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Research Article

Art outcome in combined group of women with premature ovarian failure and menopausal women

Rekha Rajendrakumar*, Purnima K. Nadkarni

Department of Reproductive Medicine, Nadkarni Hospital and Test Tube Baby Centre, Killa Pardi- 395125, Valsad, Gujarat, India

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***Correspondence:**

Dr. Rekha Rajendrakumar,

E-mail: dr_rajendrakumar60@yahoo.co.in

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ABSTRACT

Background: It is to present an overview of the study of the ART cycles in combined group of women with premature ovarian failure (POF) and menopausal women in 1 year period. Purpose of the study was to know the pregnancy outcome in this combined group. Since majority of the patients who entered our tertiary hospital had already received various treatment methods such as gonadotropins, long protocols and ultra-short protocols in previous hospitals with no positive result, we had to take them directly to the ovum donation (OD) or embryo donation (ED).

Methods: A simple study was performed from 1st January, 2015 to 31st December, 2015. Women with POF and menopause were enrolled and complete follow up of them was done from their first visit till stable pregnancy of 14 weeks was achieved. While doing this, we considered various parameters which can affect the ART outcome, for e.g. endometrial evaluation, hysteroscopy findings, proliferative phase preparation, leuteal support, semen analysis etc. The study outcome results included pregnancy rate and miscarriage rate.

Results: In spite of good efforts, ultimately, stable pregnancy rate (beyond 14 weeks gestation) of these women was only 35% that was almost one third of the total study population that too with the help of OD and ED. Pregnancy rate was actually 42%, out of which 7% had miscarriage. With all the cost, efforts and time involved, 65% (2/3rd) of women could not achieve successful pregnancy.

Conclusions: Since the possibility of pregnancy gradually declines after the age of 30 and a steep fall in fertility after the age of 35, women should be advised not to postpone marriages and should be encouraged to have children earlier.

Keywords: Premature ovarian failure, Menopause, Antral follicle count, Infertility, Ovum donation, Embryo donation

INTRODUCTION

Incidence of premature ovarian failure (POF) is gradually increasing, as present generation women are delaying having families. Other causes noted are autoimmune, genetic, iatrogenic like surgery on the ovary like endometriosis, teratoma or ovarian drilling, hysterectomy, radiotherapy, chemotherapy, viral oophoritis, excessive use of gonadotropins, smoking, occupational exposure to lead and heavy metals etc., Though POF related issues can be usually managed well

with hormone replacement therapy (HRT), in an infertility context, POF poses a challenge to the treating physician, as the loss of ovarian function means that the probability of pregnancy with own eggs is greatly reduced.¹ Most of the women with poor ovarian reserve are deeply upset by the time they realize that they are infertile. Absence of fertility is due to absence of follicles and the inability of remaining follicles to respond to stimulation. Ovulation is erratic, rare and unpredictable and therefore, successful spontaneous pregnancy can occur in only 5-6% of POF patients. Though recombinant

follicle stimulating hormone (rFSH), gonadotropin releasing hormone agonist (GnRH a) flare up protocol, long luteal protocols, GnRH antagonists, use of corticosteroids and growth hormones all have been tried, they have not rendered encouraging response.^{2,3}

Only treatment possible which can give best result is with the help of donor eggs. Success rate with ovum donation (OD) is only 30%.⁴ In this study, we have studied the success rate with OD and embryo donation (ED) in patients with POF and menopausal age group.

METHODS

A simple observational study was conducted for a period of 1 year from 1st January, 2015 to 31st December, 2015. Of the whole outpatient and inpatient population, the patients of POF and menopause were selected for the study. Based on the values of anti mullarian hormone (AMH), follicle stimulating hormone (FSH) and antral follicle count (AFC) of both the ovaries together, cut off values were decided and women who would fit into these criteria were included in the study (Table 1).

This sample size was 46. Out of this, 3 women were lost to follow up after about 3 months of study. So, the effective sample size dropped to 43.

These 43 women were analysed on the basis of following parameters: Age, effective married life, primary or secondary infertility and menstrual cycle patterns. Effective married life of all women was more than 3 years. Since menopausal women also had the same scenario of infertility problems and same expectations as of POF group, they too were included in the study group.

Few menopausal women had genuine reasons to get into the study like 2nd marriage or death of the previous child. Menstrual pattern in some indicated gradual deterioration of fertility as oligomenorrhoea or hypomenorrhoea whereas in others, it was having regular cycles followed by abrupt cessation of menses. 47% of them had regular on-going cycles (Table 2).

Under investigations, semen analysis was one of the important parameters. Azoospermic men were encouraged to proceed to percutaneous epididymal sperm aspiration (PESA) or testicular sperm aspiration (TESA) depending on the case. They were informed that if PESA or TESA turns out to be positive, they had bright chance of becoming genetic fathers. Out of the 7 azoospermic men, PESA/TESA was positive in 3. Rest 4 who were negative, were encouraged for ED. Out of the 21% men who had oligoasthenoteratospermia, 14% were considered for OD + intra cytoplasmic insemination (ICSI) from husband's sperm as we could retrieve some good sperms. Rest 7% were taken for ED because of abnormal semen parameters. However, 63% of men had normal seminogram (Table 3a).

100% of the women underwent hysteroscopy as part of basic investigation to rule out intrauterine problems. Those were cleared then and there. Majority of them (81%) had normal hysteroscopy findings. Pin hole and occluded ostia were not further evaluated since all of them were for embryo transfer. Endometrial scratching was done for all and endometrial sample was taken for tuberculosis polymerase chain reaction (TB PCR) testing in all 43 women. TB PCR was positive in 7 (16%) of the patients and negative in 84 %. Anti tuberculous treatment (ATT) for 6 months was given for TB PCR positive women. But we imbibed them into the study and treatment of infertility, after 1 month of ATT (Table 3b).

Transvaginal sonography (TVS) was also done as part of the investigations. Day 2 TVS was done to count AFC, to visualize uterine architecture, endometrial and cavity abnormalities and also to rule out pelvic pathology (Table 3c).

Laparoscopy was done in only 2 patients as they had abnormality in TVS. One patient had simple ovarian cyst and bilateral hydrosalpinx. Cyst was removed, also bilateral salpingectomy to improve the pregnancy rate. Another patient who underwent diagnostic laparoscopy had 2 x 2 cms solitary subserous fibroid which was not removed.

Autoimmune profile was done for all. Thyroglobulin antibody was positive in 2 (4.65%) women. Rest of these investigations like antinuclear antibody, antiphospholipid antibody, anticardiolipin antibody and lupus anticoagulant were negative in all 43.

Karyotyping was advised for all the women with the age less than 40 years. Only 26% of them got karyotyping done and those were all normal.

General debility and psychological state of the couple were improved.

Proliferative phase monitoring and preparation

After tackling hysteroscopic and laparoscopic abnormalities in early part of the cycle, in the present month, prior to embryo transfer (ET) which is intended to be in next month, the study of endometrial response and growth with the influence of the drugs was studied.

Patient was called for the next visit on the second day of the menses and ovarian quiescence was checked before starting treatment. GnRH analogue 20 units (Triptorelin acetate 0.05mg) subcutaneous into the anterior abdominal wall daily for 3 days was given in all menstruating women, either just prior to or on 2nd, 3rd and 4th day of menstruation to prevent premature secretory changes in the endometrium consequent to the spontaneous rise in luteinizing hormone (LH).

Proper endometrial preparation was restarted with the following drugs with the intension of ET in this month.

Drugs used for endometrial preparation

Estrogen (17 beta-estradiol) cutaneous gel 2.5gms.equivalent to 1.5 mgm of estradiol gel.

Tab. Estradiol valerate 2 mg orally twice a day. Estrogen doses were titrated according to endometrial thickness and pattern which was monitored every 3rd day by sonography. Endometrial thickness was measured in the sagittal plane.

Tab. Folic acid 5 mg, tab. Aspirin 75 mg, antioxidants, and arginine sachet all one per day.

Tab. Sildenafil 25 mg for vaginal insertion twice a day.

In patients with history of repeated pregnancy wastage, recurrent implantation failure (RIF) or those with autoimmune investigation positive, prednisolone 8 mg twice a day was added.

Natural micronized progesterone supplementation in the form of 400 mg once daily vaginal tablet was started 48 hours prior to OD + ICSI or ED.

Meanwhile, partners were advised to freeze their semen sample for the fear of inability to give the sample on the day of ICSI whose wives needed OD. Also, they were instructed to give fresh sample on the day of ICSI with prior 2 to 3 days abstinence.

Once the endometrial lining has achieved the thickness of 9 mm with good triple line, they were considered for ET. In 34 (80%) women, embryos were transferred between days 14 to 16. In the rest 20%, embryo transfer was done between day 17 and day 19 of the cycle. Some women received ED because either sperms were morphologically abnormal or TESA/PESA were negative (Table 4).

2 fertilized embryos were transferred intrauterine, either on day 3 or day 5 transfers using soft catheters under ultrasound guidance (Table 5).

Leuteal phase support

Inj. Human Chorionic gonadotropin (HCG) 5000 IU on the next day of ET and then biweekly, totally 5 doses subcutaneous or intramuscular.

Natural micronized progesterone vaginally 400 mgm, twice a day.

Tab. Dydrogesterone orally 10 mg twice a day.

Inj. Low molecular weight heparin 20 units subcutaneous once daily.

Estrogen was given 2 tablets thrice a day. Rest of the medicines which were given for the endometrial preparation were continued in the same doses till beta Human Chorionic Gonadotropin (β HCG) report.

TVS was not done in the secretory phase.

RESULTS

Table 1: Inclusion criteria considered for the study.

Parameter	Values
AMH	less than 0.5 ngm / ml
FSH	more than 20 mIU / ml
AFC	less than 4 (both the ovaries included)

Table 2: History and pattern of the study group patients.

		Number of women (total 43)	%
Age	Less than 40 years	30	70
	More than 40 years	13	30
Infertility	Primary	28	65
	Secondary	15	35
Menstrual pattern	Primary amenorrhoea	0	0
	Regular cycles with good flow	20	47
	Regular cycles with hypomenorrhoea	2	10
	Secondary amenorrhoea (more than 1 year)	5	12
	Oligomenorrhoea	16	36

Table 3A: Semen analysis.

	Number of men (total 43)	Percentage (%)
Azoospermia	7	16
PESA/TESA positive	3	7
PESA/TESA negative	4	9
Oligo astheno terato spermia	9	21
Normospermia	27	63

14 days after the ET, patient was called for first serum β HCG testing. Cut off limit of this sample was taken as 50 mIU/ml. Second sample was taken one week after the first sample and cut off value considered here was 500 mIU/ml. 3 days interval was maintained between HCG inj and β HCG test. Those who turned out to be β HCG negative in the second sample were advised to stop all medication and wait for the spontaneous menstruation.

They were also counselled to report to the hospital on the second day of next menses. Those, in whom β HCG was positive, were instructed to continue with all the medications and to report at 4 weeks from the date of ET for TVS to ascertain presence of intrauterine pregnancy with the presence of gestational sac and fetal heart and also to know whether it was multiple gestation (Table 6).

Table 3B: Hysteroscopic findings.

	Number of women (total 43)	Percentage (%)
Intrauterine Septum	2	5
Endometrial polyp	3	7
Intra uterine adhesions	3	7
Normal	35	81

Table 3C: Ultrasonography findings.

	Number of women (total 43)	Percentage (%)
Atrophic ovaries	13	30
Intra uterine septum	1	2
Endometrial polyp	2	5
Ovarian cyst	1	2
Subserous fibroid	1	2
Atrophic uterus	5	12
normal	24	56

Table 4: Pattern of ET.

	Number of women (total 43)	Percentage (%)
OD + ICSI	36	84
ED	7	16

Table 5: Out of the above OD and ED cases.

	Number of women (total 43)	Percentage (%)
Day 3 embryo transfer	26	60
Day 5 blastocyst transfer	17	40

Pregnancy statistics

Pregnancy was considered clinically positive when gestational sac was visualized at 4 weeks from the day of ET. If the fetal heart had not appeared by this day, they were called for repeat scan after 1 week to ascertain the same. Women with missed abortion, in whom fetal heart was seen initially and was absent in subsequent scans,

were called for repeat scan after 1 week to confirm the diagnosis. Once the diagnosis of missed abortion was made, they were thoroughly counselled and pregnancy was terminated.

Table 6: β HCG results.

	Number of women (total 43)	Percentage (%)
β HCG positive	18	42
β HCG negative	25	58

In rest of the 15 women, pregnancy continued uneventfully and was considered stable after 14 weeks of gestational age (Table 7). These 15 pregnancies were ascertained normal by serial clinical, laboratory and USG monitoring. Sildenafil was stopped as soon as β HCG was positive.

Table 7: Pregnancy statistics and final outcome.

	Number of women (total 43)	Percentage (%)
Women who had presence of fetal heart beat	18	41.86
Twin pregnancy	2	4.65
Missed abortion	3	6.97
Pregnancy continued beyond 14 weeks	15	34.8
Pregnant women aged more than 40 years(more than 14 wks gestation)	3	6.97
Pregnant women aged less than 40 years(more than 14 wks gestation)	12	28
Women delivered during the study (from the study group)	9	20.9
On-going pregnancy	6	14

Estrogens and HCG inj. were stopped at around 14 weeks. Prednisolone was tapered and stopped at 14 weeks. Progestogens, aspirin and low molecular heparin were continued till 34 weeks.

DISCUSSION

According to Mirkin et al age has no impact on the success, once diagnosis of POF was made.⁵

In our small study, 65% of the women had never experienced pregnancy and 35% were secondarily infertile. This is to compare with study by Vegetti et al which showed the latter figure at 56%.⁶

ESHRE (December 2015, management of women with POI) suggested that routine ultrasound for AFC is not necessary as the ovarian function may fluctuate in women with POF, follicular activity may be seen subsequently during stimulation, thus not distinguishing POF from other diagnoses. We had considered AFC of all the women.⁷

Original paper by Goldberg et al did not show any follicles in the ovarian biopsy from women with FSH levels beyond 33 mIU/ml.⁸ The literature search since then resulted in number of papers using FSH cut off value for POF ranging from 20 to 40 mIU/ml (Noyas et al Del Prato, Borani).^{9,10} La Marca et al said that FSH of 26 mIU/ml is the physiological preovulatory peak.¹¹

According to Sherman et al and Brockmans et al AFC assessment is better than basal FSH.^{12,13}

Satwik R et al concluded that AMH is far better than age and FSH in predicting overall ovarian response.¹⁴ La Marca et al found that low AMH was also found in females with good regular cycles and hence women with low AMH alone should not be diagnosed as POF.¹¹

It also said that there is no guidance to include laparoscopy routinely including ovarian biopsy. In our study, we performed laparoscopy in only 2 indicated cases.

Some large retrospective studies like Remohi et al and Soares et al have not observed significant difference in outcome according to endometrial thickness, but several others like Borini et al, Teanik et al have found it to be an important prognostic factor for OD.¹⁵⁻¹⁸ According to Dessolle L, endometrium should be minimum 8 mm.¹⁹

Also, they administered single injection of 3.75 mgm depot Triptorelin in the withdrawal phase of previous cycle. We had used daily injections of Triptorelin 0.05 mg daily for 3 days. Seadat et al, Simon et al, Check et al, Dilwigi et al have shown that use of GnRH agonist during IVF cycles leads to alteration in hormonal profile of leuteal phase and endometrial histology.²⁰⁻²³

10-12% had karyotype abnormalities in a study conducted by Jino et al and Kolanlari et al.^{24,25} There was no karyotype abnormality in our study.

Most common autoimmune disorder associated with POF is thyroid autoantibody, 14-27% according to Hock et al.²⁶ In our study, 4.65% women proved positive for the same which was much lower and all other autoimmune parameters were negative. Welt et al proposed that

thyroid peroxidase autoantibody should be assayed in all patients of POF.²⁷

Two randomized trials by Badway et al and Tartagni et al demonstrated that good estrogen support is necessary for increased pregnancy rate and they had used ethinyl estradiol.^{28,29}

In our study, we explained the pros and cons of OD and ED thoroughly to the patients, success rate and that those were the only options left out for them.³⁰ We explained the fact that chance of having either spontaneous pregnancy or with the help of various other drugs (explained previously) would be only 5 to 6%, which is merely taking chance. Moreover, one of the etiologies of POF is genetic defect and it will not be transmitted to the offspring when OD or ED is done.³¹ Many studies (Lutjen et al, Sauer et al, Templeton et al, Amerathunga D et al) have made it clear that OD is the most successful treatment for infertile women with POF.³²⁻³⁵

Amerathunga D et al suggested transfer of only 2 embryos for optimal implantation rates with least chance of multiple pregnancy.³⁵ They showed pregnancy rate of 72% in an average of 2.5 cycles per patient. Shelling AN in journal of Reproduction and Sterility, November 2010, showed the successful pregnancy rate of 30% with donor egg or ED.³⁶ Our data are in accordance with the latter study and we took about 3 cycles per patient.

Though we achieved a pregnancy rate of 42%, net success rate fell to 35% after excluding missed abortions which is on par with many other studies. Incidence of miscarriage varied in different studies from 6% (Galbeya et al) to 25% (Alagana et al).^{37,38} Incidence of miscarriage was low in our study probably because of good diagnostic and therapeutic hysteroscopy, good quality of metaphase 2 (M2) donor oocytes and embryos and proper proliferative and secretory endometrial support.

Older women who were more than 40 years showed 7% pregnancy after 14 weeks, whereas women less than 40 gave 28% stable pregnancy rate. This might have been because of poor endometrial vascularity or poor intrauterine milieu related to age.

CONCLUSION

Since it is a common, serious, emotionally distressing and irreversible problem which can disintegrate families, it must be dealt on both physical and psychological platforms. Women with POF should be educated about the nature of their disease and current research efforts on fertility aspects.

Though cryopreservation of their own embryos, eggs or ovarian tissue, OD, ED and adoption are the different avenues available, they should be made to understand the importance of early marriage and early child bearing to have their own genetic child. It should not be too late that

one day the woman comes to realize the shattering truth that she is permanently infertile and can never have a progeny with her own eggs. If the couple seeks medical help at a later stage, the only option presently available to them would be OD, that too, with success not more than 30 to 35%.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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