



# Practice patterns for the treatment of idiopathic infertility: is there a role for advanced semen testing?

Vishal N. Patel<sup>1</sup>, Kevin B. Ginsburg<sup>1</sup>, Erika Etnyre<sup>2</sup>, Felix Shun<sup>2</sup>, Aram Loeb<sup>3</sup>, Stephen A. Krawetz<sup>2,4</sup>, Amarnath Rambhatla<sup>1</sup>

<sup>1</sup>Department of Urology, Wayne State University, School of Medicine, Detroit, MI, USA; <sup>2</sup>Wayne State University, School of Medicine, Detroit, MI, USA; <sup>3</sup>University Hospitals Urology Institute, Case Western Reserve University, Cleveland, OH, USA; <sup>4</sup>Department of Obstetrics and Gynecology and Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA

**Contributions:** (I) Conception and design: VN Patel, A Loeb, SA Krawetz, A Rambhatla; (II) Administrative support: SA Krawetz, A Rambhatla; (III) Provision of study materials or patients: VN Patel, KB Ginsburg, E Etnyre, F Shun; (IV) Collection and assembly of data: VN Patel, KB Ginsburg, E Etnyre, F Shun; (V) Data analysis and interpretation: VN Patel, KB Ginsburg, A Rambhatla; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Vishal N. Patel, MD. Department of Urology, Wayne State University, School of Medicine, University Health Center, 4201 St. Antoine, Ste 7-C, Detroit, MI 48201, USA. Email: vipatel@med.wayne.edu.

**Background:** For idiopathic infertile couples, normal semen parameters do not rule out infertility from a male factor. RNA sequencing of spermatozoa can provide additional measures of male fecundity, distinguishing couples likely to achieve live birth with timed intercourse (TI) or intrauterine insemination (IUI) versus more aggressive assisted reproductive technology [*in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI)]. This survey study evaluates treatment patterns of urologists for men with idiopathic infertility (IDF) and investigates attitudes regarding the utility of a novel test of sperm RNA in guiding treatment paradigms.

**Methods:** A 12-question, web-based survey was emailed to members of two male infertility societies, the Society for the Study of Male Reproduction and The American Society of Andrology. Follow-up email prompts were sent two and four weeks after initial contact.

**Results:** Of 291 invited participants, 33 (11%) completed the online survey. A majority (58%) were fellowship trained in male infertility. Respondents reported their typical treatment algorithm for most couples with IDF was: TI first line (73%), followed by IUI second line (80%), IVF third line (80%), and ICSI fourth line (85%). Most, 71%, of respondents reported a test that could identify which couples were likely to conceive with TI or IUI *vs.* proceeding directly to assist reproductive techniques beneficial. Furthermore, 52% report that knowing the results of such a test would change their practice patterns.

**Conclusions:** Variability exists in the evaluation and treatment of couples with IDF. A majority of physicians surveyed asserted that the development of a test in this space to further characterize male-factor infertility would both be helpful clinically and change practice patterns.

**Keywords:** Idiopathic infertility (IDF); RNA sequencing; advanced semen testing

Received: 19 December 2018; Accepted: 04 January 2019; Published: 16 January 2019.

doi: 10.21037/amj.2019.01.01

View this article at: <http://dx.doi.org/10.21037/amj.2019.01.01>

## Introduction

Infertility—the inability to conceive after 12 months of regular, unprotected intercourse—is a diagnosis that plagues couples attempting to have children (1) with 50%

of infertility that can be attributable to a male factor (2). Medical advances in the past decade have drastically changed the odds of conceiving for couples who have struggled with infertility (3,4). Idiopathic infertility (IDF),

is diagnosed when a full work up for infertility has failed to identify an underlying cause. Despite advances in reproductive techniques and diagnostic technology, 15% to 30% of couples are left without answers regarding the etiology of their inability to conceive and diagnosed with IDF (5,6).

Treatment for couples with IDF remains a challenge. Currently, treatments for IDF include timed intercourse (TI), intrauterine insemination (IUI) in natural cycles or in combination with ovarian stimulation IUI, *in vitro* fertilization (IVF), and intracytoplasmic sperm injection (ICSI). There remains a gap in current diagnostic tests to aid in treatment choices in couples with IDF; the ideal treatment paradigm and treatment regimen remains unknown (7,8). Logically, physicians tend to recommend non-invasive and less expensive approaches as an initial management strategy such as TI and IUI (9). Without new testing in this space, there remains the potential for wasted time, poor utilization of resources, added expense, and a decline in the couple's fertility while pursuing more conservative treatment options that will ultimately fail. Herein, we assess urologists' practice patterns treating couples with IDF and the attitude toward the utility of a new diagnostic test to aid in decisions regarding treatment.

## Methods

We performed a survey assessing the practice patterns in the management of IDF and to determine if there is a need for advanced semen testing in this setting. Members of the Society for the Study of Male Reproduction and the American Society of Andrology were invited to participate in the 12-question, web-based survey via email (Supplementary file). Emails from the two societies were cross checked to ensure that multiple responses were not received from the same individual. An initial survey was sent with follow up emails at 2 and 4 weeks to encourage participation. No financial incentive or compensation was offered to survey participants. The study was deemed exempt by the Wayne State University institutional review board.

## Results

A total of 291 members of two male infertility societies were invited to participate in the study, of which 33 (11%) completed the survey. Most participants (58%) were fellowship trained in male infertility, have been practicing

**Table 1** Demographics of survey respondents

Demographic	N [%]
Fellowship trained in infertility	
Yes	18 [58]
No	13 [42]
Years in practice	
<5	4 [13]
5–10	3 [10]
11–20	6 [19]
>20	18 [58]
Practice type	
Academic appointment	17 [55]
Private practice with academic affiliation	3 [10]
Private practice, Group	6 [19]
Private practice, Solo	2 [7]
Other	3 [10]
Region/section	
Mid-Atlantic	3 [11]
New England	3 [11]
North Central	4 [15]
North Eastern	1 [4]
South Central	3 [11]
South Eastern	5 [19]
Western	8 [30]

for more than 20 years (58%), and practiced in an academic environment (55%) (*Table 1*).

Current patterns of evaluation and treatment for couples with IDF were examined with 35% of survey respondents responding that they would perform a hormonal evaluation prior to recommending treatment while another 35% of respondents reported that they would not obtain any additional diagnostic tests prior to recommending a treatment strategy (*Table 2*). Most respondents (73%) recommended TI as their first treatment for couples presenting with IDF, followed by IUI (14%), ICSI (9%), and IVF (5%) as other first line therapies (*Table 3*). Respondents reported their typical treatment algorithm for most couples with IDF was TI first line (73%), followed by IUI second line (80%), IVF third line (80%), and ICSI

**Table 2** Additional assays ordered prior to recommending treatment in couple with idiopathic infertility and normal semen parameters (N=31)

Assay	N [%]
Hormone Panel (Testosterone, Estradiol, FSH, and LH)	11 [35]
Hormone Panel and Sperm DNA Fragmentation	2 [6]
Hormone Panel, Sperm DNA Fragmentation and DNA Methylation	1 [3]
Hormone Panel, Sperm DNA Fragmentation, DNA Methylation, and FISH analysis	1 [3]
Sperm DNA Fragmentation	4 [13]
Sperm DNA Fragmentation, and Fish Analysis	1 [3]
None	11 [35]

**Table 3** Frequency of various therapies for first, second, third, and fourth line treatments for patients with idiopathic infertility and normal semen parameters

Treatment	N [%]
<b>First line therapy</b>	
Timed intercourse	16 [73]
Intrauterine insemination	3 [14]
In vitro fertilization	1 [5]
Intracytoplasmic sperm injection	2 [9]
<b>Second line therapy</b>	
Timed intercourse	1 [5]
Intrauterine insemination	16 [80]
In vitro fertilization	1 [5]
Intracytoplasmic sperm injection	2 [10]
<b>Third line therapy</b>	
Timed intercourse	2 [10]
Intrauterine insemination	1 [5]
In vitro fertilization	16 [80]
Intracytoplasmic sperm injection	1 [5]
<b>Fourth line therapy</b>	
Timed intercourse	1 [5]
Intrauterine insemination	0 [0]
In vitro fertilization	2 [10]
Intracytoplasmic sperm injection	17 [85]

fourth line (85%).

Highlighting a need for new testing in this space, 71% of respondents reported a test that could identify which couples were likely to conceive with TI or IUI *vs.*

proceeding directly with assisted reproductive techniques would be beneficial to their clinical practice. Furthermore, a majority, 52% reported that knowing the results of such a test would change their practice patterns in managing couples with IDF. Practitioners thought that a new test could be integrated into their practice if priced between \$100 and \$500, and a reasonable turnaround time for results reporting was 1–2 weeks.

### Discussion

The majority of survey respondents were fellowship trained and experts in the field of male infertility. Despite their expertise, we noted variability in the response of the urologists regarding work up and treatment algorithms recommended for couples with IDF. A fairly large proportion (35%) of respondents from our survey would not obtain further testing for couples with IDF prior to recommending a treatment course. This suggests that currently there is a lack of helpful prognostic tests in this space, and many urologists consider that the available tests may not be helpful in guiding treatment recommendations (10). This highlights the need for further testing which can provide results that can aid in guiding treatment in these challenging couples.

Several treatment strategies and algorithms have been proposed using female age, percentage of motile sperm, and estimated spontaneous pregnancy rate in an attempt to optimize pregnancy rates (11,12). Despite these tools, there is still a significant degree in variability in the treatment of IDF. The pregnancy rates for couples with IDF per cycle of TI and life style modifications are reported to be 1.3% to 4.1%, IUI +/- ovarian stimulation 3.8% to 17.1% and IVF 21–27% (13,14). We interpret that current

management trends seen in our study are likely driven by cost with TI being the least expensive followed by IUI, IVF, and finally ICSI. The development of semen RNA testing would optimize time and cost efficiency which would help streamline treatment of IDF.

Nucleic acid sequencing-based assessment of spermatozoa may be a gateway into optimizing patient selection for treatment with IDF. For example, previous work has demonstrated the potential utility of next generation sequencing and other technologies in guiding therapy for couples with IDF (15,16) and identifying a possible cause (17). Development of this test could help guide treatment and steer a couple towards a management strategy with the highest likelihood of success while limiting the cost and morbidity of more invasive therapies when not needed. Ideally, couples that are more likely to achieve a live birth with IVF and ICSI would be able to proceed directly to these treatments without wasting time, resources, and a possible decline in fertility potential while attempting TI and/or IUI. Conversely, couples that are likely to achieve a live birth with TI and IUI can be spared the significant expense and any associated risk with IVF and ICSI. A majority of survey respondents reported that a test such as the one previously described would be both beneficial to their clinical practice as well as change their practice habits. This testing can provide vital information to facilitate recommendations and can serve as a valuable tool for infertility clinicians.

## Conclusions

Even though there has been vast improvement in infertility therapy, treatment for couples with IDF remains a challenge. Survey respondents demonstrated variability and lack of standardized treatment for couples with IDF. A majority of physicians surveyed assert that the development of a test to further characterize male-factor infertility would both be helpful and change practice patterns, aiding to limit the under-treatment and over-treatment of couples with IDF.

## Acknowledgments

*Funding:* None.

## Footnote

*Conflicts of Interest:* The authors have completed the

ICMJJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2019.01.01>). Dr. Krawetz reports Research supported in part from a Fertility Innovations grant from MERCK. The other authors have no conflicts of interest 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 deemed exempt by the Wayne State University institutional review board.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Centers for Disease Control and Prevention, Division of Reproductive Health. Available online: <https://www.cdc.gov/reproductivehealth/infertility/index.htm>
- Centers for Disease Control and Prevention: 2015 Assisted Reproductive Technology Success Rates. National Summary and Fertility Clinic Reports. Available online: <https://www.cdc.gov/art/pdf/2015-report/ART-2015-National-Summary-Report.pdf>
- World Health Organization. WHO manual for the standardized investigation and diagnosis of the infertile couple. Cambridge, UK: Cambridge University Press, 2000.
- Collins JA, Burrows EA, Wilan AR. The prognosis for live birth among untreated infertile couples. *Fertil Steril* 1995;64:22-8.
- Templeton AA, Penney GC. The incidence, characteristics, and prognosis of patients whose infertility is unexplained. *Fertil Steril* 1982;37:175-82.
- Collins JA, Corsignani PG. Unexplained infertility: a review of diagnosis, prognosis, treatment efficacy and management. *Int J Gynaecol Obstet* 1992;39:267-75.
- Sunderam S, Kissin DM, Crawford SB, et al. Assisted reproductive technology surveillance — United States, 2014. *MMWR Surveill Summ* 2017;66:1-24.

8. Reindollar RH, Regan MM, Neumann PJ, et al. A randomized controlled trial of 503 couples assigned to conventional infertility treatment or an accelerated track to IVF: preliminary results of the Fast Track and Standard Treatment (FASTT) Trial. *Fertil Steril* 2007;88:S41.
9. Quaas A, Dokras A. Diagnosis and Treatment of Unexplained Infertility. *Rev Obstet Gynecol* 2008;1:69-76.
10. Eimers JM, te Velde ER, Gerritse R, et al. The prediction of the chance to conceive in subfertile couples. *Fertil Steril* 1994;61:44-52.
11. Hunault CC, Habbema JD, Eijkemans MJ, et al. Two new prediction rules for spontaneous pregnancy leading to live birth among subfertile couples, based on the synthesis of three previous models. *Hum Reprod* 2004;19:2019-26.
12. Brandes M, Hamilton CJ, van der Steen JO, et al. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. *Hum Reprod* 2011;26:360-8.
13. Guzick DS, Sullivan MW, Adamson GD, et al. Efficacy of treatment for unexplained infertility. *Fertil Steril* 1998;70:207-13.
14. Aboulghar MA, Mansour RT, Serour GI, et al. Diagnosis and management of unexplained infertility: an update. *Arch Gynecol Obstet* 2003;267:177-88.
15. Jodar M, Sendler E, Moskovtsev SI, et al. Absence of sperm RNA elements correlates with idiopathic male infertility. *Sci Transl Med* 2015;7:295re6.
16. Krawetz SA, Kruger A, Lalancette C, et al. A survey of small RNAs in human sperm. *Hum Reprod* 2011;26:3401-12.
17. Burl RB, Clough S, Sendler E, et al. Sperm RNA elements as markers of health. *Syst Biol Reprod Med* 2018;64:25-38.

doi: 10.21037/amj.2019.01.01

**Cite this article as:** Patel VN, Ginsburg KB, Etnyre E, Shun F, Loeb A, Krawetz SA, Rambhatla A. Practice patterns for the treatment of idiopathic infertility: is there a role for advanced semen testing? *AME Med J* 2019;4:4.

## Supplementary

1. What best describes your training and practice
  - a. Urology (primarily clinical)
  - b. Urology (primarily research)
  - c. OB/GYN (primarily clinical)
  - d. OB/GYN (primarily research)
  - e. PhD (primarily research)
2. How many years have you been practicing?
  - a. Less than 5
  - b. 5-10 years
  - c. 11-20 years
  - d. More than 20 years
3. Are you fellowship trained in infertility?
  - a. Yes
  - b. No
4. What type of practice are you associated with?
  - a. Private practice, solo
  - b. Private practice, group
  - c. Private practice with academic affiliation
  - d. Academic institution
  - e. Other
5. Which AUA section are you affiliated with?
  - a. New York
  - b. Northeastern
  - c. South Central
  - d. North Central
  - e. Mid-Atlantic
  - f. New England
  - g. Western
  - h. Southeastern
6. For idiopathic infertile couples with normal semen parameters, what, if any, additional tests do you routinely order? Check all that apply.
  - a. Hormone panel (testosterone, estradiol, and gonadotropins)
  - b. Sperm DNA fragmentation
  - c. Sperm FISH analysis
  - d. DNA Methylation
  - e. None
7. What protocol do you (or your practice) follow for couples presenting with idiopathic infertility? Please select order 1 being first, 4 being last.
  - a. Timed Intercourse
  - b. IUI
  - c. IVF
  - d. ICSI
8. Would you find a test for idiopathic infertile couples to identify those likely to conceive with timed intercourse vs. proceeding directly with assisted reproductive techniques beneficial?
  - a. Yes
  - b. No
  - c. Maybe
9. Would knowing the results of such a test change your practice patterns?
  - a. Yes
  - b. No
  - c. Maybe
10. What do you think is a reasonable cost for such a test that would allow for the test to be integrated into your practice?
  - a. <\$100
  - b. >\$100-\$500
  - c. >\$500-\$1,000
  - d. >\$1,000-\$1,500
  - e. >\$1,500
11. Would it be useful if the test could simultaneously assess health status?
  - a. Yes
  - b. No
  - c. Maybe
12. What would you consider to be an acceptable turn-around time for such a test in order for usage to be beneficial in your practice?
  - a. Less than 1 wk
  - b. 1-2 wks
  - c. 2-3 wks
  - d. >3 wks