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® 2017;107: 324–8. ©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,

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semen quality begins to decline as early 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

TABLE 1

Examples of disorders that preimplantation genetic diagnosis can diagnose.

Disorder type	Disorder
X-linked	Hemophilia
	Duchenne's muscular dystrophy
	Fragile X
Mitochondrial	Mitochondrial myopathy
	Neuropathy ataxia and retinitis pigmentosa
	Leigh syndrome
Aneuploidy	Trisomy 21, 13, or 18
	Turner's syndrome
	Klinefelter's syndrome
Autosomal recessive disease	Cystic fibrosis
	Fanconi anemia
	Glycogen storage disorders
Autosomal dominant disease	Huntington's disease
	Von Hippel Lindau
	Marfan syndrome

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single pregnancies with embryos where PGD was used (13). Based on these risks and indications, what benefit can PGD provide for the aging male who wishes to conceive a child?

Other than mitochondrial DNA inherited diseases, any of the above-mentioned diseases could be inherited from paternal origin. Because of this, PGD would be indicated in a male of any age with a concern about certain genetic diseases. An older male with an older female partner in the late 30s or 40s would also be an indication for PGD as stated above.

While advanced maternal age is the most widely studied risk factor for trisomy 21 due to meiotic nondisjunction, there are paternal causes. Hassold et al. identified paternal chromosomal nondisjunction as the cause of trisomy 21 in 20% of cases (14). However, more recently Antonarakis showed that the suspected paternal contribution of trisomy 21 in a study of 200 families was only 5% (15).

More broadly, aging male sperm has shown a predisposition of aneuploidy. In a recent study from the November 2015 issue of *Clinical Medicine Insights: Reproductive Health* by García-Ferreyra et al. (16), 286 embryos, divided based on paternal age, were examined for aneuploidy. The groups were <39 years, 40–49 years, and >50 years old. The investigators showed that embryos from men older than 50 had a lower rate of blastocyst formation and a significant increase in aneuploidy rate, with an aneuploidy rate as high as 73.9%. Coates et al. showed a significant increase in sex chromosome abnormalities in blastocysts whose paternal origin came from oligozoospermic men (17). Other studies have shown no significant difference in aneuploidy as a result of aging male semen (18). Although some contrary literature is present, there appears to be a reliable amount of evidence showing sperm from the aging male can cause an increase in aneuploidy.

In conclusion, PGD/PGS using trophectoderm biopsy and 24 chromosome analysis has numerous benefits and low adverse events when performed by experienced embryologists. While the evidence is not as strong as the maternal age factor, paternal aging does appear to contribute to an increase in aneuploidy. For the older male, PGD is indicated if there is a family history of testable genetic diseases, a history of spontaneous abortion, and advanced age of the maternal partner. However, no current guidelines currently recommend the routine use of PGD/PGS based on advanced paternal age alone.

HOW TO COUNSEL THE PATIENT?

As in any procedure or patient encounter, both the risks and benefits of a patient treatment plan must be explained. As previously discussed, males are fathering children older, and patient guidelines on advanced paternal age are following suit. Aging men do have a different set of risk factors they need to be counseled on when seeking paternity. It is the provider's role to explain these risks and tailor the counseling to the specific patient's needs.

The literature has shown children conceived from advanced paternal age fathers are more likely to develop certain pathologies. While multiple pathologic states have been linked to advanced paternal age, multiple studies have shown that schizophrenia and autism spectrum disorders are conditions on which patients need to be counseled. However, the association between advanced paternal age and risk to the child is not always consistent and remains uncommon. The slight increased disease risk to offspring is reflected in current guidelines, which prefer donors younger than 40 years of age. The American Society for Reproductive Medicine practice guidelines for sperm donors state, "the donor should be of legal age but younger than 40 years of age so that potential hazards related to aging are diminished" (19). The British Andrology Society states the donor should be no older than 40 years at the time of his donation, and the legal limit to donate is 45 years of age (20).

The rate of autism spectrum disorders increases with advanced paternal age. In a study from Israel, offspring of men 40 years or older were 5.75 times more likely to be affected by autism spectrum disorders than children of men younger than 30 (21). This study controlled for socioeconomic status and maternal age. In addition, an American study showed an increase odds ratio of 1.4 for autism spectrum disorders in offspring of men older than 40 compared with those of men 25–29 when controlling for maternal age (22). Providers should counsel men older than 40 that while autism spectrum disorders in the offspring remain rare, there is a slight increase in relation to advanced paternal age.

The rate of schizophrenia is increased in association with advanced paternal age. While schizophrenia is known to affect 0.5%–1.5% of the population, children born to men older than 45 were found to be twice as likely, and to men older than 50 nearly 3 times as likely, to have schizophrenia (23). This was supported by Dalman and Allebeck, who showed the odds of having a schizophrenic child were 2.8 times greater in men over 45 years of age than in men younger than 25 (24). Despite these findings, this represents only a slight increase in overall absolute risk. Of note, the 2001 study by Malaspina et al. did not now show an increased rate in other psychiatric disorders (23). A man older than 40 should be advised that his offspring are at least twice as likely to

have schizophrenia than the offspring of someone 10 years younger.

In addition to the disease risk of the offspring, fertility and health counseling should be performed on an older male seeking paternity. Medical comorbidities and the related medications do affect fertility. A patient must also be healthy enough to engage in sexual activity. While accounting for less than 1% of all myocardial infarctions, sexual activity has been shown to increase the relative risk of a cardiac event by up to 3 times (25). Of the sudden cardiac deaths associated with sexual activity, 75% were associated with extramarital affairs with younger women. The American Heart Association states that men can engage in sexual activity if they can tolerate mild to moderate physical activity without cardiac symptoms. Table 2 shows a list of comorbidities, which a physician must consider when counseling a patient. The overall health of the father should also be taken into consideration, and current screening tests should be up to date. A 50-year-old healthy male who is up to date with current health screening tests is far different than a 50-year-old male who is obese, has baseline cardiac disease, and a shorter overall life expectancy. Erectile dysfunction and hypogonadism, if present, should be addressed and treated. Of note, exogenous treatment of hypogonadism will further exacerbate infertility and is best treated with therapy to increase endogenous T production. Financial concerns may also play a role, and the patient should be counseled on expected fees. Table 3 summarizes the counseling guidelines found for this review. The overall health of the patient including a recent wellness check and physical exam with up-to-date medical screening tests should be performed for the aging male seeking paternity.

SHOULD MALES CRYOPRESERVE SPERM WHEN YOUNG?

Sperm cryopreservation is commonly used for a variety of indications. While the medical, ethical, and legal implications of cryopreservation have evolved with time, it is now used in practice for certain clinical situations. The effects of aging on semen factors have previously been discussed. There are also known deleterious effects of cryopreservation on sperm. Given these findings, the question arises, should younger men cryopreserve sperm to use later in life because of the decreased fertility and increase in certain diseases associated with advanced paternal age?

TABLE 2

Medical comorbidities and their effect on fertility.

Disease	Effect on fertility
Heart disease	Risk of sexual activity, increased rate of erectile dysfunction
Hypertension	Medications leading to erectile dysfunction
BPH medications	Retrograde ejaculation
Depression	SSRI therapy (resulting in delayed ejaculation)
Prostate cancer	Prostatectomy, hormonal castration

Note: BPH = benign prostatic hypertrophy; SSRI = selective serotonin reuptake inhibitors.

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TABLE 3

Patient counseling summary.

General counseling area	Specific counseling area
Decreased fertility risk	Up to 20% increase in failing to conceive after 1 y in men over 40
Advise about the slight increased absolute risk of certain diseases such as	Down syndrome Autism spectrum disorders Schizophrenia Aneuploidy
General screening guidelines for men	Abdominal ultrasound in smokers over 65 Colonoscopy in men over 50 PSA testing beginning at age 50 Alcohol abuse screening Blood pressure and cholesterol screening Depression Lung cancer screening in prior smokers beginning at age 55
Financial costs	Average IVF/ICSI costs in patient's area PGD/PGS Cryopreservation Physician office visits

Note: ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; PGD = preimplantation genetic diagnosis; PGS = preimplantation genetic screening; PSA = prostate-specific antigen.

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Sperm cryopreservation is indicated for donor insemination or used in conjunction with IVF-ICSI and IUI. Sperm can be preserved for years, and subsequent embryos are screened using PGD as previously mentioned. Preservation before IVF allows couples with a variety of maternal and paternal infertility factors to conceive a child together. For male factor this includes obstructive azoospermia or severe nonobstructive oligozoospermia (26). Cryopreservation is also indicated before surgical or medical treatment for malignancy such as chemotherapy or retroperitoneal lymph node dissection for testicular cancer. Preserving sperm before military deployment or situations where the patient is placed at an increased risk of death or decreased future fertility is also indicated. As will be discussed later, cryopreservation has also been used in perimortem and postmortem conditions. Sperm cryopreservation indications can be expected to evolve with time.

Cryopreservation has shown deleterious effects on semen parameters under certain clinical situations. Sperm preserved from patients undergoing infertility evaluation showed less preservation of sperm motility than donor sperm (27). This does not affect ICSI as the sperm is injected directly into the egg but does have a deleterious effect on IUI. The media used to preserve the sperm have also shown a varied impact of sperm parameters (28). In addition to poor motility, Donnelly et al. showed that sperm DNA integrity was harmed by cryopreservation in infertile men but not in normal patient populations (29). The adverse effects of cryopreservation also include financial strain on the patient. Given both the biologic and financial implications of

cryopreservation, it would be difficult to recommend young men bank sperm only to offset the deleterious effects of aging on semen parameters.

Young men using cryopreservation to offset the aging process could also raise ethical and legal concerns. Many of these issues have been addressed. Patients who have died after cryopreserving sperm or when sperm is cryopreserved in the postmortem state have provided examples of ethical dilemmas. Guidelines are in place to help navigate such situations. Guideline examples include [1] that the patient had a desire for paternity prior to death, [2] legal consent from the patient before death or consent from the wife, [3] that the death was sudden, and [4] agreement to a 1-year waiting/bereavement period before the sperm can be used (30). If young men begin to bank sperm frequently to be used at a later date, new guidelines would need to be developed proactively or as a result of legal and ethical cases.

As previously discussed, men are fathering children at an older age, and these men need to be counseled on the risks associated with advanced paternal age. While some studies have failed to show a regression in semen parameters, the majority of the literature published does support a gradual decrease in fertility as men age. There is also an increase in Down syndrome, autism spectrum disorders, and schizophrenia associated with advanced paternal age. Despite these findings, currently there are no specific guidelines regarding semen testing specifically for older males or the use of PGD/PGS for advanced paternal age as the sole indication. Men must still be counseled about these risks, but when compared with the cost and the effects of cryopreservation on semen, there is no literature showing an indication for young men to preserve sperm to offset the deleterious effects aging has on fertility.

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