Original Article

Factors associated with undergoing microdissection testicular sperm extraction among men with non-obstructive azoospermia following evaluation by a reproductive urologist

Daniel R. Greenberg[1#], Alexander V. Stanisic[2#], Minh N. Pham[1], Matthew T. Hudnall[1], Siddhant S. Ambulkar[2], Robert E. Brannigan[1], Richard J. Fantus[3], Joshua A. Halpern[1]

[1]Northwestern University Feinberg School of Medicine, Department of Urology, Chicago, IL, USA; [2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]The University of Kansas Hospital, Department of Urology, Overland Park, KS, USA

Contributions: (I) Conception and design: DR Greenberg, AV Stanisic, JA Halpern; (II) Administrative support: RE Brannigan, RJ Fantus, JA Halpern; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: DR Greenberg, AV Stanisic, MN Pham, MT Hudnall, SS Ambulkar; (V) Data analysis and interpretation: DR Greenberg, AV Stanisic, JA Halpern; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as the co-first authors.

Correspondence to: Alexander V. Stanisic, BS. Northwestern University Feinberg School of Medicine, 420 E Superior St, Chicago, IL 60611, USA. Email: alexander.stanisic@northwestern.edu.

Background: Microdissection testicular sperm extraction (mTESE) is the gold standard treatment for men with non-obstructive azoospermia (NOA). However, many men do not elect to pursue this surgical intervention. We aimed to identify factors associated with NOA patients undergoing mTESE after initial evaluation by a reproductive urologist (RU) through a retrospective cohort study.

Methods: We retrospectively reviewed NOA patient who underwent evaluation by a RU between 2002-2018. Demographic and clinical data were collected. Our primary outcome was electing to undergo mTESE.

Results: 44.4% (75/169) of NOA men underwent mTESE. These patients earned significantly higher median neighborhood income ($133,000 *vs.* $97,000, P<0.001), spent fewer years trying to conceive before seeking care {1.3 [interquartile range (IQR): 1–3] *vs.* 2.3 (IQR: 1–5), P=0.012}, and were more likely to be married (79.7% *vs.* 53.9%, P=0.001). On univariate analysis, married men [odds ratio (OR) 3.37, 95% confidence interval (CI): 1.67–6.79, P=0.001] and men with higher neighborhood income (OR 1.14, 95% CI: 1.06–1.21, P<0.001) were more likely to undergo mTESE, while couples attempting to conceive for a longer period of time prior to initial evaluation were less likely to undergo mTESE (OR 0.79, 95% CI: 0.68–0.92, P=0.003). On multivariable regression analysis, marital status and years attempting to conceive remained significantly associated with NOA patients undergoing mTESE (OR 4.61, 95% CI: 1.16–18.25, P=0.03; OR 0.67, 95% CI: 0.52–0.88, P=0.003, respectively).

Conclusions: Higher neighborhood income and marital status were positively associated with patients undergoing mTESE, while couples who attempted to conceive for a longer period of time before seeking infertility care were less likely to undergo mTESE.

Keywords: Male infertility; azoospermia; microdissection testicular sperm extraction (mTESE)

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Introduction

Infertility, defined as 1 year of appropriately timed unprotected intercourse without conception, is a common medical condition that affects between 8–12% of reproductive-aged couples (1,2). Men are implicated as the sole reason for the inability to conceive in approximately 20–30% of cases (3). Within the United States, 5–15% of men evaluated for infertility are azoospermic and 60% of these men are diagnosed with non-obstructive azoospermia (NOA). NOA results from impaired spermatogenesis due to either inadequate gonadotropin production or intrinsic testicular failure. Among men without sperm in the ejaculate, NOA is distinguished by testicular size and serum follicle-stimulating hormone (FSH) (4,5). Unless there is an identifiable reversible cause of azoospermia such as hypogonadism, treatment for NOA requires surgical intervention for sperm retrieval to facilitate in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) if couples desire biological children (6).

Microdissection testicular sperm extraction (mTESE) was first described by Schlegel *et al.* in 1999 and is now considered the gold standard treatment for men with NOA (7,8). This procedure allows for successful sperm retrieval in approximately 50% of men and is associated with lower rates of vascular injury, fibrosis, loss of testicular volume, and acute and chronic testicular injury compared to conventional testicular sperm extraction (TESE) and fine needle aspiration (FNA) (9-11). However, mTESE is a highly specialized and resource-intense procedure requiring uniquely trained surgeons and laboratory personnel, which can also be associated with high costs.

Despite the proven efficacy of mTESE, there is a paucity of data examining barriers in access to mTESE for men with NOA. Health insurance coverage, education level, marital status, household income, and the availability of a specialty-trained reproductive urologist (RU) have been previously shown to impact the medical treatment and management of male infertility. However, there are no studies examining access to definitive surgical care for NOA. We sought to identify demographic and clinical factors associated with undergoing mTESE among men with NOA after evaluation by a RU. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-76/rc).

Highlight box

Key findings

- Higher neighborhood income and marital status were positively associated undergoing microdissection testicular sperm extraction (mTESE) for non-obstructive azoospermia (NOA) while couples who attempted to conceive for a longer period of time before seeking infertility care were less likely to undergo mTESE.

What is known and what is new?

- mTESE is the gold standard treatment for men with NOA, but not all patients pursue this option even after evaluation by a reproductive urologist.
- Our findings highlight patient clinical and demographics factors associated with undergoing mTESE among men with NOA.

What is the implication, and what should change now?

- This study helps to understand the patient population of men with NOA who pursue surgical treatment for infertility.

Methods

Study design and patient population

We queried the Northwestern Medicine electronic database to identify adult men (≥18 years of age) who underwent semen analysis (SA) for fertility evaluation within our academic health system. We subsequently performed a retrospective review of men evaluated for NOA who were evaluated by a fellowship-trained RU between 2002–2018. Out of 669 azoospermic patients who underwent fertility evaluation during the study period, 169 met diagnostic criteria of NOA. Only patients that had all variables present were included in the final analysis. To meet the clinical definition of NOA, patients required two SAs demonstrating azoospermia, bilateral testicular volume <15 cc based on clinical exam by RU at time of initial evaluation, and index FSH >7.6 mIU/mL (4,12). Index SA and laboratory values were obtained by either a referring provider or upon initial evaluation by a RU. At our institution, mTESE is offered to all men who meet the clinical definition of NOA, and extensive counseling regarding the procedure, expected recovery, chance of successful sperm retrieval, and expected cost, is provided to the patient in detail. We used a large, retrospective database to prevent limitations and bias from sample size. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was reviewed and exempted from requiring approval by the Institutional Review Board (IRB) at Northwestern University Feinberg School of Medicine. Individual consent for this retrospective analysis was waived.

Study variables

Demographics including age at index semen analysis, race and ethnicity, body mass index (BMI), median income, geographic distance traveled from home to the RU clinic, marital status, age of partner, and type of insurance (private, public, or self-pay/other), were collected at the time of initial evaluation. Income was defined according to the median income reported by zip code of the patient's residential address defined by the 2018 United States Census Bureau American Family Survey. Geographic distance to RU clinic was measure in kilometers and was obtained by determining the distance from the center of a patient's zip code to the RU clinic using ArcGIS 10.6 (Redlands, CA, USA). The RU clinic is a subdivision within the Department of Urology at our academic institution. Clinical data including FSH, luteinizing hormone (LH), testosterone (T), testicular volume, history of sexual dysfunction, testosterone use, and prior genitourinary surgery were also analyzed. Prior pregnancies by either partner and time spent trying to conceive prior to initial evaluation by a RU were included.

Outcome measures and covariates

The primary outcome for the retrospective analysis was undergoing mTESE following evaluation and diagnosis of NOA. Covariates for multivariable analysis were chosen either *a priori* (as previously identified factors shown to be barriers to care in infertility treatment) or following significance on univariate analyses. These included patient age at index SA, race, insurance status, marital status, years spent trying to conceive, prior partner pregnancies, distance to RU, and median income.

Statistical analysis

Data were analyzed using Stata v15.1 (StataCorp. 2020. College Station, TX, USA) statistical software. Categorical variables are presented as n (%) and were analyzed using Fisher's exact test or χ^2 as appropriate. When normally distributed, continuous variables are presented as mean ± standard deviation and were analyzed using the Student's *t*-test. Nonparametric data was presented as median [interquartile range (IQR)] and were analyzed using the Mann Whitney U (Wilcoxon rank sum) test. Univariate and multivariable logistic regression was used to determine the association of demographic and clinical factors associated with our primary outcome. All tests of significance were two-sided, and a P value of <0.05 was deemed statistically significant.

Results

In total, 169 men met clinical diagnostic criteria for NOA, 75 (44.4%) of whom underwent mTESE during the study period. Demographic and clinical data are shown in *Table 1*. The average age of all NOA patients at time of index semen analysis was 34.2±8.1 years with no difference between mTESE and non-mTESE patients [33.0 (IQR: 29.0–36.0) *vs.* 34.0 (IQR: 29.0–40.0), P=0.40]. Seventy-seven (45.6%) of the NOA men were white, and the significant majority had private insurance (75.7%). Patients who underwent mTESE earned significantly higher neighborhood median income ($133,000 *vs.* $97,000, P<0.001), spent fewer years trying to conceive before seeking infertility treatment [1.3 years (IQR: 1.0–3.0) *vs.* 2.3 years (IQR: 1.0–5.0), P=0.012], and were more likely to be married at the time of initial evaluation (79.7% *vs.* 53.9%, P=0.001).

On univariate logistic regression analysis, being married was associated with a significantly higher likelihood of undergoing mTESE compared to single and non-married men [odds ratio (OR) 3.37, 95% confidence interval (CI): 1.67–6.79, P=0.001]. Men with higher neighborhood income were also more likely to undergo mTESE (OR 1.14, 95% CI: 1.06–1.21, P<0.001) (*Table 2*). However, couples attempting to conceive for a longer period of time were less likely to undergo mTESE (OR 0.79, 95% CI: 0.68–0.92, P=0.003). On multivariable regression analysis, marital status and years attempting to conceive remained significantly associated with NOA patients undergoing mTESE (OR 4.61, 95% CI: 1.16–18.25, P=0.03; OR 0.67, 95% CI: 0.52–0.88, P=0.003, respectively) (*Table 3*).

We performed sensitivity analysis defining NOA exclusively according to elevated FSH (>7.6 mIU/mL) regardless of testicular size (n=322). On multivariable analysis, years spent trying to conceive (OR 0.76, 95% CI: 0.63–0.91, P=0.002) and higher median income (OR 1.11, 95% CI: 1.03–1.20, P=0.009) remained significantly associated with undergoing mTESE for men with NOA (*Table 4*).

Discussion

This is the first study to investigate factors associated with receipt of definitive treatment (mTESE) in men with NOA,

Table 1 Demographic and clinical characteristics of men with NOA who did and did not undergo mTESE

Characteristics	No mTESE (n=94)	mTESE (n=75)	P value
Demographic characteristics			
Age (years)	34.0 (29.0–40.0)	33.0 (29.0–36.0)	0.40
BMI	26.5 (23.7–32.1)	26.5 (23.7–30.1)	0.99
Race/ethnicity			0.08
White	37 (39.4)	40 (53.3)	
Black	9 (9.6)	6 (8.0)	
Asian	6 (6.4)	3 (4.0)	
Declined/unknown	28 (29.8)	10 (13.3)	
Other	14 (14.9)	16 (21.3)	
Marital status			0.001
Married	49 (53.9)	59 (79.7)	
Non-married/unknown	42 (46.1)	15 (20.3)	
Partner age (years)	33.0 (30.0–36.5)	32.0 (28.0–35.0)	0.25
Insurance status			0.29
Private	67 (71.3)	61 (81.3)	
Public	3 (4.2)	1 (1.6)	
Self-pay/other	1 (1.4)	2 (3.1)	
Unknown	23 (24.5)	11 (14.7)	
Distance to RU clinic (km)	21.3 (10.4–41.3)	19.4 (3.3–38.0)	0.19
Income (median per zip Code, $10k)	9.7 (7.1–13.3)	13.3 (8.8–18.4)	<0.001
Clinical data			
FSH (mIU/mL)	23.3 (15.1–32.9)	26.3 (18.2–35.1)	0.18
Testicular size (mL)	9.0 (5.0–12.0)	8.0 (4.5–10.0)	0.43
Right	9.5 (5.0–12.0)	8.0 (5.0–10.0)	0.59
Left	8.0 (4.0–12.0)	8.0 (4.0–10.0)	0.40
Semen volume (mL)	2.6 (1.4–3.2)	2.6 (1.6–4.4)	0.10
Erectile dysfunction	21 (22.3)	9 (12.0)	0.11
Ejaculatory issues	10 (10.6)	5 (6.7)	0.43
Testosterone use			0.06
Current	7 (7.5)	0 (0.0)	
Prior	3 (3.2)	4 (5.3)	
None	24 (25.5)	25 (33.3)	
Unknown	60 (63.8)	46 (61.3)	
Prior genitourinary surgery			
Orchidopexy	8 (8.5)	3 (4.0)	0.35
Varicocelectomy	1 (1.1)	1 (1.3)	0.99
Family history of infertility	4 (4.9)	9 (12.9)	0.09
Previous pregnancy by male partner	11 (12.0)	4 (5.5)	0.18
Previous pregnancy by female partner	15 (20.3)	6 (9.1)	0.10
Time trying to conceive (years)	2.3 (1.0–5.0)	1.3 (1.0–3.0)	0.012

Categorial data presented as n (%) and continuous data presented as median (IQR). NOA, non-obstructive azoospermia; mTESE, microdissection testicular sperm extraction; BMI, body mass index; RU, reproductive urologist; FSH, follicle stimulating hormone; IQR, interquartile range.

Table 2 Univariate logistic regression analysis of demographic and clinical characteristics associated with undergoing mTESE

Characteristics	mTESE OR (95% CI)	P value
Age of male at initial SA (years)	0.98 (0.95–1.02)	0.35
Race		
White	Ref.	–
Black	0.62 (0.20–1.90)	0.40
Asian	0.46 (0.11–1.98)	0.30
Other	1.06 (0.45–2.46)	0.90
Insurance status		
Private	Ref.	–
Public	0.37 (0.04–3.61)	0.39
Self-pay/other	2.20 (0.19–24.84)	0.55
Marital status		
Non-married/unknown	Ref.	–
Married	3.37 (1.67–6.79)	0.001
Time trying to conceive (years)	0.79 (0.68–0.92)	0.003
Previous pregnancy by male partner	0.42 (0.13–1.40)	0.16
Previous pregnancy by female partner	0.39 (0.14–1.08)	0.07
Distance to RU clinic (km)	1.00 (0.99–1.01)	0.51
Income (median per zip code, $10k)	1.14 (1.06–1.21)	<0.001

mTESE, microdissection testicular sperm extraction; SA, semen analysis; RU, reproductive urologist; OR, odds ratio; CI, confidence interval; Ref., reference.

specifically after evaluation by a RU. We chose to examine this particular clinical scenario because it is one of the few male infertility conditions with a "gold standard" treatment, as noted in the most recent joint guidelines from the American Society of Reproductive Medicine and American Urological Association, and where initial access to care (i.e., consultation with a RU) has already been obtained (8). As such, factors negatively associated with mTESE in the current study can be considered specific barriers to access for mTESE but may also represent important barriers to care for a broader range of male infertility conditions and treatments. We found that married men with higher median neighborhood income were more likely to undergo mTESE, whereas couples attempting to conceive for a longer period prior to initial evaluation by a RU were less likely to undergo mTESE.

Our findings reflect the financial burden associated with Assisted Reproductive Technology. In our study, the median neighborhood income among men undergoing mTESE was approximately $30,000 more than men who did not undergo surgical intervention. Our result is even more revealing given that the median neighborhood income among all men in our cohort was approximately $50,000 more than the median household income in the United States in 2018 (13). Moreover, 95% of the men in our cohort utilized private insurance, suggesting that referral and evaluation to a specialist for male factor infertility is less accessible to uninsured patients or those with public insurance. Surgical treatment for azoospermia can range from $500 for testicular biopsies to more than $5,000 in out-of-pocket expenses for mTESE. IVF and ICSI, both necessary in the context of surgical sperm retrieval, are expensive therapies with an average cost per cycle accounting for 50% of a couple's annual disposable income (14). When combined with reported live birth rates of approximately 50% per intended egg retrieval cycle, couples may require multiple cycles to achieve pregnancy, ultimately rendering the cumulative process cost-prohibitive (15). Recent studies

Table 3 Multivariable logistic regression analysis of demographic information and clinical characteristics associated with undergoing mTESE

Characteristics	mTESE OR (95% CI)	P value
Age of male at initial SA (years)	0.90 (0.81–1.01)	0.07
Race		
White	Ref.	–
Black	0.71 (0.09–5.52)	0.75
Asian	0.29 (0.03–2.55)	0.27
Other	4.49 (0.09–1.64)	0.20
Insurance status		
Private	Ref.	–
Public	–	–
Self-pay/other	1.30 (0.01–235.67)	0.92
Marital status		
Non-married/unknown	Ref.	–
Married	4.61 (1.16–18.25)	0.03
Time trying to conceive (years)	0.67 (0.52–0.88)	0.003
Previous pregnancy by male partner	0.34 (0.06–1.97)	0.23
Previous pregnancy by female partner	3.46 (0.39–30.70)	0.27
Distance to RU clinic (km)	1.09 (0.94–1.00)	0.04
Income (median per zip code, $10k)	1.09 (0.96–1.22)	0.18

mTESE, microdissection testicular sperm extraction; SA, semen analysis; RU, reproductive urologist; OR, odds ratio; CI, confidence interval; Ref., reference.

show that this financial burden is even greater in low- and middle-income countries (16). The current study reinforces prior literature demonstrating significant financial barriers to definitive fertility treatment (17).

We found that time spent attempting to conceive, and not age of either partner, was a strong predictive factor associated with undergoing mTESE. Longer time spent trying to conceive could result from inadequate referral patterns from primary care providers or other healthcare providers, delaying access to care for male partners. Eisenberg *et al.* showed that female partners are more likely to undergo infertility evaluation in couples encountering difficulty with conception, whereas 18–27% of males with self-reported infertility do not undergo male evaluation as part of the couple's initial infertility assessment (18). Alternatively, time spent attempting to conceive may be a surrogate for other factors such as motivation to conceive or knowledge and awareness regarding infertility—motivated couples with greater knowledge may seek care earlier when trying to conceive and are therefore more willing to explore all options (including surgery) and incur greater financial burden in order to achieve pregnancy. Unfortunately, due to the retrospective nature of this study we were unable to assess couples' motivation for seeking male evaluation of infertility.

Not surprisingly, married men with NOA were more likely to pursue mTESE compared to non-married men. Using the National Survey of Family Growth, Persily *et al.* showed similar results among men seeking evaluation for self-reported subfertility and infertility (19). They found that unevaluated men were over three times more likely to be divorced or separated compared to evaluated men and were almost eight times more likely to have never been married. Our findings highlight the fact that many of the same barriers and factors associated with limited access to initial evaluation by a RU persist when determining who pursues surgical standard of care for NOA.

Our study must be considered within the context of

Table 4 Multivariable logistic regression analysis of demographic information and clinical characteristics associated with undergoing mTESE using broader criteria for NOA defined as FSH >7.6 mIU/mL

Characteristics	mTESE OR (95% CI)	P value
Age of male at initial SA (years)	0.92 (0.87–0.98)	0.012
Race		
White	Ref.	–
Black	1.33 (0.35–5.11)	0.68
Asian	0.93 (0.20–4.25)	0.92
Other	1.84 (0.65–5.15)	0.25
Insurance status		
Private	Ref.	–
Public	–	–
Self-pay/other	1.73 (0.31–9.77)	0.53
Marital status		
Non-married/unknown	Ref.	–
Married	2.15 (0.97–4.76)	0.06
Time trying to conceive (years)	0.76 (0.63–0.91)	0.002
Previous pregnancy by male partner	0.57 (0.22–1.50)	0.26
Previous pregnancy by female partner	0.77 (0.27–2.20)	0.63
Distance to RU clinic (km)	1.00 (0.99–1.00)	0.39
Income (median per zip code, $10k)	1.11 (1.03–1.20)	0.009

mTESE, microdissection testicular sperm extraction; NOA, non-obstructive azoospermia; FSH, follicle stimulating hormone; SA, semen analysis; RU, reproductive urologist; OR, odds ratio; CI, confidence interval; Ref., reference.

certain limitations. First, due to the retrospective nature of the study, we relied on previously collected data in the electronic data repository which may be subject to incomplete reporting or incorrect coding. Second, we were only able to identify patients who underwent mTESE within our integrated, multi-site academic health center. As such, there may be men who initially presented for fertility evaluation and ultimately received definitive surgical care at another institution, which would have resulted in overestimation of our reported number of patients not undergoing mTESE. Third, our entire cohort received treatment in the state of Illinois, which does have mandated insurance coverage for IVF and other fertility services. While the insurance mandate does not include mTESE, coverage for associated IVF may reduce aggregate financial costs, thereby mitigating financial barriers to treatment. As such, these data may not be generalizable to states without insurance mandates. Lastly, we utilized neighborhood income as a surrogate for individual patient income, which may either overestimate or underestimate individual patient incomes.

Conclusions

In our retrospective analysis of men evaluated for NOA at our institution, higher neighborhood income and marital status were positively associated with undergoing mTESE, whereas couples who attempted to conceive for a longer period of time before seeking care by a RU were less likely to receive the gold standard treatment. These data suggest that future efforts to decrease time to evaluation and costs of treatment may improve access to gold standard care for men with NOA.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-76/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-76/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-76/coif). The authors have no 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and exempted from requiring approval by the Institutional Review Board (IRB) at Northwestern University Feinberg School of Medicine. Individual consent for this retrospective analysis was waived.

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