CLINICAL EXPERIENCE WITH ORAL MICRONIZED ESTRADIOL VALERATE IN ENDOMETRIAL PREPARATION

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Abstract

The success rates of in-vitro fertilization (IVF) have plateaued over the last few years. Various factors affect the outcomes, endometrial receptivity being one such. In IVF with own oocytes, endometrial growth is brought about by the estrogen secreted by the multiple follicles recruited as a result of controlled ovarian hyperstimulation. In donor egg IVF however, endometrium has to be prepared artificially with hormone replacement. Various regimens have been suggested for the same but a consensus regarding the optimal method is still lacking. This small observational study takes a look at the efficacy of oral micronized estradiol valerate in improving endometrial thickness in women undergoing donor-egg IVF both with fresh and frozen-thawed embryos.

Keywords: Endometrial receptivity; Donor-egg IVF; Micronized estradiol

Introduction

During the menstrual cycle the endometrium undergoes cyclic proliferative and secretory changes in preparation for implantation. If this preparation is not sufficient, then implantation will fail. Successful implantation is dependent on close interaction between the embryo and the endometrium. In a normal ovulatory cycle, endometrial development is controlled by the hormonal secretions of the ovary, which undergoes a series of predictable changes associated with follicle development, ovulation, and transformation to a corpus luteum. Each of these stages is associated with a specific sequence of hormonal signals that travel through the circulation and stimulate the endometrium to first proliferate and then transform to a receptive state. The IVF success rates have plateaued over the last few years propelling scientists to look at various ways to improve outcomes. One of them is to try and improve the endometrial receptivity.

During the proliferative phase, the endometrium grows in response to the increasing levels of estradiol, in a process that involves not only direct stimulation of mitosis but also inhibition of apoptosis, along with increased vascular permeability, giving more access to circulating growth factors. The glands and the stroma proliferate, the endometrial lining thickens and the estrogen receptor content also increases. After ovulation, secretory events ensue in the estrogen primed endometrium.

Repair of the endometrial surface is already initiated during the menstruation process in the remaining basal layer, prior to any increase in estrogen concentrations. Proliferative activity in the basal layer remains constantly low, and once estrogen concentrations increase, proliferative activity in the developing functional layer of the human endometrium is induced. Proliferative activity peaks between cycle days eight and ten. An adequate endometrium thickness and appearance play a key role in the implantation of embryo and achievement of pregnancy. Thin endometrium is said to result in impairment of blood flow impedance through the endometrium and hence poor receptivity.

A variety of regimens for the induction of endometrial receptivity have been described. These vary in the dose and route of administration of estrogen (E2) and progesterone (P), in the duration of administration of E2 before initiating P, and in the duration of P administration before embryo transfer. A recent Cochrane review concluded that there is insufficient evidence to recommend one particular protocol for endometrial preparation over another with regard to pregnancy rates after embryo transfer.

This study aims to determine the efficacy of micronized estradiol valerate (Valest, Walter Bushnell Pvt. Ltd, India) in improving endometrial thickness in women undergoing donor-egg IVF.

This drug is structurally similar to endogenous estrogen and hence naturally replenishes the estrogen level and is better accepted by physiological systems of the body. Being a natural estrogen, it is potentially safer than its synthetic counterparts. Micronization (particle size < 10µ) enhances dissolution, thereby improves absorption, consequently bioavailability and clinical efficacy of estradiol valerate.

Aim

To determine the efficacy of micronized estradiol valerate (Valest, Walter Bushnell Pvt. Ltd, India) in improving endometrial thickness in women undergoing donor-egg IVF.

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**Study design**

Prospective open label, uncontrolled, drug utilization study to evaluate the role of micronized estradiol valerate in endometrial priming.

**Methodology**

Women below the age of 50 years requiring donor egg IVF were recruited for this study. This could be either fresh donor egg IVF or with frozen-thawed embryos of donor eggs. The excluding criteria included any endometrial pathology on transvaginal ultrasound scan.

After the initial consultation, all women underwent baseline blood tests including Anti-Mullerian hormone (AMH), FSH (Follicle stimulating hormone), thyroid function tests and random glucose estimation.

The indications for which women were offered donor egg IVF included: premature ovarian failure (cessation of menstruation at < 40 years in the absence of other causes), poor ovarian reserve (AMH < 1 ng/ml and/or FSH > 10mIU/mL), repeat IVF failures (≥ 2), postmenopausal (more than 40 years and cessation of menstruation for > 12 months with an FSH > 30 mIU/mL).

A transvaginal ultrasound scan was done in the same sitting with 7.5-10 MHz probe to rule out any endometrial pathology. Once recruited, the endometrial thickness was measured on day second or third of their menstruation or of withdrawal bleed. Women undergoing fresh donor egg IVF were given ovarian suppression with combined oral contraceptive pill [Ethinyl estradiol 0.03 mg + Desogestrel 0.15 mg]. Those undergoing frozen-thawed embryo transfers had a GnRHa (gonadotropin releasing hormone analogue, Leuprolide 3.75mg) given around day 21 of the preceding month. From day second or third, oral micronized estradiol valerate was started at a dose of 2mg three times a day. A week later a transvaginal scan was repeated and estradiol dose titrated up if needed. Embryo transfer was done between day 18-23 of the cycle ensuring at least 14 days (no longer than 18 days) of estradiol priming. In cases of day three embryos, intramuscular progesterone 50 mg was given for three days and in case of blastocyst transfers, it was given for five days followed by embryo transfer the next day under ultrasound guidance. The endometrial thickness was last measured on the day of starting the progesterone. Total dose of estradiol required until the time of embryo transfer was calculated.

Following the embryo transfer, luteal phase support continued in the form of progesterone 50 mg intramuscular and oral estradiol valerate 2mg three times a day. Serum βhCG (human chorionic gonadotropin) level was done two weeks following the embryo transfer. If ≥ 30 mIU/mL, it was considered as positive result and a transvaginal scan was performed two weeks later. Demonstration of an intrauterine gestational sac with/without contents such as yolk sac, foetal or cardiac activity was considered as clinical pregnancy.

Women were recruited between November 2015 and April 2017. Fifty cycles of donor egg IVF were studied.

**Outcome measures**

Primary endpoints- To analyse the endometrial priming with micronized estradiol valerate by measuring the difference in endometrial thickness on transvaginal ultrasound scan

Secondary endpoints- To determine the pregnancy outcomes in terms of clinical pregnancy, abortions and livebirths

Ethical consideration: This study was approved by Institutional Ethics Committee and all participants signed an informed consent form.

**Results**

Table 1 highlights the demographic features of the study participants. The mean age of the recipients was 37.6 (±4.7) years and that of the donors was 27.2 (±1.4) years. The most common indication for undergoing donor egg IVF was repeated IVF failures (46%) with own eggs, followed closely by poor ovarian reserve (40%). Forty one women underwent fresh cycle of IVF with donor eggs and nine underwent frozen-thawed embryo transfers with donor eggs. In 46 women day three embryos were transferred and four women had day five embryos (blastocysts) transferred.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (years)</td>
<td>37.6 (4.7)</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>27.2 (1.4)</td>
</tr>
<tr>
<td>Infertility duration (years)</td>
<td>7.6 (4.4)</td>
</tr>
<tr>
<td>Type of infertility</td>
<td>Primary 39 Secondary 11</td>
</tr>
<tr>
<td>Indication for DE IVF *</td>
<td>RIVFF- 23 POR- 20 RPL- 3 POF- 2 PM - 2</td>
</tr>
<tr>
<td>Type of DE IVF</td>
<td>Fresh 41 Vitrified 9</td>
</tr>
<tr>
<td>Sperm quality**</td>
<td>N 40 O 6 DS 4</td>
</tr>
</tbody>
</table>

DE IVF- Donor egg IVF
* Indications
POF- Premature ovarian failure
POR- Poor ovarian reserve
RIVFF- Repeat IVF failures
RPL- Recurrent pregnancy losses
PM- Postmenopausal
** Sperm quality
N- Normal, O- mild oligospermia, DS- donor sperms
The mean starting endometrial thickness was 5.3 mm (±1.4) and the mean maximum thickness achieved was 8.8 mm (±1.33). The mean difference in endometrial thickness that was achieved was 3.57 mm (±1.45). The mean total dose of micronized estradiol valerate required per patient was 82.8 mg (±14.34) with the minimum requirement being 64 mg and the maximum being 118 mg. During the final measurement of the endometrial thickness, 45 (90%) women showed a triple line pattern and five (10%) showed homogenous pattern (Table 2).

### Table 2. Outcomes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial thickness difference (mm)</td>
<td>3.57 (1.1, 7)</td>
</tr>
<tr>
<td>Endometrial pattern***</td>
<td>A: 45, B: 0, C: 5</td>
</tr>
<tr>
<td>Dose of estradiol valerate (mg) [Mean (range)]</td>
<td>82.8 (64, 118)</td>
</tr>
<tr>
<td>Number of embryos transferred [Mean (range)]</td>
<td>2.76 (2, 4)</td>
</tr>
<tr>
<td>Number with positive βhCG</td>
<td>28 (56%)</td>
</tr>
</tbody>
</table>

*** Endometrial pattern A- Triple line, B- Isoechoic, C- Homogenous

Twenty eight (56%) women had a positive βhCG. Of these 27 (54%) showed clinical pregnancy. Seven women underwent abortion, twelve women had given livebirth and eight women are currently ongoing pregnancies (Table 3).

### Table 3. Pregnancy outcomes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=28</td>
<td></td>
</tr>
<tr>
<td>Livebirths</td>
<td>12</td>
</tr>
<tr>
<td>Ongoing Pregnancies</td>
<td>8</td>
</tr>
<tr>
<td>Abortions</td>
<td>7</td>
</tr>
<tr>
<td>Biochemical</td>
<td>1</td>
</tr>
</tbody>
</table>

### Discussion

This small study has shown encouraging effect of oral micronized estradiol valerate on the endometrial thickness. In 1996, Hoffmann et al in their study concluded that 'endometrial thickness ≥ 7 mm in hormone replacement cycles predicts in phase endometrial histology and can replace the endometrial biopsy'. For all practical purposes an endometrial thickness of ≥ 7mm is considered as optimal for good implantation of embryos though a more recent meta-analysis by Kasius et al has advised clinicians against using it for cycle cancellation. Our study had a mean endometrial thickness of 8.8 mm at the end of estrogen administration which was a reasonable endometrial thickness.

In 2011, Sunkara et al presented their analysis of 1900 FET cycles after dividing them into those with prior pituitary suppression and those without. They noticed that 'there was a significantly higher clinical pregnancy rate achieved in cycles without downregulation where the duration of estrogen supplementation was < 20 days compared to cycles where the duration of estrogen supplementation was ≥ 20 days'. However, there was no significant difference in the clinical pregnancy rate in relation to the duration of E2 supplementation in FET cycles where pituitary suppression was used prior to E2 supplementation. They hence concluded that 'in medicated FET cycles, prior down regulation protects against the detrimental effect of prolonged E2 supplementation before starting progesterone therapy'. All our study subjects had been given pituitary suppression in the previous month. We varied the dose of estradiol to our subjects based on the endometrial response seen on the transvaginal scan. Most other studies have analysed the duration of estrogen supplementation rather than the total dose used. Hence we are unable to say if the dose required by some of our women was in a higher range. However, even if it were, the effects were probably offset due to the previous pituitary suppression as suggested by Sunkara et al.

Our clinical pregnancy rate of 54% was very encouraging. However other factors may have contributed apart from the endometrial response, such as embryo quality and maternal BMI, which have not been accounted for in our study, making it a limitation worth bearing in mind.

Various studies have compared oral with transdermal and vaginal routes of administration of estrogen in FET. Transdermal estrogen does not undergo metabolism in liver and hence estradiol concentrations exceed the weaker estrone concentrations, resulting in a more physiological estradiol/estrone ratio (approximately 1) as against that achieved by oral preparations (0.2). Moreover the serum lipid, coagulation factors and renin substrate remain unaffected by transdermal preparations. Davar et al whilst comparing transdermal and oral estradiol valerate found significantly high serum estradiol levels on the day of starting the progesterone, in women on oral preparations. Though the pregnancy rates were comparable in the two groups, there was a tendency towards lower pregnancy in women on oral preparation and high serum estradiol levels. Hence transdermal approach might be worth considering but in the meantime as mentioned earlier, prior pituitary suppression may offer protection with excessive serum estrogen levels with oral estradiol.

Vaginal estradiol has been associated with local irritation and its absorption may be impeded by concomitant use of progesterone pessaries for luteal support.

### Conclusion

Oral estradiol valerate appears to be effective in endometrial priming in women undergoing donor egg IVF- with fresh donor oocytes as well as in those undergoing frozen embryo transfers.
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**Conflict of interest:** None

**References**


