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Original Article

Can hormone replacement therapy prior to oocyte donation cycle in women with premature ovarian failure improve pregnancy rate?

Lt Col Nikita Naredi^{a,*}, Lt Col K. Sandeep^a, Maj V.D.S. Jamwal^b^a Classified Specialist (Obstetrics & Gynaecology) & Trained in ART, ART Centre, Army Hospital (R&R), New Delhi 110 010, India^b Graded Specialist (Anatomy), ART Centre, Army Hospital (R&R), New Delhi 110 010, India

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ABSTRACT

Background: Infertility is an important issue in women with Premature Ovarian Failure (POF). With no conclusive treatment available to enhance fertility in these women, it is the use of donor eggs with In-Vitro Fertilization (IVF) which can fulfil their desire to become a mother in a novel way. Hormone replacement therapy (HRT) in POF apart from correcting the endocrine defect also helps in improving the milieu of the uterus by improving its vascularisation and the sub endometrial blood flow. We thus aimed to carry out a study to find out whether hormone replacement therapy if administered prior to the oocyte donation cycle in patients of premature ovarian failure improves the pregnancy rate.

Methods: A comparative study was carried out incorporating 46 subjects with 23 in each group. Group A received HRT prior to their oocyte donation cycle while the second group entered into the oocyte donation programme directly after an artificially induced menstruation.

Results: It was observed that, although the HRT group had a slightly higher pregnancy rate, with a better mean endometrial thickness as compared to the non HRT group it was not statistically significant.

Conclusions: Institution of hormone replacement therapy does improve the vascularisation of the uterus, corrects the histologic features of the uterine lining and makes the endometrium receptive but whether it enhances the pregnancy rate needs to be elucidated with further studies.

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Introduction

Premature ovarian failure (POF) a syndrome, characterised by the cessation of ovarian function before the age of 40 years

with associated elevated gonadotropin levels (FSH $\geq$ 40 mIU/ml), affects 1–3% women of reproductive age.¹ It comprises a triad of amenorrhoea, hypergonadotropinism, and hypo-estrogenism. A diverse aetiology for POF has been postulated,

* Corresponding author. Tel.: +91 08800504222 (mobile).

E-mail address: nikitanaredi@gmail.com (N. Naredi).

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like auto immune disorders, infectious and genetic causes, but most of the cases have been found to be idiopathic.² There are myriad health and psychological issues pertaining to this syndrome, but the inability to conceive, is the aspect which is most distressing and challenging. Currently, no treatment has been conclusively resulted in enhancement of fertility in women with POF, thus the use of donor eggs with In-Vitro Fertilization (IVF) is a practical treatment strategy and a hope for women with this endocrinopathy to become a mother.

Hormone replacement therapy (HRT) after the diagnosis of POF may be initiated, as untreated patients are at a great risk of bone loss due to increased osteoclast activities, resulting in osteopenia as well as osteoporosis.³ Furthermore, most of the patients develop symptoms of oestrogen deficiency, including vasomotor flushes and vaginal dryness, both of which respond to oestrogen therapy effectively. Apart from these health benefits it is also believed that endometrial blood flow increases in response to hormone replacement therapy (HRT) and therefore makes the endometrium more receptive in women with premature ovarian failure. Thus this study was carried out with an aim to evaluate if hormone replacement in patients with premature ovarian failure just prior to their oocyte donation cycle improves the pregnancy rate.

Material and methods

This was a comparative study carried out at our Assisted Reproductive Technology Centre over a period of one year (01 January 2011 and 31 December 2011). Patients diagnosed to have premature ovarian failure based on their menstrual history, gonadotropins levels (FSH > 40 mIU/ml on two occasions 6 weeks apart) and ultrasound picture (no or minimal demonstrable follicles on transvaginal sonography) were enrolled in the study. Karyotypic analysis was carried out for all POF patients and only patients with normal karyotype were part of the study. Subjects with ovarian failure secondary to radiation, chemotherapy or extensive surgery were excluded. The male factor needed to be normal for women to be part of the oocyte donation cycle. The patients were part of the study only if they had not been on regular or irregular HRT for 6 months prior to the commencement of their treatment cycle.

Approval from the institutional ethics committee was obtained and 46 sub fertile subjects with POF were made part of the study after meeting the inclusion and exclusion criteria. They were randomly divided into two groups based on their initial registration numbers. The women with the even numbers belonged to group A and received hormone replacement therapy for 3 months prior to their oocyte donation cycle while the ones with the odd numbers included in group B were HRT naive and directly went for the oocyte donation programme after an artificially induced menstruation with combined contraceptive pills. Hormone replacement was administered in the form of conjugated oestrogens 0.625 mg/day (Premarin 0.625 mg, Wyeth–Ayerst) for cycle days 1–28 and progesterone in the form of Medroxy progesterone acetate 10 mg/day orally (Deviry 10 mg, Elder) from cycle days 15–28. After a withdrawal bleed oestrogens were started for the preparation of the endometrium in both the

groups from day 2 of the cycle with Estradiol Valerate 2 mg (Tab Progynova 2 mg, Schering AG, Germany) two times a day for 4 days increasing to 2 mg 3 times a day for the next eight days. The patients were called for a transvaginal scan on day 12 to measure the endometrial thickness (ET) and colour Doppler study to see for the sub endometrial blood flow. If the ET was greater than 7 mm with good endometrial blood flow the subject was started on injection micronized progesterone 100 mg intramuscularly and oral Dydrogesterone 10 mg (Duphaston 10 mg, Solvay, New Zealand) twice a day and planned for embryo transfer after two days. However if the ET was not good (<7 mm) the dose of Estradiol Valerate was increased to 2 mg four times a day and in addition tablet Sildenafil Citrate 50 mg was to be applied intravaginally at bed time. The patients were called for alternate day TVS and if the endometrial growth was not adequate in spite of 20 days of priming the endometrium, the cycle was cancelled and embryo transfer was not carried out for the lady. Concurrently, the donors underwent controlled ovarian hyperstimulation after down regulation with GnRH analogue followed by superovulation with gonadotropins as per standard protocol. They were then taken up for transvaginal ultrasound-guided oocyte retrieval 36 h following ovulation trigger. Insemination of the donated oocytes with the prepared semen from the recipient's husband was done and if fertilisation occurred and led to cleavage of the fertilized oocytes into the 4 to 6 cell stage, the patients with a good endometrial thickness (>7 mm) underwent a day 2 embryo transfer. Two Grade 1 embryos were transferred under transabdominal ultrasound guidance. Luteal support for all the women who underwent embryo transfer was carried out with injection micronized progesterone 100 mg intramuscularly daily along with tab Dydrogesterone 10 mg twice daily. The women also continued with their Estradiol Valerate in the prescribed dosage. Serum β human chorionic gonadotropin (β hCG) was carried out 16 days after embryo transfer as per our institutional policy and a TVS for presence of gestational sac was done 3 weeks after the transfer. β hCG value greater than 50 mIU/ml was taken as positive result with foetal cardiac activity at 6 weeks as a positive pregnancy.

For statistical analysis, chi-square test, analysis of variance or Fisher's exact test was applied where appropriate. P-values <0.05 was considered statistically significant.

Results

A total of 46 patients with POF were part of the study after meeting the strict inclusion and exclusion criteria. 23 women were part of the observation in each group. The clinical and demographic characteristics of the patients have been depicted in Table 1. The mean age of the patients was 29.2 ± 3.6 years in the HRT group and 30.3 ± 4.1 years in the non HRT group which was comparable. In both the study groups secondary amenorrhoea was more common as compared to primary amenorrhoea. Good endometrial thickness (>7 mm) developed in 82.6% patients who were exhibited HRT as opposed to only in 60.8% HRT naive women. However it was not statistically significant. Subjects who could not attain the target endometrial thickness were also greater in the non HRT

Table 1 – Patient characteristics of both the study groups.

Characteristics	HRT group (n = 23)	Non HRT group (n = 23)	t/Z value	P value
Mean age (N = 23)	29.2 ± 3.6	30.3 ± 4.1	0.967	0.339
Mean ET (N = 23)	7.2 ± 1.1	6.5 ± 1.8	1.623	0.112
Type (N = 23)				
Primary (%)	34.8	17.3	1.047	0.295
Secondary (%)	65.2	82.7	1.046	0.295
Pregnancy rate (%)	40.0	25.0	0.822	0.411
Dropout rate (%)	34.8	47.7	0.683	0.495

group. The primary outcome measure i.e. the pregnancy rate in women after an oocyte donation cycle was 40% in subjects who received hormone replacement prior to their cycle but only 25% conceived in the non HRT group but not statistically significant.

Discussion

Premature ovarian failure (POF) characterised by a cessation of normal ovarian function before the age of 40 is a clinically challenging entity as the unrecoverable loss of oocytes results in a bleak fertility prognosis for these women. Of the diverse etiologies of POF it is the idiopathic variety, which is most commonly encountered, but occurs only in 1–3% of women in the general population.⁴ Various treatment modalities have been recommended to combat this endocrine disorder of which HRT is the most important. HRT is required to control vasomotor symptoms, minimise risks of cardiovascular disease, osteoporosis as well as to maintain sexual function.⁵ In addition to the aforementioned health consequences of the depleted ovarian function, the loss of reproductive capabilities is the most distressing element, and deserves maximum medical and psychological assistance.

The various therapeutic interventions which have been tried to induce and enhance fertility in POF patients include: clomiphene citrate, gonadotropins, oestrogens, GnRH analogues, oral contraceptives, corticosteroids, dehydroepiandrosterone (DHEA) or a combination of these.⁶ However none of these have demonstrated any significant improvement in ovulation and pregnancy rates.⁷ Thus the last and the most promising measure resorted to is egg donation. In-Vitro fertilisation using donor oocytes has demonstrated high pregnancy rates in women with premature ovarian failure.⁸ Nevertheless, it is known that in ART-induced pregnancies, successful Embryo Transfer depends on several factors: the quality of the oocytes and embryos, the number of embryos transferred, the quality of the transfer, uterine contractions, endometrial thickness and echogenicity, good homogeneity of the endometrial transformation, and vascularisation.⁴ The last three factors being implantation parameters, decrease the chance of pregnancy when the endometrium is less than 6 mm thick and uterine vascularisation is poor.⁴ Hormone replacement in a POF patient for a variable duration prior to the egg donation cycle may restore these parameters and enhance effective uterine receptivity during and after embryo transfer. Apart from the endometrial receptivity, synchronisation between embryonic development and endometrium is also of paramount importance. During oocyte

donation cycle, events of ovarian stimulation of the donor and endometrium of the recipient are completely separated. Thus, the recipient has to receive incremental oestrogen replacement of flexible length during the follicular phase of the donor's stimulated cycle followed by progesterone to synchronize the recipient's endometrium to the transferred embryo.

Although no randomised studies have been carried out to prove the efficacy of HRT in improving pregnancy rate in patients with POF who enter an oocyte donation cycle, workers have definitely shown that standard HRT in women with premature ovarian failure enables restoration of endometrial blood flow to normal which imply better uterine receptivity after oocyte donation.⁹ The present comparative study, the first study of this kind, although comprised a small sample size demonstrated an improved pregnancy rate in women who were administered HRT vis a vis in women who were not. It also shows that the mean endometrial thickness was better in the HRT group on endometrial priming as compared to the women who were not administered HRT. Li et al demonstrated that when the endometrial response to hormone replacement therapy in women with premature ovarian failure was examined by serial ultrasonographic measurement of endometrial thickness and histological study of endometrial biopsy was carried out on day 19 of the cycle it was seen that women with idiopathic ovarian failure had significantly better response than women with Turner's syndrome, whereas women with premature ovarian failure associated with previous chemotherapy had an intermediate response. However, all endometrial biopsies studied revealed secretory changes.¹⁰ The present study however included only the karyotypically normal and idiopathic POF subjects and found a better endometrial response. In an oocyte donation program in a French public hospital, the maintenance of uterine trophicity under HRT resulted in 30%–50% of clinical pregnancies with fresh embryos and 15%–25% with frozen-thawed embryos.⁴ The clinical pregnancy rate of 40% in our study is comparable to the aforementioned study but the cycle was carried out with only fresh embryos.

HRT although improves the endometrial blood flow and increase the uterine receptivity but is also known to induce resistance over a period of time, in certain patients as evident by inappropriate uterine response despite high doses of oestrogen.¹¹ Adjuvant drugs like aspirin, high dose Vitamin E, Pentoxifylline (PTX) have also been used to improve uterine parameters in hormonal replacement therapy resistant women with premature ovarian failure. It has also been reported that uterine radiation-induced fibrosis is reversible by combined PTX–Vit.E treatment.⁴ Letur-Konirsch et al have

elucidated that in women with POF with uterine resistance to HRT; combined PTX–Vit.E reduces fibro atrophic uterine lesions and improves the uterine response to HRT, thus allowing embryo implantation and ongoing pregnancy.⁴

Conclusion

Thus we can say that in spite of HRT's conclusive role in circumventing the negative impact of hypoestrogenism in women with POF; its role in ART for improving the pregnancy outcome is not confirmatory for want of literature and work on this topic. The present study, a first work of its kind however, does demonstrate the benefit of HRT in POF women in terms of improved pregnancy rates but has its limitations in view of a small sample size. Nevertheless oestrogen-progesterone replacement therapy may still be administered in POF patients prior to their oocyte donation cycle as it improves the sub endometrial blood flow and uterine vascularisation till larger studies prove its role in increasing the implantation rate in a more conclusive manner to make it a standard protocol.

Intellectual contribution

Study concept: Lt Col Nikita Naredi, Lt Col Sandeep K.

Drafting & manuscript revision: Lt Col Nikita Naredi, Maj VDS Jamwal.

Study supervision: Lt Col Sandeep K.

Conflicts of interest

All authors have none to declare.

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