Original Article

Prognostic factors affecting outcome of intrauterine insemination procedures at a fertility center in Ondo, South West Nigeria

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ABSTRACT

Background: There is a recent resurgence in the use of intrauterine insemination (IUI) in Nigeria. However, there is a need for a rational use of the procedure so that couples do not waste time and money on ineffective therapy if it is not indicated.

Objective: The objective of this study was to identify the possible prognostic factors affecting outcome of IUI among patients undergoing the procedure.

Patients and Methods: This is a retrospective review of the case files and treatment protocols of fifty consecutive couples who had IUI procedure following the established diagnosis of Infertility at the Paramount Fertility Center of Paramount Specialist Hospital Ondo, Nigeria, over a period of 1 year (February 2016 to January 2017).

Results: There were ten (20.0%) pregnancies recorded, of which three (6%) clients had first-trimester miscarriages (between the 5th and 13th weeks), one (2%) had an ectopic pregnancy, whereas six (12%) were carried to the age of viability and delivered. Forty (80%) clients did not achieve pregnancy. The postwash concentration of sperm was noticed to be the only parameter significantly affecting the rate of pregnancy in our treatment cycles with $P < 0.05$. There was also a trend toward a reduction in pregnancy after the age of 40.

Conclusion: This study shows that the postwash sperm count and age of the female have the most predictive value for IUI clinical pregnancy outcome in our center.

Key words: Infertility; intrauterine insemination; prognostic factors.

Introduction

Intrauterine insemination (IUI) is a procedure that places washed active sperm past the cervix and in a woman's uterus around the time of ovulation. This makes the journey to the fallopian tubes much shorter, and there is a better chance that more sperm will encounter the egg. The goal of this procedure is to improve a woman's chance of getting pregnant.

The use of intrauterine artificial insemination for the management of infertility underwent a decline following the emergence of the human immunodeficiency virus (HIV) as well as the complications associated with the use of neat semen.

Sperm preparation methods developed for *in vitro* fertilization (IVF) and embryo transfer, such as the wash,

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swim-up and swim-down techniques, and the use of density gradients, have led to a resurgence of interest in IUI. The use of washed prepared sperm for IUI has also resulted in a significant reduction in the side effects associated with the use of neat semen for IUI (which never should be used), such as painful uterine cramps, collapse, and infection.[1]

This resurgence has led to the abuse of the procedure in patients who will not benefit from the procedure, leading to unnecessary psychological and/or financial burden.

This study reports on the outcome of fifty consecutive IUIs at a private health facility in Nigeria with the aim of documenting prognostic factors that can be used in decision-making and patient counseling.

Patients and Methods

Couples who had IUI treatment following the established diagnosis of Infertility at the Paramount Fertility Center of Paramount Specialist Hospital Ondo, Nigeria, over a period of 1 year (February 2016 to January 2017) were enrolled in the study.

This is a retrospective review of the case files and treatment protocols of couples who had IUI procedure during the study period.

The IUI treatments were performed after patients were adequately counseled, and written consent was obtained and then recruited for the procedure before ovulation induction was commenced.

A baseline serum concentration of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and estradiol on day 2 or day 3 of the menstrual cycle preceding the treatment cycle was done to assess the ovarian reserve. A hysterosalpingography was also performed on day 10 of the menstrual cycle to assess the tubal patency, and a baseline semen analysis was done to assess the sperm count. Couples were also screened for HIV, hepatitis B and C, and syphilis using the Venereal Disease Research Laboratory test. The blood group and haemoglobin genotype was performed for patients considering donor sperm so as to be able to choose the appropriate semen from the sperm bank.

The semen was collected preferably by masturbation (or coitus interruptus with spermicide-free condoms where masturbation was not possible) about 35 h after human chorionic gonadotropin (HCG) trigger. Sperm wash technique with SpermGrad (Vitrolife Sweden AB, Goteborg Sweden) gradient sperm preparation medium was used for 10 min at 2500 rpm. The final sample was simply washed with G-MOPS PLUS (Vitrolife Sweden AB, Goteborg Sweden) for 5 min at 2500 rpm and incubated at 37°C for 5 min before insemination.

The patients were placed in lithotomy position; cleaning of the perineum, vulva, and vagina was done with normal saline, and a sterile speculum was inserted to expose the cervix. Air was withdrawn into the IUI catheter (SUNN IUI SAR Healthline (P) Ltd., India) to serve as an air plug before drawing the prepared sperm to prevent regurgitation. The sperm(0.3-0.5ml) was then injected into the uterus slowly and the catheter withdrawn when pushing the air plug. The patients were under rest for 15 min in Trendelenburg position after insemination. Normal sexual intercourse was encouraged within the next 72 h.

The luteal-phase support was commenced on the 5th day postinsemination with intramuscular hydroxyprogesterone caproate (Proluton Bayer Schering Pharma, Germany) 250 mg depot. Biochemical pregnancy was determined by maternal serum HCG level on day 15 postinsemination, while clinical pregnancy was confirmed by ultrasound detection of a gestational sac at 4 weeks' postinsemination.

Our primary end point was the live birth rate (per insemination), and the secondary end points were chemical and clinical pregnancy rates and spontaneous miscarriage rates. The data regarding pregnancy follow-up and delivery were also extracted.

Ovulation induction protocols included clomiphene citrate (CC) 100 mg daily for 6 days (Ovumine, Baroque Pharmaceuticals Pvt. Ltd., India) alone, or in combination with metformin 500 mg twice daily for 10 days or letrozole 2.5 mg daily for 6 days, and controlled ovarian hyperstimulation (COH) with human menopausal gonadotropin (HMG IVF-M injection menotropin, LG Life Sciences) 75 IU daily for 10 days starting from day 2 to day 5 of the menstrual cycle. Ancillary medications given include M2-Tone Herbal one tablet twice daily for 10 days (Charak Pharma Pvt. Ltd., India) and folic acid 5 mg daily. The ovarian response to stimulation was monitored by transvaginal ultrasound assessment of follicular and endometrial growth on days 9 and 11 of menstrual cycle. A pre-HCG scan was done on day 11 or day 12 and ovulation was triggered by a single injection of 5000 IU of HCG (Diclair-HP HCG, R Germany) when at least a matured sized follicle or more had reached the diameter of 18 mm or more and trilaminar endometrial thickness of 8–12 mm. IUI was then carried out between 36 and 40 h post-HCG trigger.

The results were analysed by Statistical Package for the Social Sciences (SPSS) software version 17.0 SPSS Inc. Chicago

IL, USA. The results were presented as mean ± standard deviation. The statistical significance of differences between groups for continuous variables was assessed and differences in proportions were assessed using Mantel–Haenszel's test or Fisher's exact test, where appropriate. $P < 0.05$ was considered statistically significant.

Results

Between February 2016 and January 2017, fifty procedures were done in the IUI section of the fertility center. There were ten (20.0%) pregnancies recorded, of which three (6%) clients had miscarriages between 5th and 13th weeks of gestation. One (2%) had an ectopic pregnancy, whereas six (12%) were carried to the age of viability and delivered. Forty out of the fifty (80%) clients did not achieve pregnancy. The details are summarized in Table 1.

Table 2 shows the relationships between the various factors and pregnancy rates. The mean female age was 33.8 ± 7.9 years.

Cause of infertility was ovulatory in 18%, tubal factor (one patent fallopian tube) in 14%, cervical factor in 10%, male factor in 26%, and unexplained in 32% of the patients. The postwash concentration of sperm was noticed to be the only parameter significantly affecting the rate of pregnancy in our treatment cycles with $P < 0.05$.

Discussion

In our study, we made an effort to determine the prognostic factors that would determine the success of ovulation induction and IUI. The variables selected were patients' parameters such as age of the woman, parity, cause of infertility, choice of ovulation induction agent, insemination time post-HCG trigger, and concentration of semen. Parameters related to ovulation induction included number of follicles and endometrial thickness. Laboratory parameters such as days of abstinence, postwash motility, and morphology were recorded.

Among the patients' parameters, female age is important as declining oocyte quality associated with increasing age is well documented.[2] Even more effective treatment options such as IVF cannot completely overcome the negative impact of age.[3] In our study, the trend toward reduction in success rate with ovulation induction and IUI was noted in women aged >40 years, although the difference was not statistically significant. However, many studies have documented a significant drop in the success rate beyond the age of 40 years, with reported live births being as low as 1.4%.[4] Put together, for women over 35 years, ovulation induction and IUI as a treatment option need careful consideration, and for women over the age of 40, IUI is a poor treatment option.

Table 1: Pregnancy rate following intrauterine insemination

Outcome	Frequency (%)
Nonpregnant	40 (80.0)
Miscarriage	3 (6.0)
Ectopic	1 (2.0)
Live birth	6 (12.0)
Total	50 (100.0)

Table 2: Factors affecting the pregnancy rates in intrauterine insemination

Parameters	Outcome		Frequency (%)	*P*
	Nonpregnant	Pregnant		
Female age (years)				
20-24	1	0	1 (2)	0.490
25-29	4	3	7 (14)	
30-34	15	3	18 (36)	
35-39	17	4	21 (42)	
40-44	3	0	3 (6)	
Parity				
0	29	10	39 (78)	0.317
1	6	0	6 (12)	
2	4	0	4 (8)	
3	0	0	0 (0)	
4	1	0	1 (2)	
Cause of infertility				
Ovulatory	8	1	9 (18)	0.749
Tubal	6	1	7 (14)	
Cervical	3	2	5 (10)	
Male	10	3	13 (26)	
Unexplained	13	3	16 (32)	
Ovulation induction agent				
CC alone	15	4	19 (38)	0.987
CC + metformin	7	2	9 (18)	
CC + letrozole	3	1	4 (8)	
Letrozole + metformin	1	0	1 (2)	
HMG	13	3	16 (32)	
Natural cycle	1	0	1 (2)	
Insemination time (h) post-HCG				
<36	1	0	1 (2)	0.845
36-38	12	3	15 (30)	
38-40	25	7	32 (64)	
>40	2	0	2 (4)	
Postwash sperm concentration (million/ml)				
<20	6	0	6 (12)	0.006
21-40	10	1	11 (22)	
41-60	3	0	3 (6)	
61-80	10	0	10 (20)	
81-100	7	3	10 (20)	
>100	4	6	10 (20)	

HCG – Human chorionic gonadotropin; HMG – Human menopausal gonadotropin; CC – Clomiphene citrate

No difference was noted in the success rate with regard to the cause of infertility. Among indications for IUI, the success rate was higher in male factor (use of a donor sperm) and unexplained infertility as compared with tubal and ovulatory factors, although the difference did not reach statistical significance. Some studies found that unexplained factors have a better prognosis in clinical pregnancy compared to other etiological factors.[5] However, some studies noted that moderate male factors and anovulation have the highest clinical pregnancy rates in IUI.[6]

An unexplained infertility couple may have problems with egg quality, the ability of the sperm to fertilize the egg, undiagnosed tubal dysfunction, implantation failure, or genetic causes.[7] Ovarian factors may be related to elevated LH levels that affect the egg quality by resumption of early meiosis and premature oocyte maturation that will lead to inability to be fertilized or miscarriages.[8]

Ovarian stimulating agents for COH affected the clinical pregnancy rate of IUI. It has been observed that the chances of getting pregnant in IUI using COH were double with the addition of COH compared with IUI alone.[9] The drug regimens that are mainly used for IUI were CC and gonadotropins (rFSH, HMG, and HCG).[10] In our center, we used CC alone or in combination with metformin or letrozole. We also use HMG alone or in combination with other drugs for ovarian stimulation. In most of the studies, the use of gonadotropins has a better clinical pregnancy rate compared to CC.[6] However, this regimen would increase the risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Therefore, the use of gonadotropin in unexplained factors may not be appropriate for these reasons.[11]

Minimal stimulation using combination of both CC and gonadotropins in IUI seems to be the ideal regimen. This protocol could reduce the risk of multiple pregnancies and achieve the main objective of obtaining a few dominant follicles with less complication of OHSS.

Another important prognostic factor for IUI success is the sperm quality. We assessed our results based on the sperm concentration which had significant influence on the clinical pregnancy rate. Our study showed that patients with sperm concentration >80 million had a better outcome. This proves that male patients with oligozoospermia (low count in sperm) and asthenozoospermia (low progressive motility in sperm) were associated with a poor outcome. IUI is not a good option for these patients. Intracytoplasmic sperm injection (ICSI) during IVF should be considered instead.

There was a significant difference in the clinical pregnancy rate when postwash sperm concentration was >80 million/ml ($P = 0.006$). In most studies, the density gradient method has been shown to confer advantages in sperm recovery compared to swim-up method. This method not only yields the highest number of motile sperm but also reduces the bacterial contamination and processing time.[12] Furthermore, this technique has a higher percentage of morphological sperm recovery, better DNA quality, and chromatin packaging.[13-15]

There are many studies that stated the suitable number of sperm recovery after preparation. The minimum number of motile sperm varies from 0.8 to 10 million/ml.[16,17] In our cases, patient with normal sperm count had a good recovery of motile washed sperm compared with patients with low sperm count. However, the sperm recovery after postwash for oligozoospermia patients in gradient method did not improve the count and motility.

Conclusion

Ovulation induction and IUI are important treatment options for varied indications, especially when female age is <35 years. Definitive prognostic factors for predicting success will help in counseling patients regarding the modality of treatment. We concluded that the female age and sperm count have the most predictive value for IUI clinical pregnancy outcome in our center. Other factors such as type of infertility, etiological factors, stimulation protocol, timing of insemination, and parity do not have a significant effect on the IUI successful rate. Hence, female patients with advanced age and male patients with low sperm count would benefit from IVF/ICSI rather than IUI.

Study limitations

A limitation of the study is the retrospective design. Although the sample size is small, our study provides an important finding/evidence that there is good clinical pregnancy with an increased sperm concentration in IUI procedures in Nigeria. Another limitation of the study is the fact that there was no uniformity in the ovulation protocol used. We did not assess cycle cancelation rates or OHSS rates. Further studies with larger series of women are needed to confirm these useful findings in our low-resource setting.

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Conflicts of interest

There is no conflict of interest.

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