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RESEARCH ARTICLE

ANALYSIS OF ASSISTED REPRODUCTION TECHNIQUE CYCLES IN YOUNG WOMEN WITH AFC COUNT LESS THAN FIVE IN A PUBLIC SECTOR CENTRE.

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Abstract

Aims and Objective(s):
1. To estimate the ART (Assisted Reproductive Techniques) outcomes in young women with AFC count less than five in a public sector ART centre in a developing country.
2. To compare the stimulation protocols used in these women
Design: Retrospective data analysis.
Method(s): Three year ART data analysis of 87 embryo transfer cycles in women, aged 20-35 years with AFC count less than five in a public sector ART clinic in a developing country. The data was analyzed in two groups based on the ART stimulation protocol used. We used Chi square and T tests used for statistical analysis.
Results: Pregnancy rate of 44% was noted following fresh transfer cycles and 35.4% following Cryo ET cycles in women with AFC count less than five. The pregnancy rates in the agonist stimulation group and flexible antagonist groups was 46.13%and 42% respectively and comparable. Good quality embryo yield was 1.28 in antagonist group and 1.6 in agonist group ($p > 0.05$). Cycle cancellation due to non-recruitment was minimal in both groups. Day 5 embryo transfers, was significantly more in the long agonist group while cleavage stage embryo transfers were more in the antagonist group.
Conclusions: Our stimulation protocols helped achieve satisfactory reproductive outcomes in young women with basal antral follicle count less than five. Both long agonist and antagonist stimulation protocols were comparable in their reproductive outcomes. The costs incurred in either regimen were not significantly different.

Introduction:-

Assisted reproductive techniques (ART) have opened up new frontiers in the management of sub-fertility. It provides an opportunity to those with decreased reproductive potential to have biological offspring, which grants them the joy of parenthood and a respite from the myriad of social, cultural and psychological problems that sub fertility causes.

Current research and evidence show that ART success depends on the number of healthy oocytes retrieved [Fauser et al 2005]. Understandably, poor ART outcomes are noted in women with low antral follicular count in whom lesser oocytes are retrieved. [Himabindu et al 2013, Brigga et al 2015]

In developing countries, the couple undergoing IVF/ICSI (In vitro fertilization, Intra cytoplasmic sperm Insemination) cycles, find the expenses heavy and burdensome. [Shahin2007] The patients spend huge amounts to buy the hormones required for controlled ovarian stimulation. The women with low ovarian response particularly those with diminishing ovarian reserve as evidenced by low antral follicular counts (AFCs) need more gonadotropins than a normal responder for controlled ovarian stimulation [Pandyan et al 2010]. Thus, their treatment cycles are even more expensive.

Our centre is a Government run ART centre in a developing centre catering to patients from poor economic background. We conduct around 300 IVF ET (In vitro fertilization and embryo transfer) cycles per year. Amongst the women, undergoing controlled ovarian stimulation cycles 13- 15% women have low antral follicle count. This data review aims to assess the reproductive outcomes of our ART regimens and to find whether any stimulation regimen was better in terms of pregnancy outcomes and cost effectiveness.

Study duration 2012 to 2015- two years:-
Sample group- Women who underwent IVF/ICSI and ET at our centre.
Inclusion criteria
Women undergoing COHH
AFCS count less than five
Age 20 to 35 years
Exclusion criteria
Women recruited for donor oocyte/donor embryo cycles

Aim:-
To estimate the ART outcomes

- Oocyte yield
- Embryo yield
- Good quality embryo yield
- The day of embryo transfer
- Pregnancy rates

To compare the two stimulation protocols used in these women

Material and Methods:-

We conducted this review from the data records of patients attending our public sector ART clinic in a developing country. Eighty-seven women satisfied the inclusion and exclusion criteria and their records reviewed. The women underwent controlled ovarian stimulation by either long agonist or antagonist protocol followed by fresh or segmented cycle embryo transfer. The data was analyzed in two groups based on the ART stimulation protocol used. We used Chi square and T tests for statistical analysis, and significance determined by P value < 0.05.We had randomly allocated the patients to either the long agonist or antagonist -stimulating regimen. The long agonist and antagonist protocols we used in these patients are briefed below.

The long agonist protocol:-
Injection Leuprolide acetate (GnRH agonist) 0.5 mg subcutaneously daily was started from day 21 of previous cycle. This dose changed to 0.3 mg daily from second day of the ensuing menstrual cycle and gonadotropin stimulation started. The gonadotropin and its dose for ovarian stimulation was determined based on the basal estradiol, FSH and LH values. The GnRH dose further reduced to 0.2mg daily from the sixth day of stimulation and maintained so until the day of hCG (human chorionic gonadotropin) trigger. All women received between 9-11 days of gonadotropins. The gonadotropins used were recombinant FSH or highly purified HMG or a combination based on the hormone levels and follicular monitoring. The follicular monitoring done by transvaginal ultrasound and the follicular recruitment, endometrial thickness noted. When more than three follicles of 17mm were recruited, the hCG trigger was given followed by oocyte retrieval under general anesthesia after 34 hours. IVF/ICSI done and the

embryos cultured and were transferred on either day2, day3 (cleavage stage) or day 5 (blastocyst) based on the embryo quality. Luteal phase support given with injectable and vaginal natural micronized progesterone. The patients reported after two weeks following the embryo transfer to test for pregnancy by urine pregnancy kit as well as serum BhCG estimation. Pregnancy test considered positive when BhCG levels were more than 30 mIU/ml. Women who were unfit for transfer had all their embryos vitrified on day 3 and segment warmed embryo transfer done later. Same cycle embryo transfer was deferred if the endometrial thickness at the time of oocyte pickup was less than 7mm.

Antagonist cycle:-

Here, we started the gonadotropins on day 2 of the period based on patient history, and hormonal profile. The flexible regimen for starting antagonist (Cetrorelix 0.25mg SC daily) followed. The antagonist overlapped when there were more than three recruited follicles of 11mm or one follicle of 13mm. The patient received between 9-11 days of gonadotropins either rFSH, HMG HP or both based on patient profile and follicular monitoring. The trigger and subsequent management of the ART cycle was the same as in long agonist protocol.

Results:-

Patient profile:-

The demographic profiles of our patients were as shown in the tables below. Eighty-seven women satisfied the inclusion criteria and their age distribution is in Table 1. Their mean basal hormonal profiles on Day 2 were FSH - 7.8 IU/ml and LH-4.5 IU/ml. Primary infertility accounted for 61(70.11%) while 26(29.89%) had secondary infertility. The main etiology for infertility (table 3) among these women was tubal pathology (47.13%) and 43.68% had history treatment for genital tuberculosis. More than eighty (86 %) percent of the women reviewed belonged to poor socio economic background.

Table 1:- Age distribution of patients.

Age	Number (%)
20-25	8(9%)
26-30	37(43%)
31-35	42(48%)
Total	87(100%)

Table 2:- Reasons for ART and associated pathology noted.

Etiology for undergoing ART other than low AFC	Numbers	Tuberculosis treatment in the past in woman
Tubal factor	41(47.13%)	24(59%)
Male factor	15(17.24%)	5(33%)
Unexplained	11(12.64%)	7(64%)
Endometrial pathology	7(8.05%)	2(29%)
Endometriosis	13(14.94%)	0(0%)

Of the women included 34 (39.08%) were stimulated by the long agonist protocol and 53(60.92%) by antagonist protocol. The causes for infertility in both long agonist and antagonist groups were comparable (p value >0.05)) (table3)

Table 3:- Comparison of etiological factors in agonist and antagonist groups.

	Agonist (n=34)	Antagonist (n=53)	P value
Tubal disease	15(44%)	26(49%)	>0.05
Endometriosis	4(12%)	9(17%)	
Tuberculosis history	17(50%)	26(49%)	

Comparison of ART outcomes based on protocols used in women with AFCs less than 5 (table 5)

The mean oocyte yield (the number of oocytes retrieved per patient was significantly more in the agonist group (10.33) compared to the antagonist group (6.23). On the other hand, fresh transfers were 93.4% in the antagonist group and this was significantly more than the agonist group. Of the 34 patients in agonist group, six had segmented

embryo transfers due and poor endometrial build up but none had OHSS (ovarian hyperstimulation).Two patient in the agonist group had to cancel their cycles due to non-recruitment.

In the antagonist group, only three women had segmented IVF due to poor endometrial build up and none had cycle cancellation.

The embryo yields were comparable in both groups, but day 3 transfers were significantly more in the antagonist group. In contrast, the agonist group had significantly more day 5 transfers.

Table 4:- ART outcomes.

	AGONIST N=34	ANTAGONIST N= 53	pvalue
Mean oocyte yield per patient	10.33	6.23	<0.0001
Number of fresh transfers	26(76.47%)	50(94.34%)	.01440
Total embryos for fresh transfer	68	113	.8114
Mean Embryo yield/patient for fresh transfer	2.61+/_ 1	2.36 +/_ 0.9	0.2468
Good quality embryo yield	1.28 +/_ 0.99	1.6 +/_ 0.96	0.1239
Day 2 transfers	1	7	.1711
Day 3 transfers	10	37	.0024
Day 5 transfers	15	6	< .0001
FET	6	3	.0573
Non recruitment and cycle cancellation	2	0	.0826

Tests- chi square, t test

Table 5:- Pregnancy rates.

Pregnancy Rate	Stimulating Regimen		P Value
	Agonist N=34	Antagonist N=53	
Pregnancy rate fresh transfer	46.13%	42%	.5688
Live birth rate	33%	30.3%	.5442
FET(Frozen embryo transfer) pregnancy rate	37.5%	33.3%	.5556
Live birth rate	30.2%	29.6%	.3968

Our review revealed a pregnancy rate of 44% following fresh transfer cycles and 35.4% following Cryo ET cycles in women with AFC count less than five. The pregnancy rates in the agonist stimulation group and flexible antagonist groups was 46.13%and 42% respectively and comparable.

As shown in table 5 above, the vitrified warmed embryo transfer outcomes in both groups were also similar between the two stimulation groups. The mean good quality embryo yield was 1.28 in antagonist group and 1.6 in agonist group and difference not significant.

Significant difference (p-value 0.05) noted in the number of Day 5 embryo transfers, which was significantly more in the long agonist group. Cycle cancellation due to non-recruitment was minimal in both groups, two (5.88%) and none in the antagonist cycle.

Table 6:- Average Gonadotropin Consumption.

Total dose of Gonadotropins	Mean no of days of stimulation	Agonist (N=34)	Antagonist (N=63)	P values
Recombinant FSH (rFSH) only	9.2	N= 6 1641 IU	N=7 1854IU	0.3267

Highly purified HMG	10.3	N=7 3300 IU	N=23 3182 IU	0.2501
rFSH +HMG HP	9.6	N=21 1411IU +1893 IU	N=23 1538IU + 986IU	0.2161 <0.01 Total <0.01

We noted that the average total doses of gonadotropins in women who received either rFSH or HMG HP for stimulation was comparable in both agonist and antagonist groups (table 6). In the subset of women who needed both FSH and HMG the average total dose of HMG as well as the combined average dose was significantly lesser in the antagonist group.

In the long agonist cycle the patient received subcutaneous daily doses of leuprolide for an average of 24.6 days the cost of which was significantly lesser than the 3-5 doses of cetrorelix used to regulate the antagonist cycle. Thus, overall we found no significant difference in the average costs incurred by the patients between both groups.

Discussion and Conclusions:-

Eighty-seven women with age between 25 and 35 underwent IVF treatment at our centre over two years from 2013. They constituted 14.2 % of women undergoing ART cycles in our centre.

Tubal disease and genital tuberculosis contributed to causative pathology in almost half of these women, emphasizing the high prevalence of tuberculosis induced infertility in our patient subset.

The pregnancy and live birth rates in women aged between 25-35 years of age with antral follicle count less than five was above 40% and 30% respectively. Thus, we were able obtain satisfactory reproductive outcomes in women with low ovarian reserve.

Both long agonist and antagonist protocols of ovarian stimulation showed comparable pregnancy and live birth rates. The pregnancy rates in the agonist stimulation group and flexible antagonist groups were 46.13%and 42% respectively. In contrast to Pandian et al [Pandian et al 2010], the oocyte yield in the long agonist group was significantly better amongst our patients although the clinical pregnancy rates in both groups were similar.

The fresh and vitrified –warmed embryo transfer outcomes in our patients were comparable in both groups.

Our study did not find significant difference in the costs incurred per cycle of stimulation between the two groups.

More cleavage stage embryos embryo transfers were done in the antagonist cycles while significantly more transfers of blastocysts were possible in the antagonist cycles. There were no cycle cancellations due to non-recruitment in the antagonist group.

Thus, we were able to achieve satisfactory reproductive outcomes with optimal stimulation regimens in young women with basal antral follicle count less than five. Both long agonist and antagonist stimulation protocols were comparable in their reproductive outcomes. The costs incurred in either regimen were not significantly different and benefitted in view of the satisfactory reproductive outcomes.

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