CLOMIPHENE CITRATE, DEXAMETHASONE AND HUMAN CHORIONIC GONADOTROPIN FOR INDUCTION OF OVULATION

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SUMMARY

Ultrasonographic monitoring of ovulation was practised in 38 patients undergoing induction of ovulation with clomiphene or clomiphene and dexamethasone combination, over a period of 11 months. hCG was administered to initiate follicular rupture when the dominant follicle was 18-20 mm and copious cervical mucus secretion was present. Post-ovulatory events including pregnancies were monitored by sonography.

A three-fold increase in pregnancy rate (13.33% versus 36.36%) with optimally timed administratoin of HCG convincingly proves the importance and need for sonographic monitoring and adjunctive hCG therapy.

DEX therapy in combination with CC in randomly selected subjects or cycles did not yield improved pregnancy rate (14.70%) when compared to employing CC alone (13.33%). Perhaps, DEX has to be reserved for CC failures evidencing elevated DHEAS levels.

The very high pregnancy rate of 83.33% in subjects with secondary amenorrhoea (evidencing endogenous estrogen and having no galactorrhoea) is significant and it indicates: (i) Detailed work-up such as HSG, laparoscopy or RIA hormone studies are not needed for beginning CC therapy, and with proper clinical evaluation and progesterone challenge test suitable candidates should be recruited, and (ii) antifertility effect of clomiphene (poor cervical mucus and luteal insufficiency) is an insignificant cause of clomiphene failures, and such subjects should undergo a detailed evaluation to unearth other causes for infertility.

Since all the 16 pregnancies were recorded within 4 treatment cycles, and 82.25% of the pregnancies occur within 2 treatment cycles, failure to conceive within 4 ovulatory cycles could be the indication for detailed work-up.

Reduced pregnancy wastage (5.88%) and absence of multiple

pregnancies in this series, perhaps, are attributable to sonographic monitoring of cycles and timely hCG administration. Early pregnancy sonographic monitoring ensures identification of healthy pregnancies and offers proper guidance to the patients.

Introduction

Clomiphene Citrate (CC) has been used to induce ovulation for more than 2 decades, and despite the availability of the newer ovulogens CC remains the most common single agent to be employed for ovulation induction. Women with oligomenorrhoea/secondary amenorrhoea due to minor hypothalamic-pituitary dysfunction without estrogen deficiency have a much great incidence of ovulation following treatment with CC.

A marked discrepancy between the rates of ovulation and pregnancy has been reported in most studies (Kase *et al* 1967; Garcia *et al*, 1977; Gysler *et al*, 1982 and Wu., 1984). There has been continuous attempt at improving the success rate of clomiphene therapy by various alterations and modifications of the treatment protocol. The schedules advocated are: (i) Initiation of therapy early in cycles, perhaps 2nd or 3rd cycle day (Wu, 1984). (ii) Discriminatory use of estrogens for the few selected subjects to oppose the antiestrogenic effect on the cervical mucus (Gysler *et al*, 1982). (iii) Adjuctive therapy with dexamethasone in patients known to have an adrenal androgen excess (Maroculis, 1981; and Daly *et al*, 1984. (iv) Combined clomiphene and bromocriptine therapy in some subjects with hyperprolactinaemia (Pepperell, 1983). (v) Incremental CC therapy employing individualised graduate treatment regimen (Pepperell, 1983), (vi) Monitoring of ovulation induction using ultrasound (DeCherney and Laufer, 1984), and (vii) precisely and optimally timed administration of human Chorionic Gonadotropin (hCG) to initiate follicular rupture (Pepperell, 1983; Thorneycroft, 1984; Wu, 1984 and Ritchie, 1985).

In our earlier communication we have reported a pregnancy rate of 46.34% for 41 anovulatory subjects treated with clomiphene and monitored by the clinical parameters (Rajan *et al*, 1984). Since then we have modified our treatment protocol by including the following schedules to CC therapy: (i) Administration of the CC on the 2nd or 3rd cycle day. (ii) Adjunctive use of Dexamethasone (DEX), (iii) Selective use of midcycle estrogen therapy. (iv) Monitoring the follicular dynamics by employing ultrasonography, and (v) timely administration of hCG to induce ovulation (Rajan, 1985; and Rajan and Rajan, 1985). The data collected over the last one year employing the modified treatment protocol is presented in this communication, and herein we discuss the impact of adjunctive therapy (DEX and hCG) on the success rate of CC treatment.

Study Design

Subjects with ovulatory disorders, exhibiting delayed cycles, oligomenorrhoea or secondary amenorrhoea (evidencing positive progesterone challenge), and excluding those with galactorrhoea, were recruited for this study. Male factor was excluded by clinical examination and semen study, and PCT was performed as part of monitoring of the induced cycle. A pelvic factor was excluded by clinical examination, and not all women were subjected to HSG or laparoscopy evaluation at the beginning of the study. These tests were considered

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mandatory when repeated attempts at ovulation induction failed to result in conception. Our stand was the same for endocrine evaluation (RIA studies) as well. Unless the patient presented with hypoestrogenism, galactorrhoea or marked hirsutism, or failed to achieve ovulation by repeated attempts at CC induction we do not order for endocrine profile.

Following spontaneous menstruation or induced bleeding (with 75 mg progesterone i.m.) CC was started in a dose of 50 mg daily for 5 days beginning on the 2nd or 3rd cycle day, sometimes 4th or 5th day and never after 5 days. Occasionally a 100 mg dosage has been employed. DEX therapy was randomly combined in the different cycles of the same patient or in all cycles of randomly selected subjects. DEX, in a dose of 0.5 mg/day, was begun early in the cycle along with CC and was administered late in the night. If the subject failed to menstruate after 30 days of therapy the drug was discontinued, otherwise the treatment is continued through the next cycle.

For monitoring the CC induced cycles 3 parameters have been employed: namely, (i) BBT, (ii) cervical mucus study, and (iii) follicular sonography. We feel that all these 3 parameters are complementary in identifying (i) follicular maturation, (ii) ideal time for performing PCT, (iii) the need for estrogen therapy for improving cervical mucus, (iv) optimal day for administration of hCG, (v) occurrence of ovulation, (vi) quality of corpus luteal function, and (vii) early sign of pregnancy. Moreover, sonography aids in identifying multiple follicular maturation and a decision of withhold hCG administration, and monitoring of early pregnancy. Quite often 'ovulation pain' has been identified as a subjective symptom of ovulation.

From the 10th or 11th day of beginning of CC therapy follicular dynamics were watched daily by sonography. Concurrently, nature of cervical os and quality of cervical mucus were evaluated. When cervical mucus was copious *in vivo* sperm penetration was studied. When the dominant follicle reached 18 to 20 mm and if cervical os was open with copious cervical mucus and preferably if BBT evidenced nadir, hCG was administered in a dose of 10,000 i.u. (in some subjects 5000 i.u. was given). In the earlier part of the study a follow-up dose of 1500 i.u. was given on 4th and 7th post-ovulatory days. If more than 2 dominant follicles were located hCG administration was withheld. A poor cervical response even after the follicle had reached 18 mm diameter was considered an indication for estrogen administration, and only after achieving reasonable mucus secretion and a positive PCT decision was made to administer hCG. If all the parameters were not satisfactory or if patient compliance was inadequate hCG was not administered.

Ovulation was evidenced by the replacement of the dominant follicle by a reduced sized crenated body with fill-in echos, or by the disappearance of the follicle. Fluid in cul-de-sac and changed endometrial pattern were other sonographic evidences of ovulation. Concurrently, ovulation pain, altered cervical mucus secretion and BBT rise were looked for to support the diagnosis of ovulation. Ideally, a sharp BBT rise occurred within 48 hours of ovulation and was sustained for a minimum period of 12 to 14 days. Ovulation was evidenced with 24 to 48 hours after the administration of hCG. Sonographic imaging of cumulus and sonolucent halo evidenced imminent ovulation in many subjects.

Following treatment, if the patients fails to menstruate, sonographic diagnosis of pregnancy was reported to between 35th and 38th day of LMP. Sonography was

repeated around 8th week to evidence fetal pole, measure CRL and to identify fetal cardiac activity. If these criteria were met possibility of safe continuation of pregnancy to viability is 92.59% (Rajan and Rajan, 1986).

Results

Beginning from March, 1985 and through January, 1986, over this period of 11 months 38 patients with ovulatory disorders were recruited to be treated employing CC by the modified protocol. Among them 34 subjects could be regularly monitored and treated for atleast 3 cycles, and their included 6 subjects with secondary amenorrhoea, 10 with oligomenorrhoea, and 18 with delayed cycles, and pregnancy was recorded in 5 (83.33%), 2 (20.00%), and 9 (50.00%) subjects respectively (Table I). For the total 34 subjects regularly monitored, 17 achieved a conception, giving a pregnancy rate of 50%, and all these conceptions were achieved within 1 to 4 treatment cycles, with 13 occurring in 1 to 2 treatment cycles (82.25%) (Table II).

Age group of the patients ranged from 21 to 35 years, with majority in the 25 to 30 years bracket. Depending on the adjunctive therapy employed they could be subdivided into 4 groups: (i) CC alone, (ii) CC and hCG, (iii) CC and DEX, (iv) CC, DEX and hCG. The 34 patients had a total of 90 treatment cycles, and the breakdown figures are as follows: (i) CC alone for 30 cycles, CC and hCG for 11 cycles, CC and DEX for 34 cycles, and CC, DEX and hCG for 15 cycles, and the number of pregnancies and the pregnancy rate for treatment cycles were 4 (13.33%) for CC, 4 (36.36%) for CC and hCG, 5 (14.70%) for CC and DEX, and 4 (26.67%) for CC, DEX and hCG (Table III).

While adjunctive DEX therapy has not improved the pregnancy rate, properly timed administration of hCG appears to be certainly beneficial in improving the success

TABLE I
Clomiphene Theray for Ovulatory Disorders
(March, 1985 to January, 1986)

Menstrual disorder	No. recruited	No. followed	No. pregnant	Percentage
Secondary amenorrhoea	6	6	5	83.33
Oligomenorrhoea	12	10	2	20.00
Delayed cycles	20	18	10	55.56
Total	38	34	17	50.00

TABLE II
Pregnancies Occurring in Clomiphene Treated Cycles
(No. = 17)

Treatment cycle	No. pregnant	Percentage	Cumulative pregnancy No.	Cumulative pregnancy rate
1st cycle	8	47.05	8	47.05
2nd cycle	6	35.29	14	82.25
3rd cycle	1	5.88	15	88.24
4th cycle	2	11.76	17	100.00

TABLE III
Different Treatment Schedules and Pregnancy Rate

Treatment schedules	No. of treatment cycles	No. of pregnancies	Percentage
CC and hCG	11	4	36.36
CC, DEX and hCG	15	4	26.67
CC and DEX	34	5	14.70
CC alone	30	4	13.33
hCG as adjunct	26	8	30.77
no hCG	64	9	14.06

rate of CC therapy. Among the 21 subjects not treated with hCG pregnancy occurred in 9 (42.86%), whereas, of the 13 subjects receiving hCG pregnancy occurred in 7 (53.85%).

Among the 90 monitored cycles, where a pregnancy was conceived in 17 patients, early pregnancy monitoring by sonography revealed one pregnancy wastage in the form of blighted ovum (5.88%) and no incidence of multiple pregnancy, tubal gestation or molar pregnancy.

Discussion

Although preovulatory positive estrogen-LH feedback is usually preserved in clomiphene treated patients with anovulation and intact hypothalamus-pituitary axis, many women will manifest a significant rise in estrogen production and adequate follicular growth but fail to ovulate spontaneously (Pepperel, 1983). Inspite of normal threshold levels of estradiol LH surge seldom occurs spontaneously. Increased size of the cohort of follicles recruited and supported in induced cycles produce a supraphysiological level of folliculostatin, and this in turn interferes with the normal positive feedback response of estrogen on LH (Fritz and Speroff, 1983). Since LH surge seldom occurs in induced cycles hCG is usually required to achieve the final stages of maturation and to induce ovulation (Hodgen, 1982; Pepperel, 1983 and Ritchie, 1985).

After inducing follicular growth with clomiphene hCG has to be administered when the follicle has a normal complement of granulosa cells with adequate LH receptors. It has been observed by DeCherney (1982) at follicular sonography, that follicles with a diameter between 18 and 25 mm have a normal complement of granulosa cells. This signifies the importance of ultrasound monitoring of CC induced cycles. After daily sonographic monitoring, hCG is ideally administered when atleast one follicle is grown to 18 to 20 mm in diameter and there is copious cervical mucus secretion. Administering hCG too early may produce follicular atresia, and delaying giving hCG may result in entrapment and postmaturity of oocyte and down regulation of LH receptors (Garcia *et al*, 1983). Hence empirical use of hCG will prove disappointing and timely administration under sonographic guidance will enhance the success rate (Pepperel 1983). The value of sonography in these cycles also seems to be in making decisions to withhold hCG when multiple large follicles are demonstrated (DeCherney) and Laufer, 1984).

Our study reasonably proves the significance and the superiority of ultrasonogra-

phic monitoring of CC induced cycles and timing hCG administration. While the pregnancy rate for 30 treatment cycles employing CC alone was 13.33%, almost a 3 times higher success rate (36.36%) was observed when hCG adjunctive therapy was employed. Moreover, considering all the 90 treatment cycles the pregnancy rate was 30.77% with hCG and 14.06% without hCG. There was an overall increased pregnancy rate of 11% in 13 subjects when hCG was employed as against the 21 subjects in whom hCG was not employed. Thus it is quite convincing that hCG administration under sonographic monitoring of follicular growth enhances the success rate of clomiphene therapy.

Cortiocosteroid therapy employing dexamethasone or prednisolone in combination with CC has been a well documented effective regimen, and is useful in patients known to have an adrenal androgen excess or a mixed adrenal-ovarian androgen excess (Daly *et al* 1984 and Wu 1984). Such subjects are identified by elevated levels of dehydroepiandrosterone sulphate (DHEAS), and in them DEX combined with CC can achieve conception where CC alone fails (Pepperell, 1983). In our study DEX has been administered in the randomly selected cycles and randomly selected subjects. And we observe that the pregnancy rate has not been improved by this adjunctive therapy (14.70%) as against CC therapy (13.33%). Hence we feel DEX adjunctive therapy has no role as a routine schedule for all subjects. It should be reserved for clomiphene failures, preferably after ensuring that DHEAS level is elevated.

We observe in these sonography monitored cycles a very high pregnancy rate of 83.33% for subjects with secondary amenorrhoea, next best results (55.56% for those with delayed cycles and lowest pregnancy rate (20.00%) for subjects with oligomenorrhoea. We also realise that conceptions occur within 1 to 4 treatment cycles with majority (82.25%) in 1 to 2 treatment cycles. Hence there is a right place further evaluation of infertility status of the couple if conception does not occur within 4 ovulatory cycles. The extremely high degree of success rate in amenorrhoeic subjects denote that antifertility effect of clomiphene is a very insignificant cause for failures and other fertility disorders should be identified and corrected.

The reduced incidence of pregnancy wastage (5.88%) and particularly the absence of multiple pregnancies (inspite of early pregnancy scanning) are, perhaps, the benefits of careful sonographic monitoring of the CC induced cycles and precise timing of hCG administration. Extension of scanning facilities in the postconceptional phase offers to identify the healthy pregnancy and prognosticate the pregnancy outcome.

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