



How do we counsel men with obstructive azoospermia due to CF mutations?—a review of treatment options and outcomes

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Contributions: (I) Conception and design: All authors; (II) Administrative support: JB Persily, V Vijay; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Obstructive azoospermia (OA) is a rare cause of male infertility, with Congenital Bilateral Absence of The Vas Deferens (CBAVD) being a major cause. A wealth of literature has established an irrefutable link between *CFTR* mutations and CBAVD, with CBAVD affecting almost all men with cystic fibrosis (CF) disease and a significant portion of men that are *CFTR* mutation carriers. In the past two decades, assisted reproductive technologies have made the prospect of fathering children a viable possibility in this subset of men, using a combination of sperm extraction techniques and intracytoplasmic sperm injection (ICSI). In order to assess techniques for sperm retrieval, as well as reproductive outcomes, a systemic search of the MEDLINE database was conducted for all articles pertaining to management options for CBAVD, and also all reports describing outcomes of these procedures in the CBAVD population. Both epididymal and testicular sperm extraction (TESE) are viable options for men with CBAVD, and though rigorous data are lacking, live birth rates range from 8% to 50% in most small retrospective series and subset analyses. In addition, there does not appear to be significant differences in the rate of live birth or complications and miscarriages between the various techniques, though further investigation into other factors that limit reproductive potential of men with *CFTR* mutations and CBAVD is warranted.

Keywords: Cystic fibrosis (CF); azoospermia; Congenital Bilateral Absence of The Vas Deferens (CBAVD); infertility; testicular sperm extraction (TESE)

Submitted Oct 30, 2019. Accepted for publication May 26, 2020.

doi: 10.21037/tau-19-681

View this article at: <http://dx.doi.org/10.21037/tau-19-681>

Introduction

Azoospermia, defined as the absence of sperm in the ejaculate, is identified in up to 15% of infertile men, and falls into three general categories: pre-testicular azoospermia (often a hormonal issue), testicular (non-obstructive) azoospermia, and post-testicular azoospermia (1). Obstructive azoospermia (OA), a form of post-testicular azoospermia, results from blockage or loss of the male reproductive tract that leads to complete lack of sperm in the ejaculate (2). OA is the cause of azoospermia in up to

51% of cases, though epidemiological studies tend to favor non-OA as the slightly more common cause (3-5). Though many causes of non-OA have treatment options, OA lends itself to a broader set of corrective measures (6-9).

OA can be caused by obstruction of the ductal male reproductive tract at any point. Specific causes include both idiopathic and post-vasectomy vasal obstruction, epididymal obstruction, ejaculatory duct obstruction, and absence of the vasa deferentia. OA conditions include Congenital Bilateral Absence of The Vas Deferens (CBAVD), in which segments of the male ductal reproductive tract are absent.

These missing segments can start anywhere from the mid-portion of the epididymis (leaving only the head/caput of the epididymis), to the seminal vesicles (10).

CBAVD is present in only roughly 1–2% of all infertile men, but aside from vasectomy, it is the most common cause of OA (11). The link between CBAVD and mutations in the Cystic Fibrosis Transmembrane-Conductance Regulator (*CFTR*) gene has been extensively demonstrated (11–13). The *CFTR* gene is found on chromosome 7 and encodes the CFTR protein, which is the main regulator of an outward flowing chloride channel (14). This protein is critical for salt homeostasis in various epithelial tissues including the lung, pancreas and reproductive tracts (15). Since its discovery in 1989, over 2000 different *CFTR* mutations have been identified, the most common of which is the F508del mutation, which accounts for approximately two thirds of all abnormal *CFTR* alleles (16). These mutations have a variety of effects on CFTR function, which have resulted in an ever-growing number of broad classes of mutations, and an even wider range of patient phenotypes (12,17). Adding to the diversity, the disease presents differently in the heterozygous and homozygous forms. When a mutant allele of the *CFTR* gene is passed down from both parents, the child can develop cystic fibrosis (CF), a debilitating multi-organ disease involving the lungs, pancreas, gastrointestinal, and reproductive system. Compound heterozygous individuals, who receive two different mutant alleles, typically present with an intermediate or variable phenotype (18). When only one allele containing a *CFTR* mutation is passed down from one parent, the child will be a CF carrier and may have mild or completely absent symptoms (12).

Nearly all (roughly 98%) of patients with symptomatic CF are noted to have CBAVD on physical exam (19,20). Though there are cases of CBAVD that are not associated with *CFTR* mutations, 80–97% of patients with CBAVD have identifiable mutations in the *CFTR* gene. Additionally, CBAVD is associated with hypoplastic seminal vesicles, seminal hypovolemia and acidic ejaculate (pH <7) (20). For these reasons, these patients historically had poor fertility outcomes.

With the marked increase in life expectancy in patients with CF disease and advances in assistive reproductive technology (ART) over the past 2 decades, there has been increased interest in fertility treatment in men with OA due to CF mutations and men diagnosed with CBAVD. Men in these categories who seek biological fertility must undergo surgical collection of sperm, as very few of these men have enough healthy/present tissue to make reconstruction of the

tract possible (21). Over the past two decades, the surgical options of sperm extraction have expanded and been refined to optimize reproductive outcomes (22). After successful sperm extraction, sperm can be used for fertilization of the oocyte using in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), or frozen for later use.

Despite the relatively rapid rise in sperm retrieval options, there is still a paucity of rigorous outcomes data evaluating the available surgical options for men with OA due to *CFTR* gene mutations. This review will distill down the diagnostic considerations, treatment options, and existing outcomes data for OA in men with CBAVD, empowering physicians to better counsel men with CBAVD about why their experience with sperm retrieval and pregnancy may differ from other men with OA.

Diagnostic considerations: OA, CF, and CBAVD

Infertile men are at risk for a wide range of genetic abnormalities, including but not limited to mutations in the *CFTR* gene, and as such, specific genetic tests should be based on the clinical context. Relevant to the current discussion, initial assessment of infertile men must attempt to differentiate between obstructive and non-obstructive causes using a combination of history, physical exam including a thorough scrotal and vasal exam, semen analysis and serum lab tests in order to look for potentially correctable hormonal abnormalities (23).

OA patients have normal testis volume and normal levels of FSH, indicating a functional hypothalamic-pituitary-gonadal axis. Men with CBAVD will have reduced ejaculate volume, typically less than 1 mL, due to their hypoplastic seminal vesicles (24). While men with OA have normal spermatogenesis, testicular biopsy is not necessary to make the empiric diagnosis of OA (25,26). Diagnostic biopsy should instead be considered when there is clinical uncertainty whether the patient has obstructive or non-OA or when the patient has risk factors for testicular germ cell tumors (family history, history of cryptorchidism, suggestive US characteristics) (27,28) In the setting of OA with low semen volume, *CFTR* genetic analysis is always warranted, even if the vasa are present, because reproductive tract abnormalities secondary to *CFTR* mutations are not limited to the vasa (29).

Upon physical exam, CBAVD patients may not only have absent vasa deferentia, but may also have absent epididymal segments or irregular or indurated epididymal tissue. However, the caput of the epididymis is of different

embryologic origin and is almost always present in men with CBAVD (30). In men with Congenital Unilateral Absence of the Vas Deferens (CUAVD), renal ultrasound is performed to rule out renal agenesis, because concomitant vasal abnormalities and renal agenesis is indicative of a broader mesonephric duct abnormality that is not secondary to *CFTR* mutations (31-33). Renal ultrasound should also be performed in men with CBAVD without identified *CFTR* mutations (28).

While a complete discussion of the *CFTR* mutation profile of CBAVD patients is beyond the scope of this review and is discussed in more depth in another article in this focused issue, a few key points are worth noting. As was stated earlier, men with clinical CF nearly always present with CBAVD, while anywhere from 78–97% of men with CBAVD are found to have at least one *CFTR* mutation (12). However, patients may present with two *CFTR* mutations but not have clinical features of CF aside from CBAVD. It is hypothesized that these phenotypic differences are related to alternative mRNA splicing in different tissues, and specifically inefficient splicing in the vas deferens that locally compromises *CFTR* function (34,35). When CBAVD is the only presenting feature in a patient with at least one *CFTR* mutations, the disease is sometimes referred to as the joint CF-CBAVD. These presentations are often characterized by higher frequencies of atypical *CFTR* gene variants, including the IVS8-5T polymorphism, the TG variant, and more frequent class IV and V *CFTR* mutations.

Treatment options

Many forms of OA, especially OA secondary to vasectomy, are amenable to microsurgical tract reconstruction. The technical aspects of these procedures are the focus of other reviews (36,37). However, cases of reconstructive failure and OA not amenable to reconstruction were often considered hopeless until the advent and widespread adoption of ART in the early 1990s. A number of procedures have been developed and refined that allow for extraction of sperm from the epididymis and testicles. These techniques include microscopic epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), testicular sperm extraction (TESE), and percutaneous testicular sperm aspiration (TESA). Of note, sperm obtained from chronically obstructed duct systems, or prior to complete maturation in the epididymis, tend to have poor motility,

and thus, retrieved sperm from CBAVD patients should be used for ICSI, and not intra-uterine injection or other IVF methods.

MESA

Epididymal sperm offers the advantage of longer transit and maturation time relative to testicular sperm. MESA in particular offers the advantage of sperm aspiration under direct vision of the epididymal tubules (38). Through a small scrotal incision, the testis is delivered, the tunica vaginalis is opened, and the epididymis is inspected under 16–25× magnifications using the operating microscope. The standard approach is to search for superficial dilated tubules, make small incisions to extract fluid, and check the fluid for sperm under a microscope. If no sperm are found, the process is repeated at a more proximal part of the epididymis (39). Of course, in cases of CBAVD when only the caput of the epididymis is present, the relatively limited real estate for extraction must be taken into account. Gentle compression of the testis and epididymis can enhance flow from the incised tubule. Sperm can then be cryopreserved in multiple aliquots so that several ICSI cycles can be attempted.

PESA

Though PESA is considered by some to be less reliable than open epididymal sperm retrieval, given that the small quantities of sperm are sometimes inadequate for cryopreservation, reported pregnancy rates in general are similar to those achieved with open techniques without requiring microsurgical skill (40). A recent surgical video highlighted the simplicity of this technique, which involves the use of a hypodermic needle attached to a 1 cc syringe, which is inserted through the skin into the corpus or caput of the epididymis and used to aspirate and then quickly analyze sperm content (41). The blind approach can necessitate multiple passes, increasing the risk for scrotal hematoma. Given the increased risk, and potential for lower quantity of sperm, epididymal sperm retrieval under direct vision is considered the preferred technique by many, especially in the context of the cost and effort that goes into IVF to begin with (42,43). That said, MESA entails the cost associated with the use of the surgical microscope as well as longer time under anesthesia, and thus, both procedures have pros and cons.

TESA and TESE

TESA or TESE are typically indicated when there is a failure to find sperm in the epididymis, or in some cases of CBAVD, when there is not enough viable epididymis present. TESA is the least invasive method, though it may require 10–20 passes using a high-suction glass syringe and a 23-gauge needle (44,45). TESA has the same technical advantages as PESA, in that no microsurgical skill is required, and only local anesthesia is used. The drawback of these techniques is that testicular sperm tends to be immature and immobile because of the lack of epididymal maturation. As with other blind procedures, the risk of hematoma, vascular injury, and post-procedure pain are increased with TESA.

TESE, and testicular biopsy in general, can be helpful for distinguishing OA from non-OA, though if OA is suspected, testicular biopsy is not required before sperm retrieval and ICSI are attempted (46). TESE, and microsurgical TESE (micro-TESE), offer the same advantage as MESA, in that extraction can be performed under direct vision. Open TESE, and micro-TESE in particular, allows retrieval of a large number of sperm for potential cryopreservation and the use for multiple cycles of ICSI.

The diversity of options has drastically changed both the management of and fertility-related outcomes in men with CBAVD. Given the phenotypic range in this population, and in particular, the range in length of viable epididymal tissue, TESE in combination with ICSI have maximized the options available those who provide infertility services to these couples. However, given the superior maturity of epididymal sperm, a comparison of outcomes, both in terms of sperm retrieval rates and also pregnancy-related outcomes, is warranted.

Sperm retrieval and pregnancy-related outcomes in the CF/CBAVD population

Unfortunately, very few studies were designed to look specifically at sperm retrieval outcomes in the CF/CBAVD population. Many of the studies to be presented do fortunately provide subset analyses that look specifically at men in the study with these conditions. However, very few speak specifically about the variation in CF mutations present, and many of the sample sizes were made quite small by the subset analyses. There are no randomized controlled trials that attempt to answer which method for sperm retrieval is superior, and the studies consist of mainly

retrospective analysis, case-control studies, and a few prospective studies. Additionally, because the goal is always adequate sperm retrieval and subsequent fertilization, implantation, and a successful pregnancy, many studies consider not only a primary technique of retrieval, but also a reflex secondary technique. These studies will be discussed under both relevant sub-sections. Sperm retrieval rates and outcomes are presented in *Table 1*. ICSI/pregnancy outcomes are presented in *Table 2*.

MESA

A group led by Schroeder-Printzen *et al.* was one of the earliest to publish robust sperm retrieval data for men with non-reconstructable OA, a group that likely included men with CBAVD, though the paper did not specify (47). Of the 93 men in the cohort that underwent MESA, sperm were retrieved from 88 of them, a retrieval rate of 94.6%. Mean sperm concentration was $40.9 \times 10^6/\text{mL}$, and global motility rate was on average 24.8%. This group also achieved a pregnancy rate of 42.4% after 33 ICSI cycles with frozen sperm.

Silber and colleagues were the first to publish more specifically on the use of MESA for CBAVD, and also on the outcomes of ICSI in men with CBAVD (55,59,60). Given that these reports were made during the early days of ICSI, the initial reports focused on a comparison between MESA followed by IVF and MESA followed by IVF/ICSI, but the IVF/ICSI data will be highlighted. The group first published a series of 72 consecutive MESA followed by IVF/ICSI cases (55,59). ICSI resulted in fertilization and embryo transfer in 90% of cases, leading to an ongoing or delivered pregnancy rate of 46% per transfer and 42% per cycle. Notably, the pregnancy and live-birth baby rates were 53% and 42% respectively with ICSI. Similarly, Hubert *et al.* looked at 23 men with CF who chose to proceed with sperm retrieval and IVF/ICSI and found a similar pregnancy rate per cycle (40%), clinical pregnancy rate (63%) and live-birth rate (47%), concluding that this technique can be an effective option in men with CBAVD (48).

McCallum and colleagues conducted a retrospective analysis looking at MESA outcomes specifically in men with the F508del *CFTR* mutation (50). Of the nine men, eight underwent MESA, five couples went on to achieve a pregnancy, and four couples delivered seven kids. This equated to a fertilization rate of 75% and a life birth rate per cycle of 43.75%. Interestingly, the author's key take away was that physicians involved in the reproductive care

Table 1 Sperm retrieval outcomes

Study	Number of procedures	CBAVD only?	Sperm Retrieval rate, %	Amount of sperm (per mL)	% Motile	% Cryo ^a
MESA						
Schroeder-Printzen 2000 (47)	93	NO	94.60	40.9×10 ⁶	24.80	N/A
Hubert 2006 (48)	23	YES	82.60	N/A	N/A	N/A
Buffat 2006 (49)	83	YES	N/A	N/A	N/A	N/A
Mccallum 2000 (50)	8	YES	100	36.3×10 ⁶	N/A	N/A
Yamamoto 1997	32	YES	100	25.1×10 ⁶	34.50	N/A
Llabador 2015 (51)	47	YES	43.5	N/A	N/A	N/A
Janzen 2000 (42)	141	NO	100.0	N/A	100	23.40
PESA						
Glina 2003 (52)	65	NO	82	N/A	N/A	43
Kovac 2014 (53)	51	NO	100	N/A	N/A	21.60
Esteves 2015 (41)	32	YES	98.60	N/A	N/A	21.90
Semião-Francisco 2010 (54)	171	NO	100	N/A	93.60	N/A
TESE						
Llabador 2015 (51)	61	YES	100	N/A	N/A	N/A
TESA						
Semião-Francisco 2010 (54)	103	NO	100	N/A	58.90	N/A
Glina <i>et al.</i> 2003 (52)	14	NO	100	N/A	N/A	N/A

^a, % of men with retrieved sperm who proceeded with cryopreservation. ICSI, intracytoplasmic sperm injection; CBAVD, congenital bilateral absence of the vas deferens; MESA, microscopic epididymal sperm aspiration; PESA, percutaneous epididymal sperm aspiration; TESE, testicular sperm extraction; TESA, testicular sperm aspiration.

of CF patients should be optimistic about the prospects of fatherhood, which they considered “excellent” given the current state of the technology even in 2000.

Finally, Llabador and colleagues looked at both MESA and TESE used to retrieve sperm from men with CBAVD (51). The sperm retrieval rate for MESA alone was 43.5%. They did find an overall fertilization rate of 67.1%, an implantation rate of 15.3%, and clinical pregnancy and birth rates of 26.5% and 22%, respectively. It is interesting to note that these authors found differences in spermatogenesis quality within this cohort of men with CBAVD, and that poor quality predicted poor fertility outcomes. This variation may also contribute to the low sperm retrieval rates, but it is unclear why this cohort differed from the cohorts in other studies.

Given these results, MESA appears to be a viable option for men with CBAVD seeking infertility treatment and

sperm extraction, despite concern about variable quality epididymal tissue. Though sperm retrieval outcomes were insufficiently reported in many cases, most groups were able to retrieve sperm in roughly 80–100% of men. IVF/ICSI is a viable option for couples where the man has CBAVD, with fertilization rates between 60% and 75%, and live birth rates per cycle between 18% and 45%. Standard reporting of fertility and pregnancy outcomes would have aided the analysis, as would prospective study designs.

PESA

Though MESA is still considered the gold standard for epididymal sperm retrieval, a number of studies have assessed the viability of PESA as a less invasive alternative for sperm retrieval in CBAVD patients. Lu and colleagues completed a single center retrospective analysis of 945

Table 2 ICSI/pregnancy outcomes

Study	ICSI cycles	CBAVD only?	Fertilization rate, %	Implantation rate, %	Pregnancy/cycle, %	Birth/cycle, %	Miscarriage/cycle, %
MESA							
Silber 1995 (55)	72	YES	90	N/A	N/A	N/A	N/A
Hubert 2006 (48)	40	YES	61	N/A	40	27.50	10
Buffat 2006 (49)	125	YES	58.90	N/A	22.10	N/A	13
McCallum 2000 (50)	16	YES	75	N/A	N/A	43.75	20
Yamamoto 1997	N/A	YES	78.1	N/A	37.5 ^a	N/A	N/A
Llabador 2015 (51)	200	YES	67.10	15.30	26.50	22	15.10
van Wely 2015 (39)	280	NO	N/A	22.00	47.00	39	8.00
PESA							
Lu 2014 (56)	531	YES	70.00	40.20	49.70	35	23.90
Meniru 1997 (57)	140	YES	53	19	14.30	7.90	10
Esteves 2013 (58)	32	YES	61	N/A	55.20	34.40	25
Kamal 2010 (25)	331	YES	62.20	20.80	42.30	N/A	19.20
Kovac 2014 (53)	434	NO	76.50	N/A	45.10	N/A	N/A
Semião-Francisco 2010 (54)	171	NO	22.10	10.50	32.50	N/A	18.00
Glina 2003 (52)	587	NO	67	N/A	38	N/A	N/A
TESE							
Llabador 2015 (51)	70	YES	65.20	11.80	24.30	17.10	23.50
Buffat 2006 (49)	41	YES	51.90	N/A	24.30	N/A	35.70
van Wely 2015 (36)	94	NO	N/A	15	30	24	6.00
TESA							
Kamal 2010 (25)	790	YES	68	19.93	43.20	N/A	22.20
Semião-Francisco 2010 (54)	103	NO	57.90	9.40	31.90	N/A	31.80
Glina 2003 (52)	153	NO	61	N/A	16	N/A	N/A

^a, pregnancy rate per couple was the only statistic reported. ICSI, intracytoplasmic sperm injection; CBAVD, congenital bilateral absence of the vas deferens; MESA, microscopic epididymal sperm aspiration; PESA, percutaneous epididymal sperm aspiration; TESE, testicular sperm extraction; TESA, testicular sperm aspiration.

patients and 1,414 ICSI cycles, with the goal of comparing ICSI outcomes in men with CBAVD and men with acquired OA. The group found significantly lower rates of live birth per embryo transferred, and significantly higher rates of miscarriage and ectopic pregnancy per embryo transferred in the CBAVD group (56). The authors hypothesized that the higher rates of *CFTR* mutations in the CBAVD group may have explained the increased rates of miscarriage and stillbirth. In this group of Chinese men, only 13% of men with CBAVD had *CFTR* mutations compared to Western

studies which demonstrate approximately 78% to 97% of CBAVD patients harbor at least one *CFTR* mutation (19,61). The authors suggest that the prevalence and/or type of *CFTR* mutation may have a clinical impact on fertility outcomes.

In an older, smaller retrospective review, Meniru and colleagues compared men with CBAVD to men with failed vasectomy reversal using PESA and that the pregnancy rates between the groups did not significantly differ (14.3% for the CBAVD group *vs.* 12.1% for the non-CBAVD

group) sperm (57). Similarly, Esteves *et al.* retrospectively compared PESA outcomes based on the cause of OA in 146 men in a single center, and found a 96.8% sperm retrieval rate with PESA alone in CBAVD patients, while only 3.2% of men with CBAVD required rescue TESA after PESA (58). The group achieved clinical pregnancy in 16 men (55.2%) of the CBAVD group, resulting in 11 live births, one still birth, and 4 miscarriages.

An additional study by Kamal and colleagues sought to assess whether the cause of OA affected ICSI outcomes, using both PESA and TESA depending on the situation. TESA outcomes will be discussed later. PESA resulted in 331 ICSI cycles in men with CBAVD, resulting in a fertilization rate of 62.2%, an implantation rate of 20.8%, a rate of clinical pregnancy of 42.3%, yet a rate of miscarriage of 19.2%. These numbers were similar to a study by Glina and colleagues, which examined the results of 587 ICSI cycles and found a 67% fertilization rate and a 38% clinical pregnancy rate per implantation cycle. However, this study was not limited to CBAVD causes of OA (52).

Thus, though MESA is still considered by many to be the gold standard for sperm retrieval, PESA is an additional viable option for sperm retrieval. The studies did not speak to complication rate, and rarely mentioned the challenge of completing PESA in men with less substantial epididymal tissue, and so again, standardizing outcomes and discussing sperm retrieval characteristics relative to the specific nature of the CBAVD anatomy would aid in the development of a more robust comparative framework for the two procedures. In addition, only one group attempted to compare outcomes of fresh *vs.* frozen sperm, another possible useful line of inquiry that has yet to be adequately studied in the literature (53). The last challenge in making a definitive statement is that many of the comparative studies on this subject focus on epididymal *vs.* testicular sperm, but few if any focus on different retrieval methods for sperm from the same location. Given the aforementioned differences in procedure morbidity and invasiveness, these procedures warrant further comparison. In terms of available data, retrieval rates with PESA do not seem substantially inferior to those with MESA, though there appears to be greater variability in fertilization rates with PESA. Though the studies are weak, clinical pregnancy rates and life birth rates also do not appear to differ between PESA and MESA.

TESE

Few studies have reported CBAVD-specific TESE outcomes,

though it is important to note that there is data going back as far as 1995 that testicular sperm can be as effective as epididymal sperm when combined with ICSI (55). Llabador *et al.* looked at MESA and TESE, because in 43.5% of cases, MESA was followed by TESE in the same surgical session because no sperm were found in the epididymis (51). Sperm was retrieved in all 61 men who had reflex TESE performed. The group found a non-significant difference in the delivery rate (27% with MESA and 18.6% with TESE), and also a non-significant difference in miscarriage rate (15.1% with MESA and 23.5% with TESE), though there was a trend pointing to the superiority of MESA. Of note, most clinical pregnancies required no more than two ICSI cycles, despite the relative immaturity of testicular sperm.

Buffat *et al.* compared outcomes using epididymal and testicular extraction methods, and found that fertilization and clinical pregnancy rates did not differ between the two. The group found that the miscarriage rate was statistically significantly higher in the TESE group than in the MESA group (37.5% in the TESE group *vs.* the 12.5% in the MESA group). Given the increased miscarriage rate, the group concluded that testicular sperm lacked some characteristic required to ensure a viable pregnancy, and that epididymal sperm should be used when available (49).

Though lacking CBAVD stratification, a useful comparison between MESA and TESE was conducted by van Wely *et al.* (39). The analysis included 374 total ICSI cycles and found MESA had a superior live birth rate (39% from MESA *vs.* 24% for TESE), and that MESA had an adjusted multivariable logistic analysis OR of 1.82 (95% CI: 1.05–3.67) for on-going pregnancy compared to micro-TESE. Despite this large sample size, and a clear distinction in the text about CBAVD patients, no sub-analysis was carried out, making a direct assessment of CBAVD/CF outcomes difficult.

The paucity of data in men with OA and then specifically CBAVD-OA makes drawing conclusions about the use of TESE for CBAVD patients difficult. Some data suggests slightly lower fertilization rates, lower clinical pregnancy rates, and higher rates of miscarriage with testicular sperm compared to epididymal sperm. However, these results are based on limited comparative data and more rigorously designed comparative studies are warranted and necessary.

TESA

CBAVD specific TESA outcomes are rarely reported in

the literature. Kamal *et al.* performed TESA followed by 221 cycles of ICSI using sperm from men with CBAVD, and found a fertilization rate of 68.2%, an implantation rate of 21.56%, a clinical pregnancy rate of 46.2%, but a miscarriage rate of 22.2%. Semião-Francisco and colleagues conducted a retrospective analysis that did not stratify based on CBAVD, but included 103 total ICSI cycles and found a sperm retrieval rate of 100% (54). Unfortunately, pregnancy outcomes were not stratified by CBAVD. However, in the same study, the group compared TESA to PESA, and found that, though the fertilization rate was greater for PESA, when retrieved sperm were used for ICSI, there was no difference in clinical pregnancy and implantation rates. Glina and colleagues also conducted a retrospective analysis of men with OA, however they reported that the most common cause was vasectomy, and did not specify the causes in other cases. Motile sperm were only found in 65 of 79 PESA procedures, and the remaining 14 men had to undergo salvage TESA (52). Thus, CF/CBAVD outcomes specific to TESA are rare, but the literature may suggest, based on miscarriage rate alone, that epididymal sperm is superior when available in patients with OA.

As a final point about all four procedures, though sperm retrieval outcomes are presented in *Table 1*, retrieval rates and outcomes in this population are severely lacking in the literature. Even papers about the efficacy and feasibility of the procedure failed to report standard sperm parameters, including amount of sperm and motility, in many cases. Additionally, though there are papers comparing fresh and frozen sperm from these various procedures in other populations, and also CBAVD, few papers reported the rates at which couples decided to cryopreserve sperm, or the rates at which sufficient tissue was obtained for cryopreservation, severely limiting the interpretation and comparison of sperm retrieval rates between the different techniques in the CBAVD population (53).

Discussion and future directions

Despite rapid and robust developments in the genetic characterization of CBAVD, there is a dearth of specific fertility outcomes on this sub-set of men. From the limited data, it appears as though the literature demonstrates that all sperm retrieval modalities are reasonable options for men presenting with CBAVD, given that groups have had success with all techniques. Men should be counseled that testicular sperm may have slightly lower rates of pregnancy compared to epididymal sperm, keeping in mind that the amount of

viable epididymal tissue differs within this cohort of men.

To illustrate the gaps in the literature, a number of additional studies warrant discussion despite their lack of a CBAVD focus. A study by Naru *et al.* compared PESA and TESE, but failed to mention CBAVD despite the fact that a proportion of men in any cohort of OA would be expected to have CBAVD (62). Bernie and colleagues presented the pros and cons of MESA in the context of other OA and non-OA treatment modalities. The article included a pertinent review of technique modification, such as changing the gauge of the needle used for TESA (small needle, large needle, and core needle), and provided a more granular review of TESE *vs.* micro-TESE (45,63–65). Though this paper's useful summary presented sperm retrieval rates between 95 and 100%, as well as sperm yields for each technique, it did not stratify by origin of OA or between non-OA and OA. In addition, a 2008 meta-analysis on the topic, which did not find a significant difference in efficacy between testicular and epididymal retrieval techniques, did not stratify by origin of OA, and noted above all the lack of high quality comparative, randomized, and controlled data on the topic (66). Thus, given the general clinical equipoise up to this point, future studies in this cohort should seek to prospectively enroll men with CBAVD to not only directly compare testicular and epididymal techniques, but also compare the different methods of extraction at each site. The studies must publish robust reproductive outcomes, including quantity of sperm retrieved, number of ICSI cycles, and granular pregnancy outcomes, so that providers have access to a more nuanced set of outcomes data when counseling their patients.

In addition, an early meta-analysis raised the important question as to why, independent of method of sperm retrieval, CBAVD patient may have reduced fertility relative to other patients with OA. The leading theory is that a subset of CBAVD patients may have a degree of diminished spermatogenesis, resulting in decreased sperm quality, regardless of sperm retrieval modality (67,68). Previous literature has elucidated the role of the *CFTR* gene in various aspects of spermatogenesis. Men with CBAVD who underwent ICSI were more likely to have miscarriage or still birth and less likely to have a live birth, indicating that *CFTR* mutation is potentially associated with sperm function (56). Higher rates of *CFTR* mutations have been found in men with poor semen quality (56,67,69,70). At least 5 different *CFTR* mutations have been linked with non-OA or oligozoospermia (68). While the underlying mechanism is not fully understood, the *CFTR* gene is thought to be a key regulator in maintaining the luminal microenvironment of

the male reproductive tract, which in turn has an impact on spermatogenesis and sperm maturation (68,71).

A related issue, brought into focus by the conflicting results from the study by Lu and colleagues, is that many of these studies were done at a time where the panel of *CFTR* mutations that was regularly tested was not nearly as expansive as it is now. This issue, as well as regional and ethnic differences in mutational frequency and incomplete characterization of CBAVD as a systematic disease entity, limits the conclusions that can be drawn about mutational variants and their effect on reproductive outcomes. In addition, discussions of fertility management in patients with *CFTR* mutations will continue to make their way into the greater reproductive ethics and ethics of assisted reproductive technologies discussion, as people wrestle with the fact that individuals with an increasingly wide range of phenotypic presentations of CF, who were once considered infertile, can now be rendered fertile through the help of these ever expanding technologies. This discussion will invariably include whether or not the female partners of these men should undergo *CFTR* mutation analysis. This may be even more important in men with CBAVD and no identified common *CFTR* mutations, given that they may have *CFTR* mutations that are less commonly tested for.

Conclusions

As assisted reproductive technologies continue to develop for both men and women, the reproductive prospect for patient with CF/CBAVD has shifted dramatically, from that of a state of complete infertility, to the current state of the field, where OA can be managed with a spectrum of interventions. As these techniques continue to be employed, additional rigorous retrospective analyses, as well as prospective comparative trials, will be necessary to determine whether there is an ultimately superior technique that should be offered to men with CBAVD. Though current data point toward the use of epididymal sperm, testicular sperm still provides a viable option for reproduction, and the possibility of pregnancy loss should be discussed, regardless of the source of sperm. The future continues to look bright for these men, though there is still much to be learned about the ever-increasing number of *CFTR* mutations and their impact on male fertility.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Keith Jarvi and Jared Bieniek) for the series “Genetic Causes and Management of Male Infertility” published in *Translational Andrology and Urology*. The article was sent for external peer review organized by the Guest Editors and the editorial office.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau-19-681>). The series “Genetic Causes and Management of Male Infertility” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Persily JB, Vijay V, Najari BB. How do we counsel men with obstructive azoospermia due to CF mutations?—a review of treatment options and outcomes. *Transl Androl Urol* 2021;10(3):1467-1478. doi: 10.21037/tau-19-681