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According to Marshall, the basic fundamentals of the rhythm method have been known to physicians for the past 35 years; however, this form of family planning has failed to obtain the confidence of a significant segment of the Catholic population. Even highly motivated and properly instructed patients frequently fail to accomplish their objective because of an unsuspected premature or late ovulation in an otherwise fairly predictable ovulatory pattern. These rhythm failures would imply that the responsible body processes which regulate the time of ovulation are not perfect and possess intrinsic peculiarities which prohibit repeated perfect timing of ovulation. Hypothalamic disturbance is but one example of how the pituitary-ovarian axis might disturb ovulation timing.

During the past decade, many steroid compounds have been made available for use in the area of family planning and their efficacy has been virtually 100 per cent. Their mode of action is attributed to a three-fold mechanism, namely: (1) Inhibition of ovulation, (2) production of a hostile cervical mucus, and (3) interfering with implantation of a fertilized egg by altering the endometrial environment.[1,2,5-10,12] It is not within the scope of this presentation to discuss the morality of their use.

The purpose of this report is to discuss our experience with clomiphene citrate and its ability to regulate the time of ovulation. Clomiphene is a new orally administered non-steroid compound which is an analogue of the weak estrogen TACE. Clomiphene was made available in 1960 for infertile anovulatory patients. When administered to these patients, ovulation occurred and is characterized by all scientific criteria of ovulation, including pregnancy. In a summarized report by Johnson et al,[4] it was noted that 1809 out of 2616 anovulatory patients ovulated following the administration of clomiphene citrate and approximately 40 per cent became pregnant during the first three clomiphene treated cycles. The mechanism of action of clomiphene is by the direct stimulation of the ovary[11] or by the stimulation of the hypothalamico pituitary axis.[3]

In a careful review of the literature, there are no published reports concerning the use of clomiphene citrate in normal women for the regulation of ovulation time. The purpose of this study was to see if clomiphene citrate would regulate the time of ovulation and make the

practice of the rhythm method more effective.

## MATERIAL AND METHODS

The 96 normal patients participating in this study were a group of highly motivated patients wishing to space or limit the number of children in their families by the use of the rhythm method. Their ages varied between 20 and 40 years of age with an average parity of four. Before admitted to the study, each patient presented documented evidence of six months of basal body temperature graphs. The administered dose of clomiphene citrate was 50 mgs. daily for 5 days beginning on the fifth day of the menstrual cycle. Basal body temperature graphs were maintained by each patient while on clomid therapy. Patients were seen in the office each month for pelvic examination, cervical mucus study, B.B.T. graph review, vaginal cytology and, in selected cases, endometrial biopsy for histologic and histochemical analysis. This phase of the study was considered important to assure that no adverse changes occurred at or following ovulation which might interfere with the normal physiologic events leading to conception and implantation. One might conclude that these precautions were unnecessary, since previous documented studies[4] dealing with 2616 anovulatory patients treated with clomiphene citrate responded favorably with ovulation and pregnancy.

## RESULTS

Utilizing basal body temperature as an indicator of ovulation, comparisons were made of the patients' ovulatory patterns before and during clomiphene citrate erapy. Since the phrase "variation f ovulation" is repeatedly used ough- out this study, an explan ion of this phrase may be neces y. For instance, during the 6-mont control period of B.B.T. recording during the 6 months of clomid th apy, if a patient ovulated betwee day 14 and 16 of her cycles, then his patient had a variation of ov tion of three days. Therefore, the sults of this phase of our study may be reported as follows:

1. During clomiphene therapy, ovulation was controlled within 3 days in 94 patients (97.9 %) compared to 24 patients (25% during the control period.

2. During clomiphene therapy ovulation time was controlled within 2 days in 89 patients (92.7%) compared to 18 patients (19% ) during the control period.

3. In general, 95 out of 96 patients exhibited a significant improvement in their ovulatory pattern while on clomiphene therapy. With one exception, no premature or late ovulations occurred in patients under clomiphene therapy.

Viewing these results from a slightly different perspective, it was important to note when ovulation occurred following the last administered dose of clomiphene citrate. The overwhelming majority of ovulations (90%) occurred 6-8 days after the last dose of clomiphene citrate.

If the normal corpus lutein phase of the menstrual cycle is approximately 14 days, then clomiphene treated patients exhibited a corpus lutein phase of nearly 15 days. This is indirect evidence that clomiphene stimulates, rather than suppresses, pituitary gonadotropic secretions.

The menstrual cycle length under clomid therapy exhibited excellent regularity with an overall increase in the cycle length of nearly 2 days. The character of the menses were normal in all but 5 patients. The latter reported heavier periods when compared to their pre-clomid therapy menses.

Side reactions to clomiphene therapy included ovulatory pain (8), hot flashes (4), questionable hair loss (2), weight gain (1), itching (1), blurry vision (1), and moderate ovarian enlargement (3). All side reactions were considered mild and transient by the patients and investigators.

Studies on cervical mucus, vaginal cytology, and on endometrial biopsies were normal. Exhaustive laboratory studies have been documented by previous competent investigators in treating 2616 anovulatory patients with clomiphene citrate.[4] These studies were designed to evaluate the pituitary, adrenals, thyroid, liver, blood and other body systems. No adverse functions to clomid therapy were encountered.

## CONCLUSIONS

Out of 96 normal patients participating in this preliminary study, all but one exhibited a beneficial effect in regulating menstrual cycle length and ovulation time.

The most common time for ovulation to occur is 6 to 8 days after the last administered dose of clomiphene. It should be emphasized that clomiphene does not induce a stereotype response of ovulation time in all patients. Though variations in ovulatory response exist between patients, each patient responds rather consistently during clomid therapy. Therefore, each patient should be managed individually and not on a collective basis in determining their fertile and infertile periods.

The sequence of events concerned with fertilization and implantation are not affected adversely by clomiphene citrate therapy. This conclusion is based on the present observations and documented reports by previous investigators.

It should be emphasized that clomiphene citrate stimulates the processes concerned with ovulation rather than suppresses ovulation.

It is the authors' opinion that clomiphene citrate is a useful agent in regulating ovulation time and perfecting the practice of the rhythm method. More important than attempting to predict and pinpoint ovulation time is the ability of clomiphene citrate to prevent unexpected premature or late ovulations. It is hoped that further studies with clomiphene citrate will suggest that patients practicing the rhythm method of family planning may discontinue the tedious task of B.B.T. recording while they remain on stabilized clomid therapy.

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