Original Article

The Effect of Female Age on the Outcome of Intrauterine Insemination Treatment in a Public Hospital-Assisted Reproduction Technology Unit

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Abstract

Objective: The objective of the study is to evaluate the effect of female age on the outcome of ovarian stimulation (OS) and intrauterine insemination (IUI) treatment. **Methodology:** This was a 36 months' retrospective analysis of all IUI treatment cycles with prior OS. Based on the age of the women, 4 groups were identified for comparative analysis, namely women below 30 years, between 30 and 34; 35–39 years, and women aged 40 years and beyond. **Results:** Two hundred and seventeen IUI procedures were conducted during the study and 39 had a positive pregnancy test outcome (a pregnancy rate of 18%). Majority of the women were 35–39 years (41.5%), while 12% were 40 years and above. The pattern showed that the pregnancy rate was highest in the younger age group who were below 30 years, 6/18 (33.3%) and 30–34 years, 19/83 (22.9%) compared with women 35–39 years, 12/90 (13.3%) and ≥40 years, 2/26 (7.7%). The difference in the linear association of each age class compared to the next was significant ($P = 0.06$ and $P = 0.007$, respectively). The trend revealed that baseline follicle stimulating hormone increased with age and the youngest age group required significantly fewer units of human menopausal gonadotropin to achieve adequate response to OS compared to the oldest age group ($P < 0.001$). **Conclusion:** Advanced age negatively affects OS and IUI outcome. Treatment is associated with better pregnancy outcome in women under 35 years compared to women who were 40 years and beyond. This fact should be clearly emphasized at counseling of the 40-year-old that may opt for IUI treatment.

Keywords: *Age, assisted reproduction, infertility, intrauterine insemination, ovarian stimulation*

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Introduction

Age is an important factor influencing the likelihood of pregnancy in natural or conventionally treated cycles and even in assisted reproduction treatment (ART) cycles.[1-3] In the developed world, delay of marriage and elective deferment of childbearing in marriage are resulting in a number of couples desiring pregnancy relatively late in life. More so, the decline in fertility rate from the combined effect of reduced natural pregnancy rate and an increase in pregnancy wastage in this older age further compounds the outcome of infertility treatment. The developing countries, hitherto known for early marriage and childbearing, the quest for socioeconomic emancipation and educational attainment has created a new trend toward increased age at marriage and motherhood.[4-7] This trend has attendant consequences for the infertile couple (particularly women) and especially in the developing country where a woman's status is often solely defined by motherhood. Thus, for now, there is a sizeable population of the older women in the developing countries (just as in the developed countries) who require ART services to overcome their lower pregnancy rate potential.

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ART services have advanced worldwide in range and variety with good pregnancy outcome in all ages including the older women in whom without ART (third party treatment) childbearing would be extremely low or zero. However, the high cost of ART services is a major constraint especially in the low-resource settings where additionally there is reduced accessibility due to paucity of a trained workforce for ART services.[8] Ovarian stimulation (OS) with intrauterine insemination (IUI) is a relatively cheaper ART services than the *in vitro* fertilization (IVF) and embryo transfer (ET) variety. IUI is mainly intended for the women with normal ovarian reserve, uterus, and tubes whose husband semen analysis is normal or has mild-to-moderate oligospermia. The pregnancy rate for IUI is much lower than with IVF-ET but better than both the natural rate and conventional treatment cycles.[9,10] Despite a lower pregnancy rate, the lower cost and noninvasive nature of IUI treatment makes it a common choice for couples in all age group in our setting.

Although several prior studies[11-13] have documented the poor pregnancy rate outcome of OS and IUI in women aged 40 years and above, we at our setting have continued to provide this services for women who fulfill the criteria without age restrictions as the demand for OS/IUI in the older women is high because of the much lower cost. Thus, using age as a dependent variable, this study was designed to attempt a comparison of OS/IUI treatment cycles in older and young women with a view to using outcome to strengthening treatment planning and future counseling.

Methodology

This was a retrospective study of IUI procedures conducted from March 2012 to March 2015 (36 months) at the Human Reproduction Research Programme unit[8] of the Department of Obstetrics and Gynecology University of Benin Teaching Hospital; a tertiary care referral center with ART services in southern Nigeria. The study received ethical approval from the hospital ethics committee.

The study population comprised couples with at least 1-year history of infertility and had normal baseline infertility evaluation including semen analysis and tubal patency by hysterosalpingography or laparoscopy. The treatment was offered to couples with unexplained infertility, anovulatory or moderate male factor infertility. The ovulation stimulation was with clomiphene citrate in combination with human menopausal gonadotrophin (hMG) (Menogon®; Ferring Pharmaceutical, India). The clomiphene citrate tablet 100 mg was started from day 2 of menstrual cycle for 5 days with injection hMG 150 IU administered at variable dose from day 3 or 5 depending on follicular response as assessed on transvaginal ultrasound (TVS) folliculometry. The assessment of follicular response was done with TVS; first on cycle day 3 to establish a baseline and exclude residual follicles, then on cycle day 8; the TVS was performed, and further stimulation with gonadotrophin was done according to follicular response. The aim was to achieve a monofollicular response. However, if there were at most not more than three mature follicle (>17 mm) developed, the treatment cycle was continued, and the couples were advised on the possibility of multiple pregnancy, but when there were 5 or more mature follicles the cycle was either cancelled or converted to IVF treatment. Once a follicle of >17 mm size was identified, injection human chorionic gonadotropin (hCG) 5000–10,000 IU (hCG) was administered as an ovulation trigger and a single IUI was done at 36–48 h following the hCG injection.

On the day of IUI, the husband was instructed to produce semen by masturbation into a sterile jar after 3–5 days of sexual abstinence. After liquefaction and initial sperm analysis, the standard sperm preparation technique was used, employing the density gradient centrifugation method.[14] Furthermore, the woman had a transvaginal scan done to assess for ovulation as evident by collapse of the previously observed dominant follicles with or without fluid in the pouch of Douglas. If, however, some follicles were still unruptured a repeat IUI was performed without further repeat hCG 24–48 h after the first one. When ovulation is confirmed the IUI was performed under aseptic conditions using an IUI catheter (Kremer Delafontaine; Prodimed, Neuilly-en-Thelle, France or Sunn Catheter; SAR Healthcare Ltd., India) with a 1- or 2-ml syringe. The catheter was gently passed through the undilated cervical canal and the sperm suspension expelled into the uterine cavity with an insemination volume range of 0.5–2 ml. The women remained supine for 10–20 min after IUI. All the women had luteal phase support with natural micronized progesterone vaginal pessaries (cyclogest®) for 15 days after which a pregnancy test was performed.

When the pregnancy test is positive, a TVS was done 2 weeks later to confirm a clinical pregnancy. When an intrauterine gestational sac was observed, the women were followed up thereafter till delivery and the pregnancy outcome was recorded.

Statistical analysis

The variables selected for analyses were: age of the woman, duration of infertility, and cause of infertility. Others were baseline follicle stimulating hormone (FSH) and luteinizing hormone, semen count, duration of

stimulation and quantity of drug required, number of follicles, endometrial thickness, and interval between the ovulation trigger and IUI was recorded.

From the study cohort, four groups were identified based on age, namely women below 30 years, those between 30 and 34; 35–39 years; and women aged 40 years and beyond. Data were entered into SPSS version 20.0 (SPSS IBM. Corp, Armonk, NY, USA). The continuous variables and their means were compared using the independent *t*-test while the categorical variables were compared for significant differences using the Chi-square test. $P < 0.05$ was considered to be statistically significant.

Results

During the study period there were 217 IUI treatment cycles of which 39 had positive pregnancy test giving a pregnancy rate of 18%. However only 36 women (16.6%) had clinical pregnancy confirmed on ultrasound.

Majority of women were aged 35–39 (41.5%) and 30–34 (38.2%) while only few (12%–8.3%) women were aged 40 years and above and <30 years, respectively.

In Table 1, the variation in clinical characteristics and treatment response with respect to age is shown. There were more cases of primary infertility in the younger women (33.3% vs. 32.5% vs. 20% vs. 7.7%; $P = 0.035$), the duration of infertility ranged between 1 and 17 years and the mean was found to increase as age increased ($P = 0.0001$). With regard to the cause of infertility and indication for IUI, overall male factor was the most common and subgroup analysis showed that the younger women had significantly higher proportion of male factor infertility (<30 years [55.6%] vs. 30–34 [44.6%] vs. 35–39 [36.7%] vs. ≥40 [23.1%]) while a higher incidence of unexplained infertility was observed as age increased (5.5% vs. 30, 1% vs. 30% vs. 30.7%) $P = 0.006$.

The mean FSH was 7.6 ± 3.4, baseline FSH increased with age 7.1 ± 2.6 (20–29 years); 6.2 ± 2.2 (30–34 years); 8.5 ± 3.9 (35–39 years); and 8.8 ± 3.1(≥40 years), $P < 0.001$, [Figure 1]. In terms of patients response to treatment, the younger age group required significantly fewer units of hMG (Menogon) to achieve an adequate response to controlled OS compared to the older age group ($P < 0.001$); [Table 1]. Subanalysis showed that there was no difference between age group in the number of recruited follicles and size of dominant follicle on the day of hCG injection. Majority (77.4%) of the study population were on their first treatment cycle, although more of the older age group had IUI previously, the difference between age group was not significant, ($P = 0.05$). Furthermore, a repeat insemination or difficulty with insemination was not influenced by age.

As shown in Table 2, overall the pregnancy rate was highest in the younger age group who were under 30 years (6/18 [33.3%]) and 30–34 years (19/83 [22.9%])

Table 1: Association of clinical and treatment variables with age

Clinical characteristics	<30 (*n*=18)	30-34 (*n*=83)	35-39 (*n*=90)	≥40 (*n*=26)	*P*
Infertility type					
Primary	6	27	18	2	0.035
Secondary	12	56	72	24	
Duration infertility (mean±SE)	3.5±0.3	4.0±0.2	7.3±0.4	9.5±0.8	0.001
Etiology, *n* (%)					
Female factor	6 (33.3)	16 (19.3)	18 (20)	5 (19.2)	0.006
Male factor	10 (55.6)	37 (44.6)	33 (36.7)	6 (23.1)	
Unexplained infertility	1 (5.5)	25 (30.1)	27 (30)	8 (30.8)	
Combined	1 (5.5)	5 (6.0)	12 (13.3)	7 (26.9)	
Previous IUI					
No	17	57	74	20	0.05
Yes	1	26	16	6	
Total hMG units used	620.8±488.6	747.3±535.7	1129.2±546.5	1295.2±601.7	0.001
Day of hCG	11.6±0.5	11.9±0.2	11.6±0.2	11.9±0.3	0.770
Repeat IUI					
No	10	56	67	18	0.414
Yes	8	27	23	8	
Insemination					
Easy	16	75	79	24	0.434
Mild difficult	1	8	10	2	
Difficult	1	0	1	0	

SE=Standard error; IUI=Intrauterine insemination; hMG=Human menopausal gonadotrophin; hCG=Human chorionic gonadotropin

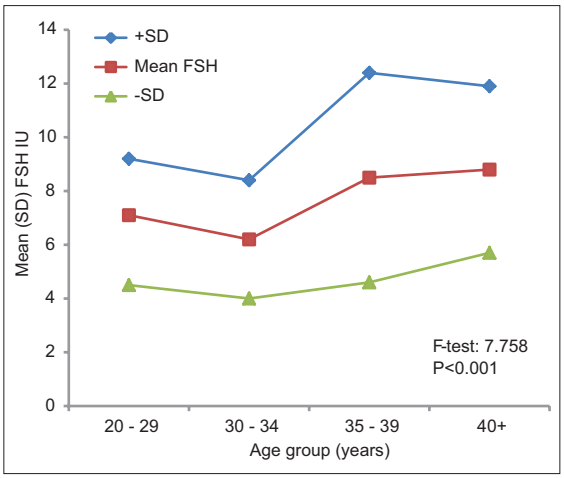

Figure 1: Relationship between mean standard deviation follicle stimulating hormone and age (*F*-test: 7.758, $P < 0.001$)

Table 2: Age group and pregnancy outcome in the study

Outcome	<30 (*n*=18)	30-34 (*n*=83)	35-39 (*n*=90)	≥40 (*n*=26)	*P*	Linear association
Pregnancy test						
Negative	12	64	78	24	0.06	0.007
Positive	6	19	12	2		
Miscarriage	1	2	2	2		
Live birth	5	16	10	0	0.094[×]	
Ectopic	0	1	0	0		

[×]Miscarriage rate <35 versus ≥35 years

versus 35–39 years (12/90 [13.3%]) and 40 years and more (2/26 [7.7%]). Although the difference in outcome across the age group was not significant, a linear association of each age class compared to the next was significant ($P = 0.06$ and $P = 0.007$, respectively). Of the 36 pregnancies, 31 (86.1%) had live births, 4 (11.1%) spontaneous miscarriage, and 1 (2.7%) was an ectopic gestation. There were 9 (25%) multiple pregnancies; of which 8 were twins and 1 triplet pregnancy. Only one of the twin pregnancies ended in spontaneous miscarriage. Further analysis with 35 years as cutoff age showed a significant decline in pregnancy rate above age 35 ($P = 0.05$). Also in Table 2, the older age group experienced more miscarriages compared to the younger age (3/25 [12%] vs. 4/24 [16.7%] $P = 0.094$).

Discussion

In this study, we observed that age significantly influenced the success of OS/IUI treatment. A trend toward reduction in success rate with OS/IUI was noted in women with age >35 years, and this became more marked at the age of 40 years and beyond, and particularly there was no recorded live birth after age of 40 years. Our findings support the documented negative impact of female age on infertility treatment. In agreement with these findings, many studies have reported a significant drop in the success rate of IUI beyond the age of 40 years.[8,11,12] Furthermore, a high prevalence of aneuploidy has been reported in association with older women due to chromosomal errors in the aging oocyte.[12] Some researchers have recommended that, for women over 35, OS/IUI as a treatment option needs careful consideration, and for women over 40, IUI is a poor treatment option.[3,10] On the other hand, IUI has been suggested as a potential treatment even for selected patients over 40 years.[13]

The impact of age on infertility treatment was confirmed from the observed significant positive correlation between age and infertility type and duration. More of the older women had a higher prevalence of secondary infertility increased. Furthermore, the majority of patients were more than 35 years and had a mean infertility duration >7 years suggests that most infertile couple would have attempted various infertility treatment methods inclusive of un-orthodox and conventional orthodox methods which failed before resorting to ART.[6,7,15] Furthermore, previous studies have confirmed that the success rate of IUI was significantly lower, as the duration of infertility increased.[16,17] With regard to infertility duration, we did not determine any particular cutoff beyond which IUI could be discouraged, but the trend by pregnancy outcome in the study suggest that IUI as an option appears to be less effective for patients with a long-standing duration of infertility.

The decline in oocyte quality with increasing age was corroborated with our finding of a significant increase in FSH levels with age, reflecting a declining ovarian reserve. This is supported in this study by the fact that the younger patients required less amount of hMG (for OS) to achieve satisfactory ovarian response. Several other reports have documented decreased oocyte quality with age.[13,18,19] Age-associated decline in uterine receptivity has been reported as an important factor affecting outcome,[20,21] but in this study, endometrial response to stimulation was the same in all the age groups.

There was a preponderance of male factor among the younger couples with primary infertility. In such cases, treatment with OS/IUI is ideal as it promises a better ovarian response to stimulation in the younger women and potential to overcome the semen abnormality by sperm preparation/IUI procedure, with consequent better pregnancy rates as observed in this study. Previous studies have identified several parameters which favors treatment success including age and cause of infertility, with the success rate being higher

in anovulatory and unexplained infertility patients as compared with endometriosis, advanced age, and male factor infertility.[10,22-24] Our study was limited as we did not analyze husbands age and postpreparation count and motility which have been demonstrated to impact on outcome.

Conclusion

From the foregoing, we can sum that the older age has declining ovarian reserve, requires a higher dosage of drugs for OS; with increased incurred cost and consequent decreased pregnancy and live birth rate in an OS/IUI treatment cycle. Albeit owing to its IUI comparatively low cost to IVF treatment, IUI could still be considered for selected older women especially in resource limited settings like ours. We can suggest that an older age is a predictor of unfavorable IUI outcome and thus with increasing age as well as increasing infertility duration, IUI as an option appears to be less effective and should not be choice treatment for women over 40 years. However, for women under 40 years, OS/IUI as a treatment option could be considered.

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Conflicts of interest

There are no conflicts of interest.

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