

Peer Review File

Article information: <http://dx.doi.org/10.21037/tau-20-919>.

Reviewer A

COMMENT 1:

Though this study is retrospective with a small number of patients, the authors are congratulated on presenting an interesting analysis of primary aromatase inhibitor use for testosterone deficiency in overweight subfertile men.

Reply 1: Thank you

Changes in text: None

COMMENT 2:

Methods

Please mention that BMI >25 is considered overweight, and that is why this BMI cutoff was used for this study.

Reply 2: This was added to our methods section.

Changes in text: Page 5, lines 11 – 12: “Hypogonadal, subfertile men with BMI \geq 25 kg/m² who were treated with anastrozole (1 mg daily) between 2008 and 2014 were included in this study as BMI \geq 25 kg/m² is considered overweight.”

UPDATED VERSION: Page 6, lines 12 - 14

COMMENT 3:

Please further explain criteria for placing patients on primary aromatase inhibitor therapy for hypogonadism, rather than an alternative therapy such as clomiphene citrate. Were any other criteria used such as have been used in other studies, including an estradiol level >60 pg/mL, symptoms of hyperestrogenemia or a T:E ratio <10:1.

Reply 3: Hypogonadal patients with BMI \geq 25 kg/m² were considered for anastrozole but no other strict criteria was considered. Treatment options were discussed with the patient and decision to prescribe anastrozole was through shared decision making.

Changes in text: None

COMMENT 4:

Please clarify the specific lab assay used for hormonal measurements, as it is recommended that testosterone be measured using liquid chromatography/mass

spectrometry for most accurate measurements.

Reply 4: Commercial laboratories performed the hormonal analysis, direct chemiluminescent immunoassays were used to measure testosterone, along with a repeat test to confirm levels.

Changes in text: Please see page 5 line 23/24 and page 6 line 1 “Commercially available laboratories were used for the hormonal testing and testosterone was measured via direct chemiluminescent immunoassays.”

UPDATED VERSION: page 7, lines 5 - 7

COMMENT 5:

Discussion

The authors present interesting data on pregnancy rates in their cohort. Please consider discussing how the rates of IVF and IUI in this population compare to those in men being treated with clomiphene citrate or with idiopathic male subfertility.

Reply 5: We thoroughly did a Pubmed search and were unable to come across specific rates quoting success specifically of IVF/IUI with clomiphene citrate and idiopathic male subfertility or clomiphene citrate and patients with BMI > 25 as in the subset in our study. A lot of the fertility data available was poorly accrued or included data using all forms of pregnancy (natural to ICSI) and as such, did not feel that we could reliably include this data in our discussion.

Changes in Text: None

COMMENT 6:

Sperm morphology is thought to have the least impact on fertility, would not put so much emphasis on this in the discussion, consider removing lines 10-14, page 10.

Reply 6: Thank you, we do acknowledge this and will remove.

Changes in text: Page 10 Lines 10 – 14 removed regarding sperm morphology

UPDATED VERSION: correlates to Page 12, line 23

COMMENT 7:

Future Directions

Are the authors considering any future directions for their study? It would be interested to compare responses to aromatase inhibitors in men with normal BMI versus the patients with BMI >25 included in this cohort.

Reply 7: We are interested in a future study regarding response rates to aromatase

inhibitors in men with normal BMI versus the patients in this cohort.

Changes in text: Page 11 Line 1 – 3: Additionally, a future prospective randomized clinical trial regarding response rates to aromatase inhibitors in men with normal BMI versus men with BMI > 25 kg/m² would be of great interest as well.

UPDATED VERSION: page 13, lines 14-16

COMMENT 8:

It was acknowledged in the limitations of the study that BMI is non-specific and does not necessarily correlate with elevated body fat composition. Has any thought been given to using alternative measures of body fat composition?

Reply 8: We agree that BMI is non-specific to body fat composition, and agree in future studies, alternative to BMI should be considered such as the gold standard dual-energy X-ray absorptiometry (DXA) scan.

Changes in text: Page 10 lines 19 – 21 “In future studies, alternatives to BMI for body fat composition should be considered, such as the dual-energy X-ray absorptiometry (DXA) scan.

UPDATED VERSION: page 13, lines 7-8

Reviewer B

COMMENT 1:

This is a retrospective study to determine the impact of anastrozole treatment on obese, sub fertile men on hormone profiles, semen parameters, and fertility outcomes.

Reply 1: Agreed

Change in text: None

COMMENT 2:

The authors found significant improvement from baseline to follow up in testosterone, T/E ratio, sperm concentration, and TMSC. Overall pregnancy rate was nearly 50% for the cohort.

Reply 2: Agreed

Change in text: None

COMMENT 3:

The study design is sound and statistical methods are appropriate. It does however suffer the limitations of retrospective studies. There is no way to fully control for variance in patient history prior to the study period. It might have made sense to exclude

patient who had varicocelectomy in order to best isolate the effects of anastrozole. Overall n is low and single-institution studies must be cautiously interpreted in terms of global applicability.

Reply 3: Agreed, however difficult given the retrospective nature. For future studies, we would consider excluding patients with varicocelectomy to avoid confounding and include studies at multiple institutions to capture a global patient subset.

Change in text: None

COMMENT 4:

What were the causes of “secondary infertility” for the three patients that carried this label?

Reply 4: We defined secondary infertility as couples who previously had a successful pregnancy and now were unable to achieve pregnancy after 1 year of trying. We were not able to determine the cause in these cases.

Change in text: None

COMMENT 5:

There are several grammatical errors so I encourage the authors to carefully edit their manuscript before final submission.

Reply 5: Thank you, edited.