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Conventional stimulation protocol failed to produce mature oocytes : rescue ivm resulted in six pregnancies after invitro fertilization and embryo transfer

Sulochana Gunasheela*, Devika Gunasheela, Santosh Gupta and Joshua Peter

Gunasheela Surgical & Maternity Hospital, Bangalore, No.1, Dewan Madhawa Rao Road, Basavangudi, Bangalore, - 560004 Karnataka, India

Abstract
When conventional stimulation protocol in IVF cycle fails to produce mature oocytes, many a times, the cycle is cancelled and the patient is disappointed. Now that in-vitro maturation of oocyte is possible in view of commercial availability of media, perhaps it may be mandatory to retrieve immature oocytes and mature them in-vitro, freeze them if necessary and fertilize, develop embryos for transfer in order to help couples to achieve pregnancy. Thus maturation in-vitro of GVs has become an important adjuvant for treating PCOS and in particular poor responders to gonadotrophin stimulation. Our study is interesting because in spite of conventional stimulation protocol, we failed to recover any mature oocytes in eleven women when the average follicles size being 17mm at the time of hCG. However, maturing these oocytes in-vitro, as a rescue measure, resulted in 50% of these women becoming pregnant after embryo transfer.

Keywords: Immature Oocytes, GV, In-vitro Maturation, Rescue IVM, IVF.

INTRODUCTION

In vitro maturation is a practice of intentionally retrieving immature oocytes from small antral follicles and maturing them in vitro. It has potential to substitute or at least adds as an adjuvant to standard IVF protocols. IVM also reduces the time cost and inconvenience related to gonadotropin stimulation and almost eliminates the risk of OHSS (1)

Various Indications of IVM are PCOS, threatened OHSS, poor response to gonadotrophins and fertility preservation in cancer patients but interestingly it can be used as rescue measure in conventional IVF stimulation by maturing retrieved GVs in-vitro which is termed as “rescue IVM” (2,3).

Very often in IVF cycle protocol, a mixed cohort of matured oocytes (MII), MI, and post mature along with GVs are obtained (4). Competence of these immature oocytes retrieved is being questioned several times (5). The aim of the present study was to investigate the role of IVM of oocytes as a rescue measure in IVF cycles, when they produce only immature oocytes in spite of stimulation with gonadotrophins.

MATERIALS AND METHODS

From March 2004 to September 2010, eleven women who underwent conventional IVF stimulation failed to produce any mature oocytes; but only GV stage oocytes were retrieved. Seven women who were between 23-39 years of age (average age 28.6 years), underwent down-regulation stimulation protocol while four were directly stimulated with recombinant FSH (rFSH). When atleast three follicles reached 17mm in diameter, 10,000 IU hCG (Profasi) was administered and 34 – 36 later oocyte pick up was scheduled. Average E2 was 2107.g on the day of hCG which ranged between 531 – 6950 in these women. A total of 108 GV stage oocytes were obtained from eleven women. Immature oocytes were incubated in IVM media and checked for maturity periodically between 12 to 48 hours. Only oocytes with 1st polar body extrusion were considered as mature and taken for ICSI. Fertilization was assessed 16 -18 hrs after ICSI .Cleavage stage embryos were transferred on day 2 after partial laser assisted hatching of the zona (6).

Luteal phase support was by vaginal insertion of micronized progesterone pessary, 300mg twice a day starting from the day of ICSI and continued till 12th week of pregnancy. Serum βhcg was done on day 18 post ET.

RESULTS

A total of 108 GVs were obtained from eleven patients with an average of 9.81 GVs per patient of which 72.22% oocytes matured in-vitro with fertilization rate of 75.64% and cleavage rate of 94.91 %. Average number of embryos available was 5.09 per patient. Embryos were transferred in ten cases (90.9%) in the same cycle. In one case, only 3 GV stage oocytes were retrieved and none of them matured in-vitro. Average number of embryos transferred per patient was 2.63 and 36.36% patients had extra embryos to freeze (See Table 1).

Out of ten patients who had fresh embryo transfer, five pregnancies were achieved with a pregnancy rate of 50% per ET. One patient was pregnant with frozen embryo transfer. Thus a total of six pregnancies achieved among eleven cases with augmented pregnancy rate of 50.46% per patient. Out of six pregnancies, four resulted in full-term singleton live-births, one triplet pregnancy which

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*Corresponding Author

Sulochana Gunasheela
Gunasheela Surgical & Maternity Hospital, Bangalore, No.1, Dewan Madhawa Rao Road, Basavangudi, Bangalore, - 560004
Karnataka, India

Tel: +91-8041312600; Fax: +91-8026670379
Email: gunasheelaivf@gmail.com

was reduced to twins by foetal reduction, unfortunately aborted at 17 wks; one missed abortion at six weeks and the same woman came for frozen embryo transfer after 3 months, became pregnanct and delivered a full-term singleton baby. Take home baby rate (THBR) was 36.36% (4/11). No significant anamolies were seen at birth among the babies delivered.

Table 1. Clinical and laboratory outcome of rescue in vitro maturation

		%
No of patients	11*	
Average Age	28.6 yrs	
Average no of GVs / Pt	9.81	
Maturation rate	78/108	72.22%
Fertilization rate	59/78	75.64%
Cleavage rate	56/59	94.91%
Average no of embryos/pt	5.09	
Av no of embryos transferred / Pt	2.63	
ET done	10/11	90.9%
Extra embryos to freeze / Pt.	2.45	
Pregnancy rate / ET	5/10	50%
Pregnancy rate / Pt.	5/11	45.5%
Clinical pregnancy rate / ET	5/10	50%
Augmented pregnancy rate / Pt	6/11	50.46%
THBR	4/11	36.36%

*** In one case, none of the oocytes matured invitro**

DISCUSSION

In 1994, Trounsen et al. (7), first reported a successful pregnancy following in vitro maturation of oocytes collected by transvaginal ultrasound guided aspiration of small follicles from unstimulated ovary in a PCO patient. Since then IVM has been used intentionally for PCOS, threatened OHSS and poor responders. Interestingly, it can also be used to rescue immature oocytes in IVF cycle when conventional protocol fails to produce mature oocytes, in spite of the average number of follicles reaching 17mm in diameter. The exact etiology of retrieving only GVs are not known. However, there are some studies which describe about intrinsic factors which may be responsible for maturation failure (8).

Most of the studies have discussed about intentional IVM for different indications (9). Our study of eleven patients suggests that immature oocytes obtained from large follicles can be matured in vitro, fertilized and good cleaving embryos could result in pregnancy. Our maturation rate was 72.22%, fertilization rate 75.44%, cleavage rate 94.91%, which seems that the oocytes were competent enough to produce clinical pregnancy rate of 50% and live birth of 36.36%. In our experience, clinical pregnancy rate and THBR are almost equal to the conventional IVF cycles. Most of the studies have shown that, in IVM, pregnancy rates are lower and abortion rates are higher than IVF cycles (10). In our study average age of the patients were 28.63 years, which may be a contributing factor for better success rate. Although the causes of maturation failure are multiple (11,12,13), we have been able to overcome by in vitro maturation, fertilization and establishing pregnancies resulting in four live births post ET. However, the number of cases are too small to arrive at any significant data in this study.

CONCLUSION

Intentional IVM is a promising technology which can reduce the cost, cancellations, time consumed and inconvenience to the patients. Rescue IVM is an added important tool in ART which can result into viable pregnancies resulting in live births. Hence ART practice should include IVM technology to help couples to overcome cancellations and disappointment.

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