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Medical Implications of the Male Biological Clock

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THE PHRASE "BIOLOGICAL CLOCK" IS MOST COMmonly used by physicians to refer to the declining fertility, increasing risk for fetal birth defects, and altered hormone levels experienced by women as they age. Abundant scientific evidence suggests that men also may have a biological clock.[1,2] Men and their physicians must therefore understand the effects of the male biological clock on sexual and reproductive health, as well as its potential contributions to major medical consequences such as diabetes, cardiovascular disease, and the metabolic syndrome.

Aging, Male Infertility, and Birth Defects in Offspring

Male fertility clearly declines with age.[3] Studies demonstrate that men older than 35 years are twice as likely to be infertile (defined as the inability to initiate a pregnancy within 12 months) as men younger than 25 years.[4] Among couples undergoing fertility treatments with intrauterine insemination, the amount of time necessary to achieve a pregnancy increases significantly with the age of the male member of the couple. Furthermore, after controlling for maternal age, couples in which men are older than 35 years have a 50% lower pregnancy rate compared with couples in which men are 30 years and younger.[5]

Although the association between advancing maternal age and an increased incidence of birth defects has long been recognized, paternal age has been considered to be less relevant. Recent data suggest that paternal age does matter and the genetic quality of sperm does decline with age. For example, Reichenberg et al[6] recently reported a significant association between advancing paternal age and the risk of autism spectrum disorder (ASD) in their children. Offspring of men 40 years or older were 5.75 times more likely to have ASD compared with offspring of men younger than 30 years, after controlling for year of birth, socioeconomic status, and maternal age. Advancing maternal age showed no association with ASD after adjusting for paternal age.

In a study reported by Malaspina et al,[7] older men were at higher risk of fathering a child with schizophrenia. Men older than 40 years were more than twice as likely to have a child with schizophrenia as men in their 20s. A similar influence of paternal age on the risk of having a child with Down syndrome also has been reported,[8] with paternal age a factor in half the cases of Down syndrome when maternal age exceeded 35 years. Other investigators found that the rate of miscarriages increased with advancing paternal age when maternal age was older than 35 years.[9] Thus, there is convincing evidence for an effect of paternal age alone as well as a combined effect of advancing paternal and maternal age on increased risks of genetic abnormalities leading to miscarriage or disease in their children.

Women should thus no longer be viewed as solely responsible for age-related fertility and genetic problems. Infertility is not just a woman's problem and awareness of the effects of the male biological clock will allow couples and their physicians to proceed with proper testing, diagnosis, and (if needed) treatment of the male partner. Still, knowledge of the contributions of male-factor infertility are just emerging and much more research is needed to fully characterize the risks associated with the metabolic, genetic, and functional changes brought on by the male biological clock. These changes include, but are not limited to, factors such as declining sperm counts and motility, sperm dysmorphology, erectile dysfunction, age-related hypogonadism, and genetic anomalies in sperm or cofactors found in semen.

Declining Testosterone Levels

Similar to women, aging in men also is associated with declines in sex hormone levels. The decrease in hormone levels in men is not as steep or as sudden as that associated with hormone declines during menopause in women, but its effects can be significant. The approximate 1% per year decline in testosterone levels after age 30 years has been termed *andropause*,[10] although this is a somewhat imprecise term because testosterone levels do not actually "pause" in the same way that estrogen levels do. A more technically accurate (though clumsy) description might be "symptomatic hypogonadism in the aging male." Hypogonadism is not defined by a specific level of serum androgens because tes-

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tosterone levels causing dysfunction vary widely among individuals.[11]

However defined, low testosterone levels are associated with a host of symptoms and signs, which are estimated to affect between 2 million and 4 million men in the United States alone.[12] These symptoms include decreased muscle mass and bone mineral density, decreased libido and energy; and increased fat mass, central obesity; insulin resistance, emotional irritability, and dysphoria.

Low testosterone may also increase mortality. In a recent article in which low serum testosterone was defined as a total testosterone level of less than 250 ng/dL (8.68 nmol/L), or a free testosterone level less than 0.75 ng/dL (0.03 nmol/L), men with low testosterone level had a mortality rate of 35% over the 8-year study period compared with a mortality rate of only 20% among men with normal testosterone levels. This trend persisted even after controlling for other relevant variables in the study population.[13]

Medical Conditions

A link between the male biological clock and diabetes is also emerging. Both type 2 diabetes and the metabolic syndrome (which involves prediabetes symptoms as well as cardiovascular risk factors) are strongly associated with below-normal levels of testosterone (hypogonadism).[14] Grundy[14] found that 40% of men with type 2 diabetes between the ages of 40 and 49 years were hypogonadal—and the rate was nearly 55% among men in their 70s. The low testosterone levels found in men with type 2 diabetes may be related to the correspondingly high prevalence of erectile dysfunction (ED) among men with diabetes, a rate estimated to range between 35% and 75%.[15]

An increasing body of evidence has revealed important associations between ED and 3 other disease states common among older men: cardiovascular disease (CVD), depression, and benign prostatic hyperplasia (BPH). Assigning causation between hypogonadism and these conditions is not simple because each disease state can adversely affect the other in reciprocal, complex relationships, and the role of declining androgens in ED is similarly complex. Broadly speaking, ED is clearly associated with age-related biological changes and, hence, the biological clock is also implicated in these other chronic, frequently progressive, and disruptive conditions.

For example, the prevalence of ED is significantly higher among patients being treated for heart disease and hypertension.[16] Treatments for hypertension may contribute to ED, which may help explain the increased incidence of ED in these patients. But the reverse relationship is also true: ED should be considered a marker for hypertension and other cardiovascular complications.[17]

Depression may both contribute to and link ED and CVD. Erectile dysfunction is associated with well-established negative psychological effects, primarily depression and anxiety.[18] Separate findings have established a 16% to 18% prevalence of major depression in CVD patients.[19,20] Patients with ED are more likely to become depressed than those without ED and therefore may have an increased risk of developing CVD.

Several recent studies have described the comorbidity of ED and BPH, which correlate with diminished quality of life.[21] Erectile dysfunction, CVD, depression, and BPH are all common conditions among older men and because these conditions appear to be strongly correlated, a multidisciplinary approach to future research and clinical practice is warranted.

Testosterone Replacement Therapy

Growing recognition of the morbidity and mortality risks associated with low testosterone levels has spawned an increased use of various forms of testosterone replacement therapy. Current treatments for hypogonadism, such as exogenous testosterone replacement and stimulation of endogenous testosterone production, are gaining in popularity. Sales of prescription testosterone products in the United States have increased significantly in recent years. In 2005, according to IMS Health Inc, a total of 2.3 million prescriptions for testosterone products were written in the United States. This represents a 50% increase from 2001 and a 210% increase from 1999.[22] This enormous increase is not without risks. Indiscriminate use of testosterone supplements can increase the risks of prostate hyperplasia (and possibly cancer), coagulation disorders (resulting in cerebral vascular injury), dyslipidemia, and infertility.[12] Simply replacing (or boosting) testosterone is an inadequate and ineffective approach to treating chronic progressive conditions with multiple causal factors (such as smoking, unhealthful diet, lack of exercise, and genetic predispositions). On the other hand, a rigorous study reported by Marks et al[23] suggests that the risks to men undergoing controlled testosterone replacement therapy for laboratory-confirmed hypogonadism may be less than previously thought.

The increase in testosterone replacement therapy seen in the United States may be because the problem of androgen deficiency is being overmedicalized and testosterone therapies are being overprescribed. Physicians must acknowledge the effects of hypogonadism and appropriately treat documented cases of endocrine dysfunction. At the same time, it is important to avoid prescribing hormone therapy merely for physical enhancement (such as for boosting muscle mass or energy in otherwise healthy men). Currently, testosterone replacement products are approved by the US Food and Drug Administration for "conditions associated with a deficiency or absence of endogenous testosterone."

Conclusions

A number of important clinical consequences occur as the male biological clock winds down. An improved understanding of the associated cellular and biochemical mecha-

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nisms of gonadal aging is needed so that safe and effective ways to delay this process or in effect, rewind the clock might be possible. A better understanding of the male biological clock may reduce adverse outcomes in offspring of older fathers and may help facilitate progress to reduce the risks of metabolic syndrome, BPH, diabetes, depression, and CVD.

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EDITORIALS

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PSA Testing
Public Policy or Private Penchant?

Peter C. Albertsen, MD, MS

PHYSICIANS ORDER PROSTATE-SPECIFIC ANTIGEN (PSA) tests for many reasons: to confirm the presence of suspected cancer, to monitor progression of prostate cancer or the effect of treatment, or to predict the likelihood that prostate cancer will occur in the future (ie, screening). In this issue of *JAMA*, Walter et al[1] document that many clinicians in the Veterans Affairs medical system order PSA tests for elderly male patients. In 2003, 56% of men older than 70 years who had no previous history of prostate cancer, elevated PSA level, or prostate cancer symptoms had a PSA test performed. Among men older than 85 years, 34% of those in good health and 36% in poor health had a PSA test performed. Most guidelines do not recommend PSA testing in elderly men, so why would physicians perform these screening tests? Why does practice not comply with policy?

Five key questions should drive the decision to perform a screening test.[2] Is the disease a significant, serious disease? Is the test accurate? Will the test improve the outcome of the disease? Will the test result cause the patient any harm? Is screening likely to do more harm than good? A review of these 5 key questions should help in understanding why PSA testing has been performed so frequently.

Does a PSA test screen for a significant, serious disease? After lung cancer, prostate cancer is the second leading cause of cancer death in men in the United States. While the lifetime risk of a prostate cancer diagnosis is about 16%, the lifetime risk of prostate cancer death is only 3.4%.[3] Of the

See also p 2336.

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