Management and counseling of the male with advanced paternal age

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Increasing percentages of children are being born to older fathers. This has resulted in concerns about the potential adverse effects of advanced paternal age. To help clinicians counsel couples, a systemic review was performed to attempt to address questions that these couples may ask: Should routine sperm testing be performed in older males? Should preimplantation genetic diagnosis (PGD) be performed? How do providers counsel patients about risk? Should young males freeze sperm if they plan to delay paternity? Using the terms "advanced paternal age", "semen testing", "preimplantation genetic diagnosis/screening", and "cryopreservation", a comprehensive search was performed in PubMed and the Cochrane Library, and numerous international societal guidelines were reviewed. In total, 42 articles or guidelines were reviewed. There were no limits placed on the timing of the articles. Thirty articles were found to be relevant and beneficial to answering the above questions. Each question was answered separately by the supporting literature. While primary research exists to support the role of semen testing, PGD/preimplantation genetic screening, and sperm banking in males who may be affected by advancing age, comprehensive studies on the possible clinical benefit of these interventions have yet to be performed. As a result, societal guidelines have yet to incorporate distinct best-practice guidelines on advanced paternal age. (Fertil Steril® 2016;■: ■–■. ©2016 by American Society for Reproductive Medicine.)

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Older men are fathering children. In a 1993 study from England and Wales, fathers 35–54 years of age accounted for 25% of live births. Ten years later, these percentages increased to 40%. Likewise, the number of fathers in the 50–54 age group have seen a notable increase (1). With the maturation of the baby boomer population, the number of older fathers is expected to increase. To help clinicians counsel couples, a systemic review of the literature was performed to address questions that these couples may ask: Should routine sperm testing be performed in older males? Should preimplantation genetic diagnosis (PGD) be performed? How do providers counsel patients about risk? Should young males freeze sperm if they plan to delay paternity?

DATA EXTRACTION

While this is an evolving topic, and minimal prospective studies have been performed, primary research and guidelines were identified. The terms "advanced paternal age", "semen testing", "preimplantation genetic diagnosis/screening", and "cryopreservation" were used for the search. No time limitations were placed on the search. After searching PubMed, the Cochrane Library, and numerous international societal guidelines, 42 articles were identified. Articles were excluded if they did not pertain to fertility in the aging male, the role of cryopreservation, or the specific clinical implications of advanced paternal age. Thirty articles were found to be relevant in answering the described questions.

SHOULD ROUTINE SPERM TESTING BE PERFORMED?

Reproductive function gradually declines with advanced paternal age from a variety of causes. In contrast to female reproductive physiology, male functions do not cease at a defined time such as menopause, and androgen production and spermatogenesis continue throughout life. The most objective and researched cause of decreased fertility is a decline in semen quality. While some literature suggests there is no significant decrease in semen parameters (2), most sources suggest semen quality does decrease with age. While no consensus exists, semen quality begins to decline as early

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as 35 years of age, and pregnancy rates may be similarly impacted. Kidd et al. compared semen parameters between 30 and 50 year old men and showed a decrease in semen volume ranging from 3% to 22%, in sperm motility from 3% to 37%, and in sperm concentration from 4% to 18% (3). In support of this, Dunson et al. showed that semen parameters start to decline noticeably after 35 years of age and continue to decrease after age 40, while controlling for female age (4). Pregnancy rates may be similarly impacted by age, although studies of pregnancy in older couples are confounded by the profound effects of age on fecundity in the female partner. The percentage of couples failing to conceive within 12 cycles increased to an estimated 18%–28% between male ages 35 and 40 years (4). However, despite these decreases, male fertility is basically maintained until very late in life and has been observed in men over 90 years of age.

Given the previously stated changes in semen parameters, what role would sperm testing play in the older male? The American Urological Association (AUA) guidelines state infertility workup should begin after 12 months of unprotected intercourse or sooner if the patient is thought to have infertility risk factors. Older males may benefit from earlier semen analysis (SA) as studies have shown decreased fertility rates (4). Earlier semen testing would allow couples to progress to further options such as IVF-intracytoplasmic sperm injection (ICSI) sooner. Based on much of the literature investigated for this review, there seems to be sufficient evidence that aging males are at risk for having abnormal semen parameters.

There is a wide range of semen testing currently available. A basic SA can provide quick inexpensive answers. According to the AUA guidelines, in addition to a history and physical examination, any male presenting for infertility should have an SA, which includes sperm concentration, total sperm number, percent motility, and forward progression scale. When indicated, sperm agglutination testing for antisperm antibodies should be performed (5). It is recommended to repeat an SA for confirmation if the first result is abnormal.

More detailed semen tests are available in certain situations. The AUA guidelines recommend against sperm morphology testing due to poor predictive values of fertility. There is insufficient evidence to recommend DNA integrity testing to evaluate DNA fragmentation percentage. However, of note, Colin et al. showed that semen from the aging male showed increased apoptotic markers, leading to an increased rate of DNA fragmentation (6). These markers could be an avenue where future research could lead to DNA integrity as testing becomes a more utilized semen parameter in the aging male. More specialized tests such as computer-aided SA have a role in specialized situations but are not recommended for routine testing. The European Association of Urology reflects the AUA guidelines on infertility (7). In summary, the same semen testing should be performed on any male patient who has failed to conceive after 12 months of unprotected intercourse. The timing for the aging male is a topic of debate.

While the aging male has known risk factors for infertility based both on semen parameters and overall erectile function, there are many clinical scenarios that make each patient different. Many aging males who had children in the past are looking to have children with a new partner of equal or younger age. This differs from an older male who has never had a child. Men who are known to be fertile from prior children need to be counseled that while most male fertility remains throughout life, it can decrease with age. Couples where both partners are of advanced age are obviously at increased risk of infertility. Each of these certain patient scenarios needs to be considered when semen testing is ordered. In conclusion, based on the current literature, there is no clear indication to do more advanced semen testing in the aging male on a routine basis. There may be some benefit in obtaining a routine SA in an older male sooner than after 12 months of failed conception. The absolute time period or age guidelines are not present in any current fertility guidelines.

SHOULD PGD/PREIMPLANTATION GENETIC SCREENING (PGS) BE PERFORMED?

PGD and PGS have been used for nearly 20 years and can provide key information for couples undergoing IVF. PGD is used to test a single embryo gene for a distinct pathologic condition, while PGS is a screening test offered to couples to detect aneuploidy. Currently, PGD or PGS are indicated in couples who have a history of multiple spontaneous abortions, a family history of X-linked disease or certain single-gene diseases, and advanced maternal age. PGD acquires cells from embryos or oocytes before embryo implantation. Blastomeres can be harvested at the cleavage stage, from polar bodies or trophectoderm. Checking for maternally derived genetic abnormalities is best accomplished using first or second polar bodies from the maternal oocyte (8), but polar bodies do not reflect mitotic contributions to genome instability. PGD is more disruptive and less accurate than analysis of trophectoderm. Fluorescent in situ hybridization, polymerase chain reaction, array comparative genomic hybridization (aCGH), single nucleotide polymorphism, and next generation sequencing (NGS) analysis allow healthy, euploid embryos to be implanted during ICSI. PGD/PGS improves the embryo implantation rate for IVF-ICSI. Embryos screened with PGD have up to 18% higher implantation rate in women older than 40 years of age (9). However, Staessen et al. concluded that PGD did not increase embryo implantation rate during IVF for women under the age of 36 (10). PGD/PGS for aneuploidy screening, especially when performed using trophectoderm biopsy and 24 chromosome detection by aCGH or NGS, can lower miscarriage rates and increase implantation rates (11).

While first used for Mendelian disorders and X-linked diseases, PGD has expanded its capability to detect chromosomal translocations, mitochondrial diseases, late-onset autosomal dominant diseases, and aneuploidy (12). Please refer to Table 1 for more detailed examples of diseases PGD can diagnose.

PGD or PGS may add significant cost to the already costly IVF-ICSI process. There is a risk of embryo death and an increased rate of cryopreservation failure, although trophectoderm rather than blastomere biopsy and vitrification have significantly reduced these risks. The literature has shown an increased rate of perinatal death in multiple but not in single pregnancies with embryos where PGD was used (13).