IN VITRO FERTILIZATION (IVF) OUTCOMES AND PREDICTING FACTORS IN A RESOURCE-LIMITED SETTING

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ABSTRACT

INTRODUCTION: Ethiopia has only one public In-vitro fertilization (IVF) center which was opened in 2019. The aim of the study is therefore to determine predictors of the outcome of IVF in the only public fertility center in Addis Ababa, Ethiopia.

METHOD: The study is conducted in the public IVF center in Ethiopia between; April 01, 2019, to March 30, 2020. A retrospective cross-sectional study design was employed. All IVF clients meeting the inclusion criteria were included in the analysis.

RESULT: There were a total of 199 couples included in the study. The clinical pregnancy rate was found to be 30.1%. The odds of getting pregnant is 61% less among participants with female partners age ≥35 years, AOR 0.39, CI 0.18-0.83 with a p-value of 0.015. Good responders ((≥4 oocytes retrieved) accounts for 152(76.4%) of the cases. Age of female partner, day 3 Follicle Stimulating Hormone (FSH), and Antral Follicle Count (AFC) count ≥5 were significantly associated with good ovarian stimulation response with a p-value of 0.050,0.002 and 0.005 respectively.

CONCLUSION: Even though near two-thirds of the study participants did not know their exact date of birth, the reported age of female partner <35 years is associated with both good ovarian response and occurrence of pregnancy, emphasizing its importance for clinical decision making. Day 3 FSH and AFC ≥5 were associated with good ovarian stimulation response. Therefore, we recommend the combination of female partner age, day 3 FSH, and AFC ≥5 to predict ovarian response in low resource settings, since variables can be readily available without much cost to patients. Furthermore, we recommend follow up studies with a large sample size and prospective cohort design to appropriately compare the different predictors of ovarian response in our setting to develop evidence-based set up specific IVF protocols and guidelines

KEYWORDS: Pregnancy rate, IVF, Resource limited setting, Predictors, Infertility, Ethiopia

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INTRODUCTION

One in every four couples in developing countries is affected by infertility[1]. Infertility, as such, is one of the major public health problems identified in Ethiopia. It is estimated that infertility affects 15 to 20% of couples in Ethiopia[2]. Realizing the magnitude of infertility in the country, Saint Paul's Hospital Millennium Medical College (SPHMMC), in collaboration with the Ministry of Health, has opened the first public Center for Fertility and Reproductive Medicine (CFRM) with functioning IVF in the country, which was inaugurated in February 2019. Before the inauguration of the center, only one private facility has been providing IVF services for over a hundred million population. In the last three decades, huge strides have been made in terms of improving pregnancy and live birth rates for IVF cycles. Previous studies have established predictors of ovarian response such as female age, antral follicle count (AFC), serum anti-Mullerian hormone (AMH), serum FSH, and serum LH concentrations[3]. Female fecundity signifcantly declines approximately at age 35 years and more sharply after age 37 years[4], and the chances of successful pregnancy become very low after the age of 40[5-7]. Accurate prediction of ovarian response and establishing a tailored treatment strategy for those patients would improve the IVF outcomes [9-11].

Basal follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), inhibin B, and antral follicle count (AFC), have been used to predict ovarian response and IVF outcomes. Basal FSH and inhibin B were found to have low predictive power [12,13]. On the other hand, AMH and AFC seem to be the most reliable determinants of ovarian response. Some investigators concluded that the predictive accuracy of these two parameters was similar[14-17], whereas other studies have shown that AMH was superior to AFC in predicting ovarian response[18,19]. However, there is a limited number of studies that assessed AFC as a predictor of IVF outcomes in poor responders[20-22]. Mutlu et al. reported that AFC was the best and the only independent parameter to predict poor response, but the study had limited value in predicting pregnancy success[20]. In Ethiopia, there is no published research on IVF as the service was not available for the general public until recently. The aim of the study is, therefore, to determine outcomes and predictors of IVF among infertile couples managed at the SPHMMC CFRM, Addis Ababa, Ethiopia.

METHOD AND MATERIALS

Study setting, period, and design

A retrospective cross-sectional study design was employed to recruit study subjects. The study was conducted at the center for reproductive medicine (CFRM) which is a fertility center administered under the SPHMMC department of obstetrics and gynecology. SPHMMC is a tertiary teaching referral hospital under the Federal Ministry of Health (FMOH). The center is located in Addis Ababa, the capital city, and is the first public IVF center in Ethiopia. Since its inauguration in February 2019, more than 5000 infertile couples were evaluated, and more than 200 IVF cycles were provided in the center. All patients who underwent IVF at the center for reproductive medicine (CFRM, SPHMMC) from April 01, 2019, to March 31, 2020, were included in this study, except couples who have frozen embryo transfers. IVF outcomes were dependent variables. IVF outcomes were measures in terms of clinical pregnancy rate diagnosed by a serum pregnancy test and ovarian response measured by the number of oocytes retrieved. Patients with ≥4 oocytes retrieved were called good responders to controlled ovarian stimulation, while those with <4 oocytes were called poor responders. The independent variables were age, AFC, BMI, AMH, and day 3 FSH.

Treatment protocol

Treatment protocols included in the study were conventional long protocol, antagonist protocol (short protocol), and minimal stimulation protocols. For long protocol, either highly purified urinary FSH (Fostimon 75 IU) or recombinant

FSH (Gonal F 75 IU), were used for stimulation starting from day 3 of the cycle. The individual dose was calculated based on the age, BMI, and AFC of the client. Downregulation was achieved by depot Goserelin (Zoladex 3.6 mg) on the 21st day of the previous cycle. The menstrual cycles of all women using this protocol were synchronized by the use of COCs (combined oral contraceptives). A variable antagonist protocol was employed where downregulation was started with Cetrotide 0.25 mg whenever the leading follicle/s reached 12cm in diameter. For minimal stimulation protocol, Letrozole 5mg PO was started on day 2 of the cycle and continued for 5 days. On the 4th day, transvaginal ultrasound monitoring was done to assess the initial response and start hMG SC 150 mg. Once the leading follicle attained 14 mm in size, down-regulation with Cetrotide was instituted. Trigger for all three protocols was decided if 3 or more leading follicles reached 18mm or more in size or greater or equal to 5 follicles reach/exceed 16mm in size.

Data collection and measurement

Data were collected by two trained data collectors using pretested well-structured questionnaires. The medical record of patients who underwent IVF during the study period was identified from the CFRM IVF registration. The records of fertility care seekers were then reviewed, and the data were collected using an open data kit (ODK). The primary investigator supervised the data collection process on daily basis.

Data processing and statistical analysis

The data were on an open data kit (ODK) and were checked for completeness and then imported into Stata statistical software release 15 (StataCorp, College Station, TX, USA) for analysis. Univariate analyses were performed using proportions and means (standard deviation), or medians (interquartile range) when the distribution was not normal. The association of the pregnancy test result and independent variables were assessed using Fisher's exact test, independent t-test, or the non-parametric test of difference of means (Mann Whitney U test). Statistical significance was declared at p=0.05 and all tests were two-sided. A full model assessing the relationship between the pregnancy test result and predictor variables was constructed after which non-significant variables were removed by a backward procedure using the likelihood ratio test ($p<0.05$) "

Ethical Considerations

Ethical clearance and permission letter to conduct the study and publish the outcome was obtained from the Institutional Review Board (IRB) of SPHMMC. Confidentiality was maintained during data collection, analysis, and interpretation by avoiding recording of names and returning client records to their place after completion of data collection. All the datasets used and/or analyzed during the current study are included in the manuscript and available from the corresponding author on reasonable request

RESULT

There were a total of 208 couples who underwent IVF during the study period. Out of these, 9 women had their embryos frozen and did not have fresh embryo transfer making the total fresh embryo transfers during the study period 199. Semen analysis results were abnormal in 25% of male partners. Close to two-thirds of the women in the study did not know their exact date of birth (64.5%). The median reported age was 32.5 years (Table 1).

Table 1: Baseline characteristics of the study subjects

Characteristics (n=208)	No.	%
Date of birth known		
Yes	73.0	35.1
No	135.0	64.9
Female partner body mass index		
<18.3	6.0	2.9
18.3-24.9	133.0	63.9
25-29.9	44.0	21.2
30-34.9	21.0	10.1
>34.9	4.0	1.9
Marital status		
Married	208.0	100.0
Educational status of female partner		
No formal education	25.0	12.1
Completed primary level education	13.0	6.3
Completed secondary level education	70.0	33.8
Diploma and above	99.0	47.8
Male date of birth known		
Yes	30.0	14.4
No	178.0	85.6
Semen analysis result		
Normal	157.0	75.5
Abnormal	51.0	24.5
Male partner TESE done		
Yes	27.0	13.0
No	181.0	87.0

Clinical pregnancy rate and predicting factors

The long protocol was used for ovarian stimulation in 136(68.3%) of the cases. The overall pregnancy rate was found to be 30.1% (60/199). Among these, 5(25%) of them were already delivered, 21(35%) aborted and 24(40%) of the pregnancy were ongoing at the time of data collection. In bivariate analysis, significant associations were observed between the female partner age, antral follicular count (AFC), number of oocytes retrieved (good responders), one embryo transfer, grade one embryo transfer, and day 5 embryo transfer with a positive pregnancy test. However, there were no statistically significant associations between the pregnancy test result and BMI, Day 3 FSH, and AMH (Table 3).

Factors associated with controlled ovarian stimulation response

Good responders ((≥4 oocytes retrieved) accounts for 152(76.4%) of the cases. Age of female partner, day 3 FSH, and AFC count ≥5 were significantly associated with good ovarian stimulation response (Table 2).

Table 2: Bivariate analysis of factors associated with controlled ovarian stimulation response

Factor	Good responders (≥4 oocytes retrieved) n=152	Poor responders (<4 oocytes retrieved) n=56	P-value*
Age of female partner, median (IQR)	32.0 (29.0, 36.0)	35.0 (31.0, 37.0)	0.016
Age of female partner			
<35 years	95 (62.9%)	26 (47.3%)	0.050
≥35 years	56 (37.1%)	29 (52.7%)	
Female partner AFC status, median (IQR)	12.0 (8.0, 14.0)	7.0 (5.0, 10.0)	<0.001
Female partner AMH median (IQR)	0.9 (0.5, 2.6)	0.6 (0.4, 1.3)	0.110
Female partner day 3 FSH	5.5 (3.9, 6.7)	7.5 (4.3, 9.6)	0.002
Female partner AFC status categorized			
≥5	140 (95.2%)	44 (83.0%)	0.005
<5	7 (4.8%)	9 (17.0%)	
Female partner day 3 LH status, median (IQR)	5.3 (3.5, 7.7)	5.8 (4.3, 10.0)	0.230
Female partner day 3 estradiol, median (IQR)	122.4 (62.0, 243.0)	93.0 (50.4, 150.0)	0.089

**p-values are calculated based on Mann-Whitney U test for continuous independent variables and Fisher's exact test for categorical independent variables

Table 3. Bivariate analysis of independent variables by the pregnancy test result

Characteristics	Negative (n=139)	Positive (n=60)	p-value*
Age of female partner, mean	(SD)33.7 (4.5)	31.3 (4.4)	<0.001
Age of female partner			
<35 years	74 (53.2%)	44 (74.6%)	0.007
≥35 years	65 (46.8%)	15 (25.4%)	
Female partner body mass index			
<18.3	4 (2.9%)	2 (3.3%) 0.30	
18.3-24.9	86 (61.9%)	44 (73.3%)	
25-29.9	29 (20.9%)	11 (18.3%)	
30-34.9	17 (12.2%)	2 (3.3%)	
>34.9	3 (2.2%)	1 (1.7%)	
Age of male partner, mean (SD)	40.4 (6.4)	37.3 (5.2)	0.071
Male partner TESE done			
Yes	19 (13.7%)	7 (11.7%)	0.82
No	120 (86.3%)	53 (88.3%)	
Female partner day 3 FSH status, median (IQR)	6.0 (4.3, 7.8)	5.0 (3.5, 7.0)	0.060
Female partner day 3 LH status, median (IQR)	5.5 (3.8, 9.1)	5.5 (3.6, 7.1)	0.78
Female partner day 3 estradiol, median (IQR)	98.0 (51.6, 230.0)	150.0 (86.0, 279.0)	0.082
Female partner AFC status, median (IQR)	10.0 (6.0, 12.0)	12.0 (10.0, 15.0)	<0.001
Female partner AFC status categorized			
≥5	121 (90.3%)	56 (98.2%)	0.001
<5	13 (9.7%)	1 (1.8%)	
Female partner AMH serostatus, median (IQR)	0.7 (0.4, 1.2)	1.4 (0.6, 7.1)	0.061
Number of oocytes retrieved, median (IQR)	5.0 (3.0, 10.0)	10.0 (6.0, 13.0)	<0.001
Good responders	91 (65.5%)	56 (93.3%)	<0.001
Poor responders	48 (34.5%)	4 (6.7%)	
Number of embryos transferred			
1	37 (26.8%)	4 (6.7%)	0.001
2	79 (57.2%)	49 (81.7%)	
3	22 (15.9%)	7 (11.7%)	
Type of protocol used			
Long protocol	85 (62.5%)	51 (86.4%)	0.063
Short protocol	19 (14.0%)	2 (3.4%)	
Minimal stimulation	32 (23.5%)	6 (10.2%)	
Day of embryo transfer			
Day 5	68 (48.9%)	50 (83.3%)	<0.001
Day 3	71 (51.1%)	1	
Grades of embryos transferred			
1	99 (71.2%)	56 (93.3%)	0.004
2	32 (23.0%)	4 (6.7%)	
3	5 (3.6%)	0 (0.0%)	
Semen analysis result			
Normal	103 (74.1%)	47 (78.3%)	0.59
Abnormal	36 (25.9%)	13 (21.7%)	

*p-values are calculated based on independent t-test or Mann-Whitney U test for continuous independent variables and Fisher's exact test for categorical independent variables

Multivariable regression of factors associated with the pregnancy test result

Multiple logistic regression was run using variables associate with the pregnancy on bivariate analysis to control confounders. A full model assessing the relationship between the pregnancy test result and predictor variables was constructed after which non-significant variables were removed by a backward procedure using the likelihood ratio test ($p<0.05$). Likelihood ratio test (lrtest) was significant when variables number and grade of the embryo were removed by the backward procedure (see Table 4). The odds of getting pregnant is 61% less among participants with female partners age ≥35 years, AOR 0.39, CI 0.18-0.83 with a p-value of 0.015. Clients with Day 5 embryo transfer were 3.28 times more likely to get pregnant compared to those with day 3 embryo transfer, p-value=0.006, CI 1.42-7.62(see Table 4).

Table 4: Multiple logistic regression model

Pregnancy test	AOR	P>z	95% Confidence	Interval
Age				
<35				
≥35 years	0.39	0.015	0.18	0.83
AFC categorized				
≥5				
<5	0.34	0.326	0.04	2.94
Oocytes retrieved				
Good responders				
Poor responders	0.35	0.083	0.11	1.15
Embryo transfer day				
Day 3				
Day 5	3.28	0.006	1.42	7.62

DISCUSSION

Good responders ((≥4 oocytes retrieved) accounts for 76.4% of the cases in the current study. The IVF pregnancy rate at the center for reproductive medicine (CFRM, SPHMMC) was 30.1%. Good responders ((≥4 oocytes retrieved) accounts for 152(76.4%) of the cases. Age of female partner, day 3 FSH, and AFC count ≥5 were significantly associated with good ovarian stimulation response. However, given the very brief history of IVF in Ethiopia, much is to be done to contextualize the various nuisances in the field.

One unique challenge is knowing the age of women seeking the service. Although age is one of the most important predictors of ovarian response, its utility in our setting remains questionable. Most of our clients do not know their exact age and it is usually hard for the physician to ascertain the stated age as most women have no birth certificate. As described above, close to one-third (64.5%) of the study participants did not know their exact date of birth. In the literature, age has been consistently shown to be one of the most important predictors of IVF success and fertility in general [3-5]. Our study also depicted the reported age had a significant association with ovarian response and a positive pregnancy test. This underlines the importance of age, even in setups where the exact age cannot be ascertained.

In the current study day, 3 FSH was associated with a good response to ovarian stimulation. This is in line with many types of research done over the years. Muasher and collaborators[6] reported that the measurement of serum levels of FSH, LH, and E2 on day 3 of the basal menstrual cycle was a predictor of controlled ovarian hyperstimulation (COH) response and IVF outcome. Subsequent studies ascertained the clinical significance of defined thresholds for such hormones in addition to their relationship to the woman's age, thus further defining the concept of ovarian reserve[5,9-11]. It was reported that the combined use of age and basal FSH in counseling patients improved the accuracy of prognosis and provide an index of functional ovarian reserve[11].

Anti-Mullerian hormone (AMH), and antral follicular count (AFC) were also being used for predicting ovarian response (18, 19). Recently, much attention has been given to the measurement

of AMH[20]. AMH is produced solely by the granulosa cells of growing pre-antral and small antral ovarian follicles and shows little inter-and intra-cycle variability. AMH is an accurate predictor of excessive response to ovarian hyperstimulation [16,18]. However, our study failed to show a significant association. This can be explained by the small number of patients that had AMH tests done. Besides, since the investigation is expensive, we did it for those with diminished ovarian reserve to ascertain the assessment determined by antral follicle count examination. Thus, the AMH was almost exclusively done on possible poor responders which were unlikely to have a good IVF outcome. The current study showed AFC ≥5 was significantly associated with a good ovarian response which is congruent with most studies[16, 18, 19].

In the current study, multiple regression analysis showed that the reported age of female partner <35 years and day 5 embryo transfer were associated with positive clinical pregnancy rate. Female clients with age less than 35 were four times more likely to get pregnant. This reflects ovarian function and underlying ovarian response which is associated with age less than 35 in the current study. Moreover, the finding was in line with a systematic review and individual studies which showed young age to be associated with pregnancy occurrence[22-24]. The current study showed day 5 transfer to be more than three times more likely to result in pregnancy. However, many studies showed there is no difference in pregnancy rate between day 3 transfer and day 5 transfer, with fewer cycles with no transfer due to very poor-quality embryos or arrested development when pushing today 5 [25,26]. This might be because of the practice in our setting in which only patients with less number and quality of embryo undergo day 3 transfer compared to routine day 5 embryo transfer for those with good number and grade of the embryo resulting in more pregnancies. Cycle day 3 serum FSH, LH, and E2 levels, measurement of AMH, and the estimation of the basal AFC were not associated with pregnancy test result in our study. These tests are better at predicting the ovarian response than the pregnancy outcome and our study was not adequately powered to detect the relationship between these laboratory investigations and pregnancy outcome.

The current study is the first of its kind in Ethiopia and will contribute to the very few publications from the whole continent. The study explored possibly clinical parameters to predict ovarian response and pregnancy outcome in a resource-limiting setting. This will help reproductive endocrinologists to identify which parameters to use for clinical decisions. However, in the current study, we did not do multiple logistic to control confounders for outcome ovarian response because of missing values on fully model regression. Furthermore, because of the retrospective nature of the study, important variables like some demographic information, causes, and duration of infertility were difficult to retrieve from the electronic record and were not included in the analysis.

CONCLUSION

Even though nearly two-third of the study participants did not know their exact date of birth, the reported age of female partner <35 years is associated with both good ovarian response and occurrence of pregnancy emphasizing its importance for clinical decision making. Day 3 FSH and AFC ≥5 were associated with good ovarian stimulation response. Therefore, we recommend the combination of female partner age, day 3 FSH, and AFC ≥5 to predict ovarian response in low resource settings, since variables can be readily available without much cost to patients. Furthermore, we would like to recommend follow-up studies with a larger sample size and prospective cohort design to appropriately compare the different predictors of ovarian response in our setting to develop evidence-based set up specific IVF protocols and guidelines.

Abbreviations

AFC: Antral Follicular Count
AMH: Anti-Mullerian Hormone
BMI: Body Mass Index
CCCT: Clomiphene Citrate Challenge test
CFRM: Center for Reproductive Medicine
COH: Controlled Ovarian Hyperstimulation
E2: Estradiol
FSH: Follicle Stimulating Hormone
FMOH: Federal Ministry of Health.
IVF: In Vitro Fertilization
LH: Luteinizing Hormone
SPHMMC: St. Paul's Hospital Millennium Medical College

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Competing Interests.

The authors declare that they have no competing interests.

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