Biological Clock Ticks for Men, Too
Genetic Defects Linked to Sperm of Older Fathers

Paul D. Thacker

Women approaching middle age have long been aware that the consequences of a ticking biological clock include not only decreased fertility but also a sharp increase in the odds of delivering a child with Down syndrome. Older men, seemingly untouched by such biological constraints, felt free to father children as they entered middle, and even old, age.

But now it is becoming increasingly clear that the biological clock ticks for men as well as women, as researchers turn up evidence that as would-be fathers get older, they have an increased chance of passing on genetic defects to their children.

“New point mutations in humans are introduced through the male line,” says Dolores Malaspina, MD, professor of clinical psychiatry at Columbia University and the New York State Psychiatric Institute. Furthermore, she adds, the number of mutations in sperm increases as men age.

“This has been known since the 50s,” said Malaspina. “What is intriguing is why society chooses to ignore this.”

Society is starting to pay attention. With many couples now deferring childbearing until they are older, the issue of paternal age and increased risk for birth defects is gaining a higher profile. It is also possible, say some experts, that if current trends of older fatherhood continue, it could someday become a public health problem as well as a personal one.

According to the latest birth statistics released in December by the Centers for Disease Control and Prevention (CDC), the average age of motherhood is at an all-time high of 25.1 years compared with 21.4 years in 1971. Although some of this increase can be explained by the drop in teen births, another reason was an increase in older women having children. Women in two age groups—35 to 39 years and 40 to 45 years—now have children at the highest levels in 3 decades. Statisticians find that women tend to marry men of similar ages, so it can be surmised that the ages of fathers have also increased.

Interestingly, while news reports on the CDC figures by various news outlets mentioned the link between increased female age and disease risk to infants, none reported the vulnerabilities posed by aging fathers that researchers have turned up in recent years, such as the association between increased paternal age and genetic diseases such as Apert syndrome (a disorder characterized by craniofacial and limb abnormalities) and achondroplasia (a skeletal disorder that causes dwarfism). Furthermore, studies show that 2% of children born to men 50 years or older will have schizophrenia, three times the incidence of schizophrenia in offspring born to fathers in their early 20s.

Some experts in this field speculate that as the mean age of fathers increases, the accumulation of mutations in the human gene pool could heighten the risk of some recessive genetic disorders in future generations.

Malaspina notes that some European countries now ban men from becoming sperm donors after reaching certain ages.

“I wouldn’t discourage a man from having a child because the risk for many of these diseases is quite small for an individual,” she says. “But it’s quite meaningful at the population level.”

The Human Fertilisation and Embryology Authority in the United Kingdom revised the upper age of sperm donors downwards from 50 to 45 in 2000, based on the evidence that older men are more likely to pass on genetic defects to offspring.

EARLY HINTS
The first hint of a link between paternal age and incidence of birth defects was noted in 1912 by Wilhelm Weinberg, MD, who found that achondroplasia, an inherited skeletal disorder occurred more often in younger siblings than older ones, suggesting that as parents aged, the likelihood of the disorder increased. Decades later, L. S. Penrose, MD, discovered that only the father’s age that correlated with de novo incidence of the autosomal dominant disorder.

There are now approximately 20 different disorders that are correlated with paternal age. The effect is quite promi-
MEN SUCH AS Apert, Crouzon, and Pfeiffer syndromes, for which frequency increases rapidly with paternal age. Fathers of children with these syndromes are, on average, 5 years older than the mean age of fathers in the population or those of similarly affected children with familial forms of the same diseases.

The increase in such genetic disorders probably has multiple causes, including differences in how sperm are produced as well as environmental factors. In 1955, Penrose hypothesized that mutations in sperm cause disease. The copy-error hypothesis posits that mutations arise disproportionately in the male germ line, because these cells undergo many more replications than do the germ cells that give rise to eggs. Also, because the number of replications leading to sperm formation increases as men age, there are more possibilities for genetic mistakes.

Abnormal expression of paternally imprinted genes is another possible mechanism linking advancing paternal age and offspring health, suggests Malaspina. Imprinting is a phenomenon affecting certain genes that causes such genes to be expressed differently in offspring, depending on whether they are inherited from the mother or the father.

DNA DAMAGE IN SPERM

Men thus add more mutations to the gene pool than women simply because their germ cells pass through more mitotic replications. Women have only about 24 divisions in the cells that give rise to their eggs, and these divisions all occur before birth. In men, germ line cells have already passed through 30 rounds of mitosis before puberty, and then continue to divide every 16 days—a total of 23 replications per year.

By the time a man reaches age 30, the cells that create sperm will have passed through 380 mitotic divisions. At age 40, the number has climbed to 610, and at age 50, it reaches 840 rounds of replication. Each round of division creates another opportunity for an error to enter into the germ line.

“When I worked in industry before [going to] medical school, women were closely watched for their exposure to toxins in case they were pregnant,” says Malaspina. Such an approach ignores the fact that men, with their dividing germ cells, also should be protected from benzenes and other chemicals, as well as radiation.

Multiple studies have examined aging’s effect on sperm DNA. Narendra Singh, MBBS, of the bioengineering department at the University of Washington, in Seattle, and colleagues found in a study of 66 men aged 20 to 57 years, there were significantly more breaks in the DNA of sperm from older men (≥36 years) than from younger men (Fertil Steril. 2003;80:1420-1430).

“There is a gradual increase in DNA damage with age,” Singh says. “But the change was most remarkable at age 35.”

Older stem cells might simply be creating more damaged sperm. Another possibility is that protection from free radicals, which damage DNA, might decrease with age. The researchers also found that both motility and the rate of apoptosis, or programmed cell death, in sperm also fell. Apoptosis is one mechanism to keep damaged sperm from fertilizing an egg.

“This is the first study showing that apoptosis goes down as a function of age,” notes Singh. “This finding is troubling because it shows that aging predisposes the offspring for transmission of damaged DNA.” Future research might uncover strategies for either selecting healthy sperm or helping the body to cull the sperm with damaged DNA, he says.

Other studies have found high rates of point mutations in the genes associated with disease in offspring. Ethlyn Jabs, MD, a professor of pediatric genetics at Johns Hopkins University, in Baltimore, found that 99% of the Apert syndrome cases were caused by mutations from the male germ line (Am J Hum Genet. 2003;73:939-947). The incidence of these mutations increases as men age, but the higher predicted incidence of Apert syndrome in society suggests that some other process may be at work.

“It’s more complex than just the number of mutations in the sperm,” said Jabs. “There may be some sort of selection process for sperm with mutations that we can’t yet explain.”

A similar trend has been found by Norman Arnheim, PhD, professor of molecular and computational biology at the University of Southern California, Los Angeles. Achondroplasia closely correlates with male age, but its incidence is higher than can be accounted for by the frequency of mutated sperm (Proc Natl Acad Sci U S A. 2002;99:14952-14957). He has posited a number of theories to explain why sperm selection might be occurring.

“There’s a big field on sperm competition and we know that it happens in a number of animals,” he says. Some scientists suggest, for example, that it is possible that a mutation that increases the odds of a birth defect will also allow the particular sperm possessing that mutation to outcompete other sperm to fertilize the egg. “Some think it might have to do with the mitochondria that power the sperm’s flagella. I don’t know if that’s the right hypothesis, but it’s one that’s out there.”

A PUBLIC HEALTH THREAT?

Although researchers have attempted to conduct epidemiological studies to look for correlations of disease with paternal age, such studies can be difficult to perform. For one thing, data sets often lack information about paternal age. Statistics from the CDC, for example, indicate that 13.4% of birth certificates from 2002 did not list the father’s age.

This lack of information makes it difficult to ask questions about paternal age and birth defects, says Mathias Forrester, a data consultant for the Hawaii Birth Defects Program. “We’ve looked at maternal age, but we’ve never even asked the question about paternal age because it’s difficult to get good denominators out of birth certificates.”

Even when information about the father’s age is provided on a birth certificate, birth defects might be missed; they are often underreported because they are sometimes identified after the birth
Bar Codes Mandated for Hospital Meds

Tracy Hampton, PhD

To reduce the number of medication errors in hospitals, the Food and Drug Administration (FDA) will soon require bar codes—similar to those found on consumer goods—on most prescription and over-the-counter drugs.

The FDA estimates that the measure will help prevent nearly 500,000 medical mistakes over 20 years and save $93 billion in costs. According to the Institute of Medicine, as many as 98,000 individuals die each year due to medical errors, including errors involving drug administration.

“Bar coding systems have proved their dependability and effectiveness by ensuring the accuracy of a myriad of actions in commerce and industry,” said FDA Commissioner Mark B. McClellan, MD, PhD. “We’re now advancing the adoption of these systems in settings where they can help save lives.”

Getting it Right

By using bar code scanning equipment, health care professionals will be able to verify that the right drug is given to the right patient at the right time and at the right dose.

On admission to the hospital, each patient will be given a bar-coded identification bracelet to link the patient to his or her computerized medical record. Before administering a drug to the patient, a health care worker will scan the patient’s bar code, which will link to the computerized medical record. The health care worker will then scan the drug to be administered. The computer will sound an alarm if the medication is incorrect.

A large amount of information can be stored in bar code systems. For example, a bracelet scan could reveal information on a patient’s current medications, and a drug scan could give information on the expiration date and any potential adverse effects when combined with other drugs.

In addition to helping patients, the measure is expected to reduce lawsuits associated with preventable adverse events. Bar codes on medications used in hospitals will also help drug manufacturers and pharmacists keep track of inventory.

The FDA is confident that a bar code system will be effective because it has proven so at Veterans Affairs (VA) Hospitals. Since June 2000, these facilities have been using bar code medication administration. A comparison of medication error data from 1993 and 2001 at the O’Neil VA Medi-