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Original Articles

Reproductive Biology Section

Influence of the conclusion of a recent large cooperative study in changing standard protocol of inducing menses in anovulatory women with oligomenorrhea prior to initiating ovulation induction with anti-estrogens and outcome

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Summary

Purpose: To compare pregnancy rates following ovulation induction in anovulatory women with clomiphene citrate *vs.* letrozole and to determine the relative confounding effect of inducing menses or not. The study also evaluated whether starting these anti-estrogen drugs later in the menstrual cycle has less adverse effect on endometrial thickness. *Materials and Methods:* Prospective series with choice by physician of inducing menses or not or choosing clomiphene citrate or letrozole for ovulation induction. Peak endometrial thickness was compared between drugs and between those conceiving or not. *Results:* There were 21 first cycles using letrozole and 42 using clomiphene. Menses were not induced in 18/21 (86%) letrozole cycles and 24/42 (57%) clomiphene cycles. Clinical pregnancies occurred in four (22.2%) letrozole cycles without induced menses with one miscarriage *vs.* 4/24 (16.6%) clomiphene cycles, no miscarriage. One of three (33.3%) letrozole cycles with menses induced achieved a clinical pregnancy *vs.* only 1/18 (5.5%) of clomiphene cycles. There were no miscarriages. *Conclusions:* Though the endometrial thickness was higher with clomiphene without induced menses *vs.* menses induced (11 mm *vs.* 9.5 mm), one cannot explain the trend for lower pregnancy rates in women with induced menses because of thinner endometria since the thickness was 10.3 mm for clomiphene and 10.0 with letrozole.

Key words: Induced menses; Clomiphene citrate; Letrozole; Endometrial thickness.

Introduction

For many years when confronted with anovulatory women with amenorrhea or oligomenorrhea who desire to become pregnant, the treating physician would induce menses with progesterone withdrawal to establish a normal endometrium before proceeding with ovulation inducing drugs. Recently a large (n=626) multicenter randomized study evaluated pregnancy rates following ovulation induction in women with oligomenorrhea or amenorrhea according to whether menses were first induced before initiating clomiphene citrate or the drug was started without inducing menses [1]. The anovulatory women for this aforementioned study had polycystic ovarian syndrome (PCOS) [1]. The results of the study found live birth rates per ovulation of only 3% with the use of clomiphene citrate, metformin, or a combination of both taken day 3-5 after spontaneous menses, 5.4% with clomiphene taken day 3-5 after menses induced with progestin, but 19.7% when given without menses induced and with many days in the follicular phase [1]. This study was presented at journal club two months after this publication where four reproductive endocrinologists were in attendance.

Clomiphene citrate is a selective estrogen receptor modulator that occupies the same FSH pituitary receptors as estrogen but it does not inhibit release of FSH (so it acts as a competitive inhibitor) [2]. The end result is increased FSH secretion and thus ovulation induction.

Letrozole is an aromatase inhibitor and thus causes a drop in the serum E2 level which also then allows greater release of FSH from the pituitary. Most data show that it is equally effective to clomiphene citrate, and because of a shorter half-life, has a better chance of inducing monofollicular ovulation [2, 3].

The seven objectives of the present study:

1) Determine what influence the aforementioned study had on the decision of four reproductive endocrinol-

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ogists to induce menses with medroxyprogesterone acetate or not and start clomiphene citrate on day 3 or 5 or begin clomiphene citrate (or letrozole) right away in anovulatory women (but not necessarily with PCOS).
2) Corroborate or refute the results of the aforementioned study finding higher pregnancy rates without induction of menses using clomiphene citrate.
3) Determine if using letrozole following menses induction *vs.* not also shows higher pregnancy rates without menses induction.
4) Determine if the aforementioned study using clomiphene exclusively had as much influence on these doctors when prescribing letrozole *vs.* clomiphene assuming the same outcome could apply to letrozole.
5) Compare peak endometrial thickness in the late follicular phase in those women taking clomiphene on day 3-5 or much later (without induction of menses).
6. Compare peak endometrial thickness in the late follicular phase in those taking clomiphene citrate *vs.* letrozole.
7. Compare peak endometrial thickness with clomiphene and letrozole in those conceiving *vs.* those who did not.

Materials and Methods

A retrospective review was performed of first cycles of ovulation induction with clomiphene citrate or letrozole in women with oligomenorrhea or amenorrhea without estrogen deficiency subsequent to the aforementioned journal club. The starting dosage of clomiphene citrate was 50 mg x five days or letrozole 2.5 mg x five days. The cycle would be eliminated from the study if luteinization occurred without reaching the criteria of normal follicular maturation (i.e., if a mature follicle of 18-24 mm with a serum E2 of 200 pg/ml was not achieved). If menses were induced it was with 13 days of ten-mg medroxyprogesterone acetate. Intrauterine insemination was performed if the post-coital test was inadequate at the time of peak follicular maturation. Vaginal progesterone supplementation was given in the luteal phase in all cycles. Clinical pregnancy rates (ultrasound evidence of live fetus at eight weeks) and miscarriage rates were determined with both drugs. Endometrial thickness was determined at the time of peak follicular maturation. The endometrial thicknesses were compared between clomiphene *vs.* letrozole and in those conceiving and those not conceiving.

Results

There were 63 first cycles of ovulation induction with attaining a mature follicle in anovulatory women since the journal club presentation in August, 2010 (study concluded August, 2013). Clomiphene citrate was used in 42 (66.7%) and letrozole in 21 (33.3%).

Menses were induced with medroxyprogesterone acetate in 18 (42.8%) of clomiphene citrate cycles and in three (16.6%) of letrozole cycles. Ovulation drugs were started without inducing menses in 24 (57.2%) clomiphene citrate cycles and in 18 (83.4%) letrozole cycles. With menses induced there was only one of 18 (5.5%) taking clomiphene who achieved a pregnancy with no miscarriages *vs.* one of three (33.3%) taking letrozole with no miscarriages.

Without menses induced there were four of 24 (16.6%) with clomiphene citrate conceiving with one miscarriage *vs.* four of 18 (22.2%) with letrozole with one miscarriage. The average age was 28.4 for those taking clomiphene *vs.* 33.3 for those women taking letrozole. The peak endometrial thickness in the follicular phase was 11.0 mm for clomiphene citrate *vs.* 9.9 mm for letrozole. The peak endometrial thickness in those who conceived was 10.3 mm with clomiphene citrate *vs.* 10.0 mm with letrozole. Related to the small size of the study, there were no significant differences.

Discussion

Irrespective of induction of menses or not, the clinical and live delivered pregnancy rates were for the first cycle were as follows: clomiphene citrate: clinical – five of 42 (11.9%) and live delivery – four of 42 (9.5%) *vs.* letrozole: clinical – five of 21 (23.8%) and live delivered – four of 21 (19.0%). Fisher's exact test for clinical and for live delivered, p = NS. Thus letrozole seems as effective as clomiphene citrate in achieving pregnancy (possibly greater but a larger series is needed).

The data from this study are consistent with the large prospective multicenter study finding higher pregnancy rates without inducing menses when using clomiphene citrate. The numbers are too small to be meaningful but not inducing menses may not be as critical when using letrozole. Nevertheless, the data show no adverse effect of inducing ovulation with letrozole without inducing menses.

Since those conceiving with clomiphene citrate did not show a thicker endometrium compared to all cases, the concept of the theoretical advantage of starting clomiphene later for pregnancies by not having as much of an adverse effect on endometrial thickness (as suggested in the discussion of the large prospective cooperative study) does not seem to be the mechanism for the possible increased pregnancy rates with clomiphene citrate if one does not induce menses.

The aforementioned large prospective cooperative study did influence a slight majority of doctors to change prescribing habits and start clomiphene right away without inducing menses [1]. It is not completely clear why the study had a more profound influence in cycles starting letrozole with the large majority not inducing menses. A partial explanation is that one of the four reproductive endocrinologists at the meeting seemed to be most influenced to change prescribing habits and that same physician seems to favor letrozole over clomiphene citrate for ovulation induction.

The trend for higher pregnancy rates with letrozole is not clear. The patients were not younger nor was endometrial thickness increased. Possibly the trend for higher pregnancy rates was related to the tendency for the treating physicians to start the letrozole without inducing menses more often than when using clomiphene citrate.

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