RESEARCH ARTICLE

Nomogram to predict changes in semen parameters following clomiphene citrate therapy for males with abnormal semen parameters [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background:

Clomiphene citrate (CC) is known to improve semen quality for men with infertility, but there are no published algorithms to predict the changes in an individual's semen parameters following CC therapy. Since there are multiple options to treat men with infertility, a model to predict the outcomes of CC therapy would allow men to make a more informed decision on their treatment choices.

Methods:

This is a prospective study on a cohort of 121 infertile men being treated empirically with CC 25 mg every other day for a minimum of three months. Men were included if they did not have other active fertility therapies other than the use of supplements. Semen samples and a hormone profile (including total testosterone, follicle stimulating hormone (FSH) and leutinizing hormone (LH)) were provided prior to and at least three months after initiation of therapy. The patient age, pre-CC hormone values and semen parameters were used to develop a nomogram to predict the post-CC hormone values and semen parameters. The model was developed with predictors selected using backward selection methods by minimizing root mean square error evaluated on 500 bootstrap runs. A zero-inflated negative binomial modeling (ZINB) approach was used to model sperm concentration and sperm motility. A generalized linear model for the Gamma distribution was used to model testosterone. A linear model was used to model log transformed LH, FSH and semen volume.

Results:

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Post-CC sperm parameters and hormone values were predicted by the pre-CC sperm concentration, hormone values and patient. Nomograms were developed to predict the outcomes of CC therapy based on pre-CC parameters.

Conclusion:

These new models will help physicians personalize care by predicting the outcomes of therapy and allow clinicians to tailor the treatment to the individual couple.

Keywords

clomiphene citrate, male infertility, nomogram, semen parameters, testosterone level

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Introduction

Close to 15% of couples will have subfertility, with a male factor contributing to the infertility approximately 50% of the time.¹ While there are often reversible factors identified to treat men with subfertility, empiric hormonal therapy has become a popular therapy used to treat men with idiopathic infertility.

Clomiphene citrate (CC) is the most commonly prescribed medication for idiopathic male infertility in the United States.^{2,3} The use of CC for the management of ovulation predates the use for men, but there are reports dating back to the 1960s about CC use to treat infertile men with oligospermia.^{4–6} CC is an antiestrogen blocking the feedback of estradiol on the hypothalamus/pituitary axis to increase the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH).^{7,8} This in turn increases the local concentration of FSH and LH in the testis, reportedly increasing the production of testosterone and sperm.^{7–9} In a meta-analysis published in 2013, Chua *et al.*, reported that anti-estrogen use for men with infertility resulted in statistically significantly increased pregnancy rates with an OR of 2.42 (95% CI: 1.47–3.94), sperm counts with a weighted mean difference of 5.24 million/mL (CI: 2.12–8.37) and sperm motility of a weighted mean difference of 4.55% (CI: 0.73–8.37%).⁹ There was heterogeneity in the dose, type (either CC or tamoxifen) and duration of anti-estrogen analyzed for the meta-analysis.

CC is a relatively safe therapy with Guo *et al.*, reporting from a US claims database no increased incidence of side effects in those using CC, although there was a report of an embolic event occurring with CC use.^{2,10}

From these previous reports, there is evidence that the use of CC leads to improvements in semen parameters and pregnancy rates, but the magnitude of the expected response for individual patients is unknown.

The expected magnitude of change in semen parameters is critical in deciding therapies for couples with infertility. Men with total motile sperm counts (TMC) < 5 million generally will be referred for *in-vitro* fertilization (IVF), while men with TMC > 5 million are candidates for intra-uterine insemination (IUI) and men with TMC > 9 million are candidates to try to conceive spontaneously.¹ The potential goals of therapies for men with infertility is not only to achieve a spontaneous pregnancy, but also to “upgrade” semen parameters so couples might be able to conceive with less invasive assisted reproductive technologies (ARTs) (moving from needing IVF to being candidates for IUI).

Our goal was to develop nomograms based on baseline semen, hormonal and patient characteristics to predict the semen and hormonal changes following CC use. This should allow patients and clinicians to predict the individual’s expected changes in semen parameters and hormone levels following CC treatment, in turn allowing clinicians to tailor the fertility therapies and provide specific information to men on their specific expected outcomes.

Methods

This prospective cohort study took place at the Murray Koffler Urologic Wellness Centre at Mount Sinai Hospital, Toronto, Canada and was approved by Mount Sinai Hospital Research Ethics Board with approval number 14-0342-E. All participants provided written informed consent for the use and publication of the patients’ data. Patients were enrolled in this study between 2016–2019 and followed up to 2019. Men attending a specialized male infertility clinic were assessed for fertility. Standardized baseline clinical information including demographic information, fertility history, medical/surgical history and medication use was obtained on all men and prospectively recorded. A description of the initial physical finding was recorded for all men (height, weight, testicular size, presence of varicocele by physical examination).

Initial biological testing

As a part of routine care, men were asked to provide at least two baseline semen samples with two to seven days of abstinence for testing with a standard analysis of the semen samples recorded as per Bjorndahl *et al.*, 2016: sperm count and motility were measured by a standardized and validated Microptics Computer Assisted Semen Analysis Machine.¹¹ The semen testing was performed in one laboratory (FlowLabs, Oshawa, Ontario). A morning blood sample was taken for baseline hormone testing using an established commercial ELISA technique (including FSH (Cobas kit number: 11775863 122), LH (Cobas kit number: 11732234 122), total testosterone (T) (Cobas kit number: 05200067 190) and Estradiol) as per manufacturers protocol (DPC Immulite 2000, Diagnostic Products Corp., Los Angeles, CA).

Prospective clomiphene citrate cohort

As part of routine care, the men were then re-assessed in the clinic and were routinely offered empiric therapy with CC 25 mg every other day if no other specific therapies to treat the male infertility were available or planned. The CC treatment was offered independent of hormone values, semen parameters or clinical characteristics of the men. Men were also instructed to use supplements as empiric therapy if they were not already using supplements.

Exclusion criteria

Men were excluded from the study if they had evidence of infections (positive semen cultures), had a normal semen analysis, had a vasectomy or were unable to provide the samples required for the study. The presence of a varicocele was not an exclusion criterion, but men who had a varicocelectomy recently (< 3 months) or during the course of the study, were excluded from the study.

Testing while on clomiphene citrate

Men taking CC were followed with hormone assays and semen testing three months following the initiation of therapy. Men with full baseline testing and semen/hormone testing at a minimum of three months following the start of CC and who did not undergo any targeted therapy to improve fertility (e.g. varicocelectomy, infection therapy) were included in this study.

Statistical analysis

Method of nomogram development

The analyses first resulted in descriptive statistics on characteristics of the clinical parameters at baseline and following three months treatment with CC. Continuous variables were summarized using the median and interquartile range (IQR) and compared using the Mann-Whitney *U*-test.¹²

For each outcome, the full model included all variables: age, BMI, TT, LH, FSH, semen volume, percent motility, sperm concentration, and sperm morphology. To relax the linearity assumption, cubic spline terms were included for age, percent motility and sperm concentration. The knots were placed at 25%, 50% and 75% points on the distributions. The model was then developed with predictors selected using backward selection methods by minimizing root mean square error (RMSE) evaluated on 500 bootstrap runs.

A zero-inflated (ZI) negative binomial modeling approach was used to model sperm concentration and sperm motility following three months of CC. ZI models were first introduced by Lambert to account for excess zero counts.¹³ ZI models are two-part models, consisting of both binary and count model following negative binomial (NB) distribution sections in order to account for excess zero counts. In the logit section, the explanations of regression coefficients are similar to those in logistic regression. In the NB sections, the explanations are the same as in the traditional NB regression models. A generalized linear model for the Gamma distribution was used to model testosterone. A linear model was used to model log transformed LH, FSH and semen volume. All models were internally evaluated using 500 bootstrapped samples. The goodness of fit of the models was assessed by RMSE and the predictive probability curve.

All analyses were performed using the **R Stats** package version 3.4.4. A two-tailed p-value of <0.05 was considered to be statistically significant.

Results

Changes in the overall semen parameters and hormone profiles

Empiric CC therapy was used for 121 men (**Table 1**) with a median age of 36 (IQR 33.00–41.00). Following three months of CC therapy, the median T increased from 9.73 (IQR 7.0–12.0) to 16.0 (IQR 13.75–22.0) nmol/L ($p < 0.01$), median LH increased from 4.90 IU/L (IQR 3.30–6.40) to 6.0 IU/L (IQR 4.60–9.60) ($p < 0.001$) while median FSH level increased from 6.70 IU/L (IQR 3.50–9.80) to 7.85 IU/L with IQR (5.00–13.00) ($p < 0.001$). The full data set is available in the Scholars Portal Dataverse.¹⁴

There was a significant increase in the sperm concentration with an increase in the median sperm concentration from 2.4 million/mL (IQR 0.10–7.90) to 5.0 million/mL (IQR 0.4–15.6) and an increase in the mean count from 13.01 ± 3.6 million/mL to a mean of 22.12 ± 4.5 million/mL. There was no significant change in sperm motility or semen volume (**Table 1**). At baseline, 22% of the men were azoospermic, with 33% of these men having sperm in the ejaculate following CC therapy ($p = 0.08$, Chi Squared test).

Prediction of individual patient sperm concentration following three months of clomiphene citrate therapy

A model was developed (**Figure 1**) which predicted sperm concentration following three months of therapy with CC. Initial sperm concentration, LH, T, age and sperm motility were all independently predictive of the increase in sperm concentration following CC therapy (**Table 1**). These as well as serum FSH were included to provide a predicted sperm concentration for individual patients (**Figure 1**) and to provide the probability that the man's sperm concentration will be > 15million/mL (WHO normal range), total motile count > 5 million/mL (range below which IVF is often

Table 1. Model parameters for sperm concentration following three months of clomiphene citrate use.

	Estimate	z value	P	95% CI for Estimate
Negative binomial section				
(Intercept)	331.584	0.908	0.364	-384.269, 1047.437
Age_initial.form	-9.786	-0.876	0.381	-31.679, 12.107
Age_initial.form'	13.61	0.842	0.4	-18.087, 45.307
T.Pre	10.509	0.879	0.38	-12.935, 33.953
LH.Pre	-6.867	-0.851	0.395	-22.674, 8.94
FSH.Pre	2.079	0.594	0.552	-4.777, 8.935
Volume.Pre	-4.62	-0.598	0.55	-19.775, 10.535
Motility.Pre	2.595	0.875	0.382	-3.216, 8.406
Motility.Pre'	-1.229	-0.661	0.509	-4.875, 2.417
Motility.Pre=0	-115.891	-0.883	0.377	-373.104, 141.322
SpermConc.Pre	-77.842	-0.837	0.403	-260.22, 104.536
SpermConc.Pre'	-23.074	-0.004	0.996	-10222.804, 10176.656
SpermConc.Pre=0	-49.004	-0.983	0.326	-146.732, 48.724
Logit section				
(Intercept)	-0.551	-0.358	0.720	-3.564, 2.462
Age_initial.form	0.079	1.985	0.047	0.001, 0.157
Age_initial.form'	-0.107	-2.028	0.043	-0.21, -0.004
T.Pre	-0.010	-0.791	0.429	-0.035, 0.015
LH.Pre	-0.050	-2.085	0.037	-0.098, -0.003
FSH.Pre	-0.020	-1.538	0.124	-0.046, 0.005
Volume.Pre	-0.038	-0.762	0.446	-0.136, 0.06
Motility.Pre	-0.024	-1.486	0.137	-0.055, 0.008
Motility.Pre'	0.042	2.342	0.019	0.007, 0.077
Motility.Pre=0	-0.638	-1.591	0.112	-1.424, 0.148
SpermConc.Pre	0.321	10.826	< 0.001	0.263, 0.379
SpermConc.Pre'	-1.090	-10.27	< 0.001	-1.298, -0.882
SpermConc.Pre=0	0.371	0.603	0.546	-0.835, 1.577

T.Pre: Testosterone pre clomiphene citrate use; LH.Pre: Luteinizing hormone pre clomiphene citrate use; FSH.Pre: Follicle-stimulating hormone pre clomiphene citrate use; Volume.Pre: Semen volume pre clomiphene citrate use; Motility.Pre: Sperm motility pre clomiphene citrate use; Motility.Pre=0: Non-motile sperm pre clomiphene citrate use; SpermConc.Pre: Sperm concentration pre clomiphene citrate use; SpermConc.Pre=0: Azoospermic sample pre clomiphene citrate use; Final sperm concentration was significantly independently related to initial sperm concentration, age, serum LH and sperm motility.

recommended) and 0 million/mL (nomogram available at http://riskcalc.org/clomiphene_citrate/). Predictive probability of the model is shown in **Figure 2**.

Prediction of semen volume and sperm motility following three months of clomiphene citrate therapy

The final semen volume was only related to initial semen volume and none of the other tested parameters, so the model developed for final semen volume prediction only used the baseline volume (**Table 2**). Final motility was most closely correlated to initial motility, with the final model including age, T, semen volume and sperm concentration (nomogram available at http://riskcalc.org/clomiphene_citrate/).

Predicted testosterone levels following three months of clomiphene citrate therapy

The post-CC testosterone levels were most closely and significantly correlated to the pre-CC testosterone levels (**Table 3**), but the addition of information on gonadotropin levels and age significantly improved the predictive performance of the model. The nomogram is shown in **Figure 3** with the online nomogram available at (nomogram available at <http://riskcalc.org>).

Figure 1. Predicted sperm concentration following three months of clomiphene citrate therapy based on age, hormone values and initial semen parameters.

[org/clomiphene_citrate/](#)). Conversely, LH and FSH levels post-CC also correlated significantly to the pre-CC LH and FSH levels respectively and not significantly to other parameters (Tables 4–6).

Discussion and conclusion

CC is widely used as an empiric therapy to manage male infertility. Edmund Y. Ko *et al.*, in 2012 reported that CC is the most widely prescribed medication among urologists in the American Urological Association for the treatment of idiopathic male infertility.³

While certainly there are studies which do not show any benefit of CC to treat male fertility, most notably a very large, controlled trial published in 1992,^{15,16} the majority of studies do show improvements in sperm parameters and pregnancy rates with CC therapy.^{9,17,18} A meta-analysis by Chua *et al.*, published in 2013 found a 2.4 OR (95% CI: 1.47–3.94) of pregnancy in couples where the men were taking empiric CC therapies.⁹

What remains unclear is the expected response to the CC for individual patients, information which would help couples decide on therapies and allow clinicians to tailor therapies to the individual patient.

Figure 2. Predictive probability of the model for sperm concentration. (ZINB: Zero inflated negative binomial modeling).

Table 2. Model parameters for semen volume following three months of clomiphene citrate (CC) use.

Parameter	Estimate	s.e.	95% CI	p-value
Intercept	0.734	0.167	0.406, 1.062	<0.001
Volume.Pre	0.662	0.051	0.563, 0.761	<0.001

Semen volume three months following CC use was significantly related to initial semen volume and none of the other semen parameters, age or hormone values. Outcome: LH at three months; We consider model includes variable: LH. Pre, FSH. Pre, SpermConc. Pre and other parameters are tested but removed for non-improvement in outcome. (LH.Pre: Luteinizing hormone pre clomiphene citrate use; FSH.Pre: Follicle-stimulating hormone pre clomiphene citrate use; SpermConc.Pre: Sperm concentration pre clomiphene citrate use)

Table 3. Model parameters for testosterone levels following three months of clomiphene citrate therapy.

Parameter	Estimate	s.e.	95% CI	p-value
Intercept	0.064	0.015	0.034, 0.095	<0.01
Age_initial.form	0.000	0.000	0.000, 0.001	0.19
T.Pre	-0.000	0.001	-0.006, -0.001	<0.01
FSH.Pre	0.001	0.000	0.000, 0.001	0.06
Volume.Pre	0.002	0.001	0.000, 0.004	0.07
SpermConc.Pre > 0	-0.003	0.006	-0.016, 0.009	0.61

T.Pre: Testosterone pre clomiphene citrate use; FSH.Pre: Follicle-stimulating hormone pre clomiphene citrate use; Volume.Pre: Semen volume pre clomiphene citrate use; SpermConc.Pre: Sperm concentration pre clomiphene citrate use.

Figure 3. Nomogram to predict serum testosterone concentration following three months of clomiphene citrate therapy for men with infertility. (FSH: follicle stimulating hormone).

Table 4. Model parameters for leutinizing hormone levels following three months of clomiphene citrate use.

Parameter	Estimate	s.e.	95% CI	p-value
Intercept	7.157	1.029	5.118, 9.196	<0.001
LH.Pre	0.243	0.070	0.103, 0.382	<0.001
FSH.Pre	0.126	0.049	0.029, 0.223	0.012
SpermConc.Pre > 0	-2.877	0.905	-4.669, -1.085	0.002

Outcome: FSH.3m We consider a linear model for the FSH.3M outcome. The model includes variable: LH. Pre, FSH. Pre, SpermConc. Pre and other parameters are tested but removed for non-improvement in outcome. (LH.Pre: Luteinizing hormone pre clomiphene citrate use; FSH.Pre: Follicle-stimulating hormone pre clomiphene citrate use; SpermConc.Pre: Sperm concentration pre clomiphene citrate use.)

Table 5. Model parameters for FSH following three months of clomiphene citrate use.

Parameter	Estimate	s.e.	95% CI	p-value
Intercept	4.508	5.899	-7.177, 16.193	0.446
Age_initial.form	0.105	0.172	-0.236, 0.446	0.542
Age_initial.form'	-0.387	0.252	-0.885, 0.112	0.128
FSH.Pre	0.675	0.057	0.563, 0.787	<0.001
Motility.Pre>0	-0.716	1.374	-3.438, 2.006	0.603
SpermConc.Pre > 0	-2.852	1.672	-6.164, 0.460	0.091

FSH.Pre: Follicle-stimulating hormone pre clomiphene citrate use; Motility.Pre: Sperm motility pre clomiphene citrate use; SpermConc.Pre: Sperm concentration pre clomiphene citrate use.

With this present study, we have developed a nomogram (available at http://riskcalc.org/clomiphene_citrate/) using baseline values of age, FSH, LH, T levels and semen parameters (volume, count and motility) to provide the expected semen parameters and testosterone levels following CC therapy as well as the odds of having normal sperm counts and total motile counts of > 5 million sperm (level at which IUI could be considered).¹⁹ These are the first published nomograms on the expected changes in semen parameters and testosterone levels for individual men following clomiphene citrate therapy.

This nomogram will help clinicians predict the chances of clinically meaningful responses to CC therapy. As an example, a 36-year-old male with semen volume = 1.6 mL, sperm concentration = 7 million/mL and motility = 23% (sperm values

Table 6. Model parameters for sperm motility following three months of clomiphene citrate use.

	Logit section				Negative binomial section			
	Estimate	z value	p-value	95% CI for Estimate	Estimate	z value	p-value	95% CI for Estimate
(Intercept)	0.908	2.088	0.037	0.056, 1.76	3.011	5.092	0.000	1.852, 4.169
Motility.Pre	0.170	0.587	0.557	-0.398, 0.739	0.024	5.195	0.000	0.015, 0.033
Motility.Pre=0	-19.896	-1.214	0.225	-52.018, 12.227	-0.093	-0.325	0.745	-0.656, 0.469
Age_initial.form	-				-0.009	-0.809	0.419	-0.03, 0.012
T.Pre	-				0.006	0.567	0.571	-0.015, 0.027
Volume.Pre	-				0.045	1.127	0.260	-0.033, 0.124
SpermConc.Pre	-				0.001	0.462	0.644	-0.002, 0.004
SpermConc.Pre=0	-				-0.240	-0.537	0.591	-1.115, 0.635

Motility.Pre: Sperm motility pre clomiphene citrate use; Motility.Pre=0: Non-motile sperm pre clomiphene citrate use; T.Pre: Testosterone pre clomiphene citrate use; Volume.Pre: Semen volume pre clomiphene citrate use; SpermConc.Pre: Sperm concentration pre clomiphene citrate use; SpermConc.Pre=0: Azoospermic sample pre clomiphene citrate use.

where IVF might be recommended), FSH = 3, LH = 2 and T = 12, following CC therapy will have an expected semen volume = 1.6 mL, sperm concentration = 21 million/mL, sperm motility = 21%. There is a 46% chance that his sperm count will be > 15 million/ml (normal) and a 48% chance that the total motile count will be > 9 million. He would have a good chance to increase his sperm parameters to a level where a spontaneous pregnancy is possible.

As another example, a 34-year-old male with baseline semen volume = 1.3mL, sperm concentration = 3 million/mL and sperm motility = 20% (likely needing IVF) with FSH = 3.5, LH = 3 and T = 9. Following CC therapy, the expected semen volume = 1.3mL, sperm concentration = 8.6 million/mL, sperm motility = 20%. Following CC therapy, there is only a 7% chance that his sperm counts will be normal and a 4% chance that the total motile count would be > 9 million. Most likely, this couple would still need to manage the fertility with IVF even after the CC therapy. These are two examples of how this nomogram could help with treatment planning for couples with male factor infertility.

There are several limitations of this study: data comes from a single center using a single CC therapy protocol and should be replicated in other centers, the numbers of patients recruited with azoospermia (due to spermatogenic failure) is low, meaning that our nomogram is likely to be less accurate for men with spermatogenic failure and the men consumed “fertility” vitamins and minerals throughout this study. While guidelines from the American Urology Association and the American Society of Reproductive Medicine conclude that supplements are of “questionable clinical utility in treating male infertility” with non-significant effects on sperm counts, our study can’t preclude an effect of a combination of supplements and CC.²⁰

Paradoxically, the weakness of a single centre is also a strength, with one laboratory for all of the biological testing, which improves the consistency of the testing.

This is the first study to publish a predictive model for expected post therapy sperm parameters in men using CC. This is an important study since it provides clinicians with information to help personalize fertility care for the couples. This type of nomogram will allow clinicians to have a more informed discussion with patients about the expected semen parameters with CC “treatment” and allow couples to make a more informed decision to select between the many options that exist to treat and/or manage (using the Assisted Reproductive Technologies (ARTs)) male infertility.

Finally, in the future, a goal should be to develop personalized predicted pregnancy rates with the use of CC therapy. This would allow clinicians to directly compare the outcomes of CC therapy with the use of the ARTs.

Data availability

Underlying data

Scholars Portal Dataverse: Underlying data for ‘Nomogram to predict changes in semen parameters following clomiphene citrate therapy for males with abnormal semen parameters’, <https://www.doi.org/10.5683/SP2/PMZA4H>.¹⁴

This project contains the following underlying data:

- Data file: Clomid data – July 2021.tab (Study patients' pre-clomiphene citrate sperm concentration, hormone values and age; and post-treatment 3 months sperm concentration and hormone values.)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Consent

Written informed consent for publication of the patients' details was obtained from the patients.

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Faiza Alam

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It is a well-written study. The study developed nomograms based on baseline semen, hormonal and patient characteristics to predict the semen and hormonal changes following CC use. They claim it to be the first study to publish a predictive model for expected post-therapy sperm parameters in men using CC. This is an important study since it provides clinicians with information to help personalize fertility care for couples.

Need a bit of clarity regarding:

1. How was the sample size calculated?
2. What was the number of initial recruits and dropout rate?

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 01 April 2022

<https://doi.org/10.5256/f1000research.59278.r126875>

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Jay I. Sandlow

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Peter Dietrich

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1. The number of patients is somewhat small to develop a nomogram. Was there a statistician involved to determine if there was adequate power to develop this?
2. The inclusion of patients with varicoceles adds a known cause of fertility impairment to some of the cohort, which was then not added to any of the analysis. At the very least, a table row of how many patients had varicoceles and what grade would be needed.
3. Please describe "normal semen analysis" for exclusion criteria. What criteria were used? Presumably, morphology was not included in your inclusion/exclusion criteria because it is not in the table, but please comment on this as well.
4. The manuscript states sperm concentration of 5 million/mL is used to predict ability to do IUI. Please provide a reference for this. Concentration is a difficult variable to use as it does not indicate total motile number because volume is variable. Most institutions use 5-10 million total motile as an IUI cutoff.¹ Using sperm concentration also makes the data input to the nomogram less clinically applicable.
5. The table row headings are distracting as is. The table was clearly imported from R stats but is difficult to read even with the footnotes describing each row.
6. The Methods state that men were instructed to use supplements if they were not already. Why, and what supplements? The only reference used was the RCT using vitamin E. Was this the only supplement?²
7. The figures and tables are in the middle of the Discussion/Conclusion section. This is visually

confusing.

8. In the Discussion, there is a reference to a sperm concentration of >15 million/mL as “normal”. This is not true. This is just the lowest concentration in the accepted WHO reference range. I would remove that term, as it may be confusing to some readers.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: male fertility and reproductive endocrinology

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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