

Relationship of clomiphene dose and patient weight to successful treatment

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Our objective was to examine the relationship between patient weight and the dose of clomiphene required for pregnancy so as to assess the validity of recommendations that the dose of clomiphene be limited to 100 mg. We retrospectively analysed the weight–dose relationship in 1681 clomiphene pregnancies and the relationship between dose and pregnancy, births, multiple births, number of pre-ovulatory follicles and endometrial thickness in 2841 cycles of clomiphene treatment, 25–250 mg, for 5 days before intrauterine insemination (IUI). Doses of clomiphene >100 mg/day were used before pregnancies in 27.4% of patients who weighed >90 kg and in 14.7% of all pregnancies. In IUI cycles, pregnancies and births, but not multiple births or abortions, were related to dose. An increase in dose from 25 to 100 mg resulted in higher pregnancy and birth rates, and in an increase in the average number of pre-ovulatory follicles ≥ 12 mm in diameter, from 2.0 to 2.8, with no additional increase at higher doses. Endometrial thickness and cycle day of insemination were not related to dose. We conclude that doses of clomiphene may safely be increased beyond 100 mg, and that doses ≥ 100 mg are required in significant numbers of patients.

Key words: clomiphene citrate/endometrial thickness/multiple pregnancy/pre-ovulatory follicles/weight

Introduction

Since 1967, the maximum dose of clomiphene citrate approved for use by the United States Food and Drug Administration (FDA) has been limited to 100 mg/day for 5 days. Many patients require higher doses to achieve ovulation and pregnancy (Rust *et al.*, 1974; Gorfitsky *et al.*, 1978; Gysler *et al.*, 1982; Lobo *et al.*, 1982). Shepard *et al.* (1979) and Lobo *et al.* (1982) have related the need for higher doses to body weight. However, the largest of these studies comprised <200 pregnancies.

Reasons given for limiting the dose of clomiphene citrate are concerns about hyperstimulation, ovarian cysts and multiple pregnancy. The possibility of an increased incidence of abortion

at higher doses, because of chromosomal damage (Boue and Boue, 1973; Laufer *et al.*, 1982) or an anti-oestrogen effect on the endometrium (Dickey *et al.*, 1993a), has also been suggested.

Studies of the relationship between clomiphene citrate dose and the number of pre-ovulatory follicles are limited to two (Quigley *et al.*, 1984; Shalev *et al.*, 1989). Information about the relationship between clomiphene dose and multiple births is limited to four studies (Corson *et al.*, 1983; Hammond and Talbert, 1983; Groll, 1984; Dickey *et al.*, 1992). Recently, we reported an inverse relationship between clomiphene citrate dose and preclinical abortion, with no relationship between clomiphene dose and clinical abortion or multiple pregnancy, in a retrospective analysis of 1738 clomiphene citrate-induced pregnancies (Dickey *et al.*, 1996).

The objective of this study was to investigate the need for clomiphene citrate doses >100 mg/day by analysing the relationship between maternal weight at conception and clomiphene citrate dose, and that between clomiphene dose and the number of pre-ovulatory follicles, endometrial thickness, pregnancy, births and multiple births in cycles of intrauterine insemination (IUI).

Materials and methods

Patients

All pregnancies resulting from clomiphene citrate treatment from 1976 to 1995, in which maternal body weight at conception was recorded, were included in analyses. In addition, all cycles of ovulation induction with clomiphene citrate in which IUI was performed because of sperm or cervical mucus insufficiency from 1983 to 1995 were reviewed. Cycles of IUI were included for analysis if the sperm specimen in the cycle of insemination prior to preparation met criteria previously established as necessary for a $\geq 8\%$ chance per cycle of pregnancy (total count $\geq 40 \times 10^6$ spermatozoa, progressive motility $\geq 35\%$ or total number of motile spermatozoa $\geq 20 \times 10^6$, and $\geq 50\%$ normal forms; Dickey and Olar, 1993; Dickey and Holtkamp, 1996). Cycles were included for the analysis of pre-ovulatory follicle number and endometrial thickness if an ultrasound was performed on the day of the luteinizing hormone (LH) surge or on the day of human chorionic gonadotrophin (HCG) administration for IUI timing.

Ovulation induction protocol

Clomiphene citrate was administered for 5 days, at an initial dose of 25 mg/day for patients who weighed <45 kg, 50 mg/day for those who weighed 45–68 kg and 100 mg/day for those who weighed >68 kg. The dose of clomiphene citrate was increased by 25–50 mg in each subsequent cycle until a satisfactory ovarian response was evident by both biphasic basal body temperature chart and a mid-luteal phase serum progesterone concentration ≥ 2000 ng/dl. The dose

of clomiphene was decreased if symptoms of hot flushes or scintillating scotoma occurred.

Insemination

Ovulation was timed by the urine LH surge using OvuStick (Quidel Inc., San Diego, CA, USA) or Q Test (Becton-Dickenson, Sparks, MD, USA), beginning on cycle day 10. When HCG (10 000 IU) was used to facilitate IUI timing, it was given when one or more follicles was ≥ 18 mm in diameter. A single IUI was performed 34–36 h after HCG administration or between 18 and 24 h after the detection of an LH surge. A urine pregnancy test was performed 14 days after insemination. Information about semen quality, ovulation induction medication, diagnosis, age and previous pregnancy outcome were entered into a computer database at the time of insemination.

Ultrasound

Follicular development was assessed by a transvaginal ultrasound performed 5 days after the last dose of clomiphene citrate using an ATL Ultramark 4 DP ultrasound (Advanced Technology Laboratories Inc., Bothell, WA, USA) and a 5.0 MHz transducer. If no follicles were found to be ≥ 18 mm in diameter, but some were ≥ 13 mm in diameter, patients were instructed to administer HCG 1 or 2 days later if a spontaneous urine LH surge did not occur first. If follicles were < 13 mm in diameter, patients were instructed to return in 3 days for a repeat ultrasound. Wall to wall endometrial thickness was measured at the time of ultrasound for follicular size from 1991 onwards, as described previously (Dickey *et al.*, 1993b).

Pregnancy test and follow-up

All pregnancies from IUI or other treatments, including pregnancies without ovulation induction, were confirmed by serum quantitative β -HCG measurements. Pregnancies were entered into a pregnancy computer database at the time the pregnancy was confirmed, in addition to information about patient weight, age, previous pregnancy, diagnoses and treatment. All newly pregnant patients were routinely scanned by ultrasound at between 4.5 and 5.5 weeks of gestation to confirm the presence of an intrauterine gestation and to determine the number of gestational sacs. An ultrasound was repeated 14 days later to confirm fetal viability. Pregnancies were followed until 12–16 weeks of gestation, before referral for the continuation of prenatal care and delivery. Vital statistics of the birth were either self-reported by the patient or obtained from her delivery physician.

Analysis

The relationship of clomiphene citrate dose to maternal weight at conception is reported in kilograms (kg) and pounds (lb), and as the Ponderal obesity index (height in inches, divided by the cube root of weight in pounds). Results of IUI are reported as pregnancy, including preclinical abortions, clinical abortions and ectopic pregnancies, and birth rates per cycle. Statistical analyses were performed using Fisher's exact test and Pearson's correlation coefficient. Results were considered to be significant at $P < 0.05$.

Results

Relationship between clomiphene dose used at conception and patient weight

The weight and height of each patient were recorded at conception in 6117 pregnancies, including 1681 of the 1738 clomiphene citrate-induced pregnancies. The clomiphene dose taken during the cycle of conception was significantly correlated with patient weight ($r = 0.22$; $P < 0.001$) and obesity

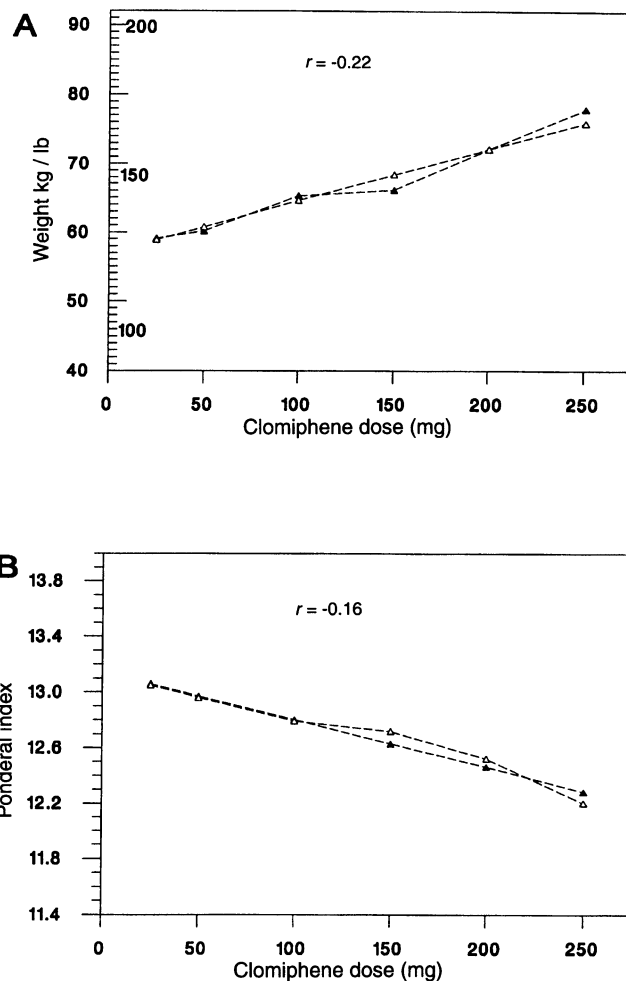


Figure 1. Relationship between clomiphene dose and: (A) mean maternal weight at the time of conception and (B) Ponderal index (height in inches/cube root of weight in pounds); (Δ) measured; (\blacktriangle) calculated ($n = 1681$). Pearson's correlation coefficient: weight $r = 0.22$, $P < 0.001$; Ponderal index $r = 0.16$, $P < 0.001$.

(Ponderal index $r = -0.16$; $P < 0.001$). The correlation between dose and obesity was not stronger than the correlation with weight alone (Figure 1). Doses of clomiphene citrate > 100 mg/day were used by 14.7% of all pregnant patients and by 27.4% of patients who weighed > 90 kg (Table I). There was considerable overlap. Doses > 100 mg/day were used by 6.8% of patients who weighed < 45 kg, while 24.5% of patients who weighed ≥ 90 kg became pregnant with doses of 50 mg/day. Clomiphene citrate (25 mg) was used by 9.1% of patients who weighed < 45 kg and by 3.3% of all patients, but by none who weighed > 74 kg.

Relationship between clomiphene dose and pregnancy, birth and multiple birth in IUI cycles

Clomiphene doses from 25 to 250 mg were used in 2841 cycles of IUI in which spermatozoa met the minimal standards needed for pregnancy. The dose of clomiphene citrate was correlated with pregnancy ($r = 0.05$; $P = 0.004$) and birth ($r = 0.04$; $P = 0.011$) rates, but not with multiple birth rates (Table II). Pregnancy and birth rates averaged 8.7 and 5.8% respectively for clomiphene citrate doses of 25–50 mg, com-

Table I. Relationship between clomiphene dose and patient weight at conception in 1681 patients who became pregnant

Clomiphene dose (mg)	No. of patients	Percentage of patients	Patient weight									
			<45 kg <100 lb		45–59 kg 100–131 lb		60–74 kg 132–164 lb		75–89 kg 165–197 lb		≥90 kg ≥198 lb	
			<i>n</i>	% ^a	<i>n</i>	% ^a	<i>n</i>	% ^a	<i>n</i>	% ^a	<i>n</i>	% ^a
25	55	3.3	4	9.1	27	3.4	23	3.9	0	0.0	0	0.0
50	782	46.5	25	56.8	430	54.4	248	42.6	56	36.3	25	24.5
100	597	35.5	12	27.3	245	31.0	220	37.2	70	45.4	49	48.0
>100	247	14.7	3	6.8	88	11.1	100	16.9	28	18.2	28	27.4
150	197	11.7	3	6.8	73	9.2	83	14.0	21	13.6	17	16.7
200	44	2.7	0	0.0	14	1.8	17	2.9	5	3.2	8	7.3
≥250	6	0.4	0	0.0	1	0.1	0	0.0	2	1.3	3	2.9
Total	1681		44		790		591		154		102	

^aPercentage of patients at this weight who became pregnant on this dose.

Table II. Relationship between clomiphene dose and pregnancy and birth rates per cycle, as well as multiple births

Clomiphene dose (mg)	Cycle (<i>n</i>)	Pregnancies		Abortions		Ectopic pregnancies % ^a	Births		Multiple births			
		<i>n</i>	%	Preclinical % ^a	Clinical % ^a		<i>n</i>	% ^b	Twins		Triplets	
									<i>n</i>	% ^c	<i>n</i>	% ^c
25	145	10	6.9	0.0 ^a	20.0 ^a	10.0 ^a	7	4.8	0	0.0	0	0.0
50	1202	107	8.9	4.7	14.0	6.5	71	5.9	6	8.4	2	2.8
75	203	33	16.2	3.0	9.1	3.0	19	9.4	2	10.5	0	0.0
100	902	96	10.6	7.3	19.8	4.2	67	7.4	6	9.0	0	0.0
150	335	44	13.1	6.8	15.9	0.0	25	7.5	2	8.0	0	0.0
200	48	7	14.6	0.0	28.6	0.0	5	10.4	0	0.0	0	0.0
250	6	0	0.0	0.0	0.0	0.0	0	0.0	0	0.0	0	0.0
Total	2841	297	10.4	5.7	16.2	4.3	193	6.8	16	8.3	2	1.0

Correlation: clomiphene dose with: (i) pregnancies: $r = 0.05$, $P = 0.004$; (ii) births: $r = 0.04$, $P = 0.011$; and (iii) multiple births: $r = 0.02$, non-significant.

^aPercentage of pregnancies.

^bPercentage of cycles.

^cPercentage of births.

pared with 11.7 and 7.8% for doses of 75–200 mg; these rates were significantly different between doses ($P = 0.002$ and $P < 0.022$ respectively).

Relationship between clomiphene dose, the number of pre-ovulatory follicles and endometrial thickness

The number of pre-ovulatory follicles and endometrial thickness were determined in 1487 cycles in which ultrasound was performed on the day of the LH surge or HCG administration. Increases in clomiphene dose, from 25 to 100 mg, were related to small but significant increases in the number of pre-ovulatory follicles (Table III and Figure 2). Doses of clomiphene citrate >100 mg/day did not result in any further increase in the numbers of follicles.

Endometrial thickness was measured on the day of the LH surge or HCG administration in 577 cycles. Endometrial thickness, determined on the day of HCG administration, was not related to clomiphene citrate dose (Table IV).

The clomiphene dose was minimally related to the day of IUI in 3127 cycles, which included cycles without ultrasound measurements and with poor semen quality. The day of IUI advanced from 12.8 days for a dose of 25 mg to 13.3 days for a dose ≥150 mg (Table IV).

Discussion

The findings of our study confirm and extend those of others who found a linear relationship between maternal weight and the clomiphene citrate dose needed for pregnancy. The large number of clomiphene citrate-induced pregnancies in our study (1681), compared with the 47 pregnancies and 117 patients treated by Shepard *et al.* (1979) and the 158 patients treated by Lobo *et al.* (1982), allow us to define more precisely the relationship between patient weight and the need for higher clomiphene citrate doses than was possible with smaller numbers of patients. Most importantly, we found that doses >100 mg/day were employed in the cycle of pregnancy by 27.4% of patients who weighed ≥90 kg and by 14.7% of patients overall. We found considerable overlap, as did previous authors. A dose of 50 mg/day was sufficient for 24.5% of patients who weighed ≥90 kg. On the other end of the weight scale, 3.3% of patients overall and 9.1% of patients who weighed <45 kg became pregnant on a dose of 25 mg/day.

Our findings are intermediate between those of Gorlitsky *et al.* (1978), who noted that 5.6% of their total pregnancies occurred at doses >100 mg/day, and Rust *et al.* (1974), who reported that 22.5% of their total pregnancies occurred at doses of 150–250 mg daily, or Gysler *et al.* (1982), who found

Table III. Relationship between clomiphene dose and the number of pre-ovulatory follicles

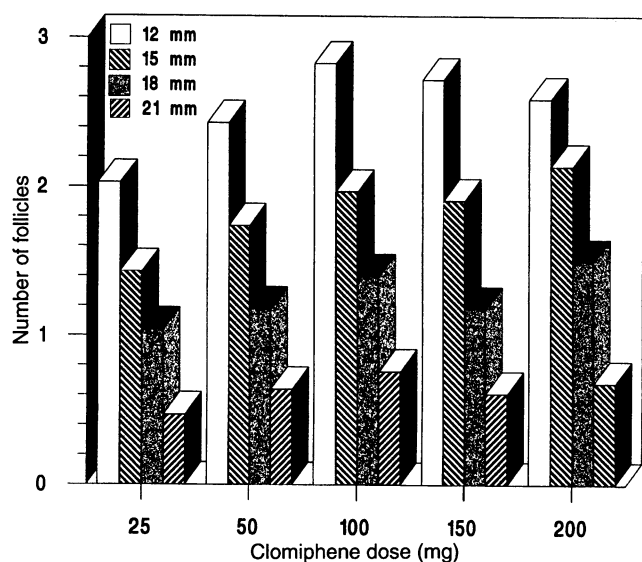
Clomiphene dose (mg)	No. of cycles	Mean (SD) no. of follicles greater than size shown			
		>12 mm Mean (SD)	>15 mm Mean (SD)	>18 mm Mean (SD)	>21 mm Mean (SD)
25	72	2.0 (1.2)	1.4 (0.8)	1.0 (0.8)	0.5 (0.6)
50	609	2.4 (1.3)	1.7 (1.0)	1.2 (1.0)	0.6 (0.8)
75	96	2.6 (1.3)	1.9 (1.0)	1.3 (0.9)	0.7 (0.8)
100	501	2.8 (1.7)	2.0 (1.2)	1.4 (1.1)	0.8 (0.9)
150	183	2.7 (1.6)	1.9 (1.2)	1.2 (1.0)	0.6 (0.8)
200	22	2.6 (1.0)	2.1 (1.1)	1.5 (0.9)	0.7 (0.8)
250	4	3.0 (1.2)	1.8 (1.0)	0.8 (1.0)	0.8 (1.0)
Total	1487				

Correlation: clomiphene dose with number of follicles: ≥ 12 mm $r = 0.13$, $P < 0.001$; ≥ 15 mm $r = 0.10$, $P < 0.001$; ≥ 18 mm $r = 0.05$, $P < 0.03$; ≥ 21 mm $r = 0.03$, P non-significant.

Table IV. Relationship between clomiphene dose, and endometrial thickness on the day of human chorionic gonadotrophin administration or cycle day of insemination

Clomiphene dose (mg)	Endometrial thickness (mm)		Cycle day of intrauterine insemination	
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)
25	24	7.5 (1.7)	212	12.8 (0.8)
50	239	8.0 (2.6)	1539	13.0 (0.4)
100	238	8.0 (2.2)	982	13.1 (1.1)
150	65	8.1 (2.4)	340	13.3 (1.2)
200	11	8.6 (1.4)	47	13.2 (1.2)
250	0	0.0 (0.0)	7	13.0 (0.5)
≥ 150	76	8.2 (2.2)	394	13.2 (1.1)
Total	577	8.0 (2.3)	3127	13.0 (1.0)

Correlation: clomiphene dose with: thickness, $r = 0.04$, not significant; cycle day of insemination, $r = 0.09$, $P < 0.001$.

**Figure 2.** Mean number of follicles ≥ 12 , ≥ 15 , ≥ 18 and ≥ 21 mm on the day of human chorionic gonadotrophin administration for a range of clomiphene doses given per day for 5 days.

that 26.7% of pregnancies occurred at clomiphene citrate doses ≥ 150 mg/day, and Shepard *et al.* (1979), who found that 28.0% of pregnancies occurred at doses ≥ 150 mg/day.

Of those who investigated the relationship between clomiphene citrate dose and pregnancy, only Shepard *et al.* (1979) compared the relationship between dose and patient weight.

These authors reported a linear correlation ($r = 0.46$) between dose and maternal weight in 56 patients who ovulated, and speculated that a closer relationship might have been obtained if dose was compared with an obesity index. They also found that oestrone concentrations were higher in obese women, and suggested that, because of this, higher doses of clomiphene citrate were required to compete with endogenous oestrogen for hypothalamic receptor sites. Lobo *et al.* (1982) confirmed a correlation between dose and maternal weight ($r = 0.93$), and also a correlation between dose and the ponderal obesity index ($r = 0.93$), in 51 patients who ovulated. In addition, they attempted to define the relationship between endogenous hormones and clomiphene citrate response. They found that serum LH, total testosterone and dehydroepiandrosterone sulphate concentrations were higher, but that serum-unbound oestradiol concentrations were no different in women who ovulated compared with those who failed to ovulate. Crosignani *et al.* (1994) found that women in the upper tertiles of body weight measured as the ponderal index who received 225 IU/day human menopausal gonadotrophin had fewer follicles and fewer oocytes retrieved than women who weighed less. In our study, the correlation between dose and maternal weight ($r = 0.22$) and between dose and the ponderal index ($r = -0.16$) during the cycle of conception was not as strong as the relationship reported by the previous authors.

The finding that doses of ≥ 100 mg/day are associated with higher per cycle pregnancy and birth rates than doses of 25–50 mg/day, with no increase in the number of abortions or

multiple pregnancies, is important, because many programmes routinely start most patients on 50 mg/day clomiphene citrate. It also suggests that patients who tolerate lower doses should be moved up to doses of 100 mg/day as rapidly as possible, and further that patients who weigh >74 kg might shorten the number of treatment cycles required for pregnancy by starting at a dose of 100 mg/day.

The failure to find a higher multiple birth rate as the dose of clomiphene citrate was increased, and any further increase in pregnancy rate when the dose of clomiphene was increased above 100 mg/day, can be explained by the relatively small additional number of pre-ovulatory follicles that occurred at higher clomiphene citrate doses. We measured follicles as small as 12 mm in diameter because we demonstrated previously that the number of follicles ≥ 12 mm in diameter was more closely related to multiple implantation than follicles ≥ 15 or ≥ 18 mm in diameter (Dickey *et al.*, 1992). In the present study, the number of pre-ovulatory follicles ≥ 12 and ≥ 15 mm in diameter increased by an average of less than one follicle per cycle as the dose of clomiphene increased from 25 to 100 mg/day, and numbers did not increase further when doses ≥ 150 mg/day were used. Quigley *et al.* (1984) found no difference between 50 and 150 mg/day clomiphene citrate in the recruitment of follicles >15 mm in diameter, even though the higher dose resulted in larger FSH and LH concentrations earlier and higher pre-ovulatory oestradiol concentrations. However, Shalev *et al.* (1989) reported an increase in the average number of follicles >15 mm in diameter from 1.0 to 2.4 in patients with regular cycles when the dose of clomiphene citrate was increased from 50 to 200 mg, and a corresponding increase in the number of follicles 8–15 mm in diameter from 0.4 to 2.1 when the dose of clomiphene citrate was increased from 50 to 150 mg, with no further increase for a clomiphene dose of 200 mg/day.

Other possible reasons for higher pregnancy rates with ≥ 100 mg/day doses of clomiphene citrate, compared with 25 and 50 mg/day, are increased FSH and pre-ovulatory oestradiol concentrations, as noted by Quigley *et al.* (1984), and increased mid-luteal oestradiol and progesterone concentrations (Dickey and Hower, 1995). However, Hammond and Talbert (1982) found that while clomiphene citrate increased progesterone concentrations in patients with luteal insufficiency, the progesterone concentrations attained were not dose related.

The evidence in our study, that doses of clomiphene citrate >100 mg/day increase per cycle birth rates and do not cause a significant increase in the number of pre-ovulatory follicles, multiple births or abortions, strongly supports the use of clomiphene citrate doses higher than the 100 mg/day limit presently imposed by the United States FDA, especially for women with excessive weight. There remain many reasons why pregnancies may fail to occur in ovulation induction cycles; having an insufficiently high dose of clomiphene citrate should not be one of them.

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