Late luteal phase dydrogesterone in combination with clomiphene or tamoxifen in the treatment of infertility associated with irregular and infrequent menstruation: enhancing patient compliance

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This pilot study was undertaken to determine whether dydrogesterone administered in the late luteal phase might have a potential benefit for infertility associated with irregular and infrequent menstruation. Between April 1994 and February 1995, 54 normo-prolactinaemic women received either tamoxifen, if there was evidence of polycystic ovaries and/or increased luteinizing hormone (LH) secretion, or clomiphene together with dydrogesterone 10 mg twice daily on days 21–26 of the menstrual cycle. A total of 23 women (42.6%) conceived (10.7% per cycle). In 192 non-conception cycles the average cycle length was 29.6 days; 182 cycles (94.8%) were 34 days or less. Patients found the rapid onset of regular menstruation to be encouraging and compliance was excellent. Controlled studies are indicated to determine whether the addition of dydrogesterone to oral ovarian stimulation is beneficial.

Key words: clomiphene/compliance/dydrogesterone/infertility/tamoxifen

Materials and methods

Our protocol for the investigation and treatment of infertility has been described in detail elsewhere (Viniker, 1996). Briefly, before the first consultation in the out-patient department, baseline investigations were organized. Blood from the female partner was sent on day 8 of the cycle for luteinizing hormone (LH) and follicle stimulating hormone (FSH) estimation and on day 21 for progesterone. A full blood count and Rubella screen were also sent with the first sample. An ultrasound of the pelvis was arranged on day 12 to assess the pelvic organs with special reference to follicular development and endometrial thickness. Patients were encouraged to keep a basal temperature chart. If the menstrual cycle was irregular, blood was also sent for prolactin and thyroid function. A semen sample was analysed.

We then discussed with the couple in general terms the causes of infertility, their investigation and treatment and then with special reference to the individual couple. The fertile phase of the menstrual cycle was emphasized and the possible benefits of urine testing for the LH surge were particularly advocated for women with irregular menstrual cycles. Sexual abstinence was not recommended before timed intercourse. To enhance patient understanding and compliance, we provided information leaflets that were developed in-house.

Oral ovulation stimulation was prescribed usually at the time of the first consultation when there was evidence of ovulatory dysfunction from the history, pre-ovulatory ultrasound scan or mid-luteal phase progesterone.

A total of 60 consecutive normo-prolactinaemic women presenting between April 1994 and February 1995 with infertility and irregular and infrequent menstruation received a prescription for dydrogesterone 10 mg twice daily on days 21–26 of the menstrual cycle, in combination with either clomiphene 50–100 mg or tamoxifen 20–40 mg on days 2–6 of the menstrual cycle. We tended to use tamoxifen if there was ultrasound evidence of polycystic ovaries or a high LH in the early or mid-proliferative phase of the cycle but otherwise clomiphene was our first choice. Patients were asked to keep a menstrual calendar. Early treatment cycles were not monitored with ultrasound follicle tracking and luteal phase progesterone estimations. Recent concerns about clomiphene, which effectively limited its use to six cycles, encouraged us to monitor response more vigorously. If the mid-luteal progesterone estimations were <30 nmol/l, we increased the dose to 100 and then 150 mg. Similarly, tamoxifen could be increased up to a maximum of 80 mg daily on days 2–6 of the cycle.

Two patients receiving dydrogesterone to initiate the withdrawal bleed before ovulation stimulation proved to be pregnant and four patients never attended for further follow-up. A total of 54 women (35 nulliparous) was known to have received at least one course of...
ovulation stimulation and dydrogesterone. Of these, 29 women initially received clomiphene and 25, who had ultrasound evidence of polycystic ovaries and/or elevated proliferative phase LH, were given tamoxifen. The outcome of the first six cycles for each patient was recorded.

Results
The average age of the women was 29.2 years (range 20–41). The average number of spontaneous menstrual cycles per annum for each patient before treatment was 5.6 (range 0–10). There were 215 treatment cycles and 23 women (42.6%) conceived (10.7% conceptions per treatment cycle). In all, 14 pregnancies occurred in the nulliparous group (40%) and nine pregnancies occurred to women with a previous child (47.46%); 12 pregnancies occurred with clomiphene (41.4%), nine with tamoxifen (36%), and two women received a combination of tamoxifen and clomiphene administered in the conception cycle.

In all, 27 patients were having six or more spontaneous cycles per year before treatment and of these, 12 conceived within the 6 months (44.4%); 27 patients were having five or fewer spontaneous periods per year and 11 conceived (40.7%).

There were 192 treatment non-conception cycles. The average cycle length was 29.6 days (range 26–90 days). There were 171 cycles of 26–31 days duration (89%); 182 cycles (94.8%) were 34 days or less. One patient taking tamoxifen and dydrogesterone had an average cycle length of 36.8 days over five cycles and conceived with the sixth course. Another patient had three cycles of 30 days and then a 90 day cycle and did not attend for further review. Four other patients experienced just one of their cycles each of >34 days.

A group of 14 women who did not conceive did not complete 6 months treatment with clomiphene or tamoxifen and dydrogesterone. Three were changed to gonadotrophins, four were lost from follow up after their second consultation and five discontinued treatment for social reasons. The partner of one patient proved to be azoospermic and one patient stopped the dydrogesterone as this seemed to be associated with headaches.

Discussion
Failure to ovulate is the cause of infertility in about 21% of couples referred to an infertility clinic (Hull et al., 1985). The commonest cause of anovulation is polycystic ovary syndrome. Anovulatory infertility is suggested by amenorrhoea, oligomenorrhoea or irregular menstruation. Occasionally, despite apparently normal menstrual cycles, evidence of ovulatory problems may be detected on ultrasound or from luteal phase serum progesterone concentrations. With the exception of premature menopause, a successful outcome can be expected in 95% of patients with infertility and amenorrhoea and in 75% when there is oligomenorrhoea.

Implantation is arguably the least understood aspect of reproduction. Endometrial function is critical. The human decidua-associated protein hDP200 may indicate the adequacy of the endometrial function (Halperin et al., 1995). We know from in-vitro fertilization (IVF) that only one in ten apparently healthy embryos successfully implants. Progesterone supplementation commencing around the time of embryo transfer is widely incorporated into IVF protocols (Lewis, 1992). Dydrogesterone supports a secretory endometrium for a limited time even in the absence of endogenous progesterone (Lenton, 1984). We chose this progestogen as one of its specific indications is for use in pregnancy. It is not a derivative of the 19-nortestosterone group which have been associated with androgenic effects on the developing female fetus. Yovich and Lower (1991) have used medroxyprogesterone (Provera: Upjohn Ltd, Crawley, W. Sussex, UK) as the support progestrone in patients with recurrent miscarriage and consider it to be safe, although the official recommendation is that pregnancy should be excluded before administration.

Before this study, patients taking clomiphene or tamoxifen would frequently have menstruation ≥7 days late and their β-HCG tests would be negative. Our initial experience with late luteal phase dydrogesterone has been that cycle regulation seems to be enhanced. Since incorporating dydrogesterone into our protocols, failure to menstruate has been almost invariably associated with positive β-HCG pregnancy tests. If conception has not occurred, the next period is clearly defined and a further course of ovulation stimulation commenced. Patients have found the rapid return of regular menstruation to be encouraging and compliance has been excellent.

Although clomiphene citrate and tamoxifen are considered to act as anti-oestrogens, their mode of action in infertility is probably complex and they seem to have different modes of action. Clomiphene modifies hypothalamic activity by binding to oestrogen receptor sites and also inhibits receptor replenishment. The hypothalamus assumes a falsely low reading of oestrogen, leading to increased gonadotrophin-releasing hormone (GnRH) activity and consequently gonadotrophin output from the pituitary. In contrast, follicular phase concentrations of gonadotrophins are not increased by tamoxifen administration, although oestradiol concentrations and luteal phase progesterone do rise (Fukushima and Maeyama, 1983; Tajima, 1984). This suggests that tamoxifen enhances folliculogenesis by direct action on the ovary rather than through the hypothalamic–pituitary–ovarian axis. Hypersecretion of LH is associated with poor conception rates and increased risk of miscarriage (Stanger and Yovich, 1985; Homberg et al., 1988; Regan et al., 1990) so that, from a theoretical point of view, tamoxifen may have an advantage as gonadotrophin levels are not increased further.

Early studies demonstrated similar success rates between clomiphene and tamoxifen (Messinis and Nilius, 1982). The majority of pregnancies will occur in the first few cycles. For early treatment cycles it has been suggested that simple monitoring with basal temperature alone is as good as urinary LH monitoring and ultrasonography (Hurd et al., 1994). If there is no success with clomiphene 50 mg then the dose can slowly be increased in 50 mg increments up to 200 mg daily for 5 days (Gorlitsky et al., 1978).

An analysis of 3837 women investigated for infertility in Seattle between 1974 and 1985 was reported by Rossing et al. (1994). There were 11 invasive or borderline malignant tumours against an expected number of 4.4. Nine of the women...
developing ovarian malignancy had taken clomiphene and five of the nine had taken the drug for 12 months or more. The relative risk for the women taking clomiphene for 12 months or more was 11.1; treatment with clomiphene for less than a year was not associated with increased risk. Subsequent to the Seattle report, the Committee on Safety of Medicines (1995), whilst accepting that further studies are indicated to investigate the possible association between clomiphene and ovarian cancer, stated that: 'We recommend that clomiphene should not normally be used for more than six cycles.'

As with clomiphene, there is concern that gonadotrophin therapy may be associated with an increased risk of ovarian cancer (Whittemore et al., 1992). This has major implications for infertility management. Should there prove to be a direct relationship between ovarian cancer and the strength of ovulation stimulation, then gonadotrophin therapy would need to be minimized. If the relationship between ovulation induction and ovarian cancer proves to be cumulative, then theoretically gonadotrophin therapy or IVF, which carry greater success rates per cycle than clomiphene or tamoxifen, would be indicated early. There has been an almost exponential increase in the use of ovulation stimulation drugs over the last 20 years; the use of clomiphene has increased 11-fold and of HMG 30-fold (Mosgaard et al., 1995). As there is a tendency towards increasing exposure of young women to these agents, careful analysis of data, as it unfolds, is essential. Tamoxifen when used for short durations does not appear to be associated with increased risk of ovarian or endometrial cancer (Cook et al., 1995).

Gulekli et al. (1993) have recommended tamoxifen for patients with polycystic ovary syndrome who prove to be resistant to clomiphene, before treatment with surgery or gonadotrophins. When clomiphene fails to achieve ovulation or pregnancy, tamoxifen may prove to be effective (Borenstein et al., 1989). Tan and Jacobs (1991) recommend tamoxifen rather than clomiphene for patients with hypersecretion of LH. In one small trial, a combination of tamoxifen and clomiphene was shown to be more effective inducing ovulation than clomiphene alone; there were also more pregnancies but no multiple pregnancies (Suginami et al., 1993).

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References


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