Paternal age and mental health of offspring

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The influence of paternal age on the risk for sporadic forms of Mendelian disorders is well known, but a burgeoning recent literature demonstrates, in addition, a paternal age effect for complex neuropsychiatric conditions, including schizophrenia, autism, bipolar disorder, and even for learning potential, expressed as intelligence. Mental illness is costly to patients, their family, and the public health system, accounting for the largest portion of disability costs in our economy. The delayed onset of neuropsychiatric conditions and lack of physical manifestations at birth are common frequencies in the population that have obscured the recognition that a portion of the risks for mental conditions is associated with paternal age. Identification of these risk pathways may be leveraged for knowledge about mental function and for future screening tests. However, only a small minority of at-risk offspring are likely to have such a psychiatric or learning disorder attributable to paternal age, including the children of older fathers. (Fertil Steril® 2015;103:1392–6. ©2015 by American Society for Reproductive Medicine.)

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Childbearing is increasingly postponed in developed countries, with any concern by clinicians and prospective parents largely focused on the age of the mother. Indeed, advanced maternal age is associated with infertility and some birth defects, and menopause imposes a clear upper limit to unaided female reproduction. One view is that fathers continue to produce "fresh" sperm, whereas oocytes age and become damaged. To the contrary, paternal age has a large influence on offspring health. As ages of mothers and fathers are highly correlated, studies that examine only maternal age can show strong effects, even if the risks are attributable to paternal age. Some conditions thought to be attributable to maternal age are additionally attributable to paternal age, including infertility and Down's Syndrome (1, 2). The evidence is clear that studies examining the influence of maternal age on reproduction and offspring health must account for paternal age effects.

The association of advancing paternal age with increasing risks for rare genetic disorders has been known for many decades, but the awareness that fathers' age can influence mental health in offspring is relatively recent. A coherent epidemiological literature with confirmatory animal studies demonstrates that the offspring of older fathers are at increased risk of mental conditions, including schizophrenia, bipolar disorder, autism spectrum disorder, poor social functioning, and lesser intelligence (3–7). Practitioners may be blindsided about the influence of paternal age on offspring mental health and learning for a number of reasons. First of all, these conditions are common, so an effect of paternal age explains only a small portion of the population-attributable risks for these disorders. Next, these conditions manifest years after birth and are generally unassociated with any congenital physical abnormalities. Finally, the later mean age of fathers in the population may have shifted notions about the definition of an older father, commonly defined as aged >40 years. However, the risk for most conditions is linearly associated with paternal aging, so the risks to offspring of fathers who are in their 30s may be doubled compared with the risks to offspring with fathers in their 20s. An autism study furthermore demonstrated that a paternal age–related vulnerability may persist across generations, with age of grandfathers independently associated with the autism risk in their grandchildren (4).

MECHANISMS

The association between increasing risks for psychiatric and cognitive

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conditions and advancing paternal age is ascribed to the introduction of de novo mutations into the population. Spermatogonia acquire genomic alterations over the repeated cell replication cycles, as occurs in somatic cells. After puberty, spermatogonia undergo 23 meiotic events per year, so at ages 20 and 40 years, a man's germ cell precursors have undergone approximately 200 and 660 such meioses, respectively. Thus, during a man's life, the proportion of spermatogonia carrying de novo mutations steadily increases (8).

Moreover, some mutations may confer a selective advantage to spermatogonia, allowing these clones to expand at the expense of other clones as men age.

In the "selfish spermatogonia" model (9), which has been applied to psychiatric conditions (10), mutations that favor within-testis expansion of specific mutant clonal lines skew the mutational profile of sperm as men age. Some of the genetic architecture supporting this expansion could affect neurodevelopment, increasing the risk for brain disorders, or for dopamine metabolism, increasing risks for psychosis. This is feasible, because mutations in the paternal germline show a propensity to occur in the tyrosine kinase receptor–RAS–MAPK (mitogen-activated protein kinase) signaling pathway and provide a selective advantage of specific sperm clones harboring these mutations to outcompete the others, and they seem to be significantly overrepresented. A recent study evaluating the germline mutation rate in teenage and elderly fathers on short tandem repeats showed that the paternal germline mutation rate is strictly monotonic increasing and that the lowest mutation rates occur in the age range of 15 to 25 years (23–25 certain paternal mutations observed) (11).

In addition to paternal aging, other potential damaging exposures to the male germline could increase mutation rates, including toxic exposures, infections, nutritional deficiencies, and even psychological stress of the father, particularly in puberty. Epigenetic processes are compelling mechanisms to explain some of the epidemiological associations between environmental exposure and disease. Life course exposures can certainly alter our gene expression through epigenetic changes, but epigenetic modulation of gene expression may additionally arise through exposures of parents, or be related to their ages (12).

Greater telomere length is frequently mentioned as a potential benefit of higher paternal age, as it is a predictor of longevity. However, any value of longer telomeres does not blunt the risk for schizophrenia, as longer telomeres are reported in the disease for later paternal age in males and for a family history of psychiatric illness in males and females (13).

Advancements in fields other than psychiatry leveraged paternal-age effects in rare diseases, to make genetic discoveries. Some resistance to the hypothesis that paternal age is related to offspring mental health outcomes, a relationship that has been long accepted for maternal age and birth order, is yielding to the increasing number of consistent and rigorous studies demonstrating this effect. Here, we consider schizophrenia and intelligence in greater depth, as these are, respectively, the most and least disabling of the psychological and learning conditions associated with paternal age.

SCHIZOPHRENIA

Schizophrenia is a severe neuropsychiatric syndrome, with a prevalence of 0.30%–0.66%, and an incidence of 10.2–22.0 per 100,000 people per year. The symptoms typically begin in late adolescence or early adulthood, whereupon lifelong disability typically ensues. Its onset is defined by the emergence of psychosis in the setting of deteriorating function and other symptoms (14). Before the onset of psychosis, during a prodromal period of several weeks to many years, nonspecific and variable subtle abnormalities worsen and coalesce into the classic disease features. These include alterations in the perception of reality, changes in the form and content of thoughts and speech, and social and emotional deficits, including a disturbed sense of self, social dysfunction, apathy, and peculiar behavior (15).

A single study in 1979 from a United Kingdom registry demonstrated that patients with schizophrenia had older fathers than other subjects (16). Further research was curtailed by the enduring interpretation that these findings just reflected delayed childbearing by genetically vulnerable men; i.e., these fathers were socially awkward or had some other schizophrenia-related constitutional impairment. Reproductive clinicians thus had not harbored concern about later paternal age and offspring mental health for seemingly healthy fathers. By contrast, the emerging data show that paternal age is higher in sporadic cases, which is consistent with de novo events.

The first study to test the hypothesis that advancing paternal age was related to an increasing risk for schizophrenia in light of de novo mutations or epigenetic effects was the Jerusalem Perinatal Cohort Schizophrenia Study (17). It demonstrated a linear increase in the risk of schizophrenia with increasing paternal age, after adjusting for mother's age. Each decade of the father's age multiplied the risk of schizophrenia by 1.4 (1.2–1.7, $P<.0001$), so that the risk ratio for offspring of fathers aged ≥ 45 years was tripled compared with that for offspring of fathers aged 20–24 years. In contrast, effects of maternal age were minimal. One quarter of all cases were attributable to effects of fathers' ages in this population. Paternal age explained one quarter of the risk for all schizophrenia in the Jerusalem cohort if categories of paternal age beginning at age 30 years were included in the calculation. The absolute number of affected cases was 1 of 198 offspring for fathers at age 20 years, 1 of 131 for those aged 30 years, and 1 of 61 offspring for those aged 50 years.

In addition, paternal aging was associated with increasing risks for schizophrenia across ethnically diverse and geographically distinct cohorts and registries, including ones from the United States (18–22), and Denmark (23, 24). Two studies that were not based on prospective cohorts or registry data did not demonstrate an effect of advanced paternal age on the risk for schizophrenia, including one that used siblings as a control group (25), and another small sample (26). These studies found that approximately 15% of the total population burden for schizophrenia was attributable to paternal age, but they calculated the effects of only categories of paternal age, beginning with ages 35 or 45 years. Although the absolute risk to children from