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Advanced Paternal Age is a Lesser Known Genetic Risk with
Potential Clinical Utility among a Group of Pediatricians

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Advanced Paternal Age is a Lesser Known Genetic Risk with Potential Clinical Utility among a Group of Pediatricians

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Abstract

Advanced Paternal Age is a risk factor for many birth-developmental defects that may be familiar to pediatricians; however, the knowledge possessed by pediatricians about advanced paternal age is unknown. An electronic survey assessed this knowledge level among pediatricians at Cincinnati Children’s Hospital Medical Center and asked whether they use advanced paternal age information in their clinical practice, why or why not, and in what context(s). Data from 130 respondents showed that most pediatricians had a low level of advanced paternal age knowledge and that most had not discussed paternal age risks in their clinical practice. Respondents expressed that advanced paternal age information has potential clinical utility and that associated risks should be discussed with patients by healthcare professionals who are educated about paternal age risks. This study demonstrated low levels of advanced paternal age knowledge but high perceived clinical utility of advanced paternal age information among a group of pediatricians.
Acknowledgement

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Introduction

What is advanced paternal age?

Advanced paternal age (APA) describes the phenomenon of elevated health outcome risks among offspring of men of increasing age. In contrast to risks associated with advanced maternal age, there are no clinical recommendations regarding implementation of APA information. Differences in male and female gamete production result in the different reproductive risks attributed to males and females with advancing age.

APA was first described as a risk factor in 1912 when a higher frequency of achondroplasia was reported among lastborn children.¹ Today APA risks are far more thoroughly described, although there is still no consistent definition of APA. Paternal age of 40 or greater when conception of a child occurs is the suggested APA criterion of The American College of Medical Genetics.² A discrepancy exists between this definition and the cutoff points utilized in many research studies, as researchers have identified males as young as 30 or as old as 55 as APA.³,⁴ Additionally, because APA risks increase continuously with age rather than drastically at one point in time, some studies have modeled age as a continuous variable.⁵ The lack of consistency in these APA definitions makes synthesizing APA risk findings more difficult, yet such correlations of APA with more than 20 congenital and adult-onset genetic diseases has been consistently demonstrated.⁶

APA associated mutations.

The problem of most concern in men of APA status is that the reliability of duplication of genetic material declines as the body ages. When DNA repair mechanisms fail to detect and/or
repair certain mutations, such mutations are then sorted into the sperm at the time of meiosis. If a mutation-affected sperm fertilizes an egg, then any resulting genotype-to-phenotype changes will likely affect the conceptus.⁵

As a man ages, the number of times that the DNA packaged in the sperm has been replicated increases. Each replication is an isolated chance for a mutation, and mutations can accrue as the DNA is copied if repair mechanisms do not detect the replication error. “Male germ cells go through 30 rounds of mitosis before a male reaches puberty and then continue to divide every 16 days- a total of 23 replications per year.”⁶ This copy-error hypothesis is the primary explanation for why reproductive risks increase with increasing male age. Other supplemental hypotheses include decreased apoptosis, abnormal expression of paternally imprinted genes, and sperm selection in favor of certain mutations.⁷ Apoptosis is a method of programmed cell death in which cells carrying mutations may be targeted for destruction, and lower frequencies of apoptosis have been shown in older men.⁶ Genetic imprinting implies that certain genes are expressed differently in the offspring depending on which parent contributed the genetic material. It has also been proposed that for unknown reasons sperm carrying certain mutations have a selective advantage toward fertilization.⁸

**Genetic conditions associated with APA.**

Over 20 conditions, including single gene disorders and complex traits, have demonstrated APA associations.⁶ Because the mutations that tend to increase with male age are spontaneous, *de novo* point mutations, many of the related conditions are linked to changes in a single gene. Such single gene conditions are subsequently inherited in an autosomal dominant fashion. This is validated by the majority of the conditions associated with APA.⁹ Noonan syndrome,
achondroplasia, Apert syndrome, Marfan syndrome, Treacher Collins syndrome, Waardenberg syndrome, thanatophoric dysplasia, osteogenesis imperfecta, neurofibromatosis, Pfeiffer syndrome, and Crouzon syndrome are single gene dominant congenital conditions shown to have an APA association.\textsuperscript{10,11,9,6} Increased risks for fetal death and certain cancers are also associated with APA due to the increase in mutations.\textsuperscript{12} Because the prevalence of each aforementioned adverse health outcome is low in the general population, even the elevated APA risk for each individual may not seem high. Yet there could be implications regarding the prevalence of these rare diseases at a population level if more older men choose to father children.\textsuperscript{12,6}

A handful of X-linked traits are also associated with APA, but because of properties inherent to X-linked transmission it is the age of the proband’s maternal grandfather at the time of conception that may confer this risk.\textsuperscript{4} X-linked conditions affected by APA include fragile X syndrome, Hemophilia types A and B, Hunter syndrome, Bruton agammaglobulinemia, and retinitis pigmentosa.\textsuperscript{6}

Several complex traits also have demonstrated associations with APA.\textsuperscript{13} Among the strongest of APA-associated risks is the psychiatric disorder, schizophrenia. Unlike single gene disorders, schizophrenia is believed to have a multifactorial etiology with some genetic component.\textsuperscript{14,5,4,3} Investigations into the APA-schizophrenia association are more abundant than investigations into the correlations of other APA-associated conditions, presumably because of the relatively high prevalence of schizophrenia. While the genetic predisposition is not fully understood at this time, APA is an accepted risk factor for schizophrenia.\textsuperscript{3}
Schizophrenia is a chronic and severe mental illness characterized by psychotic episodes that include mental disturbance, distorted perception and often hallucinations. The age of onset is usually during the late teenage years or early adulthood. Due to the debilitating nature of the disease, many people with schizophrenia do not reproduce.\textsuperscript{14,5,4,3} Given that there is a genetic component to the disease and it is not often passed on by affected individuals, the copy-error hypothesis and increased male age offer a partial explanation for the maintenance of the prevalence of schizophrenia in the human population.\textsuperscript{4}

Autism is another complex associated condition that is not evident prenatally or at the time of birth. Autism is a neurodevelopmental spectrum disorder characterized by impaired communication, social interaction, and creative/imaginative play. It has recently been demonstrated that “offspring of men 40 years or older were 5.75 times more likely to have autism spectrum disorder than were offspring of men under the age of 30 years.” This elevated risk is attributed to \textit{de novo} point mutations and possibly altered imprinting.\textsuperscript{15}

\textbf{APA, societal trends, and social perceptions}

Societal trends suggest that more males are fathering children at later ages. Social changes evident in recent history also suggest that APA may become an increasingly important matter in the future. In mating, paternal age correlates with maternal age and more couples are now starting to have children at a later age. The average maternal age in 2007 is 25.1 years compared to age 21.4 years in 1973.\textsuperscript{16,6} “The birth rate for all U.S. men increased for fathers aged 30 to 39 years and decreased for fathers aged 20 to 29 years between 1993 and 2002.”\textsuperscript{17} Another study showed that “fatherhood among men aged 35-49 has increased 40%, while there has been a 20%
decline in births fathered by men under age 30.18,19 Additionally, assisted reproductive techniques such as in vitro fertilization (IVF) allow older couples to conceive when they may not otherwise be able.20 Medications such as sildenafil citrate (Viagra) allow men of any age who may have previously lost their ability to procreate to have more chances at conception.

Even though the risks of APA have been substantiated, some think that the evidence is met with resistance due to society’s conception of masculinity and the previous belief that a man could safely father a child anytime throughout his adult life.7 A societal stigma that virility helps define masculinity has also been suggested.7 Yet a review of APA studies and related conditions suggests that such delayed childbearing practices may not be favorable in terms of genetic risk.

APA Timeline

Although the disproportionate male contribution of new single gene mutations has been mentioned in medical literature for nearly a century, the attention given to the subject in the last decade has greatly increased. Much of the research and publications regarding APA has taken place within the last decade. Additionally, many medical students should have received more comprehensive genetics education in more recent years than in the past.21,22

Research Directives

The level of APA knowledge among healthcare practitioners has never before been assessed, according to a literature search of Medline and PubMed in April, 2008. Many APA-associated conditions are birth-developmental defects familiar to pediatricians, yet no guidelines have been suggested for implementation of this information in a clinical or public health setting.
Exploration of APA awareness is the logical first step toward the potential development of formal APA educational interventions and/or clinical guidelines and toward suggesting the utility thereof. Such programs or clinical incorporations of APA reproductive risk information may subsequently assist males/couples with making educated family planning choices and may impact disease prevalence at a population level.

The current study assessed the advanced paternal age knowledge level among pediatricians at Cincinnati Children’s Hospital Medical Center (CCHMC). Also explored was whether pediatrician respondents have utilized advanced paternal age information in their clinical practice and whether they find APA information to be of clinical utility. Specific data were collected to demonstrate whether APA information has been used by CCHMC pediatricians in their clinical practice, why or why not, and in what context(s). Because of the recent attention given to APA in research and literature and because of improvements in genetics curricula, the hypothesis that pediatricians who graduated from medical school within the last decade are more knowledgeable about APA and associated risks than those who graduated earlier than 1998 was also tested. Due to the suggested social stigma of resistance to acceptance of male reproductive risks, APA knowledge levels of male and female respondents were compared.

The research questions of the current study are:

1. How knowledgeable are pediatricians about APA information?
2. Have pediatricians discussed APA information with patients in their clinical practice?
3. Is there a difference in level of knowledge between male and female pediatricians?
4. Is there a difference in level of knowledge between pediatricians who graduated from medical school more than a decade ago (prior to 1998) and those who graduated more recently (1998-present).
5. Do pediatricians believe that APA information has clinical utility?

Methods

This descriptive cross-sectional study assessed pediatricians’ knowledge about the impact of advanced paternal age on the offspring of older men and also assessed clinical applications of such knowledge.

Survey Tool

The assessment tool was a 26-item electronic questionnaire developed specifically for this project after thorough literature review using the PubMed and Medline databases in April 2007. The questionnaire collected demographic yet non-identifying information that allowed for stratification by gender and by year of medical school graduation. It also assessed APA knowledge level as demonstrated through responses to fact-based questions. The questionnaire assessed whether respondents have utilized APA information in their clinical practice and whether they perceive APA information to be of clinical value. Prior to data collection, 5 doctorate level biomedical professionals, who were not directly involved with the project, rated each questionnaire item on its clarity of wording and its relevance to the current project. Revisions were made based on results of this pre-test. Those items not considered relevant and/or clear were revised or discarded. This pre-test ensured content validity.

The questionnaire had 5 sections, and respondents were automatically directed to the appropriate subsequent section based on their individual answers. The sections included: 1) Background
information and demographics, 2) Knowledge based scored questions, 3) clinical practice assessment, 4) scenario-based questions for those who have utilized APA information in their practice, and 5) an informational paragraph and theoretical question for those who were previously unfamiliar with APA.

All respondents completed the background section. The final question in that section requested self-rated knowledge level of APA, with choices of high, medium, low, or none prior to taking the survey. Those who reported no prior knowledge were automatically directed to section 5. They did not complete the factual or clinical application questions, but instead received a brief introduction to APA-associated risks and were asked for their opinion on the clinical utility of this information. This brief introduction was developed by the principal investigator and was electronically generated when a respondent selected the response of “no prior knowledge”.

All other respondents proceeded to section 2, a 10-item fact-based portion in which one positive point was awarded to each participant for each correct answer. There was no penalty for wrong answers and each item also contained an unpenalized “don’t know” answer choice to deter respondents from guessing and/or referencing literature, internet sources, or colleagues.

Participants did not receive their score upon completion of the survey, but they were aware that their knowledge level was assessed.

Regardless of scored performance, all section 2 participants were asked about their clinical application of APA information in section 3. Those who had not applied such information clinically were asked to explain why not. They were then finished with the survey. Those who
had applied such information clinically proceeded to section 4 where the details of their application were explored. The survey was accessible on-line and supported by SurveyMonkey® (www.surveymonkey.com) using a purchased Professional Monthly Account. Completion of the survey took approximately 10 minutes per participant. The survey was available to respondents for a period of 6 weeks. SurveyMonkey® securely stored all responses and only the principal investigator had access to the data and the SurveyMonkey® account. See Appendix II for the full questionnaire.

**Setting**

Only pediatricians who are based at Cincinnati Children’s Hospital Medical Center were included in this study. The internal CCHMC e-mail system was used to contact all potential respondents. The e-mail contained a link to the SurveyMonkey® electronic survey and respondents were able to complete the survey from any computer on which they could access their CCHMC e-mail account. Survey completion likely, though not necessarily, occurred on the CCHMC campus. This study was approved by the Institutional Review Boards of both Cincinnati Children’s Hospital Medical Center and the University of Cincinnati.

**Participants**

A population of pediatricians, including pediatric faculty, fellows and residents, was selected because pediatricians are commonly educated regarding a wide array of conditions, as well as their causes and risk factors, that affect youth. Many APA-associated conditions are birth-developmental defects familiar to pediatricians. Additionally, many pediatricians serve as a family’s first contact in a diagnostic process, and referrals to genetics clinics commonly come
from pediatricians. Because families often maintain contact with an oldest child’s pediatrician, the pediatrician may have the unique opportunity to discuss risks related to future pregnancies if parents choose to expand their family as time passes. The sample population included only CCHMC pediatricians due to accessibility and convenience of that population. Only CCHMC pediatricians were eligible for participation and all other individuals were excluded from the study.

**Recruitment**

The population of CCHMC pediatricians was contacted via their institutional internal e-mail accounts and asked to complete the on-line survey. Names of these potential participants were obtained from the publicly available and quarterly updated CCHMC Medical Staff Roster (available at http://www.cincinnatichildrens.org/NR/rdonlyres/9B3D5127-34CB-4CE1-894E-80CD74DC6A75/0/managedcare.pdf?GOSEARCH.X=9\&GOSEARCH.Y=1), which includes both eligible individuals, such as Medical Doctors and Doctors of Osteopathy, and ineligible individuals such as Certified Nurse Practitioners and Registered Nurses. Using Microsoft Excel 2007, all ineligible individuals, as determined by degree, were removed from the list. The remaining 1288 individuals were the pediatric faculty, fellows, and residents at CCHMC. All internal CCHMC e-mail addresses are formatted using each individual’s first and last name, and conversion from listed names to e-mail addresses was completed in this manner. 856 eligible potential participants were successfully contacted. 432 e-mails were returned as undeliverable due to an expired account or an unknown user.
The body of the e-mail study invitation introduced the purpose of the survey, and it stated that there are no known risks of participation, that participation is voluntary, and that completion of the on-line survey implies consent for one’s responses to be included in the analysis. The link to complete the survey was included in this invitation. A reminder e-mail was sent to the same group 2 weeks after the initial invitation.

Incentives
Small incentives were offered for participation. A short informative review of APA information was electronically available following completion of the survey. This review, written by the investigators, was offered so that respondents could become more knowledgeable about the impact of APA. The answers to the fact-based questions were also explained and discussed in the review. A certificate of completion was generated at the end of the survey. It did not contain any identifying information and could be exchanged by the holder for a five dollar specialty coffee gift card. An administrative assistant who was not otherwise involved with the research facilitated the certificate-gift card exchange.

Data Analysis
Basic descriptive statistics, including measures of central tendency and variance, were utilized to describe the trends of responses from CCHMC pediatricians. Numerical scoring of section 2 items allowed for comparison of knowledge levels by demographic details such as gender and year of medical school graduation. One positive point was awarded to each participant for each correct answer. No penalties were given for other answers. The mean score was calculated in
Means of sub-groups (graduation year and gender) were also obtained. Variances were estimated for these groups.

Respondents who reported that they had never heard of APA prior to this survey were included in the initial analysis with a total score of zero inserted on the fact-based section. This allowed for analysis of all respondents and for best representation of the full population of participants. The same analysis of knowledge level was then repeated with the exclusion of respondents in this category so that trends among only those who had previously heard of APA risks could be examined separately. This exclusion also applies to trends discussed for clinical applications of APA information. The excluded group’s perception of clinical utility of APA information is also separately examined.

The sample size was determined by the number of pediatricians who chose to complete the survey. Two sample pooled t-tests assuming equal population variances were used to determine whether statistically significant differences in level of knowledge were present between physicians who graduated from medical school over a decade ago (prior to 1998) and those who graduated more recently (1998 or later), and whether there were differences in level of knowledge between male and female pediatricians.

Raw data collected with SurveyMonkey© was downloaded and coded by the principal investigator using Microsoft Excel 2005. SurveyMonkey© analysis described aggregate trends and the Microsoft Excel 2005 Statistical Package was used to perform statistical analyses. Collaboration with a Research and Development Services Systems Analyst ensured appropriate
and accurate application of statistical tools and interpretation of quantitative data. The limited qualitative data collected through this survey are presented verbatim in the results section.

**Results**

One-hundred-thirty of the 856 CCHMC-invited pediatricians participated in this study. The response rate was 15.2%. Sixty-five (50%) respondents were male and 65 (50%) were female. Fifty-nine (45.4%) graduated within the last decade (range: 1998 through 2004) and 71 (54.6%) graduated prior to 1998 (range 1973 through 1997).

**Previous Education Regarding APA**

Forty-six (35.4%) reported prior education about APA associated risks through medical school education, 38 (29.2%) reported APA education from review of primary literature and/or medical journals, and 16 (12.3%) reported APA education through attending professional conferences and/or continuing education courses. Eighteen respondents (13.8%) listed additional sources of APA education, including general public press/media, the OB/GYN physician caring for a respondent’s spouse, and personal treatment for infertility. Forty-four respondents (33.8%) reported having had no education about the impact of APA.

**Perceived Knowledge Level**

When asked to rate their knowledge level regarding the impact of APA on genetic risks to offspring born to older men, 2 respondents (1.5%) rated their knowledge level as high. Twenty-seven (20.8%) reported a medium knowledge level and 89 (68.5%) reported a low knowledge
Twelve respondents (9.2%) reported no knowledge of APA prior to participation in this study (Figure 1).

**Demonstrated Knowledge Level, Among All**

The 118 respondents who reported some (low, medium, or high) knowledge of APA were directed to the 10-item knowledge-based scored portion of the survey. 114 of these respondents (96.6%) completed this section. Four respondents (3.4%) discontinued their participation: 3 had rated their knowledge level as “low” and 1 had rated their knowledge level as “high.” Two were male and 2 were female; 2 graduated within the last decade and 2 graduated prior to 1998.

A mean knowledge score of 2.29 was demonstrated by the 126 CCHMC pediatricians who completed the questionnaire. A sum score of zero was inserted for the 12 respondents who had no prior knowledge of APA and the 4 discontinued respondents were excluded from this analysis. The possible range of scores was 0 to 10 and participant scores ranged from 0 to 9 (Figure 2). A sample variance of 5.28 was observed. No statistical difference in knowledge based on gender was seen (a=0.05, t=0.15, p=0.88). No statistical difference in knowledge based on year of medical school graduation was seen (a=0.05, t=-1.15, p=0.25).

**Demonstrated Knowledge Level Among Respondents With Prior Knowledge**

Scores of the 114 scored respondents who reported prior APA knowledge were isolated and examined. The mean score was 2.53 with a variance of 5.23. In this group, a difference in knowledge was demonstrated between those who graduated from medical school prior to 1998 (n=66 senior pediatricians) and those who graduated within the last decade (n=48 junior pediatricians).
pediatricians) (a=0.05, t=-1.99, p=0.048). Junior pediatricians had a mean score of 3.02 with a variance of 4.87 compared to senior pediatricians who had a mean score of 2.16 with a variance of 5.25. (Figure 3). This statistical difference is unlikely to confer a practical difference in knowledge, as both mean scores attained by these two groups of pediatricians indicate that neither group is well-informed about APA. No difference in level of knowledge between males and females (a=0.05, t=0.16, p=0.87) was seen in this group.

**Clinical Incorporation of APA Information**

The 114 respondents in the scored section were asked whether they have discussed risks associated with APA in their clinical practice. Seven (6.1%) had discussed APA risks and 107 (93.9%) had not. Of those who had discussed APA risks clinically, 4 (57.1%) discussed APA risks when a child born to an older father was diagnosed with a condition that is associated with APA. Four (57.1%) had also discussed APA risks when a man over a certain age indicated that a pregnancy was planned or in progress and/or when a woman expressed a planned or current pregnancy with a man of known older age.

**At What Paternal Age should APA Risks be Presented?**

Seven respondents who had discussed APA risks clinically were asked at what age they have or would incorporate such risk discussion. When a pregnancy is planned or in progress: 1 respondent (14.3%) would discuss APA-related risks with a male of any age, 1 (14.3%) would discuss risks with a male of age 35 or greater, 3 (42.9%) would discuss risks with a male of age 40 or greater, 1 (14.3%) would discuss risks with a male of age 45 or greater, and 1 (14.3%) would discuss risks with a male of age 55 or greater. If a pregnancy is not planned or in progress:
1 (14.3%) respondent would discuss APA risks with a male of any age, 1 respondent would discuss risks with males age 35 and above, 1 would discuss risks with males age 40 and above, 1 would discuss risks with males age 45 and above, and 3 (42.9%) would not offer APA risk information in this situation.

When asked to describe any other situations in which APA risks were discussed clinically, 1 (14.3%) added the comment, “Any time I discuss age effects I include advanced paternal age.”

Why Not Discuss APA?

Of the 107 who knew of APA risks but had not discussed them clinically, 66 (61.7%) said they are not well enough informed about APA risks to discuss this information, 56 (52.3%) said APA information is not relevant to the patients they see, 6 (5.6%) said they do not have enough time to incorporate APA risk discussion, and 2 (1.9%) said they do not think that APA information is currently of clinical value. Comments included, “the situation has not come up,” “traditionally, patients do not seek this information & the general public is not aware that it, too, is an issue,” “most of my male patients are infertile,” “I practice pediatrics in an emergency room setting,” and “No one seeks my advice prior to conception.”

Perceived Clinical Utility Among Respondents with No Prior Knowledge

Twelve respondents (9.2%) reported that they had never heard of risks associated with APA prior to participation in this study. These twelve were presented with an informative paragraph describing APA risks and were asked whether this knowledge may be clinically useful to them. Eleven (91.7%) responded to this question. Five (45.5%) said they may discuss APA risks after
obtaining more information, 5 (45.5%) said that APA information does not seem relevant in their scope of practice, and 1 (9.1%) said that they may discuss APA risks with an older male who expresses his intention to biologically contribute to a pregnancy. All respondents reported that APA information seems to be clinically valuable and that they would have time to incorporate discussion of APA information.

**Discussion**

**Overview**

This study assessed pediatricians’ knowledge of APA and their practices related to discussing APA with patient families. 856 CCHMC pediatricians were questioned in an e-mail survey and 130 responded (15.2%). The results indicate that respondents are largely aware that APA is a genetic risk factor, but few pediatricians in the same sample demonstrate a knowledge level sufficient to permit clinical application of this information. Most pediatricians know of this deficit and self-reported that they are not knowledgeable enough about APA to discuss associated risks with their patients.

Most pediatricians had not discussed paternal age risks in their clinical practice but do believe that APA should be discussed with patients in appropriate situations by knowledgeable professionals. A minority of APA-knowledgeable pediatricians have discussed APA risks in situations when a child born to an older father is diagnosed with an APA-associated condition, when a man over a certain age indicates that a pregnancy is planned or in progress, and when a female indicates a planned or current pregnancy with an older man.
Clinical Barriers to Pediatricians Addressing APA: Low Knowledge Level and Low Relevance

The largest reported barrier to the pediatrician addressing APA risks is a lack of sufficient knowledge; a barrier that may potentially be overcome through educational initiatives and/or standardized medical practice guidelines. Such guidelines could also define at what age males should be counseled about APA-risks, as the inconsistency in the definition of APA is observed both in the literature and in the results of this study.

Besides lack of APA knowledge, many pediatricians state that APA information is not relevant to the group of patients they see. While many APA-associated conditions are birth-developmental defects that should be familiar to a pediatrician, the specific risks may be a topic more appropriately addressed by other healthcare professionals such as obstetricians/gynecologists, geneticists, genetic counselors, and advanced practice nurses. Yet a general knowledge of APA risks among pediatricians may facilitate appropriate patient referrals in the likely event that a patient is not self-seeking age-related reproductive or diagnostic counseling. Preconception or prenatal cases involving an older father may be best addressed by an OB/GYN or a prenatal genetic counselor, while pediatric diagnoses with a possible APA- etiology may be better addressed by a pediatric geneticist or genetic counselor.

Discussion of Clinical Utility in Preconception and Prenatal Cases of APA

The desired clinical incorporation may be limited to provider-patient discussion of APA in order to promote full awareness of age-related reproductive risks. In some cases, this information may prompt a male to thoroughly consider whether having a child is personally right for him in his
later years. Likely, a man who wants a child at an older age will not be dissuaded by APA-information, but because he is well-informed may be more inclined to follow through with recommended early and thorough prenatal and pediatric care. Males who do not wish to have children in their later years may be encouraged to practice sex with contraception or may consider having a vasectomy performed. Male attitudes and responses to APA information should be investigated in the general population.

Other clinical courses for a male making fully educated family planning choices are yet to be defined; however, it seems unlikely that extreme reproductive-risk techniques such as Preimplantation Genetic Diagnosis would be feasible or desired based on the types of associated risks, associated ethical/moral issues, and the relatively low chances of any individual embryo/fetus being affected with any single condition based on paternal age alone. Additional limitations to offering APA-specific clinical options may include the timing at which associated conditions present and the inability to change the outcome.

The potential benefits and limitations of APA-risk discussion in different clinical scenarios could be separately explored. Increased-risk awareness during preconception and prenatal periods is a hypothesized benefit. Prenatal discussion of APA-risks may allow for more thorough prenatal evaluation for APA-associated conditions such as achondroplasia and congenital heart defects; however, it is important to note that currently offered prenatal screenings such as Level II Ultrasound already seek to identify prenatally detectable congenital conditions. The methodologies and resources that would be necessary to tailor any prenatal screening or diagnostic regimens to APA-risks would have to be carefully examined.
Some APA-associated conditions such as Autism and Schizophrenia cannot be detected prenatally, though there may be benefits of addressing such risks on a preconception or prenatal timeline. Hypothesized benefits include providing anticipatory guidance and risk-awareness, possibly leading to increased childhood surveillance. Additionally, this discussion may be justified by the professional’s responsibility to share with the parent/family all pertinent information.

**Discussion of Clinical Utility in Pediatric Cases of APA**

Retrospective exploration of a possible diagnostic etiology is another potential clinical benefit of APA-risk discussion. In the pediatric realm, when a patient is diagnosed with an APA-associated condition it may be the responsibility of the pediatrician to incorporate APA-issues into the discussion of etiology and natural history. Resulting parental awareness of risks may affect their feelings regarding a current diagnosis and/or their future family planning. Pediatricians’ familiarity with APA-genetic risks may also facilitate referrals to a geneticist or genetic counselor who may more thoroughly discuss the topic, including the possible subsequent inheritance pattern. Because many APA-associated conditions manifest as serious medical and/or social disabilities, it is important for a family to be aware of the possible transmission to future generations.

**Barriers and Benefits to APA Discussion**

Anticipated barriers to discussion of APA risks during or after a pregnancy are potential guilt experienced by the father and the inability to change the diagnostic outcome for the child. In
some cases, early diagnosis can lead to a better prognosis through therapeutic and treatment interventions. Whether or not the genetic risks posed to the child of any particular older man are substantial enough to change his family planning or prenatal/pediatric regimen of care is an individual issue. Yet without access to APA-information males will not be able to grant this information their consideration. Additionally, because a greater number of older men are now fathering children the population prevalence of APA-associated rare conditions may increase. This is also an important consideration when assessing the need for increased APA-educational curricula, and perhaps creating standardized counseling practice guidelines and public health initiatives.

Sources of APA Awareness

An increase in the abundance and availability of APA information may correlate with an increase in knowledge and clinical application across professional cohorts; however, this was not the case in the current study when the knowledge level of all junior pediatricians (graduates of medical school 1998 to present) was compared to all senior pediatricians (graduates of more than a decade ago). One third of all respondents indicated that APA-risks were presented in their medical school curriculum, but the schools of attendance, teaching methods, and depth of information were not examined in the current study. Such examination in a future study may be beneficial for developing targeted educational interventions.

Several respondents identified the public media as a source of APA-awareness, which suggests that males in the general population could be made aware of life-span reproductive risks through general media publicity or public health initiatives. In this event, more patients may approach the
topic with their pediatrician or other healthcare professionals and further substantiate the importance of healthcare professionals’ awareness of such risks.

**APA and Societal Trends**

A societal stigma has been proposed that masculinity is associated with lasting virility. Women in society have long been presented with their gender-age associated risks, and the suggested stigma of masculinity calls to question whether males are equally inclined to be familiar with their own increasing reproductive risks as they age. The results of this study show no significant difference in level of APA knowledge between male and female pediatricians. Males and females are equally likely to be knowledgeable about APA and to apply this information clinically. Whether a gender bias exists within other societal segments remains unknown. Many women seek reproductive counseling related to being of advanced maternal age. It has not been assessed whether men would proportionally seek reproductive counseling if the services were of equal availability.

A greater number of men are fathering children at later ages now than ever before, creating a larger target patient population. Overwhelmingly, pediatricians, both familiar and previously unfamiliar with APA, reported perceived clinical utility of APA-information. Most indicate that patients who could relate personally to APA information should be presented with such information either by the knowledgeable pediatrician or by another appropriate professional. Such clinical incorporations of APA reproductive risk information may assist males and their partners in making educated family planning choices.
Conclusions

The findings show that this sample of pediatricians affiliated with a major US research and teaching hospital has a low knowledge level regarding details of APA genetic risks. Very few incorporate APA information into their clinical practice and lack of knowledge is the largest reported barrier to doing so. Many pediatricians also do not discuss APA in their practice because it is not relevant to the group of patients they see. The belief that APA information is clinically useful in some place and some form is largely upheld. Other professional groups, such as OB/GYNs and genetic counselors, who may be knowledgeable about APA, are discussed above. Limitations of this study include the narrow group of pediatricians surveyed at only one pediatric institution.

The results suggest numerous directions for future exploration in the disciplines of APA research, multi-disciplinary professional knowledge studies, clinical benefits and limitations, and medical and public educational interventions. This study would be interesting to repeat with other professional cohorts who may encounter clinical situations where paternal age is significant. Multi-institutional studies to assess the APA-knowledge and clinical application among pediatricians and other professionals would be more informative and may better guide the development of further assessments and interventions. A general population investigation of male attitudes and responses to APA information could contribute information to further understanding of educational needs among pediatricians and other healthcare specialists.
References


Appendix I

Figure 1. Perceived APA knowledge level of all respondents. (n=130).

Figure 2. Scores attained by all respondents on the knowledge-based portion. (n=126, observed range=0 to 9, possible range=0 to 10). (Mean=2.29, Median=2, Mode=0).
Figure 3. Difference in APA knowledge level by year of medical school graduation among respondents who reported some prior knowledge. (a=0.05, t=-1.99, p=0.048).
Appendix II

Pediatrician Knowledge and Application of Advanced Paternal Age Information

Please complete the following questionnaire. Completion of this questionnaire implies your consent for your responses to be included in a Master’s thesis research project. The questionnaire is designed to assess pediatricians’ knowledge level about the impact of advanced paternal age on the offspring of older men and also to assess clinical applications thereof. Your responses will not be linked to any personally identifying information and there are no known risks of participating in this study. Following submission of this questionnaire you will be offered a short informative article regarding the impact of advanced paternal age and a certificate of completion that can be exchanged for a $5 Starbucks gift card. Completion of the questionnaire will take approximately 10 minutes.

(Please note: This survey will be administered electronically to the study population and the appropriate continuation sequence will be generated based on individual responses.)

Section I. Background Information

1. What is your age? _______ years

2. What is your gender?
   a) Male
   b) Female

3. In what year did you graduate from medical school? ________

4. What best describes your primary area of practice?
   a) Resident
   b) General pediatrics
   c) Cardiology
   d) Developmental pediatrics
   e) Endocrinology
   f) Gastroenterology
   g) Genetics
   h) Hematology/Oncology
   i) Immunology
   j) Neonatology
   k) Neurology
   l) Psychiatry
   m) Other (please specify): ________________________________

5. Have you received education about the impact of advanced paternal age on genetic risks to offspring born to older men through any of the following sources? Select all that apply.
6. How would you rate your knowledge level regarding the impact of advanced paternal age on genetic risks to offspring born to older men?

a) High
b) Medium
c) Low
d) I had never heard of any such impact of advanced paternal age before this survey  (If d, please skip to Section V below).

Section II. The following questions assess your knowledge of advanced paternal age-related information and risks that increase in the offspring of older men. Please choose the best answer.

7. Some genetic conditions occur more frequently among offspring of older men than among offspring of younger men. The biological mechanism thought to be primarily responsible for this increase in risk is:

a) Copy-errors
b) Nondisjunction
c) Recombination
d) Don’t know

8. Advanced paternal age is best known for its association with sporadic cases of genetic disorders that are typically inherited in which fashion?

a) Autosomal Recessive
b) Autosomal Dominant
c) Mitochondrial Inheritance
d) Don’t know

9. It is commonly accepted in the current literature that advanced paternal age correlates with approximately how many adverse health conditions in offspring?

a) 10
b) 20
c) 30
d) Don’t know
10. A man who biologically contributes to a pregnancy at age 40 could be counseled that the resulting child has a 1/110 chance of having:

   a) Down syndrome  
   b) Noonan syndrome  
   c) Schizophrenia  
   d) Don’t know

11-16. Is advanced paternal age a demonstrated risk factor for the following conditions?

11. Achondroplasia?
   a) Yes  
   b) No  
   c) Don’t know

12. Trisomy 18?
   a) Yes  
   b) No  
   c) Don’t know

13. Apert syndrome?
   a) Yes  
   b) No  
   c) Don’t know

14. Autism?
   a) Yes  
   b) No  
   c) Don’t know

15. Noonan syndrome?
   a) Yes  
   b) No  
   c) Don’t know

16. Diabetes Mellitus Type I?
   a) Yes  
   b) No  
   c) Don’t know
Section III. This section assesses your clinical application of advanced paternal age information.

17. Have you ever discussed risks associated with advanced paternal age in your clinical practice?
   a) Yes  (proceed to section IV)
   b) No   (proceed to the next question in this section)

18. If you have not discussed risks associated with advanced paternal age in your clinical practice, why not? Please select all that apply.
   a) Advanced paternal age information is not relevant to the patients I see.
   b) I am not well enough informed about the risks of advanced paternal age.
   c) I do not have the time to incorporate advanced paternal age risk discussion.
   d) I do not think advanced paternal age information is currently of clinical value.
   e) Other (please specify): ______________________________

Section IV. Complete this section only if you answered yes to question 17 in section III.

In your clinical practice:

19. Have you discussed risks associated with advanced paternal age when a child born to an older father is diagnosed with a condition that occurs more frequently with advancing paternal age?
   a) Yes  
   b) No   
   c) I have never encountered this situation

20. Have you discussed risks associated with advanced paternal age when a man over a certain age indicates that he has biologically contributed to a pregnancy or plans to do so?
   a) Yes  
   b) No   
   c) I have never encountered this situation

21. Have you discussed risks associated with advanced paternal age with a woman who is pregnant or expresses that she is planning a pregnancy with a man known to be of older age?
   a) Yes  
   b) No   
   c) I have never encountered this situation

22. To males of what age have you offered or would you offer advanced paternal age risk information when a pregnancy is planned or in progress?
a) any age  
b) 30 and above  
c) 35 and above  
d) 40 and above  
e) 45 and above  
f) 50 and above  
g) 55 and above  
h) 60 and above  
i) I have not and would not offer advanced paternal age risk information in this situation.

23. To males of what age have you offered or would you offer advanced paternal age risk information when a pregnancy is **not** planned or in progress?

- a) any age  
- b) 30 and above  
- c) 35 and above  
- d) 40 and above  
- e) 45 and above  
- f) 50 and above  
- g) 55 and above  
- h) 60 and above  
- i) I have not and would not offer advanced paternal age risk information in this situation.

24. Are there other situations in which you have discussed risks associated with advanced paternal age? If so, please describe:

______________________________________________________________________________  
______________________________________________________________________________  
______________________________________________________________________________  

25. Is there anything you would like to add related to information about advanced paternal age and your practice?

______________________________________________________________________________  
______________________________________________________________________________  
______________________________________________________________________________  

**Section V.** Complete this section only if you answered (d) to question 6 in **Section I**.

**Advanced paternal age (APA) describes the phenomenon of elevated health outcome risks among offspring of older men. While there is no consistent age cutoff defining APA, it is known that de novo mutations occur more frequently in sperm of older men. This occurs in part due to decreased function of DNA repair mechanisms. Over 20 genetic diseases have demonstrated APA associations. Societal trends also suggest that more males are fathering children at later ages.**

26. With this information in mind, do you expect that you would discuss such risks in your clinical setting? Select all that apply.
a) Yes, I may discuss such risks when a child born to an older father has a genetic condition that may be associated with advanced paternal age.
b) Yes, I may discuss such risks with any older male who expresses his intention to biologically contribute to a pregnancy.
c) Yes, I may discuss such risks with any older male, regardless of his intention to biologically contribute to a pregnancy.
d) No, advanced paternal age-associated risks do not seem relevant to the patients I see.
e) No, I do not have time to incorporate advanced paternal age risk discussion.
f) No, this information does not currently seem to be of clinical value.
g) Maybe, after obtaining more information.
h) Other (please specify):___________________________________