



# ACCU-VIT : a new strategy for managing poor responders

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## Introduction

In 2011, the European Society for Human Reproduction and Embryology (ESHRE) reached a consensus on the minimal criteria required to define poor ovarian response, known as the Bologna criteria. The acronyms POR and PORs were also proposed to enter into conventional assisted reproduction treatment terminology to define poor ovarian response and poor ovarian responders, respectively. Minimal stimulation protocols were evolved with the intention of providing a more natural stimulation for IVF, with one of its main advantage being production of fewer but better quality oocytes. A potential management of poor responders is to create a sufficient pool of embryos by accumulating good quality embryos by vitrification over several minimal stimulation cycles.

The aim of the current study was to evaluate the efficacy of serial minimal stimulation IVF cycles with vitrification and accumulation of embryos followed by a remote frozen embryo transfer for the treatment of poor ovarian responders as compared to conventional IVF protocols.

## Material and Methods

### Study Population

This a retrospective data analysis of patients who were classified as poor ovarian responders based on the Bologna criteria between 1<sup>st</sup> June 2010 and 30<sup>th</sup> November 2012.

### ACCU-VIT Protocol

This protocol consists of Minimal Stimulation IVF (msIVF) + Vitrification + Accumulation of Embryos + Remote Embryo Transfer (rET)

### msIVF

The minimal stimulation protocol using Clomiphene Citrate (Ovofar, MSD, India), Human Menopausal Gonadotropin (hMG) (HUMOG, BSVL, India) and GnRH Antagonist Cetrorelix (Ciscure, Emcure, India) was used.

### Vitrification and accumulation of embryos

The retrieved eggs were fertilized using either IVF or ICSI and the resulting embryos were frozen on day 3 using vitrification (Cryotech, Japan). Back to back cycles of msIVF followed by ACCU-VIT were performed till about six top grade were accumulated per patient.

### rET

A remote embryo transfer was performed when adequate embryos were accumulated. The embryos were warmed using the Cryotech (Cryotech, Japan) warming protocol. The warmed embryos were transferred on day 4, after preparing the endometrium with Estradiol Valerate tablets (Progynova, Zydus Healthcare, India).

### Conventional Stimulation Protocol

Conventional controlled ovarian stimulation protocol using Biosimilar recombinant FSH (Foligraf, BSVL, India) along with Buserelin (Busag, Zydus Gynova, India) was used. Fresh embryos were transferred on day 3.

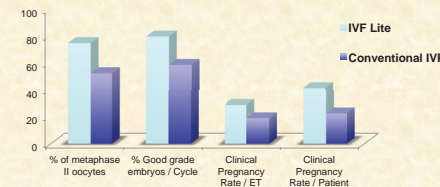
## Results

The ACCU-VIT group had a total of 55 patients who underwent 150 treatment cycles. For the conventional IVF group, a total of 85 patients underwent 149 treatment cycles. The percentage of metaphase II oocytes retrieved was 74.85 % for the ACCU-VIT group and 52.73 % for the conventional IVF group (statistically significant,  $p < 0.01$ ). The difference in the number of gonadotropin units required to produce one MII egg between the two groups was statistically significant: 579.09 units for ACCU-VIT group and 4819.98 units for conventional IVF group,  $p > 0.001$ . It is interesting to note the significant difference in the percentage of good grade embryos between the two groups ( $p < 0.01$ ).

Clinical pregnancy rate (PR) per embryo transfer was 28.50% in the ACCU-VIT group and 18.70% in the conventional IVF group. The cumulative pregnancy rate (CPR) per patient was 41.81% in the ACCU-VIT group which is much higher than the 22.35% CPR per patient in the conventional IVF group.

	ACCU-VIT	Conventional IVF	p Value
Patients (n)	55	85	
No. of initiated cycles	150	149	
Avg no. of initiated cycles/patient	2.73	2.27	
% cancelled retrieval cycles / initiated cycle	16.66% (25/125)	22.15% (33/149)	NS
% Cycle with no oocytes retrieved /retrieval cycle	7.2% (9/125)	9.48% (11/116)	NS
% Cycle with no fertilization / retrieval cycle	1.6% (2/125)	2.59% (3/116)	NS
Dosage of Gonadotropins (IU)	1482.48±881.7	12098.16±4113.9	<0.001
Dosage of gonadotropins required /MII oocyte	579.09	4819.98	<0.001
No. of oocytes / retrieval cycle	3.42±1.3	4.76±2.80	NS
% of metaphase II oocytes	74.85%	52.73%	<0.01
Fertilization Rate (%)	91.12%	90.89%	NS
Cleavage Rate (%)	97.96%	96.01%	NS
% Good grade embryos / Cycle	79.73% (1.99/2.22)	58.79% (1.17/1.99)	<0.01
No. of transfer cycles (n)	81	102	
Clinical Pregnancy Rate / ET	28.50%	18.70%	<0.05
Cumulative Pregnancy Rate / Patient	41.81% (23/55)	22.35% (19/85)	<0.01
% cycles with cancelled embryo transfers	0%	12.07% (14/116)	<0.01

Cycle outcomes for ACCU-VIT and conventional IVF groups



## Discussion

The incidence of POR is 9.24% in the patients undergoing IVF treatment. The current study was set out to assess the application of ACCU-VIT protocol as a new strategy for managing poor responders.

The minimal stimulation protocol used clomiphene citrate and gonadotropins, with GnRH antagonist. It involves a reliable cryopreservation technique such as Cryotec vitrification used for the accumulation of embryos over a few cycles followed by remote embryo transfer. Acceptable pregnancy rates have been reported in literature (20% for fresh transfers and 41% for cryopreserved embryo transfer) indicative of the fact that cryopreserved remote embryo transfers have resulted in a higher pregnancy rate when compared to fresh embryo transfers. The main advantage with the minimal stimulation protocol is that there is no resting cycle required between two treatment cycles which allows patients with poor ovarian reserve to have back to back consecutive cycles before their follicular reserve is depleted.

The study center makes use of the latest Cryotec vitrification method developed by Dr Masahige Kuwayama. The study center chose this method owing to its numerous advantages, which all cumulatively added up to an extremely high embryo survival rate.

Although there was no significant difference in the number of MII oocytes between the two groups. Interestingly, the ACCU-VIT group had MII oocytes comparable to the conventional IVF group, with significantly less gonadotropins used. The ACCU-VIT group had a significantly higher percentage of good grade embryos than the conventional IVF group. This suggests that when minimal stimulation is used, a cohort of few but better quality oocytes is obtained. The CPR observed in this study for poor responder patients in the ACCU-VIT group is comparable to the success rate in normal responding patients.

In conclusion, accumulating vitrified embryos in serial minimal stimulation cycles (ACCU-VIT) followed by a frozen embryo transfer is a better treatment option for poor ovarian responders as compared to conventional IVF. This approach allows the poor responder women to have consecutive cycles of embryo accumulation before the follicular reserve is depleted. It will maximize the ovaries' already limited life span, allowing patients the opportunity to store embryos while oocyte production is still active.