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Evaluation of Factors Influencing the Success of Intrauterine Insemination

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Abstract

Introduction : Intrauterine insemination is a fertility treatment method in which processed sperm from either the partner or the donor is deposited within the uterine cavity, usually near the time of ovulation. For the first three to four cycles, IUI is usually effective. So, in this study, we attempted to analyse the factors involved in the success of IUI.

Aim : The main aim of this study is to determine thefactors influencing and predicting the success of IUI.

Methodology :This is a cross-sectional retrospective observational study conducted at the Institute of Reproductive Medicine at MMM between January 2018 and December 2019 in subfertile women attending the IRM OPD and being scheduled for IUI. The proforma was completed, and data was analysed to determine the factors influencing IUI success.

Result :We discovered that fertility declines significantly after the age of 35, regardless of gender. As a result, it has been suggested that the reproductive age be carefully planned. Endometrial thickness was also found to be significantly thicker in the pregnant group than in the non-pregnant group. The clinical pregnancy rate increased with an increase in post-wash motile sperm count. It is worth noting that a PTMC of more than 5106/ml can also result in a successful pregnancy. Furthermore, ovarian stimulation is a good option for achieving a high positive pregnancy outcome as soon as possible. The oral ovulogens+ gonadotropins regimen is the best of the options.

Conclusion:Age, duration of infertility, body mass index, cause of infertility, number of ovarian follicles, endometrial thickness, total motile sperm count, IUI-single/double, Trigger-HCG /Urinary/Recombinant, Luteal support were all evaluated as predictors of IUI success. The best results were seen in a younger patient with a high post-wash motile sperm count. Unexplained and anovulatory infertility had a higher pregnancy rate after IUI among the underlying causes of infertility. With stimulated cycles, the live birth rate increased.

Keywords: *Intrauterine insemination, predictors of IUI,sub-fertile.*

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I. Introduction

Although the monthly rate of conception is lower in the majority of infertile couples seeking treatment, it is still possible to become pregnant naturally (ESHRE Capri Workshop group). Subfertility treatment policies should be planned carefully to prevent overtreatment, which would reduce any potential health concerns from ovarian stimulation and the overall expense of infertility care. Currently, there are many different treatment options available using assisted reproductive technologies.

Intrauterine insemination (IUI) is a type of fertility treatment that improves the chances of conception in both male and female infertility. It is used to treat infertility caused by moderate male factors, endometriosis, ovulation failure, and unexplained factors. (2,3) In comparison to in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI), IUI is a simpler, safer, and less expensive treatment protocol with a lower complication rate, making it more widely accepted by infertile patients.(4–6).

The clinical IUI pregnancy rate is also lower than the rates of other ARTs due to a variety of factors. (7,8) The reported pregnancy rates per cycle have typically ranged from 8% to 22% (Sunde et al. ; Dodson and Haney; Peterson et al; Brzechffa et al; Cohlen et al), but very low (4%) and high (40%) pregnancy rates have also been published (Karlstrom et al and Fanchin et al). The large variation in pregnancy rates may be due to the small size of the study populations, variability in subject characteristics, ovarian stimulation protocols, and insemination techniques.

Previously, only a few studies thoroughly examined the various variables influencing IUI outcome (Dickey et al; Mathieu et al., Tomlinson et al). Patient profile, duration of infertility, type of infertility, stimulation protocol, follicular response, endometrial thickness, timing of IUI, and semen parameters such as post wash motility, morphology, and total motile fraction have all been identified as prognostic factors for IUI treatment outcome (TMF). (9-12) Data on prognostic factors associated with IUI treatment using clomiphene citrate/human menopausal gonadotrophin (HMG)/human chorionic gonadotrophin (HCG) for ovarian stimulation are particularly scarce.

We attempted to identify the variables that contribute to the success of IUI treatment in this retrospective study. These data would be useful in planning subfertility treatment and predicting IUI therapy success rates in individual couples.

II. Materials And Method :

This is a cross-sectional retrospective observational study conducted at the Institute of Reproductive Medicine at MMM between January 2018 and December 2019 in subfertile women attending the IRM OPD and being scheduled for IUI. Depending on the individual factors of each patient, natural cycle/stimulus regimens were used for follicular development. Once a follicle had grown to >17 mm in size, an injection of human chorionic gonadotrophin (hCG) was administered as an ovulation trigger, and a single or double IUI was planned. After evaluating for follicle rupture, IUI was performed under ultrasound guidance. The patient is instructed to rest in bed for 10-15 minutes. After 14 days, beta-HCG was done ,if positive, a transvaginal ultrasound was done to confirm a clinical pregnancy. The proforma was filled and data was analyzed for the factors influencing the success of IUI.

Study Type: Retrospective study

Inclusion Criterion:

All Sub fertile patients who are undergoing IUIat IRM.

Exclusion Criterion:

Severe endometriosis and severe male factor infertility.

Sample size :

250 Sub-fertile women attending IRM OPD,who are being programmed for IUI from January 2018 to December 2019.

This sample size was calculated on applying the formula,$n=4pq/d^2$,

WhereP=50%(Prevalence)

So,Q=70%(1-P)

And allowable error (d) was kept at 20%.

On applying the above formula sample size n=92 which is approximately 100,In this study we took 250 sample size.

Statical analysis:

Data analysed was entered in Microsoft excel and analysed using the statistical package for SPSS version 23.0. Frequency and percentages were calculated for the discrete data and mean & SD for continuous data.If the P value was less than 0.05 then it was considered as statistically significant.

III. Results :

1. Overall pregnancy rates :

The average number of IUI cycles per patient was 2.2, the pregnancy rate per patient was 23.1%, and the pregnancy rate per cycle was 10.2%. (Table 1). Both the pregnancy rate per patient and the pregnancy rate per cycle decreased after the age of 39 years; however, only when comparing pregnancy rates per cycle was a significant difference found (Table 1). When comparing the 30 year age groups, a significant difference in pregnancy rate per patient and per cycle was observed whenbetween-group comparisons were performed (Table 1).

Table 1: Pregnancy rates per patient and per intrauterine insemination cycle with reference to the age of the woman

Age (years)	No of patients	No of cycles (IUI)	No of pregnancy (n)	Mean no of cycles per patient	Pregnancy rate per patient(%)	Pregnancy rate per cycle(%)
<25	25	59	7	2.36	28	11.86
26-30	103	196	20	1.90	19.41	10.20
31-35	87	208	27	2.39	31.03	12.98

>36	35	84	5	2.4	14.28	5.95
Mean	-	136.7	-	2.26	23.17	10.24

2. BMI and Duration of infertility :

The average female subject age in the clinically pregnant group was significantly lower (30.76 4.06 years) than in the non-pregnant group (39.62 4.84 years) (p 0.05). (Table 2). The length of infertility was discovered to be significantly related to the chances of success (Table 2).

Table 2. Comparison of the Female Age, BMI and duration of infertility Between Pregnant Groupand Non-Pregnant Group

		Non pregnant group n-191	Pregnant group n- 59	P value
Mean Female age (years)		39.62 ± 4.84	30.76 ± 4.06	0.049
BMI (kg/m^2)	< 18 to 25	33	17	0.061
	25 to 30	60	11	
	> 30	98	31	
Duration of infertility (years)	< 5	60	26	0.011
	5 to 10	128	31	
	> 10	3	2	

3. Female age :

The female study subjects were divided into four groups based on their age: (1) group a: 25 years old; (2) group b: 25-30 years old; and (3) group c: 31-35 years old. (4) Group d: over the age of 36. The clinical pregnancy rate decreased significantly with age (group A - 28 percent, group B - 19.4 percent, group C - 31 percent, and group D -14.2 percent, respectively; p = 0.022). (Table 3). The results of the pairwise comparisons for the three groups revealed statistically significant differences (p 0.05). (Table 3).

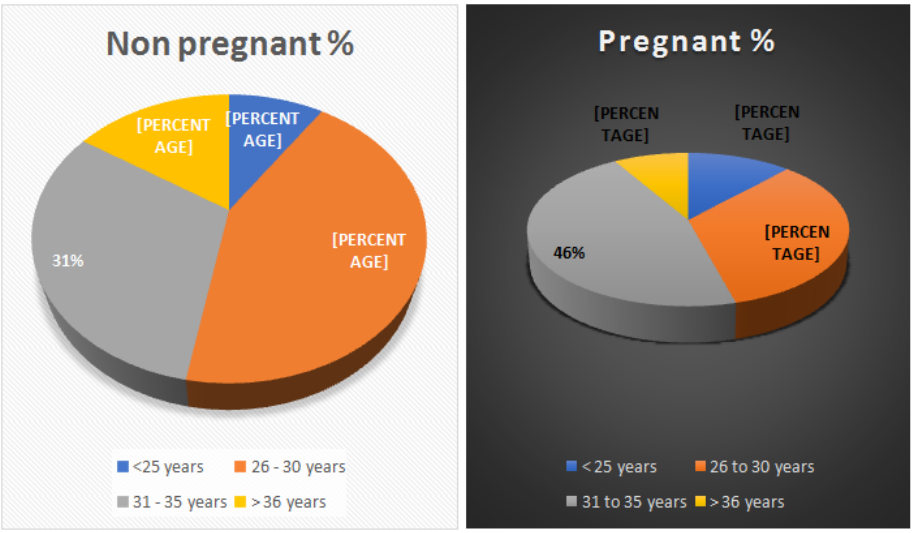
Table 3. The Clinical Pregnancy Rate According to Female Age

	Female Age (years)				
	Group A <25 n-25	Group B 26 to 30 n-103	Group C 31 to 35 n-87	Group D > 36 n-35	p value
Non-pregnant group N – 191	18	83	60	30	0.022
pregnant group n - 59	7	20	27	5	

Table 3. The Clinical Pregnancy Rate According to Female Age

The pairwise comparison results for the three groups showed statistically significant differences (p < 0.05) (Figure 1).

Figure 1. Comparison of female age distribution among non-pregnant and pregnant women.



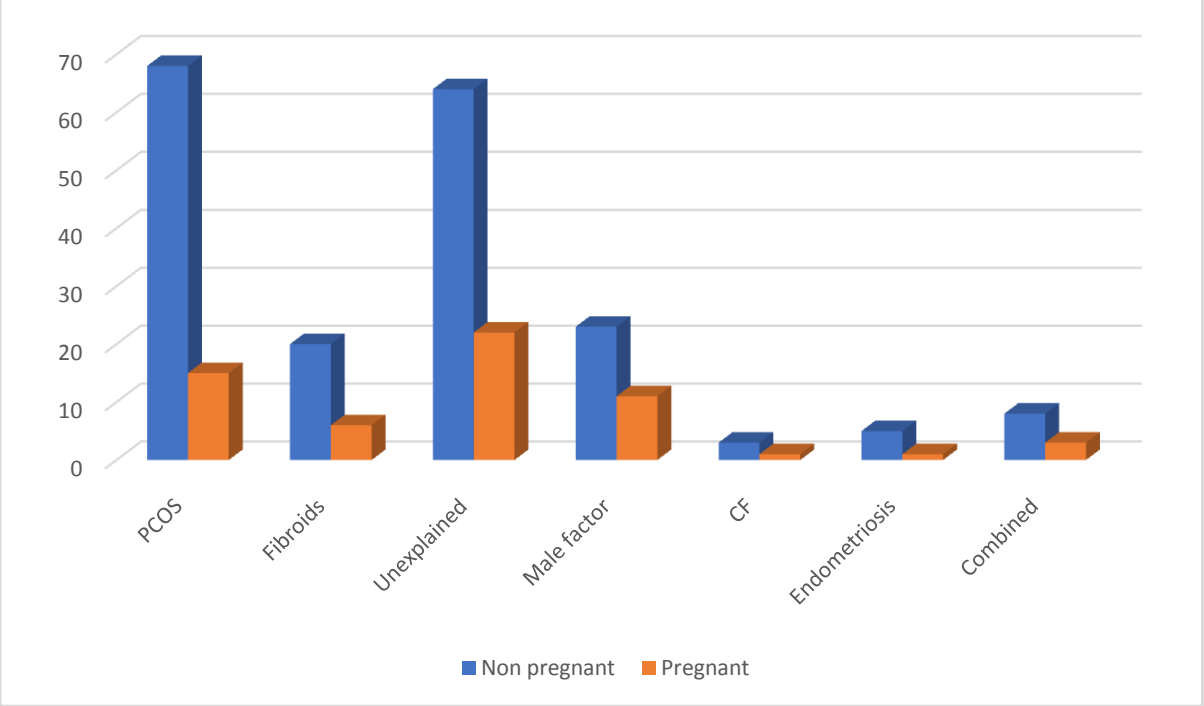
4.Causes of infertility :

In our study, we discovered that among the indications for IUI, unexplained infertility, PCOS, and male factor had higher success rates than other aetiologies. Though there was no statistically significant difference between the various causes of infertility in our study, endometriosis was found to have lower pregnancy rates.

Table 4: Cause of infertility affecting pregnancy rates in intrauterine insemination

Causes of infertility	Non-pregnant group n-191	pregnant group n-59
PCOS	68	15
Fibroids	20	6
Unexplained	64	22
Male factor	23	11
Cervical factor	3	1
Endometriosis	5	1
Combined	8	3

Figure 2. Comparison of CPR(clinical pregnancy rate) based on causes of infertility among non-pregnant and pregnant women



Timing of IUI :

The pairwise comparison results for IUI performed within 90 minutes show no statistically significant difference from IUI performed more than 90 minutes after collection. The difference in clinical pregnancy rates between single IUI per cycle and double IUI per cycle was not statistically significant ($p > 0.05$). (Table 5,6)

Table 5. The Clinical Pregnancy Rate According to the Frequency of IUI

	Single IUI		Double IUI	
	<90 minutes	> 90 minutes	<90 minutes	> 90 minutes
Non-pregnant group n – 191	165	4	21	1
Pregnant Group n-59	46	1	11	1

Table 6. The Clinical Pregnancy Rate According to the timing of IUI

	<90 minutes		> 90 minutes	
	Single IUI	Double IUI	Single IUI	Double IUI
Non-pregnant group n –	165	21	4	1

191				
Pregnant Group n-59	46	11	1	1
P value	0.117		0.427	

USG Parameters :

The clinical pregnant group had significantly thicker endometrial tissue than the control group (12.46 2.02 mm versus 10.25 2.10 mm, respectively; p 0.05). (Table 2). The cases were divided into two groups based on ET. The difference in clinical pregnancy rates between the two groups was statistically significant (p = 0.028). (Table 7). The pairwise comparison results for the two groups revealed that the clinical pregnancy rate in group b (ET> 8 mm) was significantly higher than in group a (ET 8mm) (p = 0.028). (Table 7)

Table 7. The Clinical Pregnancy Rate with respect to some ultrasound parameters

	Number of preovulatory follicles (>16 mm)			Endometrial Thickness (mm)	
	< 2	2 to 3	>3	< 8 mm	> 8 mm
Non-pregnant group n -191	162	22	7	80	111
Pregnant Group n-59	51	5	3	9	50
P value	0.278			0.028	

Sperm parameters :

The postwash motile sperm count is a significant predictor of IUI success. When the Postwash motile sperm count was greater than 10 million, we discovered a significantly higher pregnancy rate. When the post wash motile sperm count was less than 5 million, the pregnancy rate was lower. In one of the earlier studies, the authors attempted to establish a cut-off point for seminal parameters at which IUI would be beneficial in male factor infertility. A postwash motile sperm count of 1 million was linked to a low pregnancy rate.Sperm morphology appeared to play an important role when the post wash count was 5 million. Based on our findings and previous reports, we believe that in cases of male factor infertility with a population of 5 million, couples should be carefully counselled and the option of ART-IVF should be offered more liberally, especially if the female partner's age is advanced.

Table 8. Pregnancy rates after intrauterine insemination with respect to some sperm parameters

	Total sperm count		Motility (%)			Post-wash total motile sperm count ($\times 10^6$ /mL)		
	< 39	> 39	20 to < 42	42 to <80	>80	<5	5 to <10	>10
Non-pregnant group	79	112	53	135	3	5	65	121
Pregnant Group	25	24	15	44	0	1	16	42
P value	0.890		0.574			0.053		

Ovarian stimulation protocol :

The clinical pregnancy rate in ovarian stimulation cycles was significantly higher than in natural cycles (Table 9). The ovulation induction cycles were divided into five groups based on the medication scheme: Letrozole (group a); FSH (group b); HMG (group c); OI+FSH (group d); and OI+HMG (group e). When we compared groups a and c, b and c, a and d, a and e, and c and e, we discovered that different ovarian stimulation protocols were related to pregnancy outcome (P0.005) (Table 10). When compared to the other groups, group E had the highest clinical pregnancy rate. The pairwise comparison results for the five groups revealed that group E had a significantly higher clinical pregnancy rate than groups a, b, and d. (Table 10).

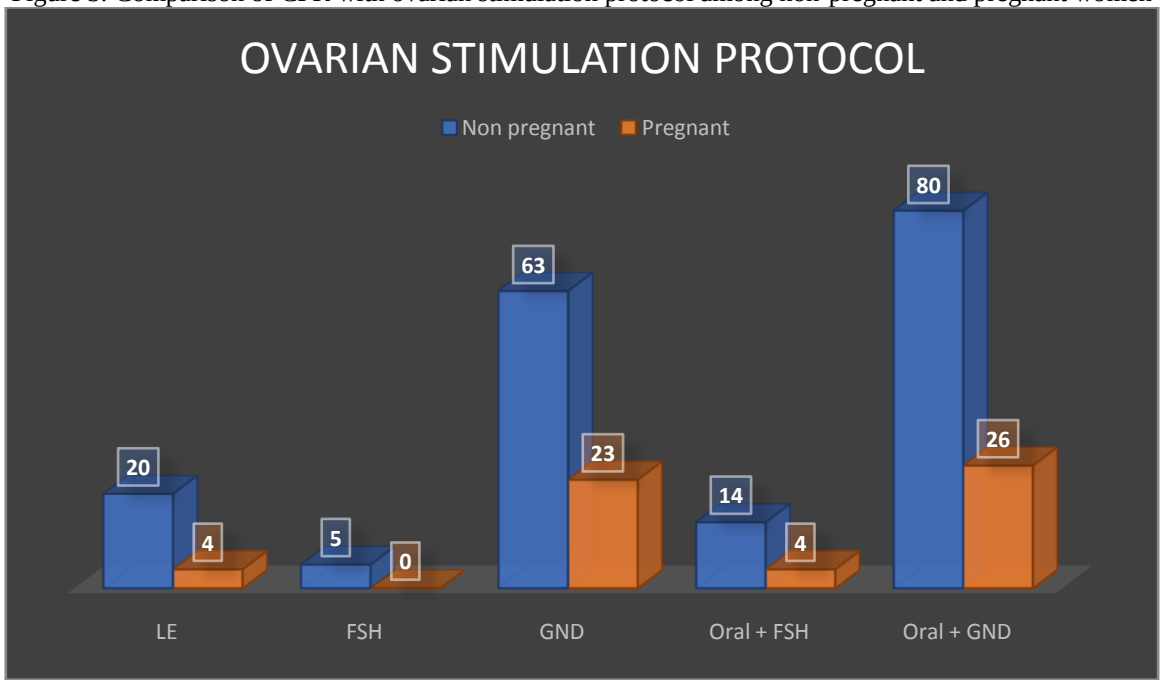
Table 9. The Clinical Pregnancy Rate According to Treatment Protocol

	Treatment protocol	
	Natural cycle	Ovarian stimulation
Non-pregnant group n -191	19	182
Pregnant Group -n 59	2	57
P value	0.543	

Table 10. The Clinical Pregnancy Rate According to ovarian stimulation Protocol

Non-pregnant group n -191				
Group A(LE)	Group B (FSH)	Group C(HMG)	Group D (OI + FSH)	Group E (OI+ HMG)
20	5	63	14	80
Pregnant Group -n 59				
LE	FSH	HMG	OI + FSH	OI+ HMG
4	0	23	4	26
P value - 0.012				

Figure 3. Comparison of CPR with ovarian stimulation protocol among non-pregnant and pregnant women



IV. Discussion

Determining how to improve the clinical pregnancy rate has been a common topic among researchers and can be discussed in regard to the following aspects.

Female Age

Previous research has discovered that age is an important factor influencing the clinical pregnancy rate in female subjects; the clinical pregnancy rate gradually decreases with increasing age. (13-15) The current study's findings support these beliefs; the data revealed that female subjects in the pregnant group were significantly younger than those in the non-pregnant group. Furthermore, female subjects aged 30 years had the highest clinical pregnancy rate when compared to other age groups; the differences were statistically significant (p 0.05). The oocyte number rapidly decreases as female subject age increases, especially once she reaches >35 years. As a result of metabolite accumulation in the body, the ovarian environment changes, resulting in deoxyribonucleic acid mutations and telomere shortening, for example, resulting in a physiological decline in oocyte quality. (16) Furthermore, endometrial receptivity decreases with age; thus, delaying implantation in endometrial window extremes can result in poor pregnancy outcomes. (17) Taken together, COH/IUI as a treatment option for women over 35 requires careful consideration, and IUI is a poor treatment option for women over 40.

Body mass index

Among the studies conducted to evaluate the success of IUI, a BMI (Body Mass Index) of 25 to 29.99 kg/m2 or 30 kg/m2 does not appear to have a negative effect on live birth after intrauterine insemination. Obesity, on the other hand, may be linked to a higher risk of biochemical pregnancy following intrauterine insemination. In our study, we also found a higher clinical pregnancy rate regardless of the patient's BMI.

Duration of infertility

The success rate was significantly lower, and the duration of infertility increased. An earlier study discovered a significant decline in IUI treatment success as the duration of infertility increased. (18) However, we were unable to identify any specific threshold above which IUI should be avoided. IUI appears to be less effective as the duration of infertility increases.

Causes of infertility

Among the indications for IUI, patients with unexplained infertility had a higher success rate than those with endometriosis or severe male factor infertility, though the difference was not statistically significant. An earlier meta-analysis documented a trend toward lower pregnancy rates in endometriosis, with pregnancy rates reduced to half when compared to other infertility indications. (19)

When the effect of infertility aetiology was examined, endometriosis patients had a significantly lower pregnancy rate than women with unexplained infertility. The pregnancy rate in the endometriosis group was 6.8 percent per cycle, which is slightly lower than previously reported (9-16), and Hughes et al concluded in his meta-analysis that a diagnosis of endometriosis reduced the effectiveness of ovarian stimulation/IUI by approximately half in the treatment of persistent infertility (unexplained infertility, male factor, and endometriosis), which is consistent with the current data. According to the current data and the published IVF results by Geber et al(20), IVF is more effective than IUI in women with endometriosis.

According to Peterson et al. (21), the average pregnancy rate per cycle for unexplained infertility using HMG/IUI was 18%. This is supported by our current research. A decreased fertilisation rate has been proposed as the cause of infertility in women with unexplained infertility, which may be overcome by superovulation therapy in conjunction with an increased number of fertilizable oocytes in IUI. In patients with unexplained infertility, current evidence suggests that IUI should be considered as a first line of treatment before more expensive IVF.

IUI Timing and Frequency

The mastery of IUI timing and frequency is strongly related to the success of an IUI. According to the current research findings, the clinical pregnancy rate was higher with double IUI per cycle than with single IUI per cycle. Ragni (22) also believed that double IUI per cycle resulted in a better pregnancy outcome than single IUI per cycle. Previous research (23), found that the majority of pregnancies occurred within the first four treatment cycles, favouring a maximum of four IUI cycles before IVF.

Endometrial thickness

A large number of studies have shown that an ET (Endometrial Thickness) of 8-12 mm has the highest clinical pregnancy rate. The current study's findings show that subject ET was thicker in the clinical pregnancy group than in the non-pregnancy group. Weissman et al (26) discovered that an ET of 7-14 mm resulted in a higher rate of implantation and pregnancy than an ET of >14 mm. According to Zhao et al (27), the clinical pregnancy rate during an EMT of >7 mm was significantly higher than during an EMT of 7 mm.Overall, a thin endometrium may reduce clinical pregnancy and implantation rates. Moffat et al (28) also reported that age, decreased ovarian reserve, endometriosis, and the hypo gonadotrophic condition all affect ET in female subjects. Low implantation and pregnancy rates can be caused by a variety of factors, including age, endometrium pattern, inflammation, and endocrine disorders, all of which affect endometrial receptivity. As a result, the effects of ET on the pregnancy rate warrant further investigation.

Pre-ovarian follicles

The number of follicles was a good prognostic predictor of IUI outcome in our study. Many studies have shown that cycles with three pre-ovulatory follicles have a higher pregnancy rate (16.3 percent), which is significantly higher than cycles with only one follicle (5.7 percent). Multi-follicular development may result in more fertilable oocytes and a higher-quality endometrium and luteal phase, improving fertilisation and implantation rates. However, we did not find a significant increase in CPR with multi-follicular development in our study. The poor outcome in cycles with only one pre-ovulatory follicle, which has been confirmed in other studies, highlights the importance of combining ovarian stimulation with IUI.

Sperm Parameters

There are differing views on the effect of Postwash motile sperm count on clinical pregnancy rate. According to the data in the current study, the Postwash motile sperm count was higher in the pregnancy group than in the non-pregnancy group. A Postwash motile sperm count of 5106/mL, on the other hand, did not result in a significant reduction in clinical pregnancy rate. Furthermore, male patients with mild asthenospermia are the best candidates for this treatment; however, as sperm activity declines, reaching a sufficient sperm

concentration becomes difficult. Other factors must be influencing the pregnancy outcome at this point. In future studies, a larger sample size would help confirm this regularity.

Ovarian Stimulation Protocol

There are differing views on the effects of various treatment protocols on clinical pregnancy outcome. Previous research [34] found no significant difference in clinical pregnancy rates between the ovarian stimulation cycle and the natural cycle. Other studies[35] have found that the ovarian stimulation scheme, as opposed to the natural scheme, significantly improves the clinical pregnancy rate. Furthermore, several studies have shown that in IUI programmes, cycles with HMG have better reproductive outcomes than cycles with CC and LE.According to the findings of this study, the clinical pregnancy rate was significantly higher in the ovarian stimulation cycle than in the natural cycle (p 0.05). The natural cycle's unstable LH peak fluctuation, on the other hand, makes determining the most appropriate insemination time difficult. Ovarian stimulation, on the other hand, would make estimating ovulation time easier. In different ovarian stimulation protocols, the clinical pregnancy rate was higher in the HMG group than in the non-HMG group. Furthermore, the LE+HMG group had the highest clinical pregnancy rate, whereas the CC group had the lowest.Dinelli[37] also believed that single CC use was ineffective in improving clinical pregnancy rates in unexplained infertility. This could be due to CC's anti-estrogen effect on the endometrium. However, by combining CC and HMG, the follicle number can be appropriately increased, thereby increasing the oestrogen level, increasing ET, and improving the clinical pregnancy rate to some extent. LE is a third-generation aromatase inhibitor that increases pituitary follicle stimulating hormone (FSH) release by inhibiting oestrogen synthesis, promoting follicle growth and development[38]. As a result, the pregnancy rate in the LE+HMG group was higher than in the HMG group.

V. Conclusion

Finally, regardless of gender, fertility declines significantly after the age of 35. It has been suggested that the reproductive age be arranged in a reasonable manner. The clinical pregnancy rate rises as the postwash motile sperm count rises. It is worth noting that a postwash motile sperm count of 5106/mL can also result in a successful pregnancy. Furthermore, ovarian stimulation is an excellent option for achieving a satisfactory pregnancy outcome as soon as possible; the LE+HMG combination is ideal. Meanwhile, combining this scheme with double IUI before and after ovulation, particularly if ovulation is observed within the next day of the first IUI, would significantly increase the chances of pregnancy.

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