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## Older fathers appear to raise risks of genetic disorders

By Roni Rabin

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When it comes to fertility and the prospect of having normal babies, it has always been assumed that men have no biological clock — that unlike women, they can have it all, at any age.

But mounting evidence is raising questions about that assumption, suggesting that as men get older, they face an increased risk of fathering children with abnormalities. Several recent studies are starting to persuade many doctors that men should not be too cavalier about postponing marriage and children.

Until now, the problems known to occur more often with advanced paternal age were so rare they received scant public attention. The newer studies were alarming because they found higher rates of more common conditions — including autism and schizophrenia — in offspring born to men in their middle and late 40s. A number of studies also suggest that male fertility may diminish with age.

"Obviously there is a difference between men and women; women simply can't have children after a certain age," said Dr. Harry Fisch, director of the Male Reproductive Center at New York-Presbyterian Hospital/Columbia University Medical Center and the author of "The Male Biological Clock."

"But not every man can be guaranteed that everything's going to be fine," Fisch said. "Fertility will drop for some men, others will maintain their fertility but not to the same degree, and there is an increased risk of genetic abnormalities."

It's a touchy subject. "Advanced maternal age" is formally defined: women who are 35 or older when they deliver their baby may have "AMA" stamped on their medical files to call attention to the higher risks they face. But the concept of "advanced paternal age" is murky. Many experts are skeptical about the latest findings, and doctors appear to be in no rush to set age guidelines or safety perimeters for would-be fathers, content instead to issue vague sooner-rather-than-later warnings.

"The problem is that the data is very sparse right now," said Dr. Larry Lipschultz, a specialist in the field of male infertility and a past president of the American Society for Reproductive Medicine. "I don't think there's a consensus of what patients should be warned about."

And many men maintain their fertility, said Dr. Rebecca Sokol, president of the Society of Male Reproduction and Urology. "If you look at males over 50 or 40, yes, there is a decline in the number of sperm being produced, and there may be a decline in the amount of testosterone," Sokol said. But by and large, she added, "the sperm can still do their job."

Some advocates, however, welcome the attention being paid to the issue of male fertility, saying it is long overdue.

"The message to men is: 'Wake up,'" said Pamela Madsen, executive director of the American Fertility Association, a U.S. education and advocacy group. "It's not just about women anymore, it's about you, too."

Analyses of sperm samples from healthy men have found changes as men age, including increased fragmentation of DNA, and some studies outside the United States have noted increased rates of some cancers in children of older fathers.

Geneticists have been aware for decades that the risk of certain rare birth defects increases with the father's age. One of the most studied of these conditions is a form of dwarfism called achondroplasia, but the list also includes neurofibromatosis, the connective tissues disorder Marfan syndrome, skull and facial abnormalities like Apert syndrome, and many other diseases and abnormalities.

Some studies suggest that the risk of sporadic single-gene mutations may be four to five times higher for fathers who are 45 and older, compared with fathers in their 20s, said Dr. Joe Leigh Simpson, president-elect of the American College of Medical Genetics. Overall, having an older father is estimated to increase the risk of a birth defect by 1 percent, against a background 3 percent risk for a birth defect, he said.

Even grandchildren may be at greater risk for some conditions that are not expressed in the daughter of an older father, according to the American College of Medical Genetics. These include Duchenne muscular dystrophy, some types of hemophilia and fragile-X syndrome.

A recent study on autism attracted attention because of its striking findings. Researchers analyzed a large Israeli military database to determine whether there was a correlation between paternal age and the incidence of autism and related disorders. It found that children of men who became a father at 40 or older were 5.75 times as likely to have an autism disorder as those whose fathers were younger than 30.

"Until now, the dominant view has been, 'Blame it on the mother,'" said Dr. Avi Reichenberg, the lead author of the study, published in September in *The Archives of General Psychiatry*. "But we

found a dose-response relationship: The older the father, the higher the risk. We think there is a biological mechanism that is linked to aging fathers."

A study on schizophrenia found that the risk of illness was doubled among children of fathers in their late 40s when compared with children of fathers under 25, and increased almost threefold in children born to fathers 50 and older. This study was also carried out in Israel, which maintains the kind of large centralized health databases required for such research. In this case, the researchers used a registry of 87,907 births in Jerusalem between 1964 and 1976, and linked the records with an Israeli psychiatric registry.

According to the study's calculations, the risk of schizophrenia was 1 in 141 in children of fathers under 25 years, 1 in 99 for fathers 30 to 35, and 1 in 47 for fathers 50 and older. The study found no association between older fathers and any other psychiatric conditions.

"When our paper came out, everyone said, 'They must have missed something,'" said an author of the study, Dr. Dolores Malaspina, chairwoman of the psychiatry department at New York University Medical Center. (Malaspina was also involved in the autism study.)

But studies elsewhere had similar findings, she said: a threefold increase in schizophrenia among offspring of older fathers.

Unlike women, who are born with a lifetime supply of eggs, men are constantly making new sperm. But the spermatogonia — the immature stem cells in the testes that replenish sperm — are constantly dividing and replicating, with each round of division creating another possibility for error.

While women have only about 24 divisions in the cells that produce their eggs, the cells that create sperm go through about 30 rounds of mitosis before puberty and through roughly 23 replications a year from puberty onward. By the time a man reaches 50, the cells that create his sperm have gone through more than 800 rounds of division and replication.

Skeptics say the studies find an association but do not prove a causal relationship between an older father's genetic material and autism or schizophrenia, and note that other factors related to having an older father could be at play, including different parenthood styles. Another possibility is that the father's own mental illness or autistic tendencies are responsible both for the late marriage and for the effect on the child.

But other findings suggest implications for older fathers. Another study by Malaspina and Reichenberg, also using Israeli army data, found a correlation between having an older father and lower scores on nonverbal, or performance, IQ tests.

Fisch analyzed a New York State database of births and found that older fathers added to the risk of having a baby with Down syndrome if the mother was over 35. (The father's age seemed to have no effect if the mother was younger; younger women may have compensated for any problems of the older male.) The paper concluded that the father's age was a contributing factor in 50 percent of Down syndrome cases in babies born to women over 40.

Meanwhile, scientists have reported that sperm counts decline with age, and that sperm begin to lose motility and the ability to swim in a straight line. The researchers also reported a steady increase in sperm DNA fragmentation as men grew older, with a 2 percent increase each year in the gene mutation associated with achondroplasia, the dwarfism syndrome. They found no correlation between advanced age and the kinds of chromosomal changes that cause Down syndrome, but suggested that a small proportion of older fathers may be at increased risk for transmitting multiple genetic and chromosomal defects.

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