

The Male Biological Clock

Say “biological clock” and most people immediately think “women.” Female fertility, after all, strikes “midnight” with the cessation of menses. This occurs because of distinct—and dramatic—declines in estrogen production. And as women age, the genetic quality of their eggs and the efficiency with which their bodies reject genetically damaged embryos both decline, leading to an increased risk of genetic problems in their offspring. This triad of declining fertility, declining hormone levels, and increasing risk for genetic problems is what most people mean when they say “biological clock.”

Until recently, that is. Although it’s an idea that has not yet filtered down to the general public, we now know that men have biological clocks too. And those clocks involve the same physiological triad experienced by women. Male fertility and male sex hormones *do* decline with age. And the genetic quality of sperm *does* decline, leading to an increased risk of genetic problems in offspring above and beyond any contributed by the female. The object of this review is to describe these features of male aging and, hence, to expand the notion of “biological clock” to include *both* sexes.

Male Infertility

Data obtained in the past decade suggested a worldwide decline in male fertility. Although initially thought to be the result of external variables such as exposure to pollution, we now understand a real culprit: men are simply waiting longer to have children and aging is adversely affecting their fertility. It is well known that women are waiting longer to have children. Data from the Centers for Disease Control (2001) clearly demonstrate that over the last 30 years there has been a decline in the number of children to woman under the age of 30 with a corresponding *increase* in the number of children born to women over 30. In fact, the largest increase has been the more than doubling of the number of births to women over the age of 35. In 1970 the number of births to such women was 6 percent. That increased to 13 percent in 1999 and is undoubtedly higher now. What is less often discussed, but hardly surprising, is that there has been a parallel increase in paternal age. There was a 50 percent increase in fathers older than 35 in the past 30 years.

The increase in paternal age is both a personal problem for many couples *and* a public health problem because of the simple (but still largely unrecognized) fact that male fertility declines with age. Journal articles by Kidd et al. (2001) and Ford et al. (2000) demonstrate that men over the age of 35 are *twice* as likely to be infertile as men younger than 25. In addition, a study of couples undergoing fertility treatments with intra-uterine inseminations found that the amount of time it takes for a man to achieve a pregnancy rises significantly with age. After controlling for maternal age, men older than 35 had a 50% lower pregnancy rate than men younger than 30 (Mathieu et al 1995). Although further epidemiological research is needed to prove the point, this pattern of rising difficulty to achieve pregnancy likely holds true for the male population in general. The

bottom line: current reviews of controlled studies looking at male aging show robust positive correlations between age and infertility as well as age and the time required to achieve pregnancy.

Testosterone

As with women, the levels of sex hormones in men declines with age. The drop is not as steep or as sudden as that associated with menopause, but it can be equally significant for fertility and overall well-being. In fact changes in men's hormones are just as important as changes in women's hormones. The roughly 1 percent per year decline in testosterone levels after age 30 has been termed "andropause," though this is a somewhat unfortunate choice because testosterone levels don't actually "pause" in the same way that estrogen levels do. A more technically accurate (though clumsy) term is "symptomatic hypogonadism in the aging male." Whatever you call it, declining testosterone causes problems. Rhoden and Morgentaler (2001) estimate that between 2 and 4 million men in the US alone suffer from hypogonadism (defined as serum total testosterone levels lower than 325 ng per deciliter). The same article found that only 5 percent of these men are getting treatment for their symptoms, which include decreased libido and erectile dysfunction, loss of muscle mass and strength, weight gain, and declining cognitive function. Hypogonadism is also associated with type II diabetes, insulin resistance, central obesity and the metabolic syndrome. Newer treatments for hypogonadism such as exogenous testosterone replacement and stimulation of endogenous testosterone production are gaining tremendous popularity. Sales of prescription testosterone products have soared more than 500 percent since 1993 and show no signs of leveling off (Bhasin & Buckwalter, 2001). This enormous increase is not without risks. Indiscriminate use of testosterone supplements can raise the risk for prostate problems, blood disorders, and infertility.

Genetic quality of sperm

Although increasing maternal age has long been known to be associated with increased incidence of birth defects, the age of the male has been seen as irrelevant. New data show what we should have suspected all along: the age of the male *does* matter and the genetic quality of sperm *does* decline with age. Specifically, a 2004 study by Malaspina et al., found that older men are at higher risk of fathering a child with schizophrenia. In fact men older than forty were more than *twice* as likely to have a child with schizophrenia as men in their twenties. A 2003 study (Fisch et al.) found a similar influence of paternal age on the risk of having a child with Down Syndrome. Paternal age was a factor in half the cases of Down Syndrome when the maternal age was over 35. And a 2002 study by Rochebrochard and Thonneau of the rate of miscarriages found similar increased risks with rising paternal age when maternal age was older than 35. These and other studies clearly show that when the mother and father are both over the age of 35 years, there is a markedly increased risk of both genetic abnormalities and miscarriage. The father's contribution to these events is increased with increasing age, similar to women. As noted above, these facts are worrisome in light of the large increases in maternal and paternal age over the past 25 years.

The Male Biological Clock is Real

This brief review demonstrates a still un-appreciated reality: men have biological clocks that affect their fertility, hormone levels, and the genetic quality of their sperm. This clock plays a role on a personal level (when couples must grapple with infertility or birth defects) and on a public health level (when society must decide policies governing, for instance, insurance coverage for advanced fertility treatments such as in vitro fertilization.) Women should no longer be viewed as solely responsible for age-related fertility and genetic problems. Infertility is *not* just a woman's problem and with the new awareness of a male biological clock couples and their physicians can much more accurately proceed with proper testing, diagnosis and (if needed) treatment of the male. The field of male-factor infertility is still young, and much more research is needed to fully characterize risks and to find more effective treatments. We also need to better understand the cellular and biochemical mechanisms of "gonadal" aging in order to find safe, effective ways to delay this process and, in effect, "rewind" the male biological clock. Doing so will lessen the potential for adverse genetic consequences in offspring, improve the sexual and reproductive health of aging males, and increase a *woman's* chance of having healthy children by correcting defects in the *male* reproductive machinery.

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