Is advanced paternal age a health risk for the offspring?

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In this article we review the epidemiologic evidence for adverse health effects in offspring of fathers of advanced age. First the evidence regarding fetal survival is addressed, and afterward we review the evidence regarding morbidity in children with older fathers. The adverse conditions most consistently associated with increased paternal age are stillbirths, musculo-skeletal syndromes, cleft palate, acute lymphoblastic leukemia and retinoblastoma, and neurodevelopmental disorders in the autism spectrum and schizophrenia. Finally, we consider the public health impact of the increasing paternal age. We conclude that the adverse health effects in children that might be caused by the present increase in paternal age are severe but quantitatively of minor importance. However, identification of morbidities that are more frequent in offspring of older fathers, after having taken any maternal age effects and other confounding into account, may lead to a better understanding of the pathogenesis behind such conditions. (Fertil Steril® 2017;107:312–8. ©2016 by American Society for Reproductive Medicine.)

Key Words: Childhood cancer, congenital anomaly, paternal age, neurodevelopmental disorder, stillbirth

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The impact on offspring health of maternal age is extensively studied and described. The vast majority of epidemiologic studies consider a potential effect of maternal age on every aspect of the child's well-being, and maternal age is a strong predictor of the important perinatal outcomes: fetal death, preterm birth, and intrauterine growth (1, 2). The detrimental impact of respectively young and advanced maternal age is, however, founded on completely different mechanisms, whereby social mechanisms may account for the adverse outcomes in younger mothers and biology for the adverse outcomes in women of older ages (3).

Paternal age effects are less recognized. It is reasonable to believe that the social mechanisms responsible for adverse health in offspring of young mothers are the same for offspring of young fathers. However, biologically, the traditional view has been that the paternal contribution, the fertilizing spermatozoa, was unaffected by the age of the father. This view had to be revised in the light of seminal talks and papers by Professor James Crow around the turn of the millennium, in which he emphasized the nonlinear increase in germ-line mutations in males with age (4–6). This nonlinearity may carry the indication of when paternal age is "advanced," because there is no clear definition of advanced paternal age. Using a "standard deviation–based" definition is suboptimal, because of the strong time trends in paternal age, exemplified by the fact that the Danish proportion of children fathered by a man aged 40 years or more was 4% in 1980 and 13% in 2010. Most studies denote paternal age of 40 years or more as fathers of advanced age, but the risk increase in indisputable paternal age-related conditions starts around the paternal age of 35 years (5).

In this article we aim to provide an overview of the epidemiologic evidence regarding any adverse health effects in the fetuses and children of fathers of advanced paternal age and to discuss any possible public health implications.

ADVANCED PATERNAL AGE AND FETAL SURVIVAL

The most serious reproductive failures linked to a particular exposure are likely to be reflected in the risk of miscarriage and stillbirth, because severely affected fetuses are likely to be lost. It is estimated that approximately half of all early lost fetuses have structural and/or chromosomal defects, and the same is true for approximately one-quarter of all stillborn children. Any increased risk of congenital anomalies and other severe morbidity associated with paternal age would likely be reflected in an increased risk of fetal mortality.

More than a decade ago Nybo Andersen et al. (7) analyzed data from almost 24,000 pregnancies in the Danish National Birth Cohort and found no evidence of a paternal age relation in the risk of early fetal death (>20 weeks). This is in contrast to the findings by Slama et al. (8), who analyzed data from individuals

enrolled in Kaiser Permanente 1990–1991, a total of 5,121 pregnancies. They found that the risk of spontaneous abortion (fetal loss at ≤20 weeks) increased with increasing paternal age, so pregnancies fathered by men aged 40 and 50 years had a, respectively, 1.58-fold and 1.90-fold higher risk for spontaneous abortion compared with pregnancies fathered by a man aged 20 years. Analyses of the Jerusalem Perinatal Study from 1965–1968 displayed similar results (9). A particular difficulty arises when paternal age effects are to be studied on outcomes that are massively affected by maternal age, such as spontaneous abortion risk (1). The usually high correlation between maternal and paternal age create a risk of collinearity, but more important is the risk of residual confounding by maternal age (i.e., insufficient adjustment for maternal age). This may explain the heterogeneity in findings. The maternal age effects are large, but not massive, when stillbirth risk is considered. An analysis of more than 3 million Italian births by Astolfi et al. (10) showed a small but significant increased risk of stillbirth of approximately 1.25 when offspring of fathers aged 40 years or more were compared with fathers aged <40 years, and a comparable effect size was indicated in the analysis from the Danish National Birth Cohort (7). A robust increase with paternal age in risk of late stillbirth was also found in using the Missouri maternally linked dataset 1989–2005 (11).

Very recently we analyzed the stillbirth risk (22+ gestational weeks) according to paternal age among all live and stillbirths in Denmark 1994–2010. In this large dataset of almost 1 million births, of which more than 75,000 were fathered by a man aged ≥40 years, we demonstrated that the risk of stillbirth was significantly increased with increasing paternal age after meticulous adjustment for maternal age. Compared with offspring of fathers aged 32 years, the risk was 1.23 in offspring of fathers aged 40 years and 1.36 in offspring of fathers aged 50 years. (Urhoj SK, Andersen PK, Mortensen LH, Davey Smith G, Nybo Andersen AM. Advanced paternal age and stillbirth rate: population-based cohort study.)

ADVANCED PATERNAL AGE AND CHILDHOOD MORBIDITY
Rare Syndromes

A number of rare, well-defined syndromes have for a long time been known to be more frequent if the father was of advanced age. These are, for example, severe types of affected growth (achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta) and craniosynostotic diseases (Apert's, Pfeiffer's, and Crouzon's syndromes). The genetic background for some of the diseases, namely mutations in the *FGFR2* and *-3* genes, has been identified more recently. In addition, neurofibromatosis and Marfan syndrome have consistently been shown to be more frequent in offspring of older fathers.

Perinatal Conditions

Congenital anomalies. The reports of increased risk of congenital anomalies in fathers of advanced age go back in time. Polednak reported increased risk of syndactyly, and possibly also club foot and oral clefts (12). A study from Atlanta pointed at situs inversus in addition to the expected association between high paternal age and chondrodystrophy (13). However, appropriate adjustment for the very strong confounding effect of maternal age was not possible then. In a study from British Columbia it was reported that the risk of neural tube defects, congenital cataract, upper limb reduction defects, and Down syndrome was increased with increasing paternal age (14), and a study focused on heart defects from the same group showed a general pattern of paternal age-related increasing risk for ventricular and atrial septal defects and patent ductus arteriosus (15). A study using data from the exceptional Danish Facial Cleft Register found a relative strong paternal age effect for cleft palate, a condition with no maternal age influence (16). This was actually a replication of a finding from the Child Health and Development Study from 1959–1966 (17), and this finding was also replicated in a more recent meta-analysis (18). An analysis of the Medical Birth Register in Norway found no indication of an advanced paternal age–related risk except for "other CNS anomalies" (i.e., excluding neural tube defect, anencephaly, hydrocephaly) (19).

Our Aarhus-based colleagues analyzed the paternal age risks using data on a selected sample of first- and live-born children in Denmark, 1980–1999. In this study an increased risk of multiple systems syndromes and malformation of the extremities was found (20). The same group also demonstrated no relation between paternal age and overall heart defects but found a robust increased risk of patent ductus arteriosus in a later study using all births in Denmark (21). Analyses of the Texan Birth Defect Registry1996–2002 did not reveal any increases in risk with paternal age (22), but a similar study from California reported an increased risk of birth defects of the overall groups of the nervous system and respiratory system, the limbs, and for chondrodystrophy, but not heart defects, neural tube defect, and clefts (23). In a US national case–control study, including all birth defect categories with more the 100 cases each, an increased risk of cleft palate, diaphragmatic hernia, right ventricular outflow tract obstruction, and pulmonary valve stenosis, as well as syndromes, was shown (24). After having found an increased risk of childhood mortality attributed to musculoskeletal anomalies (25), we scrutinized the paternal age relation to subtypes of such anomalies. We found evidence for a linear increase in syndromic musculoskeletal birth defects, whereas the association with limb anomalies, craniosynostosis, skeletal dysplasias, and other anomalies remained suggestive (26).

Congenital anomaly is a poorly defined concept, encompassing very heterogeneous conditions, some genetically determined and some of developmental origin. The mechanism by which advanced paternal age directly can cause a potential detrimental effect is through a genetically mediated pathway. Consequently, the findings of paternal age–related risk associated with congenital anomalies of a probable genetic origin more plausibly reflect causal relationships.

In conclusion, several studies report increased risk of cleft palate, musculoskeletal syndromes, limb defects, and patent

ductus arteriosus. The inconsistency in findings regarding other congenital anomalies raises the suspicion that the scientific literature may be biased by positive chance findings.

Aneuploidies. Approximately one-tenth of all cases of Down syndrome are of paternal origin. Kazaura and Lie (27) made an analysis of paternal age and Down syndrome using data from 22 years of births in Norway and found a small and statistically insignificant increase in risk with paternal age after the effect of maternal age was well captured in the model. In the above-mentioned study, Zhu et al. (20) found a strong association between paternal age and Down syndrome, as did McIntosh et al. (14) in a case–control study from British Columbia. A study with particular focus on Down syndrome reported strong paternal age effects, but primarily among children born of older mothers, and this particular interaction between maternal and paternal age raises a suspicion of confounding by maternal age on the results (28). Other studies have questioned a paternal age–related increase in nondisjunction and concluded that any paternal age effect on Down syndrome and aneuploidies is "more than questionable" (29). Because confounding by maternal age is particularly severe in studies of aneuploidies and often not appropriately taken care of (30), we conclude that the evidence for any paternal age relation to aneuploidies in the offspring is weak, and more research is needed in this area.

Other perinatal conditions. Data from more than 4 million Italian births indicate a small but increased risk of preterm birth with advanced paternal age (31), whereas data from more than 2 million US live births displayed no indication of risk of preterm birth or any other of the adverse perinatal outcomes examined with increasing paternal age (32). In a smaller sample of 4,621 births from a US national sample of births 1998–2000, it was shown that paternal age of 35 years or more was quite strongly related to a risk factor for low birth weight, but gestational age was not taken into account in that study (33). Analyses of 750,000 Missouri births indicated an increased risk of preterm birth among children with fathers of advanced age, but actually at the same level as with fathers aged <25 years (11). In addition, a short report by Zhu et al. (34) based on the dataset mentioned earlier (20) demonstrated a strong and direct independent association between paternal age and preterm birth. The risk of pre-eclampsia has been reported to increase with increasing paternal age (35), but this finding has to be replicated.

Childhood Cancers

Childhood cancers have been suspected to arise from point mutations, and a paternal age relation has been studied by several authors. Retinoblastoma has been on the list of diseases with a strong paternal age–related risk. In a case–control study of the almost 1,000 cases of retinoblastoma in the Dutch register, the paternal age among cases was reported to be higher than among controls (36). The maternal age effect was the same, and the effects were not disentangled. An unadjusted North American study also reported a relatively strong crude association between increasing paternal age and risk of retinoblastoma (37).

The Swedish population-based register data were used to study parental age effects on the most common childhood cancers. The authors reported an increased risk of central nervous system cancer, particularly astrocytoma, and an indication of increased risk of Wilm's tumor with increasing paternal age (38). A study using the same data but focused on brain tumors was not able to replicate the finding (i.e., found no convincing relation with paternal age) (39). A third Swedish register study focused on leukemia and reported an increase in risk of childhood acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) but not in the risk of these diseases in adulthood (40). A meta-analysis examined the relation between parental age and respectively ALL and AML. Although the risk of AML was unaffected by advanced paternal age, the risk of ALL increased by 4% for each 5-year increment in paternal age (41).

A pooled case–control study from 5 US states found no statistically significant associations between paternal age and any cancer type after adjustment for maternal age (42), and a case–control study of risk factors for childhood cancers in England and Wales showed an increased, however statistically not significant, risk of retinoblastoma and a more convincingly increased risk of ALL with advanced paternal age (43).

In a recent analysis of almost 2 million children born in Denmark from 1978 through 2010, we found a statistically significant increased risk of ALL (hazard ratio 1.13) for each 5-year increase in paternal age. We examined all other cancer types too but found no other statistically significant positive or negative associations with other childhood cancer types. (Urhoj SK, Raaschou-Nielsen O, Hansen AV, Mortensen L, Andersen PK, Nybo Andersen AM. Advanced paternal age and childhood cancer in offspring: A nationwide register-based cohort study.)

In summary, the only childhood cancer type that has been consistently linked to advanced paternal age is ALL, but several studies point toward a relation with retinoblastoma risk, too.

Neurodevelopmental Outcomes

The literature concerning neurodevelopmental outcomes in offspring of older fathers is abundant. It was recently reviewed, and the authors concluded that the epidemiologic evidence linking advanced paternal age and complex neuropsychiatric morbidity was impossible to ignore (44). Below we have focused on population-based studies, very new studies, and studies that address the controversies within the field of advanced paternal age and offspring neurodevelopmental health.

A comprehensive study investigating the total Danish population born from Danish parents between 1955 and 2006 reported an increased risk of all groups of psychiatric diseases (except eating disorders) in offspring of fathers aged 45 years or more. In the same analyses young maternal age was uniformly related to impaired mental health in the offspring, and for several groups of diseases young paternal age was also a risk factor (45). As the authors discuss, these

results indicate that many different mechanisms are at play when the parental age relation with offspring psychiatric health is to be investigated. A direct relation between paternal age and eating disorder risk was, in contrast, recently reported from a Swedish population-based study focusing on eating disorders (46). A study, very similar to the above-mentioned Danish study, using the entire Swedish population born in the years 1973 through 2001, supported and strengthened these findings by applying a family design (comparing siblings and cousins) and thus taking some confounding factors linked to family into account. These analyses showed an increased risk of autism spectrum disorders (ASDs), attention-deficit/hyperactivity disorder, psychosis, bipolar disorder, suicide attempts, and substance use problems with increasing paternal age (47). Additionally, the results indicated impaired academic attainment with increasing paternal age. The paternal age–related neurocognitive development in childhood was also investigated in the US Collaborative Perinatal Project, and the authors reported that the neurocognitive measure scores were slightly impaired in children of older fathers (48). This supported the earlier published findings from Israeli conscription data of decreasing intelligence quotient scores with paternal age when compared with children of fathers aged 25–29 years (49). Similar data were used to demonstrate a monotonic association between paternal age and autism risk (50).

The most robust finding in the neurodevelopmental areas is that advanced paternal age is associated with ASD. This was reported in a case–control study from Middle Netherlands, in which no association to bipolar disease was found (51). A collaborative study analyzed population-covering data from the 3 Scandinavian countries, Western Australia, and Israel and demonstrated increased risk of ASD in children of older fathers (and mothers) (52). This was also found by researchers who analyzed Kaiser Permanente data (53), in population-based data from California (54), and in a case–cohort study from the US Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network (55). The uniformity in epidemiologic findings of a relation between advanced paternal age and ASD risk is consistent with recent genomic reports convincingly showing that de novo mutations, including copy number variants, contribute substantially to the development of ASD (56, 57). It has been suggested that the same mechanism accounts for schizophrenia (58), but newer studies from Denmark (59) and Sweden (60) claim, on the basis of sibling analyses, that the apparent association was a result of factors that relate to selection and not to paternal age per se. A simpler

TABLE 1

Adverse health outcomes in offspring probably affected by advanced paternal age, their occurrence, and assessed evidence for the paternal age effect (strong/medium/weak).

Adverse health condition	Population-based prevalence/lifetime risk	Evidence for a paternal age effect
Fetal death[a]		
Miscarriage (early fetal death)	1,500/10,000 clinically recognized pregnancies	Weak
Stillbirth (late fetal death)	0.4/10,000 births	Medium
Congenital syndromes and anomalies[b]		
Achondroplasia	<1/10,000 births	Strong
Thanatophoric dysplasia	<1/10,000 births	Strong
Osteogenesis imperfecta	<1/10,000 births	Strong
Apert syndrome	<1/10,000 births	Strong
Pfeiffer's syndrome	<1/10,000 births	Strong
Crouzon's syndrome	<1/10,000 births	Strong
Marfan syndrome	2/10,000 births	Strong
Neurofibromatosis (NF-1)	3/10,000 births	Strong
Syndactyly	5/10,000 births	Medium
Cleft palate	15/10,000 births	Strong
Patent ductus arteriosus	5/10,000 births (term babies)	Medium-weak
Down syndrome	5/10.000 births[c]	Weak
Club foot	15/10.000 births	Weak
Other perinatal conditions[a]		
Preterm birth	700/10,000 births	Medium
Preeclampsia	300/10,000 births	Weak
Childhood cancers[a]		
Retinoblastoma	0.6/10,000 individuals	Medium
Acute lymphatic leukemia	12/10.000 individuals	Strong
Neurodevelopmental outcomes[d]		
Autism spectrum disorders	93/10,000 individuals	Strong
Schizophrenia/psychosis	367/10,000 individuals	Strong
Attention deficit-hyperactivity disorder	192/10,000 individuals	Weak
Bipolar disorder	184/10,000 individuals	Weak

[a] If the occurrences vary substantially between countries, we have given population-based occurrence measures from Denmark, 2000–2010.
[b] Prevalence according to www.orpha.net.
[c] Prevalence among births in a population with prenatal screening and termination of pregnancy on demand. The prevalence is approximately 130/10,000 in an unscreened population, depending on parental age distribution.
[d] Lifetime prevalence according to Pedersen et al. (68).

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analysis of the same population-based register data from the 2 countries demonstrated a direct relation between paternal age and schizophrenia, and authors had earlier suggested de novo mutations being responsible for the association (61, 62). Recently a population genetic modeling study has suggested that genetic factors, shared by older fathers and their offspring and carrying liability for serious psychiatric illness, may explain the associations found (63). Almost all authors have replicated the finding of increased schizophrenia risk in offspring of older fathers (64–66), but consensus about the mechanism behind this observation remains to be established.

Finally, there are intriguing examples of nonconsistent findings obtained from population-covering analyses of the same data sources: Hvolgaard Mikkelsen et al. (67) were unable to replicate the recent findings by McGrath et al. (45) and reported no increased risk of attention-deficit/hyperactivity disorder with paternal age, neither in conventional cohort analyses nor in sibling analyses, even though data from the same population were analyzed.

In conclusion, the vast majority of studies support that risk of schizophrenia and ASDs is increased in offspring of older fathers, whereas any association with affective disorders (bipolar, eating, and attention-deficit/hyperactivity disorder) is less convincingly demonstrated. The mechanisms linking advanced paternal age and the neurodevelopmental disorders are probably diverse.

PUBLIC HEALTH IMPLICATIONS

In the first part of this article we reviewed the epidemiologic evidence regarding adverse health effects in the fetuses and children of fathers of advanced paternal age. The conditions most convincingly related to advanced paternal age, the population-level occurrence measures of the conditions, and the strength of evidence for a causal relation are summarized in Table 1.

Because paternal age is the main source of variation in mutation rate (69), there has been a concern that the increase in paternal age we have seen over the past 30 years may lead to severe populations effects, maybe concealed as minor phenotypical traits (70). We think that it is important to remember that throughout human history people have reproduced when possible, and historical data show that our contemporary impression that paternal age is very high is biased by the fact that the average paternal age was particularly low in the 1950s–1960s, compared with earlier decades (71). It might be a more relevant concern if the improvements in assisted reproductive technologies to a large extent allow otherwise nonfunctioning spermatozoa, possibly with a large number of point mutations, to fertilize ova. To address that concern an age limit for semen donation and perhaps also homologous intracytoplasmic sperm injection may be considered.

Age is definitely a biological fact, but it is also a social construct. It has been speculated that fathers of advanced age would be different in their way of interacting with the children, and that could be a reason for the associations found between paternal age and behavioral conditions. Additionally, men with mental, social, or health problems may face difficulties in mating and therefore become fathers at a more advanced age (59). Other kinds of selection (i.e., mechanisms other than point mutations) may account for the adverse perinatal conditions associated with older fathers: advanced paternal age can be a consequence of subfertility of a couple, and subfertility is known to correlate with risk of reproductive failures (72). This is mentioned to remind the readers that correlations between paternal age and adverse health outcomes in the offspring may be completely correct as observed, but not necessarily causal. In plain words: in a future situation in which fathers deliberately choose to postpone reproduction to an older age, and if fathers of older age is "the standard," it is likely that some of the observed increased risks may disappear. Indeed, this only is true for the risks caused by selection forces, and the biological deterioration of healthy reproductive ability with age in women and men is nevertheless of concern.

Still, we find it justified to remind the reader that the increased fetal mortality and the morbidity attributed to advanced paternal age is low in absolute terms, partly because of the rarity of the particular diseases and the low proportion of children fathered by men aged ≥ 45 years.

Although not of immediate public health concern, future epidemiologic studies that demonstrate paternal age correlates with specific morbidity may act as markers of probable mutational etiologies of human diseases and guide etiologic research.

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