

A Man's Shelf Life

As men age, their fertility decreases and the health risks to their unborn offspring skyrocket. But men who attend to their health can slow down the reproductive clock.

By: Mark Teich

Women have long understood that general fitness and age are both critical to conceiving a healthy child. But their partners often feel absolved of such concerns; men tend to think they can drink, carouse, smoke like coal trains, and conceive whenever they want, with no impact on fertility or their future offspring. Would that it were so.

"Everybody was familiar with the concept of women's biological clock, but when we introduced 'male' to the equation, the reaction was 'What are you talking about? Men can have children at any age,'" recalls urologist Harry Fisch, director of the Male Reproductive Center at Columbia Presbyterian Hospital in New York City and author of *The Male Biological Clock*. "It became a social issue. Men do not like to be told they have a problem."

Nonetheless, a virtual tidal wave of recent research has made it irrefutable: Not only does male fertility decrease decade by decade, especially after age 35, but aging sperm can be a significant and sometimes the only cause of severe health and developmental problems in offspring, including autism, schizophrenia, and cancer. The older the father, the higher the risk. But what's truly noteworthy is not that infertility increases with age—to some degree, we've known that all along—but rather that older men who can still conceive may have such damaged sperm that they put their offspring at risk for many types of disorders and disabilities.

"Men thought they were getting off scot free, and they weren't. The birth defects caused by male aging are significant conditions that can cause a burden to families and society," says Ethylin Wang Jabs, professor of pediatric genetics at Johns Hopkins University and leader of a study showing the link between aging paternity and certain facial deformities in offspring. "We now know that men and women alike could be increasing the risk of infertility or birth defects by waiting too long to have children." In other words, by looking for perfection in your life before you conceive, there's a very real chance you'll have less perfect kids."

Studies worldwide have found that with each passing decade of their lives and with each insult they inflict on their bodies, men's fertility decreases, while genetic risk to offspring slowly mounts. The range of findings is staggering: Several studies have shown that the older the man, the more fragmented the DNA in his ejaculated sperm, resulting in greater risk for infertility, miscarriage or birth defects. Investigations out of Israel, Europe, and the United States have shown that non-verbal (performance) intelligence may decline exclusively due to greater paternal age; that up to a third of all cases of schizophrenia are linked to increasing paternal age; and that men 40 and older are nearly six times more likely to have offspring with autism than men under age 30. Other research shows that the risk of breast and prostate cancer in offspring increases with paternal age.

Fisch has found that when both parents are over 35, paternal aging may be responsible for as many as half of all cases of Down syndrome, formerly thought to be inherited from the mother. And recent studies show that half a dozen or more rare but serious birth defects appear to be inherited exclusively from the father, including Apert syndrome, Crouzon syndrome, and Pfeiffer syndrome (all characterized by facial abnormalities and the premature fusion of skull bones) as well as achondroplasia (the most common form of dwarfism).

Male versus Female Mutations

Scientists have long known that advanced paternal age (like increased maternal age) played some role in fertility problems and birth defects. Yet because the reports mainly involved children who died before birth or who had extremely rare disorders, no one really rang the alarm. Now, with studies linking the father's age to relatively frequent, serious conditions like autism, schizophrenia, and Down syndrome, the landscape is shifting.

Women have unfairly borne the brunt of the blame for birth defects. When the conditions were familial, passed on through

chromosomal lineage, women were somehow widely believed culpable, even though such defects can be traced to either partner. "But what we're finding now is that in humans as well as in other mammals, when there's a new genetic change—called 'de novo or sporadic point mutation'—it almost always happens in the male parent," says Dolores Malaspina, chair of psychiatry at New York University Medical Center. And these de novo mutations increase in frequency with the age of the male parent.

These mutations could reflect the differences in male and female reproduction, notes Jabs. By the time females reach their teen years, their eggs have already been formed—just one new egg matures each month. Men, on the other hand, produce millions of sperm cells every time they ejaculate. After each ejaculation, they must literally replicate those cells, and each replication multiplies the chance for a DNA "copy error"—a genetic chink in the sperm DNA. The more ejaculations a man produces, the greater the chance for chinks to arise, leading to increased point mutation and thus increased infertility and birth defects. While a woman's reproductive capacity halts more or less abruptly after all her eggs have been used up somewhere in their forties or fifties, men experience a longer, more gradual winnowing and disintegration. "We believe that something in men's DNA replication machinery keeps becoming less efficient and less accurate with age, and the problems accumulate," says Jabs.

A Chilling Finding

The biggest news—the father's role in brain disorders—has come to light largely because of research from Israel, where birth records routinely include the age of the male parent. The first unsettling finding linked paternal age and schizophrenia.

"In our first study, looking at every pregnancy in Jerusalem from 1964 to 1976, we found that increased age in the father predicted increased cases of schizophrenia in the children," explains Malaspina, who was on the team doing the work. "In our second study we found that when the cases arose from new mutations—not familial inheritance—it almost always could be traced to the genetics of the father. Somewhere between a quarter and a third of the cases could be explained only by the age of the father—a threefold risk linked to fathers older than 50 compared with those in their 20s." Studies in Sweden and California produced almost identical results.

The autism findings are even more disturbing: Men 40 and older in the Israeli study were almost six times as likely to have offspring with autism than men under 30. Some researchers believe that older fathers may hold a clue to the vast upsurge in autism cases in the past decade. "With older and older couples having children—in the past two years, for the first time, more babies are being born to women over age 30 than under age 30, and on average, male partners tend to be older than female partners—it's very feasible that paternal age is a major predictor of autism," asserts Fisch.

Minor Damage is the Worst Kind

Perhaps the creepiest aspect of these findings is that a little genetic damage in men's sperm may actually be worse than a lot of damage. "When we started doing the research, our first concern was fertility, and these new studies do show that fertility maybe compromised by DNA damage. But that's not the most important thing," declares Charles Muller, lab director of the Male Fertility Clinic at the University of Washington in Seattle.

The greater threat to offspring is the less flagrant DNA damage that gets passed on. Experts like Muller believe that a substantial amount of the damage is caused by free radicals—the destructive, highly reactive particles produced by our body's energy factories, the mitochondria, as we metabolize oxygen. "One of the scariest things we're finding is that sperm DNA is damaged by even low levels of free radicals. Whereas high levels of damage lead to infertility, miscarriages, or spontaneous abortions, low levels chew up the DNA but the sperm can still fertilize," Muller states.

Complicating matters, sperm is incapable of repairing itself; Muller and his colleague Narendra P. Singh find that as men age, natural processes such as apoptosis—in which damaged cells naturally commit suicide to protect the body—become increasingly less efficient and less able to eliminate damaged DNA. Resulting defects may not show up until offspring are adults and it's too late to trace the cause. Damage may then be passed from one generation to the next.

"In short, the biggest genetic threat to society may not be infertility but fertile old men," says University of Wisconsin in Madison geneticist James F. Crow.

The Playing Field Levels

These findings have profound implications for any potential parent. Women may increasingly feel they share the onus of potential infertility and birth defects with men. Older women, focused though they are on their own reproductive timetable, may increasingly view their partner's age with a wary eye. When both parents are aging, the risks to offspring multiply. "If women are under age 35, the father's age may not matter that much, but if the mother is over 35, advanced male age can be a real problem," says Jabs.

For men, the findings may be, above all, a clarion call to take better care of themselves. "This should make men reconsider their role and responsibility in childbearing," says Barbara Willet, of the Best Start childhood resource center in Ontario, Canada. "Aging in men is an important issue, but health is the key issue. It's as if we're suddenly aware that men who want to be fathers need to be healthy, too."

One key is testosterone, necessary for the maturation of sperm. "If you have less testosterone, you have worse sperm." Testosterone naturally starts to decline in the 30s, but also varies based on factors from weight to heart health. "Fat cells in a pot belly overheat the testes and break testosterone down; clogged arteries break it down. Whatever hurts your heart, hurts your penis," Fisch states.

Men typically don't think about their health, and we need to get them to. If you're drinking or smoking, if you're working in toxic environments with pesticides, X-rays, solvents, or ionizing radiation, these things affect you as well as women, and will ultimately affect the children you conceive.

Alarming though the findings may be to some, researchers have a clear directive: "Don't panic." "The research is still fresh," says Crow, "and more needs to be done before we start making sweeping recommendations like urging people to have children younger, or telling men to freeze their sperm after their 20s. I don't advocate asking the general public to change at this point, because while some of these mutations cause very severe effects, in the totality of things that can go wrong, this is not that large a part of the picture."

Freezing sperm may sometimes be the way to go. While frozen sperm may not be quite as potent as when it is fresh, it is not a proven problem. Since the turn of the last century, sperm of domestic animals has been frozen safely for as long as 75 years, says Muller. And frozen sperm is used routinely in humans for artificial insemination. Pregnancy rates and childbirth are right up there with regularly conceived birth, and there is no substantial DNA breakdown. If you're going to get a vasectomy, join the Army, or go through cancer therapy, "I'd advise you to freeze your sperm beforehand," Muller says.

Most men can steer a gentler course just by watching their health. "Despite the new research, there's still a big difference between the female and the male biological clock," says Muller. "When the female's alarm goes off at the end, that's it. For men, the battery slowly winds down. Yes, chance of problems increase as the years pass, but some men have significant DNA damage at 35, while others go on forever—their sperm is fine in their 70s."

Men can't rewind their biological clocks, but they can slow them down, Fisch agrees. Just remember, once you're in your 40s, you're past your maintenance-free years—you have to take care of yourself. "If you want children from then on," he advises, "get into the best shape of your life."

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