Older Paternal Age Tied to Autism in Spring

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Summary

Older men are at higher risk of fathering autistic children than younger men, results of a large cohort study suggest.

After a man reaches his 20s, the risk of fathering an autistic boy or girl more than doubles with every 10-year increase in his age. This increase is independent of other factors such as the mother’s age and the family’s socioeconomic status, reported Abraham Reichenberg, Ph.D., of Mount Sinai School of Medicine, New York, and his associates.

Older paternal age at the birth of offspring is associated with several congenital disorders, and it also has been linked to schizophrenia and to decreased intellectual capacity. Previous studies examining a possible link between paternal age and autism risk have produced mixed results, but “few have systematically examined this association in rigorous designs that included adjustment for maternal age,” Dr. Reichenberg and his associates said (Arch. Gen. Psychiatry 2006;63:1026-32).

Dr. Reichenberg presented a very large population-based cohort study “specifically designed for a rigorous test of the hypothesis that advancing paternal age is associated with increased risk of ASD (autism spectrum disorder) in offspring.”

The investigators used data collected on a cohort of 378,891 Israeli-born individuals born during the 1960s to 1980s with birth dates from the 1950s to 1970s. The cohort included 3887 individuals with autism or autistic-like traits.

The initial cohort was limited to all 28-year-old residents of Israel, and the study cohort included offspring of both mothers and fathers who were alive in 2004. The cohort was limited to individuals born in Israel before 1962, and who had birth data available for at least 18 years before the study.

After excluding data on individuals with severe birth asphyxia or congenital malformations, the study cohort included 378,891 individuals born to 244,569 mothers and 384,526 fathers.

In the study, 2.38% of the children had autism or autistic-like traits, and 2.27% of the children had a maternal history of autism, compared to 1.92% of the children with a paternal history of autism. The study cohort was limited to children born to parents who were at least age 20 when the child was born and to parents who were not related or adopted.

The overall prevalence of autism spectrum disorders in this cohort was 8.4 cases per 10,000 persons.

The risk of ASDs increased significantly with advancing paternal age and was “especially strong” in offspring of the oldest men. For example, the risk of fathering an autistic child was 1.6 times higher among men in their 30s, 3.7 times higher among men in their 40s, and 14.8 times higher among men aged 50 and older. Dr. Reichenberg and his associates noted.

The risk in increased persist after the data were adjusted to account for maternal age, socioeconomic status, and other potentially confounding factors. Risk was increased for both male and female offspring.

Although all ASDs were included in this study, the researchers noted that the cohort had “autoism.” The study findings therefore may not necessarily be generalizable to the other disorders in the spectrum, such as Asperger’s syndrome and Rett syndrome. The relationship of paternal age to these disorders should be specifically examined in more contemporary cohorts,” the researchers noted.

One possible mechanism for this effect of paternal age is mutagenesis. Spontaneous mutations—either point mutations or structural chromosomal anomalies—might arise and accumulate in successive generations of sperm-producing cells.

Another possible mechanism is imprinting, a form of gene regulation in which the gene of only one parental allele is expressed and the other one is silenced. It is possible that for paternally imprinted genes, biological processes may be impaired as the father ages. Imprinted genes are known to play a key role in brain development, they added.

“These hypothesized mechanisms for paternal age effects on risk of ASD are genetic. It is important to keep in mind, however, that at age paternity is influenced by the sociocultural environment and varies across societies and over time,” the researchers wrote.

When paternal age was analyzed in the cohort of births to Israeli fathers and mothers, the risk increased even more. Paternal age increased the risk of ASD by a factor of 2.33 among 35- to 49-year-old men, and by a factor of 5.7 among men aged 50 and older. The risk increased more with advancing paternal age in the cohort of births to Israeli mothers and fathers, compared to the cohort studied previously by Reichenberg and his associates.

One study limitation was that no information was available on possible autistic traits in the parents’ parents. It is possible that if fathers were also autistic, that would contribute to their higher age at marriage and fatherhood.