Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development

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Objective: To evaluate the effects of vaginally administered sildenafil on endometrial thickness and IVF outcome in a large cohort of infertile women with poor endometrial development.

Design: Retrospective cohort analysis.

Setting: Private practice setting.

Patient(s): A cohort of 105 infertile women aged ≤40 years, with normal ovarian reserve and at least two consecutive prior IVF failures attributed to inadequate endometrial development.

Intervention(s): Patients underwent IVF using a long GnRH-a protocol with the addition of sildenafil vaginal suppositories (25 mg, 4 times per day) for 3–10 days.

Main Outcome Measure(s): Peak endometrial development, pregnancy, and implantation rates.

Result(s): Of 105 patients, 73 (70%; Group A), attained an endometrial thickness of ≥9 mm, whereas 32 (30%; Group B) did not. Implantation and ongoing pregnancy rates were significantly higher for Group A (29% and 45%) than for Group B (2% and 0). Of 11 women in Group B who had embryos transferred in that cycle, only one conception occurred, which resulted in a miscarriage. In Group B, 59% of women had a history of endometritis, compared with 44% in Group A.

Conclusion(s): Vaginal administration of sildenafil enhanced endometrial development in 70% of patients studied. High implantation and ongoing pregnancy rates were achieved in a cohort with a poor prognosis for success. Previous endometritis may decrease the response to sildenafil. (Fertil Steril 2002;78:1073–6. ©2002 by American Society for Reproductive Medicine.)

Key Words: Endometrium, in vitro fertilization, sildenafil

Estrogen-induced endometrial proliferation is in large part dependent upon blood flow to the basal endometrium. Animal research has shown that nitric oxide (NO) release can lead to relaxation of vascular smooth muscle through a cyclic guanylyl monophosphate (cGMP)-mediated pathway (1). Endothelial and inducible NO synthase isoforms have been identified in both the vascular endothelium of human endometrium and in the myometrium (2). Phosphodiesterase (PDE) is a family of isoenzymes that hydrolyzes cyclic nucleotides, such as cGMP. Inhibitors of specific PDE subtypes have been identified that can augment the effects of cyclic nucleotides on target tissues, such as human spermatozoa (3). Sildenafil (Viagra) is a type 5–specific PDE inhibitor that augments the vasodilatory effects of NO on vascular smooth muscle by preventing the degradation of cGMP. Since its introduction in 1997, sildenafil has been used with great success to treat male erectile dysfunction (4).

We previously reported that vaginally administered sildenafil suppositories could lead to an improvement in uterine blood flow and, in conjunction with controlled ovarian hyperstimulation, led to estrogen-induced proliferation of the endometrial lining in four patients with recurrent IVF failure associated with poor endometrial development (5). Although three of the women conceived in the first cycle of sildenafil treatment, the small number of patients studied precluded any definitive state-
Pathogenic factors associated with suboptimal endometrial development in women with at least two prior IVF failures due to poor endometrial proliferation who were treated with SDF.

<table>
<thead>
<tr>
<th>Factor associated with poor endometrial development</th>
<th>Total, n (%)</th>
<th>Group A, n (%)</th>
<th>Group B, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-related endometritis</td>
<td>51 (49)</td>
<td>32 (44)</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Postpartum endometritis</td>
<td>16 (15)</td>
<td>10 (14)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Septic abortion</td>
<td>26 (25)</td>
<td>18 (25)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Uterine synechiae</td>
<td>9 (9)</td>
<td>4 (6)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>DES anomaly</td>
<td>19 (18)</td>
<td>14 (19)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>18 (17)</td>
<td>15 (21)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Leiomyomatous uterus</td>
<td>9 (9)</td>
<td>6 (8)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>8 (8)</td>
<td>6 (8)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Sildenafil vaginal suppositories were prepared for us from oral tablets by a local pharmacy (at a cost of approximately $10 a piece). We have previously discussed our rational for choosing sildenafil over other potential NO donors (5). In initial attempts we used nitroglycerin patches, which were associated with an unacceptably high rate of side effects including several cases of hypotension and syncope. A vaginal route of administration eliminated these effects. Sildenafil suppositories were administered (at a dosage of 25 mg, 4 times a day) beginning with the initiation of Follistim and continued until the day of hCG administration. The dosage was extrapolated from the maximum recommended daily dose for men, given in four divided doses to minimize peak and trough effects.

Serial measurement of serum E2 levels and ultrasonographic monitoring of folliculogenesis and endometrial thickness were commenced on the 8th day of gonadotropin stimulation. Ovulation was triggered with 10,000 IU of hCG when two lead follicles were 18 mm in diameter and half the remainder were ≥15 mm. Oocytes were retrieved transvaginally under ultrasound guidance 35 hours later.

Metaphase II oocytes were inseminated with ICSI 4–5 hours after retrieval. Resulting embryos were cultured for three days, at which point up to three day-3 embryos that had cleaved to at least the seven-cell stage were transferred to the uterus under ultrasound guidance. Progesterone (in oil, 50 mg IM daily) was used for luteal support. Serum hCG levels were measured 11 and 13 days after oocyte retrieval. Vaginal ultrasound confirmation of pregnancy was performed at 6–7 weeks of gestation in women whose quantitative β-hCG levels had shown a progressive rise. A viable pregnancy was defined as fetal cardiac activity on ultrasound examination.

In our center >90% of patients with an E2 level of >300 will have an endometrial thickness of >9 mm (in greatest diameter). The pregnancy rate among women who proceed with embryo transfer despite suboptimal endometrial development is significantly lower than that for women with a lining of >9 mm. For this reason, we routinely recommend that women whose preovulatory endometrium measures <9 mm in maximal diameter not proceed with embryo transfer in that cycle, but rather have their embryos cryopreserved and stored for use in a subsequent cycle with a more optimal lining or with a gestational carrier.

A formal institutional review board approval was not obtained for this study, although the experimental nature of

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**TABLE 1**


**MATERIALS AND METHODS**

The study population consisted of 105 women of <40 years of age, with normal ovarian reserve and at least two prior, consecutive failed IVF attempts using fresh embryos, in which two or more transferred embryos were of at least seven cells on day 3 of culture. In addition, ultrasound measurement of endometrial thickness on the day of hCG administration was <9 mm in all prior IVF attempts despite adequate follicular development and elevated E2 levels. A large percentage of the patients in this cohort came to us specifically for treatment of endometrial lining issues. Many had had treatment outside our center, and demographic information regarding prior cycles was obtained from patient histories and previous medical records, which were often incomplete. The pathogenic factors associated with poor endometrial development are listed in Table 1 and included septic abortion (25%), diethylstilbestrol-related anomalies (18%) idiopathic (17%), postpartum endometritis (15%), postsurgical uterine synechiae (9%), multiple uterine leiomyoma (9%), and adenomyosis (8%).

A monophasic oral contraceptive pill was administered to all patients within 5 days of the onset of spontaneous menstruation. Daily injections of GnRH agonist (GnRH-a; Lupron; Tap Pharmaceuticals) were commenced 10–20 days later (0.5 mg daily) for 5 days, whereupon the oral contra-

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ceptive pill was stopped and the Lupron continued. As soon as menstruation occurred, the Lupron dosage was reduced (to 0.25 mg daily) and continued until the day of hCG administration. Ovarian follicular stimulation was initiated within 2–4 days of the GnRH-a–induced menstrual bleed, using Follistim (Organon Laboratories, West Orange, NJ) at an initial dose of 300–375 IU, which was decreased to and then maintained at 150 IU from the 3rd day of stimulation.

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treatment was discussed with each patient in detail before beginning therapy. A majority of patients in this study came to us specifically for treatment with sildenafil. For some women, this cycle represented their final attempt at pregnancy before considering a gestational carrier.

The 105 patients evaluated were divided into two groups based on maximal endometrial diameter as determined by ultrasound on the day of hCG administration. Group A comprised 73 women who developed an endometrial thickness of ≥9 mm, whereas Group B consisted of 32 women with a maximal endometrial thickness of <9 mm. Differences between groups were evaluated with Student’s t tests. Differences in rates and proportions among groups were evaluated by χ² tests and Fisher’s exact test where appropriate. Significance was set at P<.05.

RESULTS

Of the 105 patients treated with vaginal sildenafil suppositories, 73 (70%) developed an endometrial thickness of ≥9 mm (Group A), whereas 32 (30%) did not (Group B; Table 1). Among the patients in Group B, 11 (34%) chose to proceed with embryo transfer in that cycle despite a suboptimal lining. The overall ongoing pregnancy rate was 31% (33/105; Table 2). The overall implantation rate was 23% (51 sacs per 222 transferred embryos). The ongoing pregnancy rate in Group A (33/73; 45%) was significantly higher than that in Group B (0/11; 0%; P<.01). The implantation rate was also significantly higher among Group A (50 sacs per 172 transferred embryos; 29%), than among Group B (1 sac per 50 transferred embryos; 2%; P<.01). This finding occurred despite more embryos being transferred per patient in Group B (average of 3.2) than in Group A (average of 2.8). There were no other significant differences in the clinical and demographic characteristics between Groups A and B, although 19 of 32 (59%) women in Group B had a history of previous endometritis, as compared with 32 of 73 (44%) in Group A (P<.07; Table 1).

DISCUSSION

An endometrial thickness of ≥9 mm in the late proliferative phase, as determined by vaginal ultrasound, correlates well with the chance of pregnancy after IVF–ET, whereas a thinner endometrial lining is associated with a comparatively poorer prognosis for success (6, 7). In fact, <10% of women in our practice will achieve an ongoing pregnancy with a suboptimal endometrial lining of <9 mm (Sher G, unpublished observation). Efforts to improve endometrial proliferation during IVF through the use of estrogens and/or low-dose aspirin have met with varying degrees of success (8, 9).

Recent interest has focused on the role of NO as a modulator of uterine blood flow (10, 11). We previously reported the ability of vaginally administered sildenafil suppositories to improve uterine blood flow and endometrial proliferation in women with a history of recurrent IVF failure due to poor endometrial development (5). Three of four women conceived and gave birth after their first IVF cycle in which vaginal sildenafil was given. Though promising, the small sample size precluded any definitive conclusions. In a larger cohort of 105 infertile women with at least two failed IVF cycles associated with suboptimal endometrial development and transfer of good-quality embryos, 73 (70%) were able to develop an endometrial thickness of ≥9 mm, and 33 (45%) had ongoing pregnancies beyond 16 weeks of gestation. These are substantial numbers for a group of patients who would typically have a poor prognosis for success.

On the basis of our prior observations, that women with a maximal endometrial diameter of <9.0 mm in the presence of an E₂ level of >300 pg/mL have poor IVF outcomes (7, 8), we routinely advise all such women to abort the current cycle and have their embryos cryopreserved for subsequent use in a cycle with a more optimally prepared lining or with a gestational carrier. Despite these recommendations, 11 of 32 women in Group B chose to proceed with embryo transfer in the presence of a suboptimal lining. Among these women, only one pregnancy occurred, which subsequently resulted in a first-trimester miscarriage. Although the demographic characteristics among Group B were similar, the patients who chose to have a transfer in that cycle despite a poor lining may have had a worse chance of pregnancy than those who chose to defer the transfer. This group likely included patients in their final IVF attempt who may have felt they had nothing to lose by transferring in that cycle. This, along with the small number of patients in Group B who chose to proceed with embryo transfer, may help to explain the extremely low pregnancy rate seen in Group B.
In comparison, 33 of 73 (45%) of the women in Group A achieved an ongoing clinical pregnancy \((P<.01)\). Among the population in this study, it appears that IVF outcome was largely contingent upon adequate endometrial growth after administration of sildenafl. It is also important to note that vaginal sildenafl did not result in improved estrogen–induced endometrial proliferation in all patients, because 32 of 105 (30%) women failed to respond adequately to sildenafl treatment despite ample estrogen production. Although not statistically significant, 19 of 32 (59%) women in Group B had a history of prior pregnancy-related endometritis, which could have resulted in irreversible damage to the basal layer of the endometrium. In Group A, 32 of 73 (44%) were so affected \((P<.7)\). Thus, the use of sildenafl cannot be expected to help all patients with a thin endometrial lining. Women with intractable damage to the basal endometrium may be less likely to respond to increases in uterine blood flow. Response to sildenafl is also predicated on an adequate serum E\(_2\) concentration.

In our ongoing 3-year experience, the administration of vaginal sildenafl has been totally free of clinical side effects. Moreover, because sildenafl is rapidly and completely cleared from the body within 24–48 hours of discontinuing its administration (we always stop treatment ≥5 days before embryo transfer), the embryo is completely protected from any untoward exposure to the agent. Preliminary findings also suggest that a thin endometrial lining can often be improved by administering vaginal sildenafl suppositories for as few as 2–3 days in the late proliferative phase of the cycle.

The vaginal route of administration may provide an added benefit in terms of estrogen delivery as compared with oral or transdermal routes. Vaginal administration of sildenafl tablets may also improve endometrial development, although we have no experience with this regimen. On the basis of our findings, we conclude that selective use of vaginal sildenafl suppositories in the small subset of patients with a thin lining due to inadequate endometrial blood flow may represent a valuable addition to the assisted reproductive technology therapeutic armamentarium, although larger, randomized studies are needed to better validate its effectiveness.

References