Article

Ovulation induction with tamoxifen and alternate-day gonadotrophin in patients with thin endometrium

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Abstract

Tamoxifen has been reported to be oestrogenic on the lower genital tract. To evaluate its potential positive effect on the endometrium, and consequently early miscarriage and ongoing pregnancy rate, a prospective study was employed in patients for intrauterine insemination who failed to develop an adequate endometrial thickness in a previous ovulatory cycle. Ovarian stimulation was initiated with tamoxifen 40 mg/day from day 3 of the menstrual cycle for 7 days or clomiphene 100 mg/day for 5 days, in combination with 150 IU of human menopausal gonadotrophin on alternate days starting on day 4. Human chorionic gonadotrophin (HCG) was administered when at least one leading follicle was larger than 20 mm. Intrauterine insemination was accomplished 24–36 h after HCG injection and luteal phase supplement was achieved with micronized progesterone 200 mg transvaginally per day. It was found that tamoxifen-treated patients required more stimulation days and used more gonadotrophin, but recruited less follicles larger than 14 mm than clomiphene-treated patients. However, a significantly increased endometrial thickness ($P < 0.001$) and pregnancy rate ($P = 0.015$), decreased early miscarriage rate ($P = 0.001$) and thus improved ongoing pregnancy ($P < 0.001$) rate were noted in tamoxifen-treated patients. These results suggest that although tamoxifen may not be a first-line treatment in patients with adequate endometrium, it may be a promising alternative for patients with thin endometrium.

Keywords: *clomiphene, tamoxifen, thin endometrium, ovulation induction, pregnancy*

Introduction

Clomiphene citrate (CC) has been used in the treatment of anovulatory infertility since its introduction in 1956 (Greenblatt *et al*., 1961). By depleting the oestrogen receptors, CC acts as an anti-oestrogen on the central nervous system. This increases the pulse frequency of FSH and LH, giving a moderate gonadotrophin stimulus to the ovary, and thus overcoming ovulatory disturbances and increasing the number of follicles reaching ovulation (Adashi, 1984; Dickey and Holtkamp, 1996). Over the years, evidence has accumulated indicating that CC is successful at inducing ovulation in 50–75% of patients, but the pregnancy rate achieved after ovulation induction is much lower than expected (Drake *et al*., 1978; Gysler *et al*., 1982; Wu and Winkel, 1989). The discrepancy has been attributed to CC's prolonged peripheral anti-oestrogenic effects on cervical mucus and the endometrium (Gonen and Casper, 1990; Massai *et al*., 1993; Sereepapong *et al*., 2000). Particularly, its effect on the endometrium may explain a larger part of the lower pregnancy rate in assisted reproduction cycles (Hammond *et al*., 1983; Thatcher *et al*., 1988; Gonen and Casper, 1990). Moreover, Hsu *et al*. (1995) demonstrated that CC also interferes with uterine blood flow. Nevertheless, in order to decrease the gonadotrophin dose required for optimal stimulation, co-treatment of CC

with gonadotrophin therapy has already been an increasingly utilized method of ovulation induction for patients in whom CC treatment was unsuccessful (Dickey *et al.*, 1993a). For these reasons, a simple, inexpensive and safe alternative of CC to be used in combination with gonadotrophin in ovulation induction may be required.

Clomiphene citrate and tamoxifen citrate (TMX) are both non-steroid selective oestrogen receptor modulators. CC is part of the triphenylethylene family of compounds. It has two isomeric forms, *cis* and *trans*, which in the current nomenclature correspond to zuclomiphene and enclomiphene respectively (Sovino *et al.*, 2002). The action of zuclomiphene is mainly anti-oestrogenic, whereas enclomiphene has oestrogenic effects. TMX is also a triphenylethylene that closely resembles CC. In addition to their structural homology, both agents had been shown to be effective for ovulation induction. Klopper and Hall (1971) were the first to describe successful results with TMX for the induction of ovulation in women suffering from secondary amenorrhoea. Various researchers have described the value of TMX in cases of corpus luteum insufficiency (Fukushima *et al.*, 1982) and in conditions of inadequate cervical mucus secretion (Roumen *et al.*, 1984). However, only a few clinical trials with TMX for the induction of ovulation have been reported (Gerhard and Runnebaum, 1979; Ruiz-Velasco *et al.*, 1979; Messinis and Nillius, 1982; Boostanfar *et al.*, 2001). These reports demonstrated that the overall ovulation and pregnancy rates were similar in both groups (Steiner *et al.*, 2005). Other studies have suggested that TMX may be superior to CC in that it does not appear to have an adverse effect on the endometrium (Deligdisch, 2000). The increased oestrogenic stimulation that has been observed with tamoxifen's action on the lower genital tract may be beneficial, especially for those suffering from an adverse response following the administration of CC.

It was postulated that, by administration of TMX, it might be possible to mimic the action of CC in stimulation of ovarian follicles but to avoid the adverse effects of CC on the endometrium. In the present study, a prospective non-randomized trial was employed in a selected group of patients for intrauterine insemination (IUI) who failed to develop an adequate endometrial thickness during follicular monitoring in a previous ovulatory cycle. The aim was to evaluate the efficacy of treatment with TMX or CC in combination with alternate-day human menopausal gonadotrophin (HMG) in these patients. The potential positive effect of TMX on the endometrium, and consequently early miscarriage and ongoing pregnancy rate, was investigated in these patients.

Materials and methods

Patient selection

The study was performed between January 2002 and December 2006. All patients with infertility for at least 1 year completed a standard infertility investigation. In addition to a thorough medical history and physical examination, pelvic ultrasonography was performed to detect anatomical uterine or adnexal abnormalities. Patients with any uterine or adnexal pathology were excluded. A hysterosalpingogram was performed to verify tubal patency and patients with abnormal hysterosalpingograms were excluded from the study. A semen analysis was performed on all male partners and the World Health Organization (1999) criteria were used to confirm normality. According to previously published data, which showed a significantly decreased pregnancy rate in IUI cycles (Huang *et al.*, 1996), male partners with a total motile sperm count of less than 5×10^6, ml were excluded. Other exclusion criteria included female age over 38 years, presence of polycystic ovarian syndrome (diagnosis based on the presence of two out of three according to the Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004): oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries), previous history of adnexal or uterine surgery, or any other contraindication to ovulation induction. All the study couples had undergone at least one to three cycles of follicular monitoring with timed intercourse before undergoing ovulation induction and IUI. All those patients who failed to develop an endometrial thickness of at least 8 mm during follicular monitoring were recruited into this study. They were counselled regarding the novel use of TMX to avoid the adverse effect on the endometrium. Patients were fully informed regarding the indication, rational, mechanism of action and the possible side effects of the drugs. They were not randomized and the choice of receiving TMX or not was left to the patient. All couples underwent a maximum of three cycles of IUI treatment.

Standard ovulation stimulation and cycle monitoring protocol

Under patients' informed consent, all patients enrolled in this study were allocated into two treatment groups. After a spontaneous or progesterone-induced episode of withdrawal bleeding, all patients underwent baseline ultrasonography to confirm the absence of ovarian cysts before the drugs were given. Ovarian stimulation was performed with TMX (Nolvadex, Zeneca Pharmaceuticals, Wilmington, DE, USA) 40 mg per day from day 3 of the menstrual cycle for 7 days (Group A), or CC (Clomid; Merrell Pharmaceuticals Inc., Kansas City, KS, USA) 100 mg per day from day 3 for 5 days (Group B), in combination with 150 IU of HMG (Pergonal; Serono, Geneva, Switzerland) on cycle days 4, 6, 8 and 10 for four doses. Transvaginal ultrasonography was performed on days 11 or 12.

At each ultrasonographic scan, the internal diameter of each visible follicle was measured in two planes and the average diameter was calculated. In addition, the endometrial thickness, defined as the maximum distance between the echogenic interfaces of the myometrium, was measured in the mid-sagittal plane from the outer edge of the endometrial–myometrial interface to the outer edge in the widest part of the endometrium. The sonographers involved in this trial were blind to the kind of treatment.

Depending on the size of the recruited follicles, all patients either stopped stimulation and received a single dose of 10,000 IU human chorionic gonadotrophin (HCG; Pregnyl; NY Organon, Oss, The Netherlands) injection when at least one leading follicle was greater than 20 mm, or continued HMG injection on alternate days until at least one dominant follicle was greater than 20 mm.