Association of Age and Body Mass Index with Response to Clomiphene Citrate or Letrozole as Treatment for Anovulatory Infertility in a Sample of Filipino Women

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Background: Clomiphene citrate is used as the first line drug for anovulatory infertility treatment. When a woman fails to ovulate using clomiphene at maximum dose, letrozole is used as a second line drug.
Objective: To determine association between a patient's age and body mass index (BMI) and their response to clomiphene citrate or letrozole in the treatment of anovulation-related infertility.
Materials and Methods: The authors reviewed 147 patient records from January 2011 to August 2016 and investigated the age, BMI and response of patients when given clomiphene or letrozole for ovulation induction.
Results: Ninety-nine (99) patients received clomiphene citrate while the other 118 patients received letrozole. Those who responded positively to clomiphene were at least 35 years old (72.2%) or had above normal BMI (61.5%). Patients who responded positively to letrozole were at least 35 years old (95%) and were categorized with above normal BMI (82.9%). The authors found that patients who are older than 35 years of age are more likely to respond to letrozole compared to younger patients.
Conclusion: This study found no significant association between BMI and response to either Letrozole or Clomiphene. Patients who are more than 35 years old are more likely to respond to letrozole, compared to younger patients.

Keywords: anovulatory infertility, clomiphene citrate, letrozole, body mass index

Introduction

Clomiphene citrate is widely regarded as a first line drug for inducing ovulation due to its low cost, ease in administration and high ovulation rate (60-80%).[1-2] It is a mixed estrogen agonist and antagonist, and acts as a competitive estrogen antagonist at physiological female estrogen levels.[3,4]

Clomiphene citrate stimulates ovulation by competing with estrogen binding to the estrogen receptors in the hypothalamus. Treatment starts at a lower dose (50 mg/day) and gradually increased in subsequent cycles until ovulation. However, around 20-25% of women do not achieve ovulation even when given a maximum dose of 150 mg/day.[5] Thus, they are considered clomiphene-resistant and they fail to ovulate.

Letrozole, on the other hand, is a highly specific, third-generation, non-steroidal aromatase inhibitor with ovulation induction potential.[6] It inhibits estrogen production, which in turn, increases GnRH release and pituitary follicle-stimulating hormone (FSH) synthesis. In the 2015 study by Palihawadana, et al., they found that the ovulation response rate was 76% for patients who responded to clomiphene previously and 24% for patients with clomiphene resistance.[7]

In clinical use since the 1960s, clomiphene citrate is the most common ovulation induction first line oral agent for treating anovulatory infertility due to its low cost, lesser incidence of multiple pregnancy and ovarian hyperstimulation syndrome, and because it requires less intense monitoring.[8] When a woman fails to ovulate using clomiphene at maximum dose, or when she ovulates but does not conceive after three to six months on clomiphene use, Letrozole is used as a second line drug. This practice may lead to a waste of time and resources, and may spell the difference between success and failure to conceive, especially if the couple has limited time together. To date, there have been no studies yet that will help the general obstetrician or infertility specialist predict the ovulatory response to either Clomiphene or Letrozole based on demographic factors (age and BMI) alone and may prove to be beneficial for the clinician in making the right choice.

In this study, the authors tried to determine if there is a relationship between a patients' age and body mass index (BMI) and their response to clomiphene citrate or letrozole in the treatment of anovulation-related infertility. They aimed to describe the response to Clomiphene citrate or Letrozole, effect of BMI on the response to both drugs, and the combined effect of age and BMI on treatment response.

Materials and Methods

This retrospective analytical study was conducted in a private infertility clinic located in Pampanga, Philippines. The inclusion criteria for the study participants were adult Filipino females diagnosed with anovulatory infertility who were seen between January 2011 and August 2016. The authors excluded from the data collection and analyses those patients diagnosed with decreased ovarian reserve, or had an ovarian mass or previous ovarian surgery.

Patients were treated with incremental doses of clomiphene before shifting to letrozole. In this study, the usual starting dose of clomiphene citrate was 50 mg per day for five days with a maximum dose of 150 mg per day for five days, while the standard letrozole dose was 2.5 mg to 7.5 mg per day for five days. The authors categorized the patients into seven categories based on treatment regimen. These are:

- Clomiphene-responsive patients as patients who ovulated and were no longer given letrozole.
- Letrozole-responsive patients were those patients who ovulated and were no longer given clomiphene citrate.
- Clomiphene-resistant but letrozole-responsive patients were those patients who did not respond to clomiphene administration but ovulated after letrozole administration.
- Conversely, letrozole-resistant but clomiphene-responsive patients were those patients who did not respond to letrozole administration but ovulated after clomiphene administration.
- Clomiphene-resistant and letrozole-resistant patients were those patients who did not ovulate when administered with both clomiphene and letrozole.
- Clomiphene-responsive and letrozole-responsive patients were those patients who ovulated when administered with both clomiphene and letrozole.
- Clomiphene-resistant patients were those patients who did not respond to clomiphene administration but did not receive letrozole.

In addition, the authors also tried to look for patients who were letrozole-resistant or those patients who did not respond to letrozole administration but did not receive clomiphene.

All information collected from the subjects were encoded and analyzed using R statistical software version 3.4. The authors computed for descriptive statistics (frequency, percent) and odds ratios (with 95% confidence interval estimates) for univariable and multivariable binary logistic regression analyses, with the level of significance set at 0.05.

The authors submitted the study protocol to the Ethics Review Board (ERB) of the Angeles University Foundation Medical Center. The results were kept anonymous and the patients' personal health information were not discussed outside of

the study to ensure the patients' right to privacy and right to equity and fairness.

Results

One hundred forty seven eligible patient records were included in the study. There were 99 patients who received clomiphene citrate and 118 patients who received Letrozole.

Thirteen patients (72.2%) at least 35 years old responded positively to clomiphene while 27.8% did not. Fifty four (66.7%) patients who were younger than 35 years old responded positively to clomiphene while 33.3% did not. The odds of a positive versus negative response to clomiphene citrate was about the same for patients aged ≥ 35 years old and patients < 35 years old (p = 0.649).

Sixteen (61.5%) patients categorized with above normal BMI responded positively to clomiphene citrate while 38.5% did not. Fifty one (69.9%) patients who were either normal or underweight responded positively to clomiphene citrate while 30.1% did not. The odds of a positive versus negative response to clomiphene citrate was about the same for patients with above normal BMI and those with normal or below normal BMI (p = 0.437).

Ninety five percent of patients at least 35 years of age responded positively to letrozole while 5% did not. Sixty one (78.2%) patients who were younger than 35 years old responded positively to letrozole while 21.8% did not. The odds of a positive versus negative response to letrozole was found to be about 5.3 times higher among patients > 35 years old versus patients < 35 years old (p = 0.032).

Twenty nine (82.9%) patients categorized with above normal BMI responded positively to letrozole while 17.1% did not. 84.3% of patients

Table 1. Response to clomiphene citrate by age group (n = 99).

Age		Response to clomiphene citrate, n (%)		Total, n (%)
		(+)	(-)	
≥ 35 years old		13 (72.2%)	5 (27.8%)	18 (100%)
< 35 years old		54 (66.7%)	27 (33.3%)	81 (100%)
Total		67 (67.7%)	32 (32.3%)	99 (100%)
	Odds	1.1	0.8	odds ratio = 1.3
	95% confidence interval	[0.8, 1.5]	[0.4, 1.9]	[0.4, 4.0]

Table 2. Response to clomiphene citrate by BMI category* (n = 99)

BMI category	Response to clomiphene citrate, n (%)		Total, n (%)
	(+)	(-)	
Above normal	16 (61.5%)	10 (38.5%)	26 (100%)
Normal / underweight	51 (69.9%)	22 (30.1%)	73 (100%)
Total	67 (67.7%)	32 (32.3%)	99 (100%)
Odds	0.9	1.3	odds ratio = 0.7
95% confidence interval	[0.6, 1.2]	[0.7, 2.3]	[0.3, 1.8]

*Based on WHO classification

who were either normal or underweight responded positively to letrozole while 15.7% did not. The odds of a positive versus negative response to letrozole was about the same for patients with above normal BMI and those with normal or below normal BMI (p = 0.842).

Multivariable analysis was performed to determine the combined effect of age and BMI to the patients' response to clomiphene citrate, and authors found that the two variables taken together did not significantly affect the outcome of the drug.

Multivariable analysis of the relationship between patients' age and BMI and their response to letrozole showed a significant association between age and the outcome. Specifically, patients aged 35 years old and above were 5.3 times more likely to respond positively to letrozole as compared to patients less than 35 years old.

Table 3. Response to letrozole by age group (n = 118).

Age		Response to letrozole, n (%)		Total, n (%)
		(+)	(-)	
≥ 35 years old		38 (95.0%)	2 (5.0%)	40 (100%)
< 35 years old		61 (78.2%)	17 (21.8%)	78 (100%)
Total		99 (83.9%)	19 (16.1%)	118 (100%)
	Odds	1.2	0.2	odds ratio = 5.3
	95% confidence interval	[1.1, 1.4]	[0.1, 0.9]	[1.2, 24.2]

Table 4. Response to letrozole by BMI category (n = 118)

BMI category	Response to letrozole, n (%)		Total, n (%)
	(+)	(-)	
Above normal	29 (82.9%)	6 (17.1%)	35 (100%)
Normal / underweight	70 (84.3%)	13 (15.7%)	83 (100%)
Total	99 (83.9%)	19 (16.1%)	118 (100%)
Odds	1.0	1.1	odds ratio = 0.9
95% confidence interval	[0.8, 1.2]	[0.5, 2.6]	[0.3, 2.6]

Table 5. Multivariable analysis of the association between patients' age and BMI and their response to clomiphene citrate (n = 99).

Independent/Predictor variables	Odds Ratio	95% Confidence Interval	p-value
Age > 35 years old*	1.3	[0.4, 4.0]	0.663
Underweight**	0.3	[0.04, 1.7]	0.154
Above normal BMI**	0.6	[0.2, 1.6]	0.335

*reference category is < 35 years old
**reference category is normal BMI

Table 6. Multivariable analysis of the association between patients' age and BMI and their response to letrozole (n = 118)

Independent/Predictor variables	Odds Ratio	95% Confidence Interval	p-value
Age > 35 years old*	5.3	[1.2, 24.2]	0.032
Underweight**	0.4	[0.07, 2.7]	0.368
Above normal BMI**	0.8	[0.3, 2.5]	0.709

*reference category is < 35 years old
**reference category is normal BMI

Discussion

Anovulation accounts for 20%-40% of all infertility cases and can be severe enough to prevent conception (anovulation). The most common cause of female infertility is ovulatory dysfunction, which affects 20%-30% of couples seeking treatment.[9,10] The World Health Organization (WHO) categorized affected individuals according to the underlying pathology and baseline FSH levels. The present study focused on WHO group 2 ovulatory disorder patients, who have normal baseline FSH levels and are thus called patients with normogonadotropic hypogonadism.

Clomiphene citrate is the most common oral ovulation induction agent and is often started at a low dose (50 mg/day) and increased in succeeding cycles. If the maximum dose of 150 mg/day does not lead to ovulation, then the patients are deemed to be resistant to clomiphene citrate.

Letrozole is a third generation aromatase inhibitor that has emerged as a potential first line ovulation induction agent. Its effects are no longer present around the time of ovulation and implantation because it has a shorter half-life (45 hours) compared to clomiphene citrate (5 days). Many have begun to favor letrozole use because the unwanted anti-estrogenic effects caused by clomiphene citrate on the endometrium and the cervical mucus are not observed with its use.[11] However, many still use it as a second line agent given the limited evidence on letrozole and the lack of studies on the predictors of treatment response to it.

Previous studies have compared the efficacy of clomiphene citrate and letrozole for ovulation induction, in vitro fertilization, and intrauterine insemination settings.[12,13,14]

However, there have been no documented studies which have investigated potential factors to be considered to help shorten the time needed to ovulation.

In the 1999 study by Imani, et al., patients who were treated with clomiphene citrate and who did conceive presented more frequently in younger patients ($p < 0.0001$) and in those who presented with amenorrhea ($p < 0.05$) upon initial screening.[15] A multivariate analysis in the same study found age and cycle history (oligomenorrhea vs. amenorrhea) to be the only significant predictors of conception.[15] However, the Imani study looked at conception as the outcome and not ovulation, which is a distinct difference between studies. In terms of BMI, previous studies have indicated that it is significantly higher in patients who are resistant to clomiphene citrate when it comes to ovulation induction.[16,17]

Based on the findings of the present study, patients' response to clomiphene citrate was not significantly associated with age and BMI. In addition, there was no significant association between how patients respond to letrozole administration and their BMI. But, for those who received letrozole, patients aged 35 years old and above were found to be significantly more likely to respond to the drug compared to younger patients (those less than 35 years old). This significant finding was also the observed result even after performing additional analyses. However, when the cutoff age was lowered the result became non-significant.

The authors also performed a multivariable analysis to determine the combined effect of age

and BMI to the patient's response to clomiphene citrate. Although statistically, the authors found that age and BMI did not significantly affect the response to the drug ($p > 0.05$) clinically, they observed that lower chances of a positive response to clomiphene citrate were noted among patients with either below or above normal BMI (odds ratios = 0.3 and 0.6, respectively).

A similar multivariable analysis was conducted for letrozole and found that patients aged 35 years old and above were 5.3 times more likely to respond positively to letrozole compared to patients less than 35 years old. Additionally, although not statistically significant, lower chances of a positive response to letrozole were again observed among patients with either below or above normal BMI (odds ratios = 0.4 and 0.8, respectively).

Present study findings indicate that age, but not BMI, significantly affects whether a patient responds to letrozole treatment. This finding concurs with a previous study involving the pharmacokinetics of letrozole. In the 2011 study by Desta, et al., they found that letrozole concentrations increase with increasing age.[18] This was consistent with the study findings of Hukkanen, et al., in 2005 and Sinues, et al., in 2008.[19,20] Therefore, it is possible that patients may be undergoing certain metabolic changes such as decreasing CYP2A6 activity (which is the primary clearance mechanism for letrozole in vivo18) when they reach age 35, which is considered the start of advanced reproductive age. With plasma letrozole concentrations increasing with increasing age, older patients may have a higher chance of responding positively to letrozole exposure.

Reproductive endocrinologists and infertility experts may recommend patients who are older than 35 years old to start their ovulation induction therapy using letrozole instead of clomiphene citrate, especially those patients who are categorized. Under WHO Group 2 ovulatory disorder. Furthermore, the results of the present study may help address the lack of a standardized protocol for letrozole administration by providing evidence that could trigger the need for randomized controlled trials on anovulatory infertility treatment using letrozole for older patients.

The results of this study could possibly help reduce costs and time to ovulation because if patients who can be treated with letrozole immediately are easily identified then clomiphene citrate may not necessarily be required to be administered prior. This will also be potentially valuable for patients who have limited time together to conceive as couples such as those whose spouses are overseas contract workers.

Conclusion and Recommendations

The findings in the present study show that age and BMI are not significantly associated with how a patient responds to clomiphene citrate (i.e., neither variable seems to affect response to clomiphene citrate administration). Age, but not BMI, significantly affects response to letrozole. Patients who are at least 35 years old are significantly more likely to respond, about 5.3 times as much, to letrozole, compared to younger patients.

The retrospective nature of the study may have resulted in bias as well as certain factors, which could have potential confounding effects, not having been recorded at the point of data collection. The patients were also not randomized as in prospective clinical trials.

The authors recommend that extensive clinical trials be conducted in order to validate our findings. A randomized controlled trial with only Clomiphene-naïve and Letrozole-naïve patients may be done with a Clomiphene citrate arm (no response to letrozole), and a Letrozole arm (no response to clomiphene) with a wash out period between drugs. In addition, there should ideally be no adjunct drugs given and no change in BMI within the study period. A larger multi-center retrospective analytical study similar to this may also prove valuable in terms of identifying and generalizing the treatment response patterns of Filipino patients. Increasing the parameters assessed beyond age and BMI such as FSH / LH, and free androgen index and conducting a regression analysis on the data collected, may also yield significant results.

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