A PILOT STUDY COMPARING MILD STIMULATION INVITRO-FERTILIZATION(IVF) VERSUS LONG PROTOCOL IVF AMONG WOMEN WITH ADVANCED MATERNAL AGE IN A DEVELOPING COUNTRY

Feiruz Surur[1], Mustefa Negash[1], Abel Teshome[1]

ABSTRACT

BACKGROUND: Due to the high costs involved with conventional Invitro-fertilization (IVF) methods, access to IVF is still restricted in many low- and middle-income nations. Mild stimulation IVF has been suggested as a cheaper alternative to conventional IVF to enhance access to IVF in places with limited resources since it employs lower doses of ovarian stimulating drugs. Introducing mild stimulation IVF in Ethiopia could help increase access to assisted reproductive services. There is no previous research in Ethiopia.

OBJECTIVE: This paper aimed to examine outcomes of a mild stimulation IVF pilot program at a clinic in Addis Ababa, Ethiopia. The primary outcome of the study is the biochemical pregnancy rate.

METHODS: This study was conducted at the Center for Reproductive Medicine IVF clinic. Ethical approval was obtained before the start of the data collection. A chart review of those infertile women who had undergone IVF in the past 3 years (April 1, 2019–April 1, 2022) was done. All of the electronic registrations at the clinic were complete for the data needed, and data abstraction was done using Open Data Kit (ODK). The ODK was tested on 5% of the study population and the validity checked before the start of data collection. The data was exported to Stata 14 for analysis. Summarization using frequency distribution was done for the clients' socio-demographic characteristics. We reported only the bivariate analysis since there is no statistically significant association with the outcome variable. We did not do multivariate analysis, but the intention was to do bivariate analysis followed by the multivariate analysis for those factors that have a significant association with the outcome variable. A p-value of less than 0.05 is considered statistically significant, with a 95% confidence interval.

RESULTS: A study of 296 IVF clients found that 69.3% were women whose age was less than or equal to 35 years, while 30.7% of women were older than 35. Of the 296 women, 288 (97.3%) had their B-HCG result known, with 62.5% being negative and 37.5% positive. The purpose of the study was to determine which procedure was best for older women (age higher than 35 years). A subgroup analysis of 83 women with advanced age found that there was no significant statistical difference in pregnancy rate between mild stimulation and long protocol IVF (COR=0.78, P-value=0.727, 95% C.I=0.22-2.85). However, cross-tabulation analysis shows that among the 17 cases who were positive for pregnancy, mild stimulation had higher pregnancy rate of 13 (76.5%) compared to the long protocol with 4 (23.5%) in this age group. The long protocol cases had a mean requirement of gonadotropin medication which was threefold higher than mild stimulation IVF. Although the statistical analysis didn't show statistical association, the cross-tabulation showed that there is a higher pregnancy rate among IVF clients of advanced maternal age who had undergone mild stimulation IVF. The gonadotropin requirement for the long protocol was threefold higher

1 St. Paul's Hospital Millennium Medical College, Department of Obstetrics and Gynecology, CFRM unit

than the mild stimulation protocol, and this can be interpreted as indicating that the cost of mild stimulation IVF is threefold lower than that of long protocol IVF. Therefore, mild stimulation IVF is a cheaper alternative with a higher pregnancy rate.

CONCLUSION AND RECOMMENDATION: Even though there is no statistically significant difference between the two protocols, cross-tabulation showed that pregnancy rate is higher among mild stimulation cases. Additionally, the cost of gonadotropin treatment was three fold higher for long protocol IVF. Further prospective studies with a larger sample size should be conducted to confirm the results. However, based on the current findings, we recommend that mild stimulation IVF be considered as a better option for women with advanced maternal age in low resource settings, as it achieves a similar pregnancy rate at a lower cost.

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INTRODUCTION

In vitro fertilization (IVF) is a method of treating infertility that is gaining popularity worldwide. However, due to the high costs involved with conventional IVF methods, access to IVF is still restricted in many low- and middle-income nations[1]. Mild stimulation IVF has been suggested as a cheaper alternative to conventional IVF to enhance access to IVF in places with limited resources since it employs lower doses of ovarian stimulating drugs[2]. In Ethiopia, the prevalence of infertility is 26.7 percent overall, that is very high when compared to the global occurrence[3]. Introducing mild stimulation IVF in Ethiopia could help increase access to assisted reproductive services. This paper examines outcomes of a mild stimulation IVF pilot program at a clinic in Addis Ababa, Ethiopia. We hypothesized that mild stimulation IVF could offer favourable pregnancy rates with reduced costs compared to conventional IVF. This initial data on the efficacy of mild stimulation IVF in an Ethiopian population could help inform future efforts to expand affordable IVF services in other low-income countries.

METHODS

This study was conducted at the Center for Reproductive Medicine (CFRM) clinic. The CFRM was established on April 1, 2019, and is a branch of Saint Paul's Hospital Millennium Medical College (SPHMMC). This clinic provides all reproductive health, endocrinology, and Invitro-fertilization (IVF) services in a dedicated building. There are four outpatient clinics: two of them are for reproductive health services, and the other two are for the evaluation of infertile couples and endocrinology clients. On average, 100 infertile clients visit the CFRM clinic on working days, and the clinic is open from 8:30–12:30 am and 1:30–5:30 pm, seven days per week. The service is run by Reproductive Health and Endocrinology (REI) fellows and specialists.

Ethical approval was obtained before the start of the data collection from the Institutional Review Board of St. Paul's Hospital Millennium Medical College. A chart review of those infertile women who had undergone IVF in the past 3 years (April 1, 2019–April 1, 2022) was done. All of the electronic registrations at the clinic were complete for the data needed, thus all of the charts of women who had undergone IVF were obtained for further data abstraction using the Open Data Kit (ODK). The data collection tool Open Data Kit(ODK) was tested on 5% of the study population and the validity checked before the start of data collection. The data was entered into ODK, cleaned, and then exported to Stata 14 for analysis. Summarization using frequency distribution was done for the clients' socio-demographic characteristics. A bivariate analysis was done to test associations between categorical variables and outcome variables. The intention was to do bivariate analysis followed by multivariate analysis for those factors that had significant association with outcome variable. A p-value of less than 0.05 is considered statistically significant, with a 95% confidence interval. The outcome variable was a biochemical pregnancy which is dichotomized as "positive" or "negative". The single predictor variable was the type of protocol (long versus mild stimulation protocol). There are two main types of protocols based on the type of gonadotropin-releasing hormone (GnRH) analogue used: agonist and antagonist protocols. During the long protocol, GnRH agonists are given during the luteal phase of the menstrual cycle, and ovarian stimulation using gonadotropins is started on days 2 or 3 of the menses. For the antagonist protocol, ovarian stimulation is started using gonadotropins on days 2 or 3 of menses, and the GnRH antagonist will be started when the dominant ovarian follicle reaches a size of 14 mm. Mild stimulation is a modification of the antagonist protocol where the ovarian stimulation is started on the 2nd day of menses using an oral aromatase inhibitor (Letrozole) or Clomiphene citrate and stimulation with gonadotropins is initiated on the

4th day. The woman will be started on antagonist medication when the dominant follicle reaches a size of 14 mm. A woman whose stated age is above 35 years is considered to have advanced maternal age[4].

RESULTS

A study of 296 IVF clients found that 69.3% were women whose age was less than or equal to 35 years, while 30.7% of women were older than 35. Of the 296 women, 97.3% had their B-HCG result known, with 62.5% being negative and 37.5% positive.

Table 1 Sociodemographic characteristics of women who undergone IVF at public IVF center in Addis Ababa, Ethiopia.(n=296)

	Number	Percent
Age(Years)		
Mean±SD	33.1±4.8	
Minimum, Maximum	20, 40	
Duration of infertility(Years)		
Mean±SD	7.2±3.6	
Minimum, Maximum	1,23	
Age category		
<=35	205	69.3%
>35	91	30.7%
Parity		
Nulliparous	264.0	89.2
Parous	32	10.8
Type-infertility		
Primary infertility	206.0	69.6
Secondary infertility	90	30.4
Address		
Addis Ababa	201.0	67.9
Outside of Addis Ababa	95	32.1

The study focused on assessing which protocol was preferred for women with advanced age (age higher than 35 years). A subgroup analysis of 83 women with advanced age found that there was no significant statistical difference in pregnancy rate between mild stimulation and long protocol IVF (COR=0.78, P-value=0.727, 95% C.I=0.22-2.85).

However, the cross-tabulation of the data showed that among the 17 cases, 13 (76.5%) women with advanced age who underwent long protocol IVF had a negative pregnancy test, while only 4 (23.5%) had a positive pregnancy test. Similarly, among the 66 cases 53 (80.3%) of women with advanced age who underwent mild stimulation IVF had a negative pregnancy test, 13 (19.7%) had a positive pregnancy test. Comparing pregnancy rate between long protocol and mild stimulation protocol among the 17 women who had positive pregnancy test, 13 (76.5%) had undergone mild stimulation IVF, whereas 4 (23.5%) had undergone long protocol IVF. This suggests that mild stimulation IVF may be a better option for women with advanced age, as it has a higher pregnancy rate to long protocol IVF but requires less medication.

This study found no statistically significant difference in pregnancy rates between mild stimulation and long protocol IVF for women over 35 years old, though the sample size was small (n=83) and likely underpowered. However, cross-tabulation analysis shows that among the 17 cases who are positive for pregnancy, mild stimulation has higher pregnancy rate 13 (76.5%) compared to the long protocol 4 (23.5%) in this age group.

The mean and standard deviation of the number of gonadotropin ampules for long protocol was 39.2 and 2.1, respectively, and the range of gonadotropin ampules used were from 32 to 40. Whereas the mean and standard deviation of the number of gonadotropin ampules for mild stimulation IVF was 13.2 and 4.7, respectively. The pregnancy rate is higher among those with mild stimulation IVF. The long protocol cases had a mean requirement of gonadotropin medication which is threefold higher than mild stimulation IVF.

DISCUSSION

This study found no statistically significant difference in pregnancy rates between mild stimulation and long protocol IVF for women over 35 years old, though the sample size was small (n=83) and likely underpowered. However, cross-tabulation analysis suggested higher pregnancy rates with the mild stimulation protocol (76.5%) compared to the long protocol (23.5%) in this age group.

These findings align with other studies showing comparable or slightly higher pregnancy rates with mild ovarian stimulation IVF compared to conventional long protocol IVF in women with advanced maternal age. A study found no difference in ongoing pregnancy rates per started cycle between mild stimulation and long protocol IVF in women with advanced maternal age[5, 6]. Another study also found similar clinical pregnancy rates between mild stimulation and conventional protocol IVF in women ≥35 years[7].

Among the 17 cases of women who had advance maternal age, the majority (76.5%) of women who had undergone mild stimulation IVF had positive pregnancy compared to 23.5 % of women who had undergone long protocol. Similarly, according to a study by Youssef et al., although there was no statistically significant difference, the study found a trend towards a higher pregnancy rate with mild stimulation IVF [8].Another study showed that there is a statistically significant higher pregnancy rate for women who had undergone mild stimulation IVF compared to conventional IVF[9].

The higher gonadotropin requirements and costs associated with the long protocol found in this study have also been reported elsewhere. Studies showed that mild ovarian stimulation IVF reduced gonadotropin use and cost compared to conventional IVF[7, 8]. The lower costs with mild IVF make it an attractive option for fertility treatment, especially in low resource settings.

Some limitations of the current study include the retrospective design and small sample size in the subgroup analysis of women ≥35 years old. Other factors that may affect the pregnancy outcomes were not also considered in this study. Additional randomized controlled trials with larger sample sizes would allow for more definitive conclusions about pregnancy rates between protocols in women with advanced maternal age.

In conclusion, the study found that there was no statistically significant difference in pregnancy rate between mild stimulation and long protocol IVF for women with advanced maternal age. However, the cross-tabulation showed that the pregnancy rate was higher among mild stimulation IVF cases. Additionally, the cost of gonadotropin treatment was three fold higher for long protocol IVF.

Based on these findings, we recommend that further studies with a larger sample size be conducted to confirm the results. However, based on the current findings, we recommend that mild stimulation IVF be considered as a better option for women with advanced maternal age in low resource settings, as it achieves a similar pregnancy rate at a lower cost.

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CORRESPONDING AUTHOR

Abel Teshome

St. Paul's Hospital Millennium Medical College, Department of Obstetrics and Gynecology, CFRM Unit

Email: teshomeabela@gmail.com

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