate concentrations connected with over-riperseness ovopathy, therefore, may play a role in the causal pathway of unfavourable pregnancy outcomes. This concept not only explains the broad spectrum of chromosomal aberrations, congenital anomalies, and constitutional diseases, but also their pleiotropic pattern and male preponderance, and finally, the analogy with the above-mentioned high-risk conception categories.

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Selene, the goddess of the moon: does she shine on men only?

First of all I would like to congratulate Nawrot et al. on their convincing and important analysis on yet another selenium (Se)-dependent health issue, i.e. the inverse correlation of blood Se with blood pressure. This report represents the latest addition to an ever-growing list of sex-specific effects mediated by this particular trace element which has been named after Selene, the Greek goddess of the moon. Low Se status causes male infertility in both humans and animals, thereby its honorary title ‘XY nutraceutical’ is well deserved.6 Chemoprevention trials by Se supplementation generally report stronger effects for male participants, most pronounced usually for prostate cancer. Therefore, a large, expensive, long range, and men-only follow-up study on the chemopreventive effects of Se has recently been initiated by the NIH (www.cancer.gov/select). Moreover, a prospective multicentre study on mortality from sepsis yielded positive effects of
Se supplementation exclusively for male patients. Now the study conducted by Nawrot et al. describes the fourth sexual dimorphic major health effect of Se, beyond fertility, cancer, and sepsis. One hesitates and wonders how and why Selenne shines on men only.

The Se status is dominated by a hepatically derived Se transport serum protein, i.e. selenoprotein P (SePP). We and others have demonstrated that SePP controls Se distribution within the body and that SePP-KO mice display sex-specific Se-deficiency symptoms. SePP attaches to endothelial cells and protects from peroxynitrite-mediated damage in plasma. Moreover, we have just demonstrated that biosynthesis of selenoenzymes including SePP displays pronounced sex-specific differences, and male livers have a superior potency to translate mRNA into functional selenoproteins. Remarkably, these differences are not constant but Se-dependent.

If larger groups of people with a more divergent Se status were analysed, we would not expect such a linear correlation of blood Se with blood pressure as depicted in Figure 1. At higher Se status, all selenoproteins become maximally expressed and independent from the trace element. This kind of saturable effect has been similarly observed in both cancer prevention and sepsis studies mentioned earlier, in which participants with low baseline Se status always profited most. Consequently, successful Se supplementation will stabilize blood pressure in a healthier range.

Unfortunately, large supplementation trials are conducted mainly in the USA, where baseline Se levels are already replete because of better nutritional supply. Given the clear-cut and appealing correlation shown in the manuscript, some large-scale prospective analyses are clearly needed in Europe in order to benefit our hearts and health insurance systems. Such trials should necessarily include both men and women who are at risk of a low Se status, such as chronically ill patients, people on regular dialysis or with eating or digestion disorders, and vegans and vegetarians. Hopefully, financial support can be raised for such eagerly awaited large-scale European supplementation trials. The future shines bright, less pressure is in sight, especially at night.

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Concerns on carotid stenting in octogenarians

Zahn et al. should be complimented for creating an inter-hospital carotid artery stenting (CAS) registry and for presenting their 10 year experience, including many procedures performed on octogenarians. Although their analysis is retrospective in nature and unbalanced (321 patients >80 years vs. 2557 patients <80 years), it shows that in-hospital stroke or death rates increase significantly with older age, but the complication rate in octogenarians is not excessively high. The Zahn et al. analysis raises some concerns, however.

First, no distinction was drawn between ischemic and haemorrhagic strokes (as far as we know haemorrhagic stroke is not due to carotid disease) or between the various types of ischemic strokes (atheroembolic, cardioembolic, or lacunar infarction), so that patients with non-atheroembolic strokes should have been excluded from this analysis (it is worrying to see atrial fibrillation significantly more often in octogenarians than in the younger group). The proportions of smokers and diabetic patients or patients with hyperlipidemia were lower among the octogenarians included in the study than among younger patients, so the former would be at lower risk of atherothrombotic stroke. So, how can the authors be sure that all 184 symptomatic octogenarians had symptoms related to the carotid stenosis?

Secondly, no mention was made of the timing of CAS vis-à-vis symptom onset, and "it is an incontestable fact that carotid endarterectomy (CEA) confers the maximum benefit provided it is undertaken as soon as possible after the onset of symptoms". We were among the first groups to demonstrate as much in a 4 year prospective study on 86 patients with minor stroke, 45 of them randomized to undergo early CEA while 41 had delayed CEA.

Thirdly, since elderly patients were less likely to undergo CAS while on statin therapy, it would be interesting to know why the asymptomatic octogenarians underwent CAS, although some of them were on sub-optimal medical therapy.

Fourthly, since only in-hospital data were recorded, failure to report the event rate at 30 days prevents any comparison with other studies and casts a shadow of doubt over the study as a whole. The authors’ conviction that “clinical events are extremely low after the first days of stent implantation” is debatable. CAS was aborted in 6.9% of octogenarians and there was a residual stenosis in 10%: whatever the reasons, these should be defined as cases of treatment failure and added to all the patients who had in-hospital events after CAS.

Finally, why should octogenarians be treated with CAS? It is particularly important to demonstrate that the interventional procedure adopted is safe, and therefore that the patient would be at a higher risk of stroke if said treatment is withheld, but the results of Zahn et al.’s analysis do not support this conclusion. A few years ago, in a study on octogenarians with contralateral carotid artery occlusion, we demonstrated that these patients can undergo CEA with no more risks or complications than younger patients with contralateral carotid occlusion, and we suggested that—until prospective, randomized trials to evaluate the role of CAS have been completed—CEA should remain the standard treatment for such patients.

References

