ECONOMICAL ASSESSMENT OF RESPONSE TO CLOMIPHENE CITRATE THERAPY

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SUMMARY

Response to clomiphene citrate therapy was assessed on the basis of serial ovarian scans and pregnanediol glucuronide (PdG) estimations in 34 infertile women. The data 21 are sufficient to assess normal or abnormal follicular growth as in 17 cases (74%) rupture of the follicle occurred by day 18 and in 22 cases (96%) by day 21. PdG estimations on day 23 and day 28 could diagnose corpus luteum adequacy or deficiency with an accuracy of 100%.

INTRODUCTION

Clomiphene citrate is offered as ovulation inducing agent to infertile anovulatory women responding to progesterone challenge test as well as to those having corpus luteum inadequacy. Most commonly adopted methods to judge the response to this drug are shift in the basal body temperature (BBT), study of cervical mucus, determination of follicular growth and rupture by ultrasound (US) and of corpus luteum activity by measurement of serum progesterone or pregnanediol glucuronide (PdG), a metabolite of progesterone in urine (Baird, 1983; Chung, 1984; Queenan et al., 1980). In this paper, we analysed our data on serial ultrasonographic ovarian scans and serial urinary PdG estimations to determine the minimum number of visits that an individual has to make to the clinician or laboratory which would be adequate for judging the responses of the drug with 100% accuracy.

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MATERIALS AND METHODS

Thirty-four cycles of women (aged 29-34 years) undergoing clomiphene citrate therapy for induction of ovulation or for correction of corpus luteum function were studied comprehensively by clinical, hormonal and biophysical parameters. The drug was administered in the dose of 50 mg or 100 mg per day from 5th day of induced or spontaneous period. Transabdominal US was performed on full bladder using real time scanner with 3.5 MHz transducer. The follicles were observed from day 12 of the cycle till the day of ovulation or till a definite cyst was observed.

Daily morning urine samples were collected during luteal phase of the cycle. PdG was esti-

mated in these samples by ELISA and corpus luteal function was assessed as described earlier (Khatkhatay et al., 1987). Cycle was considered to be corpus luteum deficient if PdG concentration in most of the mid-luteal phase (MLP) samples were below the 20th centile (< 4.6 ug/mgC) of the reference group.

RESULTS

The data on 34 cycles of ovulation induction therapy was analysed. The cycle length in these women ranged from 26 to 36 days (mean cycle length 30.4 ± 2.5) and the days covering the MLP ranged from 18th to 33rd day, MLP being 4 to 9 days before ensuing menstrual period.

Out of the 34 cycles, 23 cycles were ovulatory, 2 anovulatory, in one case follicle luteinized without rupture and in 8 cystic follicles were observed. Table I shows the results of the follicular growth and rupture as visualised by US from day 15 to day 22. It can be seen that an US scan on day 18 showed rupture follicles in 17 subjects (74% of ovulatory cycles) and another examination on day 21 showed follicle rupture in 5 more cases [22/23 (96%)]. Ultrasonographic scans on day 18 and day 21 will help in identifying either a luteinized unruptured follicles (LUF) or a cyst depending upon decrease or increase (above 25 mm) in follicular size. The first scan can be carried out on day 18 as the rupture of the follicles occurred in 74% of the cycles. It is also possible to visualise a three day old ruptured follicle on US by this day. In this study we could identify cysts in 8 cases as in all these cases the follicles grew above 25 mm in size by 21st day. In one case follicle size regressed from 25 mm on day 18 to 22 mm on day 21 with ring signs and was later identified as LUF. Hence we suggest that day 18 and 21 are the most ideal days for US scans in women on clomiphene citrate therapy.

PdG levels of < 4.6 ug/mgC (20th centile of the mid-luteal phase values of reference group) in most of the MLP samples indicate deficiency in excretion of PdG by corpus luteum. Aim of the study was also to reduce number of estimations of PdG to one or two. We selected estimation of

Table - I

Ultrasonic findings of cases between days 15 and 22 on clomiphene citrate therapy

Observation	No. of cases showing corresponding observation on cycle day							
	15	16	17	18	19	20	21	22
Ruptured follicles	2	4 (6)	9 (15)	2 (17)	3 (20)	1 (21)	1 (22)	1 (23)
Multiple small or no follicles	2	2	2	2	2	2	2	2
Follicles in various stages of growth including cystic/ LUF	29	19	13	12	10	10	10 *	
Not scanned	1	7	4	3	2	1	—	

* Include 8 cystic follicles, 1 luteinized unruptured follicle and one preovulatory follicle rupturing next day.

Figure in parenthesis indicate cumulative sum of ruptured follicles.

Table - II

PdG / ug / mg C in EMU from day 20 to 30 in Clomiphene Citrate induced ovulatory cycles

Case No.	Days of Cycle											Length of cycle
	20	21	22	23	24	25	26	27	28	29	30	
1.	8.5	8.5	(12	26	24	12	23	6.4)	7	5	3.7	31
2.	5.2	9.0	9.6	11.5	11.7	(12.5	14.1	10.3	12.7	7.8	7.2)	33
3.	5.7	6.2	8.0	(5.5	5.0	4.8	5.7	4.7	3.2)	2.1	1.9	31
4.	0.3	0.6	0.9	1.5	2.9	5.2	6.8	7.0	(8.4	5.4	13.4)	36
5.	4.7	5.0	(4.7	3.5	4.8	4.7	4.8	7.5)	9.6	9.5	5.5	31
6.	4.2	8.4	(7.4	6.6	8.9	12	7.6	6.8)	5.6	3.2	2.1	30
7.	(17	20	21	18	20	16)	7	4.0	1.1	-	-	28
8.	(5.9	6.2	5.5	4.7	5	5)	5	4	2.8	-	-	28
9.	(7.1	5.6	6.1	4.9	6.4	6.3)	3.8	2.7	3.4	-	-	28
10.	4.9	(5.1	4.9	5.7	10.2	10	6)	1.4	1.7	1.8	-	29
11.	5.0	5.5	(10	8.3	5	4.8	4.8	3.8)	2.6	1.7	1.2	30
12.	2.3	2.5	4.3	4.1	7	7.5	6.6	(7.9	5.0	4.8	4.7	35
13.	2.0	2.4	2.1	2.7	5.9	(4.8	6.4	5.3	11	19	20)	33
14.	7.9	8.9	(11.3	4.9	19.0	20.0	11.0	5.6)	4.9	2.1	-	30
15.	(5.9	6.1	7.3	6.2	6.2	6.8)	3.6	3.2	2.7	-	-	28
16.	15.8	7.3	(8.4	8.2	7.9	6.3	4.6	4.9)	4.9	3.6	2.8	30
17.	15	(15	12	11	8	6	5.7)	5.2	4.9	3.8	-	29
18.	4.0	4.7	(5.1	6.2	7.8	8.0	6.4	6.3)	5.1	4.1	2.8	30
19.	3.3	1.9	1.7	2.8	(2.8	2.1	2.2	2.0	3.5	3.0)	2.1	32*
20.	2.7	3.7	(2.9	3.0	2.5	2.6	2.3	1.8)	3.2	2.4	2.2	30*
21.	2.8	3.00	3.9	(3.5	3.8	4.0	3.8	3.8	3.9)	3.3	2.4	31%
22.	-	-	-	-	-	1.8	2.4	(3.0	3.2	4.2	4.1	35*
23.	(4.2	4.3	3.9	4.1	3.3	2.8)	2.6	2.0	1.7	-	-	29*

* Denotes CLD cases

Parenthesis indicate Mid - luteal phase.

PdG in urine samples collected on days 23 and 28 as one of these days will fall in MLP for the cycles with lengths varying from 26-36 days.

Table - II gives PdG levels from day 20 to day 30 in all the ovulatory cycles. Out of 18 cases with corpus luteum adequacy (CLA) in 7 cases (Case Nos. 1, 2, 6, 14, 16, 17, 18) levels of PdG > 4.6 ug/mgC were seen on days 23 and 28 as both these days fell in the MLP of the cycles. In 4 cases (Case Nos. 4, 5, 12, 13) levels were inadequate (< 4.6 ug/mgC) on day 23 but became inadequate subsequently on day 28 as the cycle length in these cases were more than 32 days and day 23rd did not fall in MLP. In the remaining 7 cases (Case No. 3, 7, 8, 9, 10, 11 and 15) levels were high on day 23 and became low on day 29 as cycle length in these cases were more than 32 days and day 23rd did not fall in MLP. In the remaining 7 cases (Case Nos. 3, 7, 8, 9, 10, 11 and 15) levels were high on day 23rd and became low on day 28 as cycle lengths of these cases ranged between 29-30 days and day 28 did not fall in the MLP. In 5 corpus luteum deficient (CLD) (Case No. 19, 20, 21, 22, 23) on both days PdG levels were inadequate. The accuracy of diagnosis of CLA/CLD with this method was thus 100% when PdG levels on both the days were taken into consideration.

DISCUSSION

Though several parameters were used to assess the response of clomiphene citrate, ovarian ultrasonography in conjunction with progesterone assays gives accurate assessment of follicular growth and corpus luteum function. However, US monitoring has to be done serially, which is expensive and requires frequent visits with an optimum full bladder to visualise the follicles which is inconvenient to many a patients. Assessment of corpus luteal function by serum progesterone or its metabolites PdG involves serial blood or urine sampling or atleast 3 samples collected during the defined phase of the cycle (Kistner, 1965; Queenan, et al, 1980).

The aim of the study was to curtail the number of visits and laboratory analysis which would be essential for finding the response to therapy by US and urinary PdG estimations and also to suggest ideal days for such visits and sample collection. Based on our data for combined monitoring with US and PdG, we recommend day 18 for the first US scan since the ovulation was observed to have occurred in many of the cycles (74%) by that time and day 21 for observation of late ovulation and abnormal behaviour of follicles, if any. For estimation of urinary PdG, collection of samples on day 23 and day 29 will be appropriate as out of these two days atleast one sample will lie in the MLP and will be sufficient to assess the corpus luteal function. However, we are aware that it may not be of practical value when timing intercourse or postcoital test to maximise the chances of conception and programming artificial insemination by husband or by donor where the precise day of follicular rupture is needed.

In this study, we have found that CLA or CLD could be diagnosed with an accuracy of 100% when PdG levels of both the days (23 and 28) are taken into consideration. Therefore, the study suggests a novel approach for economical assessment of response to clomiphene citrate with a good accuracy.

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