A novel nomogram for prediction of spermatogenic improvement following empiric medical therapy for moderate-severe oligospermia

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BARAZANI Y, POLACKWICH JR. AS, SABANEGH JR. ES. A novel nomogram for prediction of spermatogenic improvement following empiric medical therapy for moderate-severe oligospermia. *Can J Urol* 2016;23(1):8135-8140.

Introduction: *To identify pre-treatment clinical variables and hormonal responses predictive of successful spermatogenic response to empiric medical therapy (EMT), then to create a nomogram to guide clinical therapy.*

Materials and methods: *All men who had been treated at our institution with EMT for moderate-severe oligospermia (<= 10 million sperm/mL) from 2003 to 2014 were included in our study. Men with hypogonadotropic hypogonadism, azoospermia, or those who had varicocelectomy or had received fertility altering medications within 6 months of initiating EMT were excluded, as well as those who did not obtain a follow up semen analysis.*

Pre-treatment clinical variables, hormonal responses, and spermatogenic responses were assessed. Success was defined by improvements in baseline sperm concentrations as follows: (1) cryptospermia to ≥ 0.3 million/mL, (2) > 100% increase in sperm concentration for men with baseline concentration < 1 million/mL, or (3) a 30% increase in sperm concentration for men with a baseline concentration between 1-10 million/mL.

We performed univariate analysis to evaluate for predictors of success. The Wilcoxon rank sum test was used for continuous variables and the Fisher's exact test was used for categorical variables. Multivariable logistic regression was then used to build a nomogram.

Results: *We identified 107 men who were treated with EMT for oligospermia (< = 10 million sperm/mL) who met our inclusion criteria. Forty-five men (42%) exhibited a poor spermatogenic response to EMT and 62 men (58%) exhibited a good response. Univariate analysis did not identify significant differences in any variable between the two groups. Multivariate analysis did identify predictive combinations which allowed the development of a nomogram with a high concordance index (0.78) for predicting spermatogenic response to EMT.*

Conclusions: *While none of the individual pre-treatment clinical variables or hormonal responses were predictive of success following EMT, analysis of multiple factors in concert yielded a clinically useful nomogram with a high concordance index.*

Key Words: oligospermia, empiric medical therapy, clomiphene, testolactone, anastrozole

Accepted for publication October 2015

Acknowledgement
We would like to acknowledge Tianming Gao for statistical assistance.

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Introduction

Empiric medical therapy (EMT) is a cornerstone in the management of men with moderate-severe oligospermia (< 10 million sperm/mL), and is commonly utilized to augment sperm production for either natural conception or intrauterine insemination. In fact, a recent survey of practicing American Urological Association members reported that empirical medical therapy is used by

two-thirds of survey respondents for the treatment of idiopathic male infertility. In spite of being so widely utilized, there is no clear universal pattern to the evaluation or identification of the ideal patient for such therapy, nor is there a consensus regarding the optimal medication or the proper treatment protocol for men undergoing fertility treatment.[1] Being that this is one of the most widely used treatments for idiopathic male infertility, we attempted to identify some guidance to therapy with early hormonal markers.

While guidelines for use of EMT are lacking, commonly used agents include selective estrogen-receptor modulators (SERM) such as clomiphene and the aromatase inhibitors, letrozole and anastrozole. Through the blockade of the estrogen at the level of the hypothalamus and pituitary or by decreasing the conversion of testosterone to estrogen, these medications can increase serum testosterone, LH and FSH levels, which subsequently stimulate spermatogenesis.[2] It is important to note though, that all of these agents lack FDA approval for this indication and their "off-label" use has been adapted from their fertility applications in women.

When SERMs or aromatase inhibitors are utilized, a serum hormonal response occurs in a relatively short period of time, typically within 1 month. However, improvements in semen parameters are delayed due to the long process of spermatogenesis, which takes up to 76 days.[3] Unfortunately, more than one third of men do not show improvements in sperm counts when administered EMT,[4] and no predictors have been identified to date to allow early prediction of spermatogenic response to medical treatment with these agents.

The time required to differentiate responders from non-responders to EMT potentially delays the decision to proceed with alternative therapies such as intrauterine insemination (IUI) or in vitro fertilization with intracytoplasmic sperm injection (IVF with ICSI). Thus, it would be very useful to patients and clinicians alike to identify rapidly available clinical variables predictive of successful spermatogenic response to EMT. We designed a study to identify (1) pre-treatment clinical variables and (2) early hormonal responses predictive of clinically significant increases in sperm concentration resulting from empiric medical therapy.

Materials and methods

After approval by the institutional review board, a retrospective chart review was performed to identify all men over the previous 11 year period (2003-2014) that had been treated with EMT for moderate-severe oligospermia (<= 10 million sperm/mL) at our institution. Exclusion criteria included: history of testosterone replacement therapy or anabolic androgenic steroid abuse, hypogonadotropic hypogonadism, genetic disease associated with male subfertility, azoospermia, any prior medical treatment for infertility within the previous 6 months, or a history of a varicocelectomy performed within 6 months of initiating EMT. A total of 107 men satisfied these inclusion and exclusion criteria.

For each man who underwent EMT at our institution, we collected a number of pre-treatment clinical variables including patient age, body mass index (BMI), left and right testis size, empiric medical treatment administered, as well as pre-treatment and treatment laboratory parameters including sperm concentration and a baseline hormone profile (serum testosterone, estradiol, LH, and FSH values). All testosterone values were done prior to 11 AM.

At our institution, as has been reported elsewhere,[5] the decision to use clomiphene versus aromatase inhibitor (anastrozole) depended on the testosterone:estradiol ratio. Patients were preferentially treated with an aromatase inhibitor if the T/E_2 ratio (μg/dL testosterone, pg/μl estradiol) was less than 10 or with clomiphene if T/E_2 was greater than or equal to 10.[5] After initiation of EMT treatment, we check a hormone profile at 1 month and a semen analysis at 3 months to evaluate the therapy's effect. Men were defined as responders or non-responders to medical treatment solely on the basis of improvements in sperm concentrations as follows: (1) baseline cryptospermia improving to ≥ 0.3 million sperm/mL, (2) more than a 100% increase in sperm concentration for men with baseline concentration < 1 million sperm/mL, or (3) a 30% or greater increase in sperm concentration for men with a baseline concentration between 1-10 million sperm/mL. Pre-treatment diagnoses of oligospermia were based on two semen analyses. Because many of our patients had previously been seen elsewhere, initial semen analyses were commonly done elsewhere and at times were many months prior to our consult. Therefor, for our calculations, the most recent semen analysis was used.

We then compared the spermatogenic responder group to the non-responder group. Specifically, we made comparisons of pre-treatment clinical parameters (age, physical exam findings, serum hormone levels, and baseline sperm concentrations) as well as hormonal responses to EMT. For univariate analysis, median and quartiles were given for continuous variables since the data was not normally distributed. The Wilcoxon rank sum test was used for continuous variables and the Fisher's exact test was used for categorical variables.

Multivariable logistic regression was then used to build a nomogram. Backward variable selection was performed to choose the model with the highest concordance index. The model was validated by internal bootstrap sampling.

Results

Based on the aforementioned criteria for a successful spermatogenic response to EMT, the 107 men were divided into two groups: 45 men (42%) exhibited a poor spermatogenic response (non-responder group) and 62 men (58%) exhibited a good spermatogenic response (responder group). Univariate comparison of pre-treatment clinical variables between these two groups is shown in Table 1.

Men in the non-responder and responder groups were characterized by a median pre-treatment serum FSH concentration of 4.6 mIU/mL versus 5.2 mIU/mL (p = 0.87), pre-treatment serum LH concentration of 4.4 mIU/mL versus 5.2 mIU/mL (p = 0.12), pre-treatment serum total testosterone concentration of 271 ng/dL versus 266 ng/dL (p=0.56), pre-treatment serum estradiol concentration of 21.5 pg/mL versus 27.5 pg/mL (p = 0.27), a baseline sperm concentration of 2.1 million sperm/mL versus 1.7 million sperm/mL (p = 0.83), a total testis volume of 36 cc versus 36 cc (p = 0.76), a BMI of 31.8 kg/m^2 versus 30.4 kg/m^2 (p = 0.7), and an average age of 33.5 years versus 33 years (p = 0.79), respectively. None of these differences achieved statistical significance. The responder and non-responder groups had an average post-EMT treatment sperm concentration of 15.7 million sperm/mL and 1.67 million sperm/mL, respectively.

Moreover, no statistically significant differences were observed in the hormonal responses to EMT between the non-responder and responder groups (FSH change 3.4 mIU/mL versus 3.3 mIU/mL, p = 0.27; LH change 6 mIU/mL versus 3.18 mIU/mL, p = 0.13; total testosterone increase of 375 ng/dL versus 310 ng/dL, p = 0.25), Table 2. Three men were given anastrozole in the non-responder group and five men were given anastrozole in the responder group, and this difference was also not statistically significant (p = 1). All other men were administered clomiphene citrate. Standard dosing used for clomiphene citrate was 50 mg every other day and for anastrozole, 1 mg every day.

TABLE 1. **Univariate comparison of pre-treatment clinical variables in men with a good spermatogenic response to EMT (success) versus non-responders (failure)**

Pre-treatment parameter (patients with data available)	**Group Median (quartiles)**		
	Failure n = 45	**Success n = 62**	**p value**
FSH (107)	4.6 (3.3, 7.1)	5.25 (3.3, 7.25)	0.87
LH (71)	4.4 (3.25, 5.8)	5.2 (3.95, 6.15)	0.12
T (94)	271 (185.5, 404.5)	266 (207, 368.5)	0.56
Estradiol (30)	21.5 (19, 26)	27.5 (21.5, 37.0)	0.27
Sperm concentration (107)	2.1 (0.5, 4.95)	1.7 (0.74, 4)	0.83
Total testis volume (92)	36 (28, 40)	36 (27, 40)	0.76
Body mass index (95)	31.8 (25.8, 35.3)	30.4 (27, 37.4)	0.70
Age (106)	33.5 (30, 36)	33 (30, 38)	0.79
Medication: anastrozole (8)	3	5	1

TABLE 2. **Univariate comparison of hormonal changes in men with a good spermatogenic response to EMT (success) versus non-responders (failure)**

Post-treatment parameter (patients with available data)	Group Median (quartiles)		
	Non-responder n = 45	Responder n = 62	p value
FSH change (73)	3.4 (2.15, 6.22)	3.3 (1.1, 4.5)	0.27
LH change (37)	6 (2.6, 8.4)	3.18 (0.7, 5.1)	0.13
T change (71)	375 (248, 467)	310 (191, 445)	0.25

Multivariable logistic regression was used to build the nomogram. All pre-treatment variables were evaluated as well as treatment response. Backward variable selection was utilized to identify the variables with the highest concordance index to yield a model with the greatest accuracy. The concordance index of the final model, Figure 1 is 0.78. Four parameters were used in this model: BMI, age, pretreatment LH and change in testosterone.

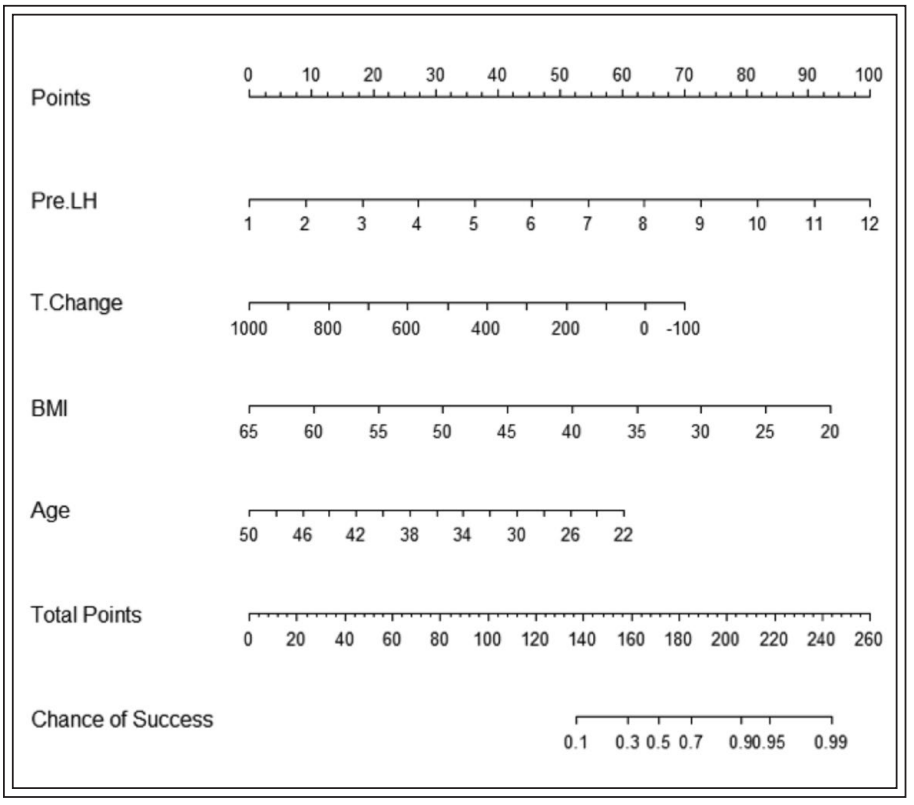

Figure 1. Nomogram for predicting spermatogenic response to EMT based on pre-treatment clinical variables and hormonal response to treatment.

Discussion

While modern assisted reproduction techniques (ART) can help achieve pregnancy even in cases of severe oligospermia, EMT is a reasonably inexpensive and safe method to improve sperm concentration and offer an opportunity for natural conception.[6] A majority of practitioners therefore utilize this therapy in the treatment of severely oligospermic patients, without knowledge of what, if any, patient characteristics are helpful in identifying those who will benefit.[1] To date, no studies have analyzed this. While we found that no single characteristic was found to be significant, we were able to develop a nomogram that could guide treatment decisions.

A number of studies have evaluated the efficacy of selective estrogen receptor modulators such as clomiphene citrate and aromatase inhibitors including anastrozole for male infertility. These studies have largely been of limited quality with few randomized controlled trials (RCT) and these have shown mixed results. While some trials have demonstrated that clomiphene has a small but significant effect on mean sperm concentrations and pregnancy rates,[7-10] a randomized, double-blind

study by the World Health Organization failed to find any impact of clomiphene on pregnancy rates.[11] In the azoospermic population, a randomized controlled trial demonstrated that medical therapy used in this fashion significantly increased MicroTESE success rates as well as restored sperm to the ejaculate in some patients receiving clomiphene citrate.[2] In the subset of oligospermic men with a low serum testosterone:estradiol ratio, treatment with aromatase inhibitors has been shown in some studies to significantly increase sperm count and motility and to correct the underlying hormonal abnormality.[12,13] But, none of these papers evaluated how to choose patients for this treatment.

In the present study, 42% of men were deemed to be non-responders to EMT because they experienced a decline or marginal improvement in sperm concentration. However, 58% of men were noted to exhibit a good spermatogenic response, with an increase in average sperm concentration to 15.7 million sperm/mL observed in this subset of patients.

Central to any study evaluating the efficacy of EMT is an inherent ambiguity with respect to what characterizes a meaningful spermatogenic response. Whether any increase in sperm concentration is meaningful or if a certain absolute or relative increase in sperm concentration defines a clinically significant response remains to be established. Making this determination is particularly challenging because oligospermic men represent a heterogeneous group; clearly, the same criteria cannot be applied to both men with cryptospermia (very rare sperm) and men with only moderate oligospermia (5-10 million sperm/mL). Because our study focused on spermatogenic response to EMT as the primary endpoint, much consideration was given to our definition of a successful spermatogenic response. Our criteria take into account the heterogeneity of men with oligospermia by establishing different thresholds for success depending on the severity of baseline oligospermia and represent a clinically meaningful increase (rather than simply any increase) in sperm concentration. Based on these criteria, more than half of men with moderate-severe oligospermia may be expected to show a clinically meaningful spermatogenic response to EMT.

A primary goal of the present study was to define which pre-treatment clinical variables (if any) are predictive of a successful spermatogenic response to EMT. Our univariate analysis comparing EMT responders to non-responders failed to find any one pre-treatment clinical variable that is predictive of success or failure. Baseline serum LH levels differed to some extent between responders (5.2 mIU/mL) and non-responders (4.4 mIU/mL), but this difference did not achieve statistical significance ($p = 0.12$). Moreover, all the other baseline variables (pre-treatment FSH, total testosterone, and estradiol levels, baseline sperm concentration, total testis volume, BMI, and patient age) were similar between the two groups. These results suggest that no single pre-treatment clinical parameter can reliably predict which patients are most likely to experience a spermatogenic benefit from EMT. This is useful to practitioners as we need not withhold therapy from patients because of certain pretreatment parameters.

The hormonal response to EMT measured at 1 month also appears not to have a direct predictive value for subsequent spermatogenic response. In fact, EMT responders and non-responders exhibited similar changes in FSH and LH levels ($p = 0.27$ and $p = 0.13$, respectively). Interestingly, there was no difference in testosterone response between the two groups (310 versus 375).

While univariate analysis did not identify a single pre-treatment clinical variable or hormonal response predictive of spermatogenic success with EMT, multivariable logistic regression analysis yielded a nomogram with high potential clinical utility. Using backward variable selection to choose a model with the highest concordance index (0.78), we have developed a nomogram that incorporates three pre-treatment clinical variables (LH, BMI and age) and one hormonal effect (change in serum T) to predict spermatogenic success. By applying this nomogram, clinicians can predict with a fair degree of accuracy which patients are most likely to experience a spermatogenic response. This is particularly important because hormonal changes are measurable within 1 month of initiating EMT, months before changes are noted in semen quality. In clinical practice, the time required to differentiate responders from non-responders to EMT potentially delays the decision to proceed with alternative therapies (ex. varicocele ligation, IUI, or IVF/ICSI), so a model that helps clinicians identify likely spermatogenic responders to EMT months before semen results are available is of great clinical value.

Our study has several limitations, including its retrospective nature and limited sample size. In particular, the smaller sample size may have limited our study's power to detect a difference between EMT responders and non-responders. Larger-scale prospective studies are needed to shed further light on which patients with moderate-severe oligospermia are most likely to respond to medical treatment as well as to identify which if any hormonal responses to EMT are predictive of spermatogenic responses. Moreover, future studies should incorporate clinical pregnancy as a clinical endpoint in addition to sperm concentration.

Conclusion

Our study represents an important first-step in distinguishing responders to EMT from non-responders. It is important for practitioners to realize there is not one hormonal parameter that predicts success, and this needs to be taken into account when counseling patients. While these two groups appear to be quite similar with respect to pre-treatment clinical variables and hormonal responses to EMT, our multivariable analysis has yielded an accurate and clinically useful nomogram, which may be incorporated into clinical practice. By applying this nomogram to oligospermic men 1 month after initiating EMT, clinicians can reliably identify the subset of men most likely to experience a spermatogenic benefit. Moreover, this information will be available months before semen quality can be reassessed for improvement, making this an invaluable tool in the management of oligospermic men. □

References

1. Ko EY, Siddiqi K, Brannigan RE, Sabanegh Jr ES. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. *J Urol* 2012;187(3):973-978.
2. Hussein A, Ozgok Y, Ross L, Rao P, Niederberger C. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. *BJU Int* 2013;111(3 Pt B):E110-E114.
3. Turek P. Chapter 20 – Male Reproductive Physiology. Wein: Campbell-Walsh Urology, 10th. Ed. Wein, Kavoussi, Novick, Partin, Peters, Editors.
4. Epstein JA. Clomiphene treatment in oligospermic infertile males. *Fertil Steril* 1977;28(7):741-745.
5. Reifsnyder JE, Ramasamy R, Husseini J, Schlegel PN. Role of optimizing testosterone before microdissection testicular sperm extraction in men with nonobstructive azoospermia. *J Urol* 2012;188(2):532-536.
6. Cocuzza M, Agarwal A. Nonsurgical treatment of male infertility: specific and empiric therapy. *Biologics* 2007;1(3):259-269.
7. Wang C, Chan CW, Wong KK, Yeung KK. Comparison of the effectiveness of placebo, clomiphene citrate, mesterolone, pentoxifylline, and testosterone rebound therapy for the treatment of idiopathic oligospermia. *Fertil Steril* 1983;40(3):358-365.
8. Check JH, Chase JS, Nowroozi K, Wu CH, Adelson HG. Empirical therapy of the male with clomiphene in couples with unexplained infertility. *Int J Fertil* 1989;34(2): 120-122.
9. Pasqualotto FF, Fonseca GP, Pasqualotto EB. Azoospermia after treatment with clomiphene citrate in patients with oligospermia. *Fertil Steril* 2008;90(5):2014.e11-e12.
10. Chua ME, Escusa KG, Luna S et al. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. *Andrology* 2013;1(5):749-757.
11. World Health Organization. A double-blind trial of clomiphene citrate for the treatment of idiopathic male infertility. *Int J Androl* 1992;15:299-307
12. Pavlovich CP, King P, Goldstein M, Schlegel PN. Evidence of a treatable endocrinopathy in infertile men. *J Urol* 2001;165(3): 837-841.
13. Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. *J Urol* 2002;167(2 Pt 1):624-629.