Human Reproduction Vol.17, No.5 pp. 1249–1253, 2002

Combined treatment by pentoxifylline and tocopherol for recipient women with a thin endometrium enrolled in an oocyte donation programme

N.Lédée-Bataille[1,5], F.Olivennes[2], J-L.Lefaix[3], G.Chaouat[1], R.Frydman[2] and S.Delanian[4]

[1]INSERM U131, Hôpital Antoine Béclère, Clamart, [2]Service de Gynécologie-Obstétrique et Médecine de la Reproduction, Hôpital Antoine Béclère, Clamart, [3]Laboratoire de RadioToxicolgie, CEA/ DSV/ DRR, Bruyères le Chatel and [4]Service d'Oncologie-Radiothérapie, Hôpital Saint-Louis, Paris, France

[5]To whom correspondence should be addressed at: Service de Gynécologie-Obstétrique, Hôpital Antoine Béclère, 157, Rue de la Porte de Trivaux, 92141 Clamart cedex, France. E-mail: Ledeenathalie@aol.com

BACKGROUND: To evaluate the effect of an antifibrotic treatment by a combination of pentoxifylline (PTX) and tocopherol (vitamin E) in patients with a thin endometrium who were enrolled in an oocyte donation programme. METHODS: Eighteen oocyte recipients who failed to develop a pre-ovulatory endometrial thickness of at least 6 mm after receiving vaginal micronized estradiol were enrolled in the study. The patients received a combination of PTX (800 mg/day) and vitamin E (1000 IU/day) for 6 months. The main outcome measurements were the change in endometrial thickness and the pregnancy and delivery rates after treatment. RESULTS: Endometrial thickness increased significantly (P <0.001), with a mean of (±SD) 4.9 ±0.6 mm before and 6.2 ± 1.4 mm after treatment, with 72% (13/18) of patients being good responders. Five patients either did not respond to the treatment or responded only slightly. Three patients, of which two had received previous radiotherapy, became spontaneously pregnant, and two became pregnant after embryo transfer. Three patients did not have embryo transfer. A total of four babies were delivered. The pregnancy rate was thus 33% and the delivery rate 27%. CONCLUSION: Treatment by combination of PTX and vitamin E appears to improve the pregnancy rate in patients with a thin endometrium by increasing the endometrial thickness and improving ovarian function. This was especially noticeable in patients who had previously received total body irradiation.

Key words: oocyte donation/pentoxifylline/thin endometrium/tocopherol

Introduction

Ultrasound assessment of the endometrium has become a standard procedure during the diagnostic work-up and treatment of infertility. Nevertheless the clinical significance of differences in endometrial thickness remain controversial, and clinicians have not been able to establish an ideal thickness for conception. Some studies have reported low pregnancy rates in the presence of thin endometrium (Glissant *et al.*, 1985; Gonen *et al.*, 1989; Check *et al.*, 1991; Sher *et al.*, 1991; Dickey *et al.*, 1992), but others could not confirm this association (Rabinowitz *et al.*, 1986; Coulam *et al.*, 1994; Bohrer *et al.*, 1996; De Geyter *et al.*, 2000). In all these studies, however, the mean endometrial thickness reported has ranged from 7–12 mm, and the concept that a minimum thickness is required to establish a clinical pregnancy is widely accepted. Those suggested vary from 5–8 mm, measured during the late proliferative to early luteal phases. We decided here to define a thin endometrium as a thickness <6 mm (Gonen *et al.*, 1991).

The incidence of preovulatory endometrial thickness <6 mm during assisted reproductive techniques (ART) is low. It is sometimes an iatrogenic response to the aggression of some medical treatment, such as repeated surgery or radiotherapy, but in most cases the causative agent remains unknown. This thin endometrium, unresponsive to intensive estrogen therapy, is associated with a poor outcome in ART (Alam *et al.*, 1993; Abdalla *et al.*, 1994, Weckstein *et al.*, 1997).

The literature on the treatment of thin endometrium is rather sparse. It has often been considered irreversible if unresponsive to high levels of estrogen. Vaginal administration of micronized estradiol, compared with oral treatment, significantly increases the serum estradiol level (279 ± 76 versus 2344 ± 398 pg/ml) and the endometrial estradiol concentration (13 ± 2 versus 918 ± 412 pg/mg protein) (Tourgeman *et al.*, 1999). Micronized estradiol, administered vaginally, has thus been described as the treatment of choice for women who have previously failed to achieve adequate endometrial thickness (Tourgeman *et al.*, 2001). Low-dose aspirin has been reported to enhance the pregnancy rate of such patients in an intrauterine insemination programme (Hsieh, 2000) and in an oocyte donation programme, although this remains controversial

Table I. Characteristics of 18 patients with a thin endometrium enrolled in the oocyte donation programme

Patients	FSH (IU/l)	Cycle	Age (years)	Aetiology for the inclusion in the oocyte donation programme	Aetiology of the thin endometrium
1	15	1	40	IVF failure, FSH ⇑	Unknown
2	36	1	43	IVF failure-, FSH ⇑	Iterative curettages
3	14	1	40	IVF failure, FSH ⇑	Unknown
4	12	1	40	IVF failure, FSH ⇑	1 curettage
5	13	1	45	IVF failure, FSH ⇑	Unknown
6	15	1	40	IVF failure, FSH ⇑	Iterative curettages
7	19	1	40	IUI failure, FSH ⇑	Unknown
8	73	0	33	Radiotherapy before medullar graft	Total body irradiation (20 gy)
9	90	0	34	Radiotherapy (medulloblastoma)	Radiotherapy (70 gy)
10	94	0	29	Radiotherapy before medullar graft	Total body irradiation (20 gy)
11	12	1	39	Chemotherapy	Chemotherapy
12	96	0	40	POF at 28 years	Unknown
13	112	0	30	POF at 28 years old	Unknown
14	113	0	30	POF at 23 years old	Unknown
15	95	0	31	POF at 23 years old	Unknown
16	81	0	28	POF at 28 years old	Unknown
17	128	0	31	POF at 27 years old	Unknown
18	6	1	30	Mitochondrial disease	Unknown

Cycle: 1 = spontaneous cycle; 0 = no spontaneous cycle, long term hormone replacement treatment; POF = premature ovarian failure.

(Weckstein *et al.*, 1997; Check *et al.*, 1998). None of these authors, however, has described any change in endometrial thickness with low-dose aspirin. It has been reported (Sher and Fisch, 2000) that vaginal sildenafil positively affected uterine artery blood flow and endometrial development in four patients.

A combination of pentoxifylline (PTX) and tocopherol (vitamin E) has been reported to be an effective treatment for musculocutaneous radiation-induced fibrosis, both in an experimental model and in humans (Delanian *et al.*, 1999; Lefaix *et al.,* 1999). According to one report, documented by hysteroscopy, this combined treatment led to complete endometrial healing after radiation-induced abrasion (Letur-Kornisch *et al.*, 2002). Another recent report describes a significant increase in endometrial thickness in six patients with radiation-induced thin endometrium (from 3–6 mm), after 12 months of this combined treatment (Delanian *et al.*, 2000). We therefore hypothesized that any thin uterine endometrium, even when the causative agent is unknown, can be treated as iatrogenically induced fibrosis.

Accordingly, we tested this treatment in 18 oocyte recipients whose endometrium remained thin in the late proliferative phase, despite vaginal treatment with micronized estradiol commencing on the first day of the observed cycle. All patients received the combination of PTX and vitamin E for 6 months. We then evaluated the effect on endometrial thickness and the pregnancy and delivery rates.

Materials and methods

Patients

Eighteen women, with a mean age of 35 ± 5 years, participated in this trial. Their characteristics are summarized in Table I. All were recipients in our oocyte donation programme who had failed to develop a preovulatory endometrial thickness of ⩾6 mm, despite vaginal administration of 2 mg of micronized estradiol commencing at the start of the observed cycle. This endometrial thickness had been observed at least twice during previous ultrasound evaluations of each patient before the pre-inclusion evaluation. We were tentatively able to identify probable causes for the thin endometrium in seven patients: previous radiotherapy (n = 3), previous chemotherapy (n = 1), previous curettages (n = 3). No cause was known for 11 patients. Inclusion in the oocyte donation programme was due to: idiopathic premature ovarian failure (POF) (n = 7), iatrogenic POF (n = 4), failure(s) of previous IVF (n = 6), and intrauterine insemination (n = 1) related to poor ovarian reserve in a woman with mitochondrial disease. Fourteen of the 18 patients underwent an endometrial biopsy on day 26 of the cycle before beginning the treatment. For all 14, the endometrium was in phase according to Noyes's criteria (Noyes *et al.*, 1950). A lymphoplasmatic infiltrate was observed in the stroma of three patients. The biopsy did not provide a histological diagnosis for the deficient endometrial proliferation. All patients provided informed consent, and our Institutional Review Board approved this investigation.

Treatments

The modalities of the treatment were determined from the pharmacokinetic data, clinical use in the treatment of other diseases, and long-term tolerance. Twice a day, each patient took a combination of 400 mg PTX (Torental 400; Pharma 2000, Magny-les Hameaux, France) and 500 IU vitamin E (Toco 500; Hoescht-Houdé, Paris, France). This combination was continued for 6 months; we then proceeded to the cycle of embryo transfer. The treatment was discontinued at the time of the transfer. For the three cases of spontaneous pregnancy occurring during the treatment period, treatment was discontinued when the pregnancy was diagnosed.

Ultrasound assessment

To standardize the data for the endometrial evaluation before and after 6 months of treatment, all patients received micronized estradiol (Provames; Cassenne, Paris, France) (2 mg daily on days 1 to 14, vaginally) before the ultrasound evaluation scheduled on day 14 of the cycle.

All scans were performed by one operator, with a SIEMENS Elegra and a 6.5 MHz transvaginal probe. The uterus was examined

Table II. Endometrial thickness and pregnancy outcome before and after 6 months of a combination of pentoxifylline and vitamin E among 18 patients with a thin endometrium

Patients	Endometrial thickness before treatment (mm)	Endometrial thickness after treatment (mm)	Pregnancy outcome
1	4.5	6.1	Spontaneous pregnancy
2	4.2	6.4	No pregnancy
3	4.5	6.5	No pregnancy
4	5.7	7	Pregnancy after oocyte donation
5	4	4	No pregnancy
6	4	4	No pregnancy
7	4.5	4.5	No pregnancy
8	5.5	6.9	Spontaneous pregnancy
9	5.3	5.6	No pregnancy
10	4,5	5.6	Spontaneous pregnancy
11	4.8	6.6	No embryo transfer
12	5	6.5	No pregnancy
13	5.5	7	No embryo transfer
14	4.5	6	No pregnancy
15	5	6.2	No embryo transfer
16	6	9.3	Pregnancy after oocyte donation
17	6	9	Pregnancy after oocyte donation
18	5	5	No pregnancy

systematically. Every time the probe was used, it was covered with coupling gel, inserted into a condom, and recoated with gel before insertion in the vagina. The uterus was viewed in the sagittal plane. Endometrial thickness was defined as the minimum distance between the echogenic interfaces of the myometrium and endometrium measured in the plane through the central longitudinal axis of the uterine body. We noted whether the endometrium was multilayered (hypoechoic inner layer and echogenic outer layer). The probe was then directed into the right vaginal fornix to identify the ascending branch of the uterine artery. A pulsed Doppler gate was placed over the vessel to record the flow velocity waveform. The probe was moved to the left fornix to identify the left uterine artery. Blood flow impedance was expressed as the mean pulsatility index of the right and left uterine arteries.

Statistical analysis

The results were expressed as mean values with their standard deviations. The paired *t*-test was used to assess the change in the endometrial thickness before and after the combined treatment and the Mann–Whitney *U*-test to assess the differences in endometrial thickness and other characteristics of patients who did and did not became pregnant. The statistical assessment used StatView software (Abacus Concepts, Inc., Berkeley, CA, USA). A P-value < 0.05 was considered significant.

Results

Short- and long-term tolerance were very satisfactory. No patients discontinued treatment, although two reported transient vertigo and dyspepsia.

The combination of PTX and vitamin E resulted in a significant increase in endometrial thickness ($P < 0.001$). The mean increase was 1.3 ± 1 mm after 6 months of combined treatment (4.9 ± 0.6 mm before and 6.2 ± 1.4 mm after). An increase in endometrial thickness in response to combined treatment was observed in 13 of 18 patients (72%) and little or no change in five patients (Table II). We observed no significant difference in endometrial thickness between the patients who did and did not become pregnant before (5.3 and 4.7 mm respectively) and after (7.3 and 5.7 mm) combined treatment. Similarly, in both groups, neither blood flow impedance nor endometrial pattern differed significantly before and after. Blood flow impedance was, however, normal before this combined treatment for 13 of the 18 patients.

Five patients became pregnant after combined PTX-vitamin E treatment. We observed three spontaneous pregnancies during month 7. Two of these women had been considered menopausal after total body irradiation before bone-marrow transplant, 7 and 10 years earlier; the third was in the oocyte donation programme after repeated implantation failure in conventional IVF with a poor ovarian reserve (FSH >15 mIU/ml). All three had normal pregnancies and gave birth to healthy babies. The other two patients became pregnant after embryo transfer. Frozen embryos were transferred because French policy does not allow fresh embryo transfers in oocyte donation programmes. The 12 week ultrasound revealed a fetal hygroma in one of these patients. Amniocentesis revealed no detectable karyotypic abnormalities, and the fetus died at 20 weeks gestation, with cardiac failure. The other patient had a normal pregnancy and delivered a healthy infant.

Three women did not undergo embryo transfer. One patient divorced before the procedure, and two others had embryos that failed to thaw successfully. Implantation failed in the ten remaining patients after embryo transfer. The pregnancy rate was thus 33% and the delivery rate 27%.

Discussion

We found in this study that combined PTX-vitamin E treatment significantly increased endometrial thickness, from 4.9 to 6.2 mm, with 72% good responders. Moreover, this effect seemed to be associated with a higher potential for pregnancy, with spontaneous pregnancies occurring.

Several pieces of biological information suggest some mechanisms by which this combination of PTX and vitamin E has proved useful in treating thin endometrium. It is well

documented that aggression to living tissue (i.e. by ionizing radiation, surgery, or chronic infection) produces free radicals that play an important role in the initial damage and in the ensuing inflammatory response that precedes fibrosis, apparently a continuous, self-maintaining local process. Tumour necrosis factor (TNF) increases free-radical leakage from mitochondria and may start this vicious circle in cells that produce TNF (Schulze-Osthoff *et al.*, 1992). TNF-α has been detected in the ovaries (Roby *et al.*, 1990) and is expressed by all types of endometrial cells (fibroblast, immunocompetent, glandular epithelial and vascular). This expression is cycle-dependent and occurs mainly in the endometrial gland (Hunt *et al.*, 1992; Philippeaux and Piguet, 1993; Tabibzadeh *et al.*, 1995; Von Wolff, 1999). Increased TNF-α expression has been associated with implantation failure (Hazout, 1995). The beginning of the implantation process can be compared to an inflammation-like reaction that is rapidly down-regulated. An excess of pro-inflammatory cytokine at this stage may have the same deleterious effects on embryo survival as it does on fetal survival in an established pregnancy. Such a phenomenon has been already observed in mice (Chaouat *et al.*, 1995, 1997).

PTX, a methylxanthine derivative, is a vasodilating agent that enhances red blood cell deformability, inhibits inflammatory reactions and reduces blood viscosity by inhibiting platelet aggregation. It has therefore been used for the symptomatic treatment of various vascular disorders, including intermittent claudication, ischemic leg ulcers, and peripheral vascular diseases. Most studies of its mechanism have focused on its effect on the production and function of TNF (Samlaska and Windfield, 1994). PTX increases the phagocytic activity of polymorphonuclear leukocytes (PMN) and monocytes, antagonizes TNF-α production and activity and reduces *in vitro* production of many cytokines, including granulocyte-macrophage colony stimulating factor (GM-CSF) and gamma-interferon (IFN-γ). In reproduction, PTX has been reported to decrease the fetal resorption rate significantly in the CBA/J×DBA/2 murine model of spontaneous abortion (Chaouat, 1995). The authors of that study hypothesised that PTX works by reducing local TNF-α production. The establishment of pregnancy has been described as a delicate equilibrium between the Th1 and Th2 cytokines (Wegmann and Guilbert, 1992): the injection of inflammatory cytokines such as IFN-γ and TNF-α can terminate normal pregnancies during early gestation. Mating between CBA/J×DBA/2 mice normally results in a high rate of spontaneous fetal resorption; this fetal loss can be prevented by preconceptional anti-BALB/c allo-immmunisation as well as by a variety of other manouvers, including injection of GM-CSF, IL10, anti-IFNγ and PTX (Chaouat *et al.*, 1985, 1995).

The physiological role of tocopherol (vitamin E) is to scavenge reactive oxygen species (ROS) at times of oxidative stress, when antioxidant enzymes such as superoxide dismutase (SOD) or catalase are unable to limit the damaging effects of ROS, and thus cannot protect cell membranes against lipid peroxidation. Found mainly in cell membranes, vitamin E is the most important antioxidant protecting membrane phospholipids against oxidative damage. In women, the antioxidant system, like the thioredoxin system, has been reported to change during the menstrual cycle in endometrial glands and stroma (Maruyama, 1997; Stark, 2001): levels are highest in the early secretory phase, that is, during the implantation window. Vascular endothelial damage and oxidative stress appear to be causally related to the pathophysiology of pre-eclampsia, which begins initially as an insufficient trophoblast invasion (Kharb, 2000). A randomized controlled trial among women at high risk of pre-eclampsia found that a combination of vitamins C and E was effective in reducing its incidence (Chappell *et al.*, 1999).

The precise mechanism by which the PTX-vitamin E combination interacts with fibrotic tissue is not yet known. In the porcine model of radiation-induced musculocutaneous fibrosis, combined PTX-vitamin E treatment induces a significant decrease in TGF-β1 levels but paradoxically no change in TNF-α levels (Lefaix *et al.*, 1999).

Five patients did not respond to the treatment. In two patients, the intensity of the uterine aggression (iterative and complicated curettages for one and radiotherapy of 70 gy for the other) may well have totally destroyed any possibility of endometrial regeneration. This might explain the lack of response. The cause of the failure to respond by the other three patients is unknown.

Three patients, two of whom had previously undergone total body irradiation (20 gy), spontaneously became pregnant, despite their documented low ovarian reserve (FSH of 17, 80 and 90 mIU/ml). This fact suggests that the treatment may influence ovarian function. We observed improvement of the endometrial thickness for these three patients and can assume that the general effect of the treatment might also affect ovarian fibrosis, especially in the two patients with previous radiotherapy. We can also suppose that some cases of ovarian failure follow—and are induced by—chronic, severe pelvic inflammation, which the treatment may reduce. The patient spontaneously pregnant after IVF failures had initially enrolled in IVF because of severe pelvic infectious disease. Specific studies are required to evaluate this interesting issue, especially since another study has already reported spontaneous pregnancies despite elevated FSH and advanced age (Check *et al.*, 2000).

Conclusion

Combined pentoxifylline and tocopherol treatment is, to the best of our knowledge, the only combination so far that seems to be effective for patients with thin endometrium unresponsive to estrogen. Larger prospective and randomized trials are needed to confirm our results. Research is required to elucidate the mechanisms by which this combined treatment affects the uterus and perhaps also the ovaries.

Acknowledgements

We thank Mrs Florence Béquet for her assistance in editing and preparing the manuscript. This work was supported by la Fondation Fertilité Stérilité.

References

Abdalla, H.I., Brooks, A.A., Johnson, M.R., Kirkland, A., Thomas, A. and Studd, J.W. (1994) Endometrial thickness: a predictor of implantation in ovum recipients? *Hum. Reprod.,* **9**, 363–365.

Alam, V., Bernardini, L., Gonzales, J., Asch, R.H. and Balmaceda, J.P. (1993) A prospective study of echographic endometrial characteristics and pregnancy rates during hormonal replacement cycles. *J. Assist. Reprod. Genet*., **10**, 215–219.

Bohrer, M.K., Hock, D.L., Rhoads, G.G. and Kemmann, E. (1996) Sonographic assessment of endometrial pattern and thickness in patients treated with human menopausal gonadotropins. *Fertil. Steril.,* **66**, 244–247.

Chaouat, G., Kolb, J.P., Kiger, N., Stanislawski, M. and Wegmann, T.G. (1985) Immunologic consequences of vaccination against abortion in mice. *J. Immunol.*, **134**, 1594–1598.

Chaouat, G., Menu, E., Delage, G., Moreau, J.F., Khrishnan, L., Hui, L., Meliani, A.A., Martal, J., Raghupathy, R., Lelaidier, C. and *et al.* (1995) Immuno-endocrine interactions in early pregnancy. *Hum. Reprod.,* **10**, (Suppl, 2), 55–59.

Chaouat, G., Tranchot Diallo, J., Volumenie, J.L., Menu, E., Gras, G., Delage, G. and Mognetti, B. (1997) Immune suppression and Th1/Th2 balance in pregnancy revisited: a (very) personal tribute to Tom Wegmann. *Am. J. Reprod. Immunol*., **37**, 427–434.

Chappell, L.C., Seed, P.T., Briley, A.L., Kelly, F.J., Lee, R., Hunt, B.J., Parmar, K., Bewley, S.J., Shennan, A.H., Steer, P.J. and Poston, L. (1999) Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet*, **354**, 810–816.

Check, J.H., Nowroozi, K., Choe, J. and Dietterich, C. (1991) Influence of endometrial thickness and echo patterns on pregnancy rates during in vitro fertilization. *Fertil. Steril.,* **56**, 1173–1175.

Check, J.H., Dietterich, C., Lurie, D., Nazari, A. and Chuong, J. (1998) A matched study to determine whether low-dose aspirin without heparin improves pregnancy rates following frozen embryo transfer and/or affects endometrial sonographic parameters. *J. Assist. Reprod. Genet*., **15**, 579–582.

Check, J.H., Check, M.L. and Katsoff, D. (2000) Three pregnancies despite elevated serum FSH and advanced age: case report. *Hum. Reprod.,* **15**, 1709–1712.

Coulam, C.B., Bustillo, M., Soenksen, D.M. and Britten, S. (1994) Ultrasonographic predictors of implantation after assisted reproduction. *Fertil. Steril.,* **62**, 1004–1010.

De Geyter, C., Schmitter, M., De Geyter, M., Nieschlag, E., Holzgreve, W. and Schneider, H.P. (2000) Prospective evaluation of the ultrasound appearance of the endometrium in a cohort of, **1**,186 infertile women. *Fertil. Steril.,* **73**, 106–113.

Delanian S. and Letur-Kornisch, H. (2000) uterine restoration by radiation sequelae regression with combined pentoxifylline-tocopherol: a phase II study. *Cancer Radiother*., **4**, 163.

Delanian, S., Balla-Mekias, S. and Lefaix, J.L. (1999) Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. *J. Clin. Oncol*., **17**, 3283–3290.

Dickey, R.P., Olar, T.T., Curole, D.N., Taylor, S.N. and Rye, P.H. (1992) Endometrial pattern and thickness associated with pregnancy outcome after assisted reproduction technologies. *Hum. Reprod.,* **7**, 418–421.

Glissant, A., de Mouzon, J. and Frydman, R. (1985) Ultrasound study of the endometrium during in vitro fertilization cycles. *Fertil. Steril.,* **44**, 786–790.

Gonen, Y. (1991) Ultrasonic evaluation of endometrial growth in women with normal cycles during spontaneous and stimulated cycles. *Hum. Reprod.,* **6**, 310–311.

Gonen, Y., Casper, R.F., Jacobson, W. and Blankier, J. (1989) Endometrial thickness and growth during ovarian stimulation: a possible predictor of implantation in in vitro fertilization. *Fertil. Steril.,* **52**, 446–450.

Hazout, A. (1995) Tumor necrosis factor and underlying infection. *Contracept. Fertil. Sex*, **23**, 631–634.

Hsieh, Y.Y., Tsai, H.D., Chang, C.C., Lo, H.Y. and Chen, C.L. (2000) Low-dose aspirin for infertile women with thin endometrium receiving intrauterine insemination: a prospective, randomized study. *J. Assist. Reprod. Genet*., **17**, 174–177.

Hunt, J.S., Chen, H.L., Hu, X.L. and Tabibzadeh, S. (1992) Tumor necrosis factor-alpha messenger ribonucleic acid and protein in human endometrium. *Biol. Reprod*., **47**, 141–147.

Kharb, S. (2000) Vitamin E and C in preeclampsia. *Eur. J. Obstet. Gynecol. Reprod. Biol*., **93**, 37–39.

Lefaix, J.L., Delanian, S., Vozenin, M.C., Leplat, J.J., Tricaud, Y. and Martin, M. (1999) Striking regression of subcutaneous fibrosis induced by high doses of gamma rays using a combination of pentoxifylline and alpha-tocopherol: an experimental study. *Int. J. Radiat. Oncol. Biol. Phys*., **43**, 839–847.

Letur-Kornisch, H., Guis, F. and Delanian, S. (2002) Complete endometrial healing by reversion of radiation-induced abrasion after combined pentoxifylline-tocopherol. *Reprod. Technol.*, in press.

Maruyama, T., Kitaoka, Y., Sachi, Y., Nakanoin, K., Hirota, K., Shiozawa, T., Yoshimura, Y., Fujii, S. and Yodoi, J. (1997) Thioredoxin expression in the human endometrium during the menstrual cycle. *Mol. Hum. Reprod.,* **3**, 989–993.

Noyes, R.W. and Rock, J. (1950) Dating the endometrial biopsy. *Fertil. Steril.,* **1**, 3–25.

Philippeaux, M.M. and Piguet, P.F. (1993) Expression of tumor necrosis factor-alpha and its mRNA in the endometrial mucosa during the menstrual cycle. *Am. J. Pathol*., **143**, 480–486.

Rabinowitz, R., Laufer, N., Lewin, A., Navot, D., Bar, I., Margalioth, E.J. and Schenker, J.J. (1986) The value of ultrasonographic endometrial measurement in the prediction of pregnancy following in vitro fertilization. *Fertil. Steril.,* **45**, 824–828.

Roby, K.F., Weed, J., Lyles, R. and Terranova, P.F. (1990) Immunological evidence for a human ovarian tumor necrosis factor-alpha. *J. Clin. Endocrinol. Metab*., **71**, 1096–1102.

Samlaska, C.P. and Winfield, E.A. (1994) Pentoxifylline. *J. Am. Acad. Dermatol*., **30**, 603–621.

Schulze-Osthoff, K., Bakker, A.C., Vanhaesebroeck, B., Beyaert, R., Jacob, W.A. and Fiers, W. (1992) Cytotoxic activity of tumor necrosis factor is mediated by early damage of mitochondrial functions. Evidence for the involvement of mitochondrial radical generation. *J. Biol. Chem.*, **267**, 5317–5323.

Sher, G. and Fisch, J.D. (2000) Vaginal sildenafil (Viagra): a preliminary report of a novel method to improve uterine artery blood flow and endometrial development in patients undergoing IVF. *Hum. Reprod.,* **15**, 806–809.

Sher, G., Herbert, C., Maassarani, G. and Jacobs, M.H. (1991) Assessment of the late proliferative phase endometrium by ultrasonography in patients undergoing in-vitro fertilization and embryo transfer (IVF/ET) *Hum. Reprod.,* **6**, 232–237.

Stark, J.M. (2001) Inadequate reducing systems in pre-eclampsia: a complementary role for vitamins C and E with thioredoxin-related activities. *BJOG*, **108**, 339–343.

Tabibzadeh, S., Zupi, E., Babaknia, A., Liu, R., Marconi, D. and Romanini, C. (1995) Site and menstrual cycle-dependent expression of proteins of the tumour necrosis factor (TNF) receptor family, and BCL-2 oncoprotein and phase-specific production of TNF alpha in human endometrium. *Hum. Reprod.,* **10**, 277–286.

Tourgeman, D.E., Gentzchein, E., Stanczyk, F.Z. and Paulson, R.J. (1999) Serum and tissue hormone levels of vaginally and orally administered estradiol. *Am. J. Obstet. Gynecol*., **180**, 1480–1483.

Tourgeman, D.E., Slater, C.C., Stanczyk, F.Z. and Paulson, R.J. (2001) Endocrine and clinical effects of micronized estradiol administered vaginally or orally. *Fertil. Steril.,* **75**, 200–202.

von Wolff, M., Classen-Linke, I., Heid, D., Krusche, C.A., Beier-Hellwig, K., Karl, C. and Beier, H.M. (1999) Tumour necrosis factor-alpha (TNF-alpha) in human endometrium and uterine secretion: an evaluation by immunohistochemistry, ELISA and semiquantitative RT-PCR. *Mol. Hum. Reprod.,* **5**, 146–152.

Weckstein, L.N., Jacobson, A., Galen, D., Hampton, K. and Hammel, J. (1997) Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study. *Fertil. Steril.,* **68**, 927–930.

Wegmann, T.G. and Guilbert, L.J. (1992) Immune signalling at the maternal-fetal interface and trophoblast differentiation. *Dev. Comp. Immunol*., **16**, 425–430.

Submitted on September 27, 2001; accepted on December 19, 2001