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

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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 (12).

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 (13). A study from Atlanta pointed at situs inversus in addition to the expected association between high paternal age and chondrodystrophy (14). 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 (15), 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 (16). 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 (17). This was actually a replication of a finding from the Child Health and Development Study from 1959–1966 (18), and this finding was also replicated in a more recent meta-analysis (19). 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) (20).

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 (21). 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 (22). Analyses of the Texan Birth Defect Registry1996–2002 did not reveal any increases in risk with paternal age (23), 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 (24). 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 (25). After having found an increased risk of childhood mortality attributed to musculoskeletal anomalies (26), 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 (27).

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 (28) made an

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