ULTRASOUND MONITORING OF CLOMIPHENE INDUCED OVULATION

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SUMMARY

This study relates to regular, daily monitoring of 97 clomiphene induced cycles, employing the following parameters: (i) follicular diameter by sonography, (ii) cervical mucus secretion, (ii) BBT.

The mean preovulatory follicular diameter in clomiphene induced cycles is 23.25 mm as against 18.88 mm in spontaneous cycles. In induced cycles ovulation seldom occurs below 20 mm, and 60% ovulate before 24 mm. Ovulation occurs between days 11 and 14 of beginning of clomiphene in 92% of cycles.

Optimal mean follicular diameter for hCG administration in clomiphene cycles appears to be slightly more (24.66 mm), and days between 11 and 14 of clomiphene seem ideal. Ovulation occurs within 24 hours of hCG in one half and within 48 hours in the rest. There is a three fold increase in pregnancy rate when hCG is employed as an adjunct.

Mutiple follicular maturation is observed in 15.46%, with 2.06% of hyperstimulation. In 82% of clomiphene cycles the cervical mucus secretion was satisfactory, and hence routine therapeutic use of estrogen is unwarrented.

hCG administration emperically, without sonographic surveillance, will not yield the desired results, and hence is not recommended if facilities are not available for sonography or estrogen study.

Introduction

Clomiphene citrate has been used to induce ovulation or improve abnormal ovulation for more than 2 decades. While successful ovulation has been estimated to occur in 70-90% of cases, pregnancy has been recorded only in 30-40% of cases. Varying dose schedules or different adjunctive therapies could not improve upon the pregnancy rate significantly. One of the obvious reasons for this poor outcome evidently is the lack of proper monitoring of subjects undergoing clomiphene induction. Careful surveillance of clomiphene cycles

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employing BBT, cervical mucus study, ultrasound imaging of the follicular dynamics and estrogen assay should improve the pregnancy rate and reduce the number of treatment cycles. In this context sonographic follicular imaging needs special mention because of its strategic role.

Sonographic follicular study has made a rapid stride in reproductive endocrinology because this is a non-invasive, simple, quick and convenient procedure, the results of which could be interpreted by the physician on the spot in his office without any delay, and could be safely repeated any number of times. The value of ultrasonography in these cycles seems to be in making a deecision to administer hCG (human chorionic gonadotropin) at the time of optimal follicular maturation, and to withhold hCG when ovulation has already occurred or when multiple large follicles are demonstrated and ovarian overstimulation, or multiple pregnancy, is to be avoided.

It has been shown that follicles with a diameter between 18 and 25 mm have a normal complement of granulosa cells producing optimal concentration of estrogens and harbour a mature oocyte (DeCherney and Laufer). While follicular size does not precisely predict the time of ovulation it is helpful as a single parameter since ovulation occurs at a narrow range of 20-25 mm diameter (DeCherney and Laufer, 1984). Of late, other sonographic parameters than follicular diameter have been employed for prediction of ovulation (Ritchie, 1985). One such sign is detection of a small echnogenic area projecting into the follicle which represents the cumulus oophorus. This may be identified in more than 20% of follicles over 18 mm in diameter. Identification of the cumulus confirms that the cystic structure is indeed an oocyte-containing follicle and that ovulation will occur within 36 hours (Hackeloer, 1984).

With the LH surge, the thecal tissue becomes hypervascular and edematous, and the granulosa cell layer begins to separate from the thecal cell layer. This feature is appreciated by the appearance of a line of decreased reflectivity around the follicle, and is consistently seen within 24 hours of ovulation. Advanced folding and separation of the granulosa cell layer from the underlying thecal layer produces a crenated pattern of lining of the follicle. This is less consistently seen but occurs when ovulation is imminent, within 6 to 10 hours.

Study Design

Ultrasonographic follicular study, diagnosis of ovulation and appearance of corpus luteum have been described in our earlier study (Rajan and Rajan, 1985). In this study we aim at studying the follicular dynamics following clomiphene therapy as related to: (i) When ovulation occurs following clomiphene treatment?, (ii) What is the maximum diameter reached by the pre-ovulatory follicle?, (iii) How many dominant follicles develop?, (iv) If hCG is administered at optimal follicular growth, what is the interval between hCG administreation and occurrence of ovulation? and (v) What is the effect of clomiphene on cervical mucus secretion?

Clomiphene citrate has been employed for induction of ovulation in anovulatory subjects (28 patients), for regulation of ovulation in subjects with abnormal ovulation or just delayed cycles (16 patients) and for timing of ovulation in AID subjects (18 patients). The standard dose employed was 50 mg per day for 5 days started on the 2nd or 3rd day of the cycle. Many of these subjects were administered adjunctive dexamethasone, 0.5 mg daily.

The total of 62 subjects studied for 97 cycles could be divided at random into two groups as to whether they received hCG at the midcycle period or not. While clomiphene citrate itself can promote follicular maturation and induce ovulation, it is quite possible that the cumulative effect of folliculostatin elaborated by the multiple follicles of the induced cycle interfere with a proper LH surge and hence the mature follicle fails to ovulate. Evidently the latter group can achieve ovulation if exogenous hCG administration to mimic endogenous LH surge is timed with optimal follicular growth.

Thus, of the 97 cycles treated, ovulation was achieved with clomiphene alone (without a mid cycle hCG) in 24 cycles (group I) and following hCG administration at a follicular diameter of 21 mm or more in 32 cycles (group II). The dose of hCG employed was 10,000 i.u. as a single injection except in 3 subjects who received 5000 i.u.. hCG in a dose of 1,500 i.u. was administered on 4th and 7th post-ovulatory days for luteal support in 4 subjects.

Observations

1. *Pre-ovulatory Follicular Diameter*: For evaluation of the maximum pre-ovulatory follicular diameter subjects who ovulated spontaneously following clomiphene therapy (Group I) alone were considered. In the 24 ovulatory cycles the maximum follicular diameter just prior to rupture ranged from 19 to 29 mm, with a mean of 23.25 mm. Except in one cycle the follicular diameter was 20 mm or more at the time of rupture. In 10 of the 24 cycles (41.67%) the follicle had reached 24 mm or more before rupture. Thus it is evident that ovulation seldom occurred before the follicle had reached 20 mm diameter in clomiphene induced cycles, and if one waited for a diameter of 24 mm to be reached already 60% would have ovulated.

In our earlier study on spontaneously ovulating subjects, the follicular diameter had ranged from 16 to 22 mm with a mean of 18.88 mm. Now, this study on clomiphene induction of ovulation evidently proves that pre-ovulatory follicular diameter is significantly greater than that of spontaneous cycles.

2. *Prediction of Ovulation*: As mentioned earlier clomiphene therapy was started on 2nd or 3rd day of the cycle, and sonographic surveillance was initiated from the 11th day of beginning of clomiphene therapy. Concurrently cervical mucus study, postcoital test and BBT recording were maintained for all subjects. The subjects were considered to have ovulated when the follicle, after having reached the maximum diameter, was replaced by a smaller irregular cyst with intra-follicular echos. By performing sonography daily in subjects who ovulated spontaenously following clomiphene therapy (group I) ovulation was evidenced to occur between 11th and 16th day of beginning of clomiphene treatment, with 91.67% (22 of 24 cycles) of ovulations clustering between 11th and 14th day of initiation of clomiphene therapy. While ovulation was recorded on 13th day in 10 cycles (about 42%), 11th day in 4 cycles (16.67%), 12th day in 3 cycles (12.5%), and 15th day. in 5 cycles (20.80%).

From this observation it is evident that ovulation occurs between the 11th and 14th day of intiation of clomiphene therapy. If one does not employ sonographic monitoring of clomiphene induced cycles, a reasonable guess of ovulation will be from 11th day to 14th day of beginning of clomiphene and coitus or insemination could be timed accordingly, particularly not to miss the 13th day.

3. *H.C.G. Administration*: hCG administration, optimally timed when the follicle was mature, is considered to improve the ovulation rate and rectify ovulatory dysfunctions. A follicular diameter of 18 mm or more, copious watery cervical mucus secretion, opening of the cervical os and BBT nadir consituted the ideal clinical condition of hCG injection. In this study, these conditions were satisfied between day 11 and 14 of beginning of clomiphene in 29 of the 32 cycles (90.65%). This figure indicates that monitoring should be started on day 11 and in all probability hCG administration could be performed within day 14 (4 days of pre-ovulatory surveillance).

The follicular diameter at which hCG was administered ranged from 21 to 30 mm with majority (65.60%) clustering around 21 to 25 mm, and the mean follicular diameter for hCG administration was 24.66. Against this, in spontaneously ovulating subjects following clomiphene therapy, the maximum follicular diameter ranged from 19 to 29 mm with 70.80% clustering around 20 to 24 mm, with a mean of 23.25 mm. Thus it becomes evident that conditions become favourable for hCG administration at a slightly greater follicular diameter than that at which spontaneous ovulation occurs following clomiphene therapy.

Of the 32 cycles studied the post-ovulatory event following hCG administration could be studied in 24 cycles. Daily monitoring after hCG administration revealed that follicular rupture had occurred within 24 hours in 13 cycles (54.17%) and within 48 hours in the remaining 11 cycles (45.83%). This brings the point that a single post-hCG monitoring 48 hours after will evidence ovulation.

4. *Pregnancy Rate*: Since the study has been initiated recently atleast 6 cycles could not be studied to evaluate the actual success rate. However, with the available data, for the 24 cycles in the clomiphene group (group I) one pregnancy was recorded, whereas for the 32 cycles in the clomiphene + hCG group (Group II) 4 pregnancies have been recroded. This is a reasonable proof justifying timely administration of hCG to trigger ovulation.

6. *Multiple Follicular Maturation*: Eventhough more number of dominant follicles does not necessarily mean multiple pregnancy, risk of multiple pregnancy is certainly more in these subjects. Among the total 87 cycles studied, there were 2 dominant follicles in 13 cycles (13.40%), and 3 dominant follicles in 2 cycles (2.06%). Two subjects in this group had signs and symptoms of ovarian hyperstimulation.

7. *Cervical Mucus Secretion*: Of the 97 cycles cervical mucus pattern was studied in 77 cycles and the following observations were made on spinbarkeit: Spinbarkeit was 15 cm or more in 12 cycles (15.58%), 10 cm or more in 23 cycles (29.87%), 5 cm or more in 28 cycles (36.36%), and scanty and poor (less than 5 cm) in 14 cycles (18.18%). This is an interesting observation against the general belief that clomiphene citrate produces antifertility effect at the level of cervical mucus. This study demonstrates that 81.82% clomiphene induced cycles have adequate cervical mucus secretion optimal for sperm transport, and the 18.18% of poor cervical mucus pattern is nothing more than what is observed as the general incidence.

Discussion

Since the advent of follicular sonography and the prevalent use of sonographic monitoring of clomiphene induced cycles a lot of observations have come to light to ensure a favourable outcome for anovulatory infertility. The decisive role of follicular

sonographic monitoring is to time hCG administration to trigger ovulation and to withhold hCG when ovulation has already occurred or when multiple large follicles are demonstrated and ovarian overstimulation, or multiple pregnancy is to be avoided.

We observe that the greatest mean preovulatory follicular diameter in spontaneous cycles is 18.88 mm, whereas in clomiphene induced cycle the mean value is certainly more and is 23.25 mm. Ovulation seldom occurs at a follicular diameter of less than 20 mm and about 60% cycles achieve ovulation before the follicle reaches 24 mm. Ovulation has been observed to occur between days 11 and 14 of beginning of clomiphene therapy in about 92% of cycles, with the maximum number of ovulations recorded on 13th day (about 42%). This observation is helpful for those who do not employ sonographic monitoring. They could consider days 11 to 14 from the beginning of clomiphene therapy as the most fertile period for timing coitus or insemination.

However, hCG administration at the optimal time following clomiphene has increased the pregnancy rate 3 folds or more. The optimal time for hCG administration is a follicular diameter of 18 mm or more, copious cervical mucus secretion with an open cervical os and BBT nadir. This study demonstrates that these criteria are fullfilled between day 11 and 14 of beginning of clomiphene therapy in 90% of cycles. From this observation and the earlier one it can be decided that regular daily monitoring of clomiphene induced cycles should be started on 11th day of beginning of clomiphene and continued for 4 days. Since one half ovulate within 24 hours of hCG injection and the rest within 48 hours, a single monitoring about 48 hours post-hCG is sufficient to diagnose ovulation.

The follicular diameter at which the cervical mucus and BBT become satisfactory for hCG administration appears to be significantly greater (mean 24.66 mm) as against the maximal follicular diameter when clomiphene alone is employed for ovulation induction (23.25 mm). The possibility of follicular rupture at sub-optimal conditions has to be seriously considered in those subjects treated with clomiphene alone, particularly because of the spectacular difference in the pregnancy rate when hCG also is combined.

More than one dominant follicle was observed in 15.46% of cycles receiving clomiphene therapy. This does not necessarily mean multiple pregnancy, but all the same these subjects are at high risk for multiple gestation. Atleast in 2 cycles (2.06%) signs and symptoms of ovarian hyperstimulation were recorded viz. severe pelvic pain and multiple follicular enlargement to less than 10 cm. None of them needed anything more than conservative treatment, and in one the cycle was suppressed by hormonal contraceptives.

A meticulous study of pattern of cervical mucus proves beyond doubt that clomiphene does not interfere with cervical mucus secretion in 82% of cycles. Hence we believe that the small percentage where cervical mucus is scanty probably is the general incidence of scant cervical mucus secretion and not particularly related to clomiphene treatment. For this reason we suggest that indiscriminate adjunctive estrogen therapy should be discouraged.

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