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Development, pharmacology and clinical experience with clomiphene citrate

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This review describes the development and pharmacology of clomiphene and those specific characteristics of both drug and patients which determine its clinical efficacy. The studies reviewed describe clinical observation of patient characteristics (age, additional infertility diagnosis, semen quality), vaginal ultrasound observations of ovaries (number and size of pre-ovulatory follicles) and endometrial lining (thickness, pattern) in 2841 clomiphene cycles in patients who required intrauterine insemination (IUI) because of poor sperm quality or an unsatisfactory postcoital test. They show that (i) conception in clomiphene cycles is related to the number and size of pre-ovulatory follicles, endometrial thickness, patient age, pelvic adhesions, type of anovulatory disorder and semen quality; (ii) pregnancy rates per clomiphene–IUI cycle are constant through at least six cycles; (iii) multiple births cannot be prevented by withholding human chorionic gonadotrophin or advising against coitus when multiple pre-ovulation follicles are present unless all follicles down to 10–12 mm diameter are counted. We also reviewed pregnancy outcome (number of gestational sacs, babies, preclinical and clinical abortion, ectopic pregnancy and birth sex) in 1744 clomiphene pregnancies from our clinic. We found that (i) preclinical and clinical abortions are increased only slightly by clomiphene use, compared to spontaneous pregnancy; (ii) clinical abortions are decreased in patients with polycystic ovaries and luteal insufficiency who use clomiphene; (iii) conception and preclinical abortions are related to endometrial thickness prior to ovulation; (iv) ectopic pregnancies are not increased by clomiphene and (v) the ratio of male births is not altered by clomiphene, except possibly in timed insemination cycles. These studies repudiate many misconceptions regarding clomiphene. They also show that clinical outcome may be improved by pre-ovulation ultrasound monitoring of ovarian and endometrial response.

Key words: clomiphene/ectopic pregnancy/follicles/multiple pregnancy/preclinical abortion

Introduction

The introduction of clomiphene citrate into clinical medicine in 1967 revolutionized the treatment of infertility in general and of polycystic ovarian syndrome (PCOS) in particular. The initial indication for use of clomiphene was treatment of PCOS and other anovulatory conditions in which ovarian activity could be demonstrated by withdrawal bleeding from progesterone (Macgregor *et al.*, 1968). Now, clomiphene alone and in combination with human menopausal gonadotrophin (HMG) and follicle stimulating hormone (FSH) is used as often to increase the number of pre-ovulatory follicles in patients with unexplained infertility and patients requiring husband or donor artificial insemination (AI) (Shalev *et al.*, 1989; Dickey *et al.*, 1992a) and to increase progesterone concentrations in patients with luteal insufficiency (Hammond and Taubert, 1982; Fukuma *et al.*, 1983; Dickey, 1984).

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Twenty-five years after its introduction into clinical medicine, less is known about the effects of clomiphene on follicular development and steroid and gonadotrophin concentrations than is known about HMG and FSH, because ultrasound and modern hormone assays were not available during the early years of clomiphene development. Likewise, much is still unknown about the effectiveness of clomiphene because of the limited number of studies that report per-cycle pregnancy rates, rather than cumulative rates.

This review examines the development and pharmacology of clomiphene from the perspective of one of its developers (D.E.H.) and of a clinician (R.P.D.) who has been involved in clinical studies of clomiphene since 1962, most recently with the aid of vaginal ultrasound. Ultrasound findings in 2841 cycles of treatment with clomiphene and intrauterine insemination (IUI) and abortion and ectopic rates in 1774 clomiphene pregnancies and 3883 pregnancies resulting from other infertility treatment at a single infertility clinic are presented. It was not our intention to present an exhaustive review of the clomiphene literature. Indeed, this would scarcely be possible. As of March 1996, there had been more than 5400 publications citing clomiphene. Rather, our objective was to present, in a single paper, a large number of studies from one pharmaceutical research laboratory and one clinical institution, performed over a number of years, in the hope that this information would contribute to the better understanding and clinical utilization of clomiphene.

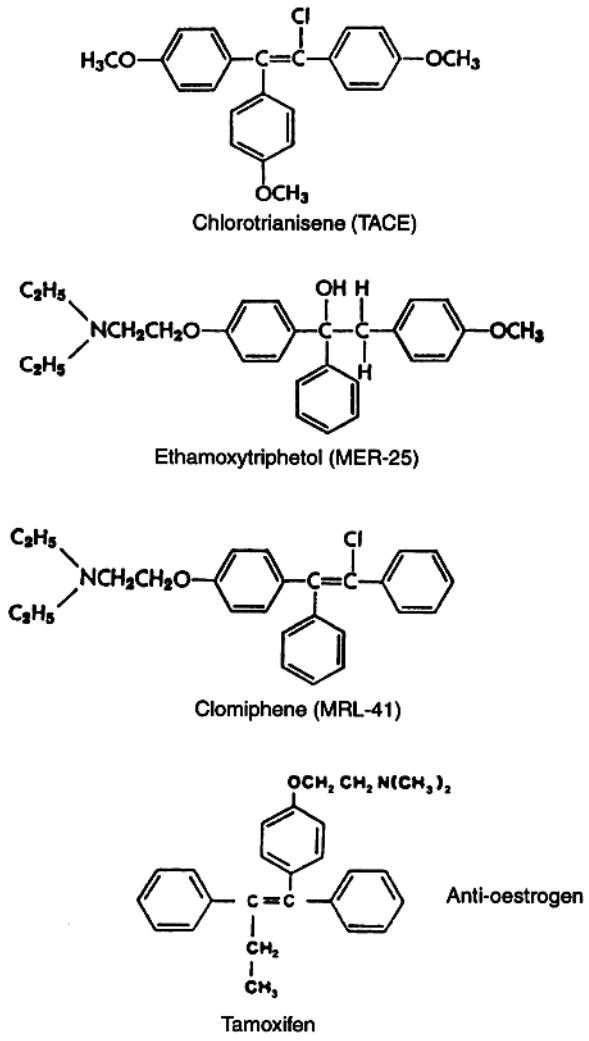

Figure 1. Chemical structures of anti-oestrogens of the triphenylethylene type.

Development of clomiphene citrate

Clomiphene citrate is an example of a pharmaceutical product of which the current use is the result of the combined and successive research efforts of industry, government, academia and private practice physicians. It is now 40 years since its original chemical synthesis and 36 years since the first clinical trials took place.

Clomiphene citrate is by chemical structure a chloroethylene. This non-steroidal structure is now well known. The first chloroethylene to be clinically important was chlorotrianisene (TACE), synthesized in 1940 in the laboratories of the then Wm. S. Merrell Company (Figure 1). It was sent to the endocrinology department of the company for biological testing in December of 1940, where it was found to have oestrogenic activity. A patent application for this substance, along with others, was made in March 1941 and the patent was issued in 1947. In 1952, Greenblatt and Brown published an article on TACE in the *American Journal of Obstetrics and Gynecology.* This paper reported the storage of oestrogenicity in human fat and provided an answer for the long-acting oestrogenic effect of TACE in the human. Overall, there have been more than 440 publications on TACE. It continues to be available and has been available by prescription since 1952.

From before 1940 and during the succeeding two decades, many hundreds of compounds with a two-carbon nucleus were synthesized and biologically tested at Merrell. One of the substances of this group of compounds came to be known as MER-25, and later as ethamoxytriphetol (Figure 1). Leonard Lerner, then of Merrell, published the first paper on this substance (Lerner *et al.*, 1958). It was never a commercially available pharmaceutical product, but underwent clinical investigation in humans as an oestrogen antagonist for two separate periods of time during the late 1950s and early 1960s. MER-25 was found to be a unique oestrogen antagonist and it is cited in over 300 publications.

Table I. Relationship of clomiphene dose to weight at conception[a]

Clomiphene dose (mg)	Total no. (%) patients	No. (%) of patients in each weight group at conception				
		<45 kg/ <100 lb	45–59 kg/ 100–131 lb	60–74 kg/ 132–164 lb	75–89 165–197 lb	90 kg/ 198 lb
25	54 (3.2)	4 (9.1)	27 (3.4)	23 (3.9)	0 (0.0)	0 (0.0)
50	784 (46.6)	25 (56.8)	430 (54.4)	248 (42.6)	56 (36.3)	25 (24.5)
100	596 (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

[a]Adapted from Dickey *et al.* (1996b). Reproduced with the permission of the publisher

In 1956, Frank Palopoli and his colleagues of the then Merrell chemistry department synthesized the substance now known as clomiphene citrate (Figure 1). A sample of this compound was submitted to the biology departments of Merrell for endocrine and other testing in January 1957. A patent application was made for this compound in August 1957 and the patent issued in November 1959 (Allen *et al.*, 1959).

Clomiphene was known in its early testing days as WSM 5008. It went through tests in 1957 with other compounds that were of more than usual interest in the endocrinology department, but at that time failed to be the object of any major interest. In the autumn of 1958 and early 1959, however, several substances were chosen for additional endocrine testing in animals and one of these was clomiphene citrate. Joseph Greslin was a colleague during this period. A biological spectrum of oestrogenicity, gonadotrophin inhibition, antifertility effect, etc. in animals was evident (Holtkamp *et al.*, 1960).

Specific animal test criteria were used in the final selection of clomiphene for safety testing in animals and for potential clinical trials. In 1959, clinical data were available on the oestrogen antagonist MER-25 for induction of ovulation, but the dosage required was too high. Tyler and Olson (1959) and Kistner and Smith (1960, 1961, 1962) reported that MER-25 could induce ovulation in women with certain types of amenorrhoea. Some of these women had polycystic ovaries. The following criteria were set forth for the selection of the new substance for clinical trial: (i) less oestrogenic than TACE, (ii) more pituitary gonadotrophin inhibiting than MER-25, (iii) some oestrogen antagonizing action, and (iv) a dosage approaching that of TACE and hopefully about one-tenth of that necessary with MER-25, which was then in clinical trial. Clomiphene citrate fulfilled the criteria in animal tests. Projected clinical uses were oral contraception, ovulation induction and use in certain types of oestrogen-dependent tumours.

Investigators outside Merrell were chosen to conduct tests in animals with this substance. James Leathem of Rutgers University tested the substance in rats with induced cystic ovaries. R.K.Meyer at the University of Wisconsin conducted various endocrine tests on this substance, as did Warren Nelson and Sheldon Segal of the Population Council, New York, USA.

The first discussions by Merrell with clinical investigators were at the time of the American Society for the Study of Sterility (ASSS), now called the Society of Reproductive Medicine (ASRM), meetings in Cincinnati, Ohio in April, 1960. The investigators with whom discussions were held during that week were Robert Greenblatt and his colleague at that time, William Barfield, and also Robert Kistner of Boston and Charles Lloyd then of Syracuse, New York. All agreed to be investigators. All saw the possibility of this compound for ovulation induction. Clinical studies began in 1960.

In October 1961, Greenblatt *et al.* (1961) reported the first results of clinical testing in humans of clomiphene, which was then known as MRL-41, in the *Journal of the American Medical Association* (JAMA). They concluded 'Although the mechanism of action of this compound is not clear at the present time, it is heartening to find a drug which holds much promise of inducing ovulatory type menses with considerable regularity in anovulatory women.' In the October 1961 issue of JAMA, there was editorial comment, of which the following is an excerpt: 'The clinical experiment opens promising new approaches to the problem of ovulation.' This editorial had references to the reports by Tyler *et al.* (1962) using MER-25. Similar editorials appeared in *The Lancet* (Editorial, 1961b) and in the *British Medical Journal* (Editorial, 1962 and 1963).

At subsequent scientific meetings, Kistner (1962), Tyler *et al.* (1962) and Vorys *et al.* (1964), who subsequently joined the clinical investigational team, each reported independently on their findings and presented the initial results of their clinical tests.

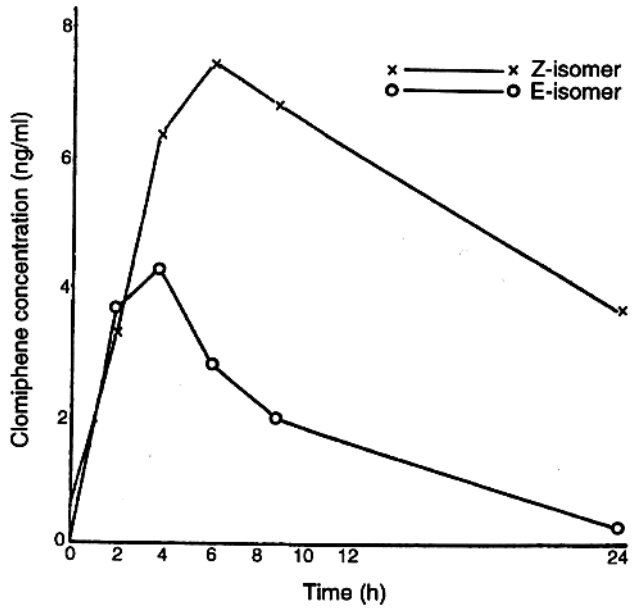

Figure 2. Mean plasma concentrations of zuclomiphene (×) and enclomiphene (○) after oral administration of one 50 mg tablet of clomiphene (n = 23). From Mikkelson *et al.* (1986). Reproduced with permission of the authors and the publisher, the American Society for Reproductive Medicine (The American Fertility Society).

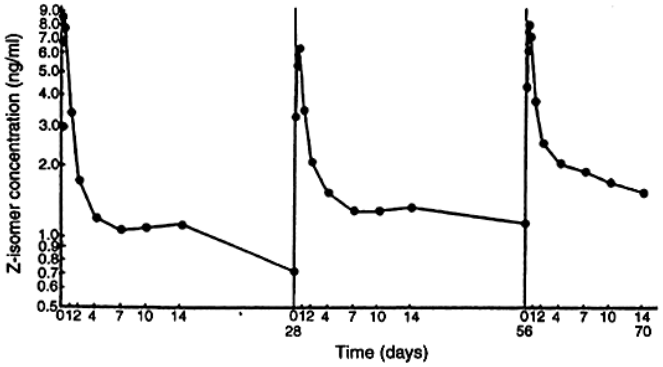

Figure 3. Mean plasma concentration of zuclomiphene after administration of one 50 mg tablet of clomiphene at 28 day intervals. From Mikkelson *et al.* (1986). Reproduced with permission of the authors and the publisher, the American Society for Reproductive Medicine (The American Fertility Society).

Under the new drug laws starting in 1963, clomiphene was studied under Investigational New Drug (IND 3). This was the third drug submitted to the United States Food and Drug Administration (FDA) for investigation under these regulations. A New Drug Application (NDA) was filed in 1965. Clomiphene was approved in 1967, when it first became available by prescription in the USA.

Increases in urine FSH and luteinizing hormone (LH) during and following clomiphene administration were first described by Dickey *et al.* (1965). Charles Flowers of Birmingham, Alabama, proposed in 1965 that clomiphene would be more effective if taken in a bolus daily rather than in divided doses because it would more readily pass the blood–brain barrier. Effects of individual isomers of clomiphene in the human were characterized by Greenblatt *et al.* (1971). Following such characterization, enclomiphene (at first known as cisclomiphene) was investigated in various clinics for ovulation induction. Paulson (1977) investigated the effect of clomiphene on spermatogenesis. A National Institutes of Health (NIH)-sponsored study group placed it in clinical trial for breast cancer. Studies were dropped by NIH when the clinical investigation of tamoxifen was broadened.

Clomiphene citrate has been marketed without interruption in the USA since its introduction in 1967. There were, however, two interruptions during the years of clinical investigation. After the start of animal investigations in 1960, there was a short interruption when there were problems in scaling up the manufacture from 10–20 g batches to kilogram size batches. Then in the autumn of 1962, Merrell again called a temporary halt to the clinical studies. The clomiphene-treated women, who were then pregnant, were followed to term and delivery of the infants. The mass of information obtained to that date from a chemical animal testing and clinical testing point of view was collated, summarized in accord with the then new drug law and submitted to the FDA in 1963. It was then that clomiphene was assigned IND 3. Clinical investigation was then started and was not interrupted again.

For several successive years during the late 1970s, the Batelle Human Affairs Research Center of Seattle, WA, USA, with the backing of the ASRM, sought a grant from NIH for the study of the outcome of pregnancies of women who had taken clomiphene. The grant was never approved. Grant requests on other subjects were given higher priority. In 1972, the present authors were in frequent conversations about the need for additional studies of the clinical activity of clomiphene. One (R.P.D.) championed investigation into the cause of a supposed increase in abortions, while the other (D.E.H.) favoured investigation into the cause of failed conception, despite apparent ovulation. As the following description of clinical studies will show, the reasons for both increased abortions and to a large extent failure of conception have now been resolved by vaginal ultrasound studies.

Pharmacology

The pharmacology of clomiphene explains many of its characteristic actions when used clinically. Clomiphene citrate, chemical name 1-[*p*(β-diethylaminoethoxy)phenyl]- 1,2-diphenylchloroethylene, is related to other trianyl-ethylene compounds, chlorotrianisene (TACE), triparanol (a cholesterol inhibitor) and tamoxifen, and is

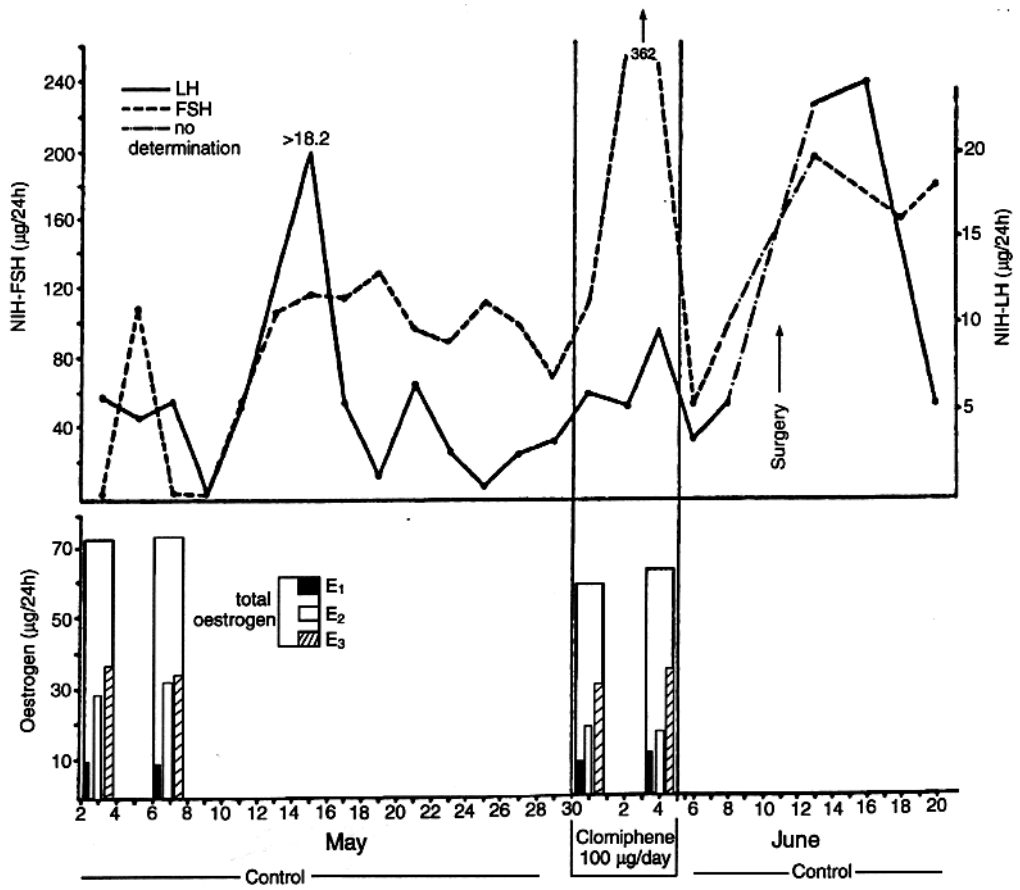

Figure 4. Excretion of follicle stimulating hormone (FSH), luteinizing hormone (LH), oestrone (E_1), oestradiol (E_2), oestriol (E_3) and total oestrogen (E) during and following treatment with clomiphene and surgery (bilateral oophorectomy) in a patient who had small normal ovaries and was amenorrhoeic for 2 years. From Dickey *et al.* (1965). Reproduced with permission of the publisher, the American Society for Reproductive Medicine (The American Fertility Society).

distantly related to the non-steroidal oestrogen diethylstilbestrol (DES; Figure 1). Owing to the presence of the diethylamino group, clomiphene is sometimes called a catechol-oestrogen. However, the catecholamino portion of the molecule appears to be completely inert and only the diphenyl portion is active. Clomiphene has code numbers of 5008 and 41, as well as a common first name, chloramiphene. Clomiphene is sold under seven different trade names throughout the world: Clomid, Clomphid, Clomivid, Clostilbegyt, Dyneric, Ikaclomine and Serophene. The two brands of clomiphene available in the USA, and a third available in Canada, are bioequivalent. Clomiphene sold in these two countries is a racemic mixture of ~38% zuclomiphene (cis isomer: formerly called 'transclomiphene') and 62% enclomiphene (trans isomer: formerly called 'cisclomiphene') (Holtkamp, 1987). Final designations were published in a correction article in 1976 (Ernst *et al.*, 1976). Zuclomiphene is mildly oestrogenic, as well as anti-oestrogenic, while enclomiphene is entirely anti-oestrogenic. Zuclomiphene is approximately five times as potent as enclomiphene in inducing ovulation.

Individual variability in metabolism of clomiphene may be substantial. Variability is, in part, related to body weight (Shepard *et al.*, 1979). For this reason, the dose of clomiphene may be required to be proportional to body weight (Table I). The total daily dose of clomiphene must be taken at one time to optimize entry into the central nervous system (CNS) and to occupy CNS and pituitary receptor sites.

Clomiphene citrate is excreted principally through the intestines. Five days after oral administration, 51% has been excreted; however, some clomiphene continues to be excreted for at least 6 weeks (Mikkelson *et al.*, 1986). Peak plasma concentrations of zuclomiphene occur 6 h after oral administration of 50 mg. A steady state, ~25%, of peak concentration is reached at 48 h and remains constant for the next 14 days (Figure 2; Mikkelson *et al.*, 1986). Serum concentrations of zuclomiphene remain at least 10% of peak levels 28 days after ingestion of a single 50 mg tablet. The effect of repeated administration of a single 50 mg tablet at 28-day intervals is cumulative, with basal levels increasing by 50% per month (Mikkelson *et al.*, 1986;

Figure 3). Owing to this accumulation, clomiphene may be more effective in inducing ovulation during the second and later cycles of treatment, even though the dose administered remains the same. Also, because of the continuing presence of clomiphene, ovulation as a result of clomiphene may also occur in the cycle following discontinuation of treatment.

Clomiphene citrate acts as a competitive antagonist of 17β-oestradiol at the level of the cytoplasmic nuclear receptor complex and possibly elsewhere (for a review, see Clark and Markaverich, 1988). Blockade of oestrogen receptors in the hypothalamic arcuate nucleus leads to an increase in gonadotrophin-releasing hormone (GnRH). Additionally, clomiphene increased the pituitary sensitivity to GnRH in a fashion similar to oestradiol (Hsueh *et al.*, 1978). As a result, FSH and LH secretion is increased during clomiphene administration (Dickey *et al.*, 1965; Figure 4). Clomiphene citrate may also have a direct effect on the ovary, making the granulosa cell more sensitive to pituitary gonadotrophin. Serum progesterone and oestradiol concentrations are increased during the luteal phase of the cycle in a direct dose–response relationship (Hammond and Taubert, 1982; Fukuma *et al.*, 1983). Increased oestrogen concentrations continue through the 16th gestational week, and increased progesterone concentrations continue until the 11th postovulation week before returning to the same value as in spontaneous pregnancy (Dickey, 1984; Dickey and Hower, 1995; Figure 5). Increased concentrations of oestradiol and progesterone as a result of clomiphene cause an increase in uterine artery diameter and moderate increase in uterine artery volume flow, but no change in resistance index (RI) during the first 9 weeks of gestation (Figure 6; Dickey and Hower, 1995).

Clinical evidence of anti-oestrogenic effects

The anti-oestrogenic effects of clomiphene are manifested clinically by hot flushes and changes in cervical mucus and the endometrium and are limited to the days tablets are taken (for hot flushes) and the following 3–5 days for other changes. In small animals with short (3–5 day) cycles, clomiphene is a contraceptive because the anti-oestrogenic effects of both the zuclomiphene and enclomiphene isomers are operative throughout the cycle. In humans and other animals with longer cycles, administration of clomiphene for 5 days is followed by ovulation 3–7 days later, after the anti-oestrogenic effect of the enclomiphene isomer has diminished.

The size of the leading follicle is significantly larger throughout the late follicular phase in clomiphene cycles compared to spontaneous cycles, although the growth rate remains the same (Randall and Templeton, 1991; Figure 7). In contrast, the endometrium is significantly thinner 4 days before the day of LH surge in clomiphene cycles, compared to spontaneous cycles, presumably due to the anti-oestrogenic effect (Randall and Templeton, 1991; Figure 8). Ultrasound studies suggest that the anti-oestrogenic effect of clomiphene on the endometrium may prevent conception, apart from the effect on cervical mucus (Table II; Dickey *et al.*, 1993a). The anti-oestrogenic effect of clomiphene on endometrium may also be a cause of preclinical (biochemical) abortions (Table III; Dickey *et al.*, 1993b). The anti-oestrogenic effect on endometrial thickness may be overridden by administration of oestrogen concurrently with clomiphene (Yagel *et al.*, 1992; Figure 9). It has been shown that high doses of oestradiol do not interfere with the ovulation-inducing effects of clomiphene (Taubert and Dericks-Tan, 1976). Because enclomiphene concentrations fall rapidly, the anti-oestrogenic effect of clomiphene on the endometrium and cervical mucus may be partially circumvented by starting clomiphene earlier, for example, on cycle day 2 or 3 instead of day 5.

Table II. Effect of clomiphene citrate (CC) and human menopausal gonadotrophin (HMG) on endometrial thickness at the time of human chorionic gonadotrophin administration and on per-cycle pregnancy and birth rates[a]

Regimen	Total no. of cycles	Endometrium ≤6 mm			Endometrium ≤8 mm			Endometrium ≤9 mm		
		No. (%[b]) cycles	No. (%[c]) pregnancies	No. (%[c]) births	No. (%[c]) cycles	No. (%[b]) pregnancies	No. (%[c]) births	No. (%[c]) cycles	No. (%[c]) pregnancies	No. (%[c]) births
CC	197	18 (9.1)	0 (0.0)	0 (0.0)	86 (43.3)	7 (8.1)	6 (7.0)	93 (47.2)	13 (14.0)	13 (14.0)
HMG	49	1 (2.0)	0 (0.0)	0 (0.0)	19 (38.8)	2 (10.5)	0 (0.0)	29 (59.2)	5 (17.2)	4 (13.8)
HMG+CC	205	23 (11.0)	0 (0.0)	0 (0.0)	114 (55.6)	11 (9.6)	8 (7.0)	68 (33.2)	10 (14.7)	8 (11.8)
None	23	2 (8.7)	0 (0.0)	0 (0.0)	13 (56.5)	2 (15.4)	1 (7.7)	8 (34.8)	0 (0.0)	0 (0.0)

[a]Adapted and revised from Dickey *et al.* (1993b). Reproduced with permission of the publisher, American Society of Reproductive Medicine (The American Fertility Society).
[b]Percentage of total cycles.
[c]Percentage per cycle.

Table III. Relationship of biochemical pregnancy and clinical abortion to endometrial thickness at the time of human chorionic gonadotrophin administration[a]

Endometrial thickness (mm)	No. (%) births	Total no. of pregnancies	No. (%) biochemical pregnancies	No. (%) clinical abortions
6–8	20 (62.5)[c]	32	7 (21.9)[b]	5 (15.6)
≥9	43 (87.8)	49	0 (0.0)	6 (12.2)

[a]From Dickey *et al.* (1993a).
[b]$P < 0.002$.
[c]$P < 0.01$.

Clinical use of clomiphene

Important clinical questions to be asked about clomiphene, as indeed they must be asked about any modality of infertility treatment, are: who should be treated, how long treatment should be attempted before turning to other more costly drugs such as HMG or FSH, and whether treatment adversely affects the outcome of pregnancy.

How long should clomiphene treatment be continued?

In initial clinical investigations of clomiphene conducted by the Wm. S. Merrell Co., pregnancy rates per cycle in patients who ovulated were recorded but, regrettably, never published. These results, shown in Table IV, demonstrate that pregnancy rates remained similar through 10 cycles in patients who ovulated, with some decline after cycle 5 or 6. This finding was subsequently confirmed in a much smaller series by life-table analysis (Table V; Hammond *et al.* 1983). In published reports of patients treated with clomiphene prior to IUI for cervical mucus or male factor infertility, pregnancy rates remained the same through the first six cycles of treatment [Table VI (adapted from Dickey *et al.*, 1992a) and Table VII (adapted from DiMarzo *et al.*, 1992)]. Such results differ markedly from those of smaller series which did not report per-cycle pregnancy rates or did not use life-table analysis; in these studies it has been implied that pregnancy rates with clomiphene fall markedly after the third or fourth cycle (Gysler *et al.*, 1982).

Effect of patient's age

The effect of the patient's age on per-cycle pregnancy rates and birth rates in one clinic is shown in Table VIII. The oldest patient to conceive was 45 years old. Pregnancy rates per cycle remained constant from <25 to age 42 years. Birth rates decreased notably after age 38 years. No twin births occurred after age 37 years; no triplet births occurred after age 32 years. The average cycle number in which conception occurred was 2.1 and did not differ for age <30 to 39 years. For ages 40–46 years, the average cycle of conception was 1.8.

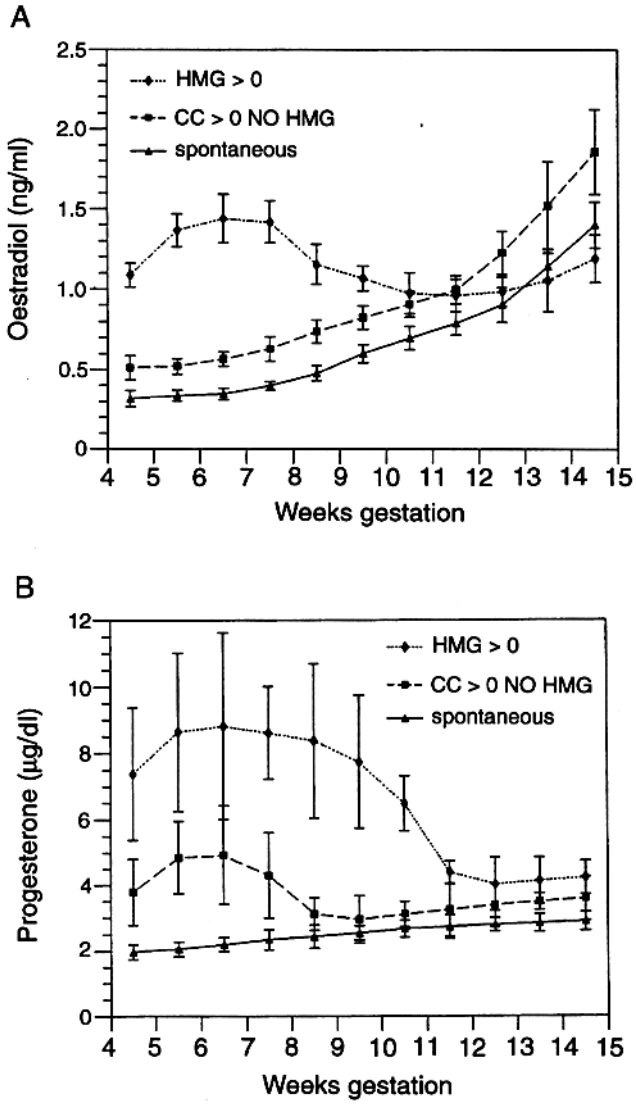

Figure 5. (**A**) Serum 17 β-oestradiol and (**B**) serum progesterone concentrations during the first 15 weeks of pregnancy, following spontaneous ovulation (group I, ▲), clomiphene citrate (CC) without human menopausal gonadotrophin (HMG; group II, ■) or CC followed by HMG (group III, ◆). Values shown are mean ± SE. From Dickey and Hower (1995).

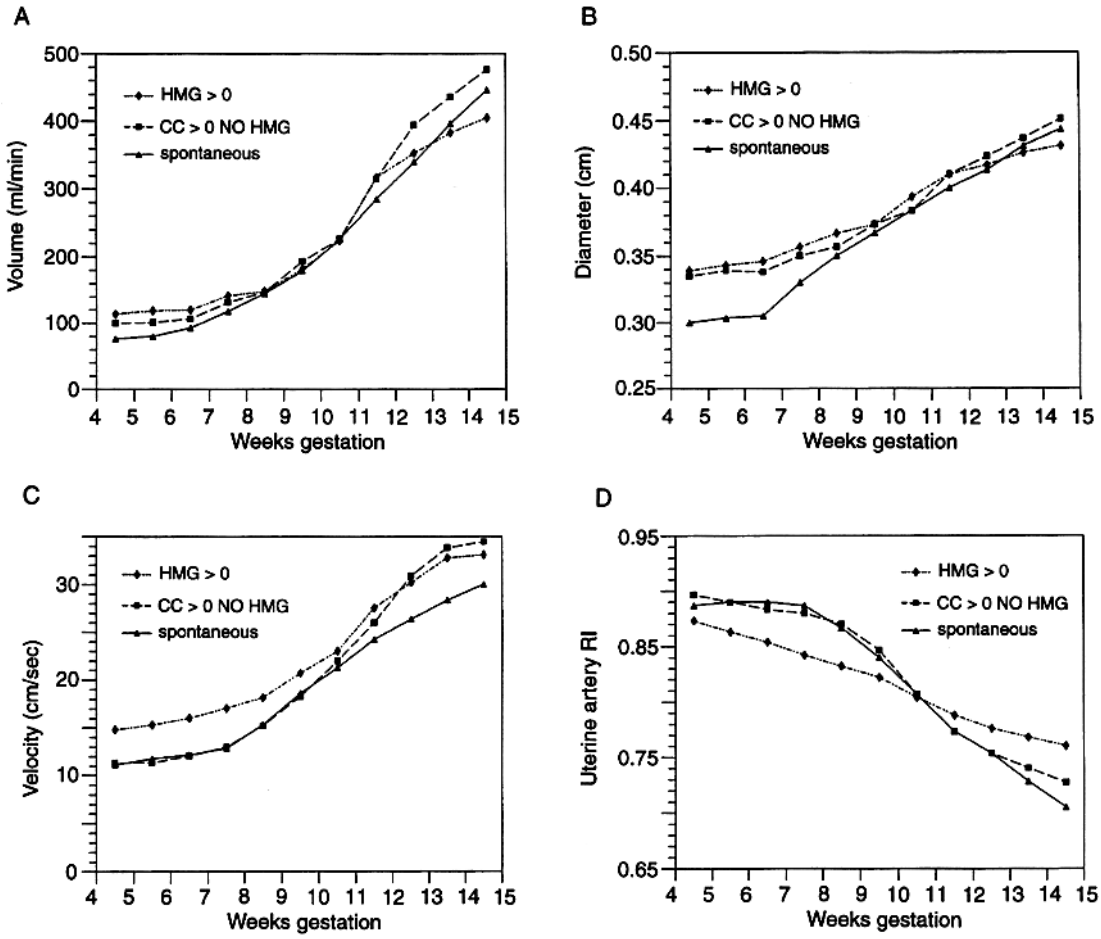

Figure 6. (**A**) Uterine artery total (right plus left) blood flow volume, (**B**) uterine artery average diameter, (**C**) uterine artery average velocity and (**D**) uterine artery resistance index (RI) during the first 15 weeks of pregnancy, following spontaneous ovulation (group 1, ▲), clomiphene citrate (CC) without human menopausal gonadotrophin (HMG; group II, ■), or CC followed by HMG (group III, ◆). From Dickey and Hower (1995).

Recently, the American Society for Reproductive Medicine (The American Fertility Society) issued a recommendation that clomiphene use be limited to six cycles. This was done primarily in response to a meta-analysis that suggested use of clomiphene was associated with an increase in ovarian cancer (Whittemore *et al.*, 1992). A review by Cohen *et al.* (1993) suggested that this meta-analysis had serious methodology problems. A subsequent cohort study concluded that any increase in ovarian cancer after use of ovulation induction drugs is limited to women who use drugs for >12 cycles without becoming pregnant (Rossing *et al.*, 1994). It would therefore seem prudent, as well as medically sound, to limit clomiphene treatment to six cycles if a term pregnancy does not occur. It is also prudent to perform pelvic ultrasound before starting the first cycle of clomiphene and to withhold treatment if any area of a suspicious nature is present in the ovary.

With regard to retreatment with clomiphene when a second pregnancy is desired, there should be less reason for concern because patients who achieve a term pregnancy will have a reduced risk of ovarian cancer. In our experience, second pregnancies occurred during the same or an earlier cycle of clomiphene treatment in 93% of cases.

Who will benefit from treatment?

Clomiphene was initially discovered to be effective in the treatment of polycystic ovarian (PCO) disease and other forms of anovulation (Greenblatt *et al.*, 1961; Kistner, 1962; Tyler *et al.*, 1962). Macgregor *et al.* (1967) summarized the results of ovulation induction with clomiphene in 4098 patients according to type of anovulatory disorder. Ovulatory response ranged from highs of 80% in patients with oligomenorrhoea and menses every 1–6 months, 76% in PCOS and 75% in postcontraceptive amenorrhoea, to lows of 60% in psychogenic amenorrhoea, 53% in oligo-ovulation with menses less frequently than 6 months and 42% in lactation-amenorrhoea syndrome, to no response in patients with pituitary disorders [now called World

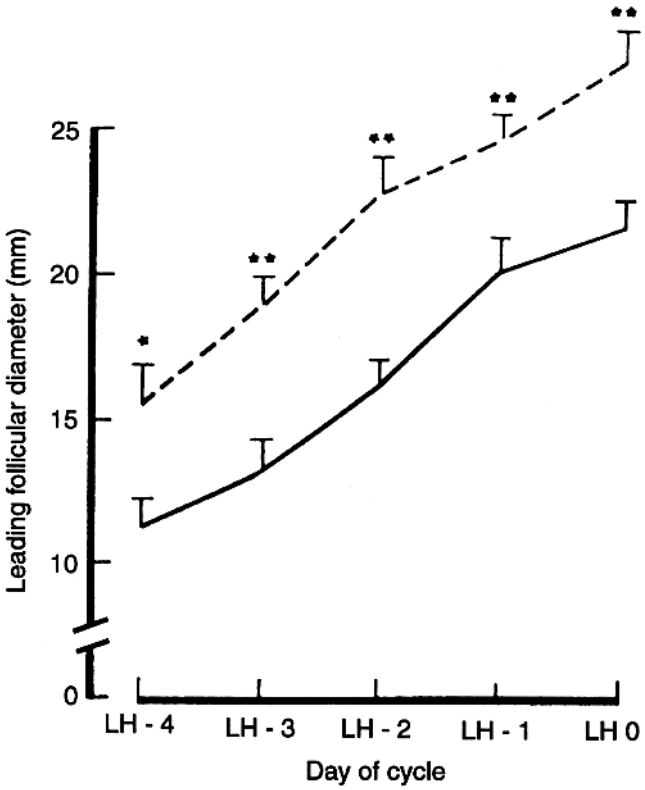

Figure 7. Daily mean leading follicular diameter in spontaneous (—) and clomiphene citrate (---) cycles. LH-0 = day of onset of luteinizing hormone surge. *$P < 0.05$; **$P < 0.01$. From Randall and Templeton (1991). Reproduced with permission of the authors and the publisher, the American Society for Reproductive Medicine (The American Fertility Society).

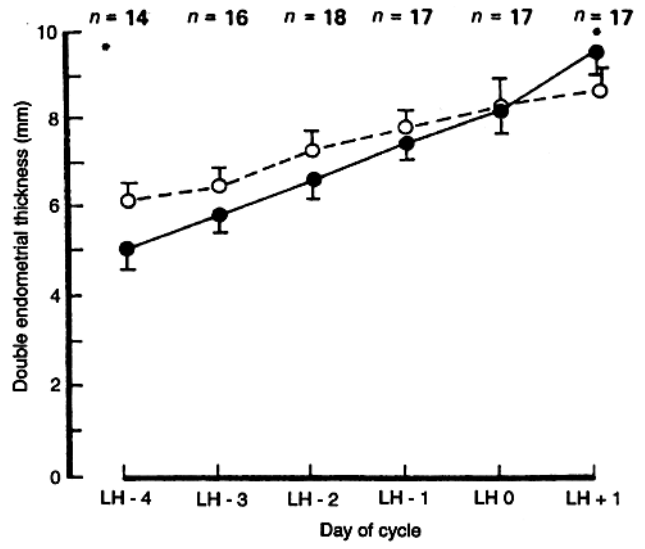

Figure 8. Double endometrial thickness (mm) in spontaneous (○) and clomiphene citrate (●) cycles (mean ± SEM). LH-0 = day of onset of luteinizing hormone surge. *$P < 0.05$. From Randall and Templeton (1991). Reproduced with permission of the authors and the publisher, the American Society for Reproductive Medicine (The American Fertility Society).

Health Organization (WHO) type I amenorrhoea]. Little has occurred subsequently to alter this evaluation of which anovulatory patients will respond to clomiphene. We have found in clomiphene-IUI cycles that when anovulation is subclassified into PCO (n = 661), luteal insufficiency determined by abnormal endometrial biopsy, or serum progesterone <1400 ng/dl (n = 709), and other causes (elevated prolactin, thyroid, adrenal; n = 94), pregnancy and birth rates were highest (20.8 and 15.1% respectively), in patients with luteal insufficiency who had no pelvic disease (Table IX). This pregnancy rate is similar to that reported by Macgregor *et al.* (1967; 20.4%) and the birth rate reported by Hammond *et al.* (1983; 15.4%).

Reasons for lower pregnancy rates in clomiphene-IUI patients compared to those in patients using clomiphene for anovulation include the presence of male or cervical factors and the method of tabulating results. Ovulation was defined as either a change in basal body temperature or occurrence of pregnancy by Macgregor *et al.* (1967). In a later paper (Macgregor *et al.*, 1968) in which all cycles were reported, the per-cycle pregnancy rate for patients treated with 50 mg of clomiphene was 8.9%, the same as we observed for clomiphene-IUI (Table VI). A third reason may be the age of the patients. Age was not reported by Macgregor *et al.* (1967) or Hammond *et al.* (1983). A fourth reason may be the presence of pelvic disease in patients who do not have solely ovulation disorders.

Table IV. Response to clomiphene in 3220 patients with ovulatory dysfunction[a,b]

Treatment cycle no.	No. of patients ovulating	No. of conceptions	% Clinical pregnancies
1	1750	373	21.3
2	1321	279	21.1
3	876	176	20.1
4	488	101	20.7
5	234	46	19.7
6	158	23	14.6
7	98	16	16.3
8	74	10	13.5
9	37	5	13.5
10	21	3	14.3
Total	5057	1032	20.4

[a]Adapted from Macgregor *et al.* (1967). Reproduced with permission of the authors.
[b]Average rate of pregnancy for cycles 1–6 was 20.7% and for [c]ycles 7–10 14.8%.

Table V. Life-table analysis of pregnancy rates in patients treated with clomiphene citrate[a]

Cycle no.	No. of cycles with ovulation	No. of pregnancies	No. lost to follow-up	% Pregnant who started	% With known outcome
1	140	26	0	18.6	18.6
2	114	16	12	14.0	15.7
3	86	7	12	8.1	8.9
4	67	6	8	9.0	11.2
5	53	6	10	11.3	14.0
6	37	2	8	5.4	6.9
7	27	4	4	14.8	17.4
8	19	4	4	21.0	26.7
9	11	3	2	27.3	33.3
10	6	3	2	50.0	75.0
>10	1	0	0	0.0	0.0
Total	561	77	62	13.7	15.4

[a]Adapted from Hammond *et al.* (1983). Reproduced with permission of the authors and the publisher.

Table VI. Relationship of treatment cycle number to pregnancy and birth rates following administration of clomiphene citrate and intrauterine insemination[a,b]

Cycle no.	No. of patients	No. (%) pregnancies	No. (%) births
1	1268	140 (11.0)	100 (.9)
2	730	83 (11.4)	58 (7.9)
3	406	40 (9.8)	33 (8.1)
4	202	19 (9.4)	13 (6.4)
5	102	10 (9.8)	10 (9.8)
6	59	5 (8.5)	4 (6.8)
7	35	4 (11.4)	2 (5.7)
8	15	0 (0.0)	0 (0.0)
9	10	0 (0.0)	0 (0.0)
10	9	1 (11.1)	1 (11.1)
11	3	0 (0.0)	0 (0.0)
12	2	0 (0.0)	0 (0.0)
Total	2841	302 (10.6)	221 (7.8)

[a]Adapted from Dickey *et al.* (1992) with revisions; additional cases were added for 1992–1995.
[b]Average pregnancy and birth rates for cycles 1–3 were 10.9 and 7.9% respectively; for cycles 4–6, 9.4 and 7.4; for cycles 7–12, 6.8 and 4.0.

Effect of pelvic disease and endometriosis

With two exceptions, Hammond *et al.* (1983) and Dickey *et al.* (1992a), per-cycle and life-table studies of clomiphene use lack information about pelvic disease and endometriosis. Hammond *et al.* (1983) reported a 50% decrease in fecundability in patients with pelvic abnormality on hysterosalpingography or laparoscopy. We initially reported a 50% decrease in per-cycle pregnancy and birth rates in clomiphene-IUI cycles for patients with endometriosis or tubal disease compared to patients who had neither (Dickey *et al.*, 1992a). Further analysis, when patients with anovulatory cycles and those who ovulated were treated separately, showed that only patients with tubal abnormalities who did not have endometriosis had significantly lower birth rates (Dickey *et al.*, 1992a; Table X). Birth rates were so low (2.9%) in patients with tubal disease but without endometriosis that other methods such as in-vitro fertilization (IVF) would be preferable means of treatment. The multiple birth rate was 10.6% in patients with anovulatory cycles compared to 5.2% in patients with regular cycles.

Use of clomiphene in IUI cycles

Most studies of clomiphene and even clomiphene with IUI do not use WHO (1992) standards (sperm concentration $\geq 20 \times 10^6$/ml, total sperm count $\geq 40 \times 10^6$, progressive motility ≥50% and normal morphology ≥30%) to determine if male factor infertility is present. A complete description of the relationship of semen quality to pregnancy in clomiphene-IUI cycles is limited to a single paper (Dickey and Olar, 1993). A re-analysis of semen quality versus pregnancy rates in clomiphene-IUI cycles in which patients with endometriosis and tubal factors have been excluded is presented in Table XI. These results indicate that sperm concentration and total sperm count values much lower than WHO standards, and sperm motility slightly below WHO standards, may result in reasonably good pregnancy rates. However, the percentage of spermatozoa with normal morphology needs to be higher than the WHO standard of 30% (i.e. IUI does not improve pregnancy rates if morphology is abnormal). Below the values of 5×10^6/ml (concentration), 10×10^6 (total count), 35% (motility), 50% (morphology), or 5×10^6 (total motile), pregnancy rates in clomiphene-IUI cycles are so low that other methods, such as IVF or donor insemination, should be used.

Table VII. Life-table analysis of pregnancy rates after administration of clomiphene citrate followed by intrauterine insemination[a]

Cycle no.	No. of cycles with ovulation	No. of pregnancies	No. lost to follow-up	% Pregnant who started[b]	% With known outcome
1	195	12	14	6.2	6.6
2	127	8	4	6.3	6.5
3	81	8	4	13.1	10.4
4	49	0	2	0.0	0.0
5	34	1	3	8.8	3.2
6	19	2	1	10.5	11.1
7–13	35	0	1	0.0	0.0
Total	540	31	29	5.7	6.1

[a]Adapted from DiMarzo *et al.* (1992). Reproduced with permission of the authors and the publisher.
[b]Average rate of pregnancy for cycles 1–6 was 6.1% of those who started.

Table VIII. Effect of patient's age on outcome in clomiphene citrate–intrauterine insemination cycles[a]

Age (years)	No. of cycles	No. (%[b]) pregnancies	No. (%[b]) births	No. (%[c]) twins	No. (%[c]) triplets
<25	99	10 (10.1)	9 (9.1)	0 (0.0)	0 (0.0)
25–26	224	23 (10.3)	16 (7.1)	0 (0.0)	0 (0.0)
27–28	416	51 (12.2)	42 (10.1)	5 (11.9)	1 (2.4)
29–30	546	55 (10.1)	37 (6.8)	1 (2.7)	0 (0.0)
31–32	488	50 (10.2)	39 (8.0)	3 (7.7)	1 (2.6)
33–34	357	44 (12.3)	29 (8.1)	6 (20.7)	0 (0.0)
35–36	319	35 (11.0)	26 (8.2)	2 (7.7)	0 (0.0)
37–38	181	16 (8.8)	13 (7.2)	1 (7.2)	0 (0.0)
39–40	110	12 (10.9)	6 (5.4)	0 (0.0)	0 (0.0)
41–42	52	5 (9.6)	3 (5.8)	0 (0.0)	0 (0.0)
> 42	49	1[d] (2.0)	1 (2.0)	0 (0.0)	0 (0.0)
Total	2841	302 (10.6)	221 (7.8)	18 (8.1)	2 (0.9)

[a]From unpublished data of the Fertility Institute of New Orleans, 1983–1995.
[b]Percentage of cycles started.
[c]Percentage of births.
[d]The oldest patient to give birth was aged 45 years.

Table IX. Relationship of type of anovulation to pregnancy, birth, and multiple births in clomiphene citrate–intrauterine insemination cycles[a]

Diagnosis	No. of cycles	No. (%) pregnancies	%[b] Abortion	%[b] Ectopic pregnancies	No. (%) births	Multiple births		
						Twin	Triplet	% Births
Ovulation total	1377	81 (5.9)	24.7	3.7	58 (4.2)	3	0	5.2
Without pelvic disease[c]	642	50 (7.8)	24.0	2.0	37 (5.8)	2	0	5.4
Anovulation total	1464	221 (15.1)	23.4	3.2	163 (11.1)	15	2	10.4
Without pelvic disease	807	132 (16.4)	20.4	2.3	102 (12.6)	10	1	10.8
Polycystic ovaries	661	84 (12.7)	23.8	0.0	64 (9.7)	7	0	10.9
Without pelvic disease	380	48 (12.6)	14.6	0.0	41 (10.8)	5	0	12.2
Luteal insufficiency	709	128 (18.0)	21.1	5.5	94 (13.2)	7	2	9.6
Without pelvic disease	389	81 (20.8)	23.4	3.7	59 (15.1)	5	1	10.2
Other[d]	94	9 (9.6)	44.4	0.0	5 (5.3)	1	0	20.0
Without pelvic disease	38	3 (7.9)	33.3	0.0	2 (5.3)	0	0	0.0

[a]Adapted from Dickey *et al.* (1992a) with revisions; additional, unpublished cycles were added for 1992–1995. Reproduced with permission of the publisher, American Society for Reproductive Medicine (The American Fertility Society).
[b]Percentage of pregnancies.
[c]Without pelvic disease = without endometriosis or tubal adhesions.
[d]Elevated prolactin, or hypothyroid, adrenal or dietary abnormalities.

Table X. Effect of additional infertility factors on fecundity and birth rate[a]

Diagnosis	No. of cycles	No. (%) pregnant	No. ectopic pregnancies	No. of abortions	No. (%) births
Anovulation	807	132 (16.4)[d]	3	27	102 (12.6)[d]
Endometriosis	1118	101 (9.0)	6	21	74 (6.6)
No tubal involvement	834	74 (8.9)	2	16	56 (6.7)
Tubal involvement	284	27 (9.5)	4	5	18 (6.3)
Tubal adhesions	274	19 (6.9)	0	11	8 (2.9)[c]
None	642	50 (7.8)[b]	1	12	37 (5.8)
Total	2841	302 (10.6)	10	71	221 (7.8)

[a]Adapted from Dickey *et al.* (1992a) with revisions; additional cycles were added for 1992–1995. Reproduced with permission of the publisher, American Society for Reproductive Medicine (The American Fertility Society).
[b],[c],[d]Significantly different from total: [b]$P < 0.05$, [c]$P < 0.01$, [d]$P < 0.0001$.

Use of clomiphene to improve pregnancy rates in IUI cycles has been investigated by several groups. The rationale for use of clomiphene in patients who require IUI is that it may increase the number of pre-ovulatory follicles. Corson *et al.* (1983) reported a 5% pregnancy rate for 202 clomiphene-IUI cycles compared to 3% for 326 cycles of IUI alone. DiMarzo *et al.* (1992) reported a 5.7% pregnancy rate in 540 cycles of clomiphene-IUI compared to 3.2% in 185 cycles of IUI alone. Others (Kemmann *et al.*, 1987; Martinez *et al.*, 1987) reported even greater improvement of results in small studies, when clomiphene was used in IUI cycles; however, Melis *et al.* (1987) found no improvement in IUI pregnancy rates when clomiphene was added, but noted a significant increase from 5 to 11% when clomiphene and FSH were given sequentially before IUI. We reported previously a 22% per-cycle pregnancy rate when clomiphene and HMG were given sequentially before IUI compared to 11% for clomiphene alone before IUI in patients who did not have endometriosis or pelvic tubal adhesions (Table XII; Dickey *et al.*, 1993c).

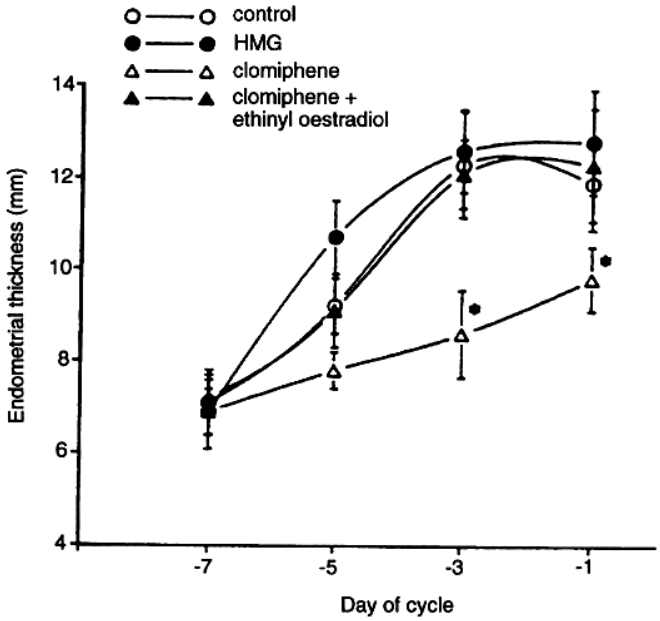

Figure 9. Distribution of mean (± SEM) of endometrial thickness at four points in the cycle. ○, Controls; ●, human menopausal gonadotrophin (HMG); Δ, clomiphene; ▲, clomiphene + ethinyl oestradiol. *$P < 0.01$ compared with the control cycle result at the same phase of the cycle. From Yagel *et al.* (1992). Reproduced with permission of the authors and the publisher, the American Society for Reproductive Medicine (The American Fertility Society).

Use of IUI in clomiphene cycles

Use of IUI to improve pregnancy rates in patients receiving clomiphene for ovulatory disorders has not been as completely studied as has the use of clomiphene in cycles where IUI is necessary because of semen or mucus quality. The presence of motile spermatozoa in an overnight cervical mucus specimen has customarily been considered sufficient to ensure pregnancy, especially if a semen analysis is normal by WHO (1992) standards. However, our studies of the relationship between pregnancy rates and semen quality before preparation for insemination suggest that high absolute numbers of spermatozoa, and especially of progressively motile spermatozoa, are more important than previously realized. We found that the pregnancy rates increased concomitantly as the total sperm count in the initial semen specimen increased from $<10 \times 10^6$ to $\geq 90 \times 10^6$ (Table XI). The upper value is more than double the WHO criterion for normal male fertility. This suggests that use of IUI might improve per-cycle pregnancy rates in clomiphene cycles in some patients whose spouse is considered to have normal semen analysis by WHO standards.

Use of clomiphene in patients with regular cycles

Recruitment of additional follicles for patients who ordinarily have single ovulations and for patients whose fecundability is limited by age would seem to be of obvious advantage, yet the relationship between the probability of conception and number of pre-ovulatory follicles available to ovulate at the time of spontaneous LH surge or administration of HCG in clomiphene patients has only been

studied infrequently. Marrs *et al.* (1984) reported that administration of 150 mg of clomiphene for 5 days significantly increased the number of pre-ovulatory follicles available for IVF, and that the final number of follicles was not affected by the cycle day on which clomiphene was started. Quigley *et al.* (1984), however, found no difference between administration of 50 mg of clomiphene and 150 mg of clomiphene in recruitment of follicles >15 mm diameter, even though the higher dose resulted in higher FSH and LH concentrations and higher pre-ovulatory oestradiol concentrations. Shalev *et al.* (1989) reported an increase in the average number of follicles >15 mm diameter in patients with regular cycles, from 1.0 for 50 mg of clomiphene to 2.4 for 200 mg; there was a corresponding increase in the number of follicles 8–15 mm diameter, from 0.4 for 50 mg of clomiphene to 2.1 for 150 mg, with no further increase for 200 mg of clomiphene. Shalev *et al.* (1989) also found an increase in the bilateral occurrence of follicles >15 mm and in overall ovulation rates with increased doses of clomiphene. These authors commented that, at least in clomiphene cycles, development of a dominant mature follicle >15 mm diameter does not appear to impede the growth of other intermediate-sized follicles, as proposed by Hodgen (1982).

Effects of follicle size and number

We investigated the relationships between pregnancy rates and the size and number of follicles seen on pre-ovulatory vaginal ultrasound and also the relationship between age and numbers of pre-ovulatory follicles, implantation rates and birth numbers (Dickey *et al.*, 1992a; Table XIII). We found that per-cycle pregnancy and birth rates were most closely related to the number of pre-ovulatory follicles ≥15 mm and were unrelated to the number of follicles ≥21 mm or ≥24 mm diameter. The highest pregnancy rate, 17.7%, occurred when there were four or more follicles ≥15 mm diameter on the day of HCG administration. We also found that all follicles ≥12 mm, or even ≥10 mm, needed to be counted when determining the risk of developing multiple implantations or births. We further found that the average number of follicles ≥12 mm that developed each cycle, which was 2.3, did not change with increasing patient age until after age 40 years, but that the number of implantations per pre-ovulatory follicle decreased after age 35 years (Table XIV and unpublished data). This suggests that the number of follicles seen on vaginal ultrasound can be used to predict the number of cycles which may be required for conception and thus, whether treatment with clomiphene will be sufficient or whether administration of HMG or FSH should be considered. For patients aged <30 years, in whom implantation occurs on the average once for every 14.5 follicles ≥12 mm and who develop five follicles per cycle, an average of only three cycles might be needed for pregnancy, whereas, for patients aged ≥40 years, in whom an implantation occurs on the average once for every 20 follicles and who develop only one follicle per cycle, an average of 20 cycles might be needed for pregnancy, and twice that number for a birth. Together, these findings indicate that clomiphene is best suited for women who are younger, who have four or more follicles develop while on clomiphene stimulation, who are free of tubal disease, who have normal cervical mucus, and who have partners who either have normal or above sperm concentration, motility and quality, or else are willing to use IUI.

Why does conception fail to occur despite apparent ovulation?

In our experience, failure to conceive in apparently ovulatory cycles is due to one of four causes: failure to ovulate despite changes in basal temperature and progesterone; failure to develop a satisfactory endometrium, which often may be treated by increasing the dose of clomiphene; failure of spermatozoa to reach the Fallopian tubes, which may be treated by IUI; and tubal disease. In addition to the reasons for failure to conceive already discussed (tubal disease, poor semen quality, poor cervical mucus quality, low numbers of pre-ovulatory follicles), endometrial receptivity and failure of ovulation may be implicated. Ultrasound observation of the endometrium prior to HCG administration in IUI cycles has provided important insight into the reason why conception fails to occur despite ovulation in some clomiphene cycles and in some spontaneous cycles as well. When endometrium wall thickness was <6 mm on the day of HCG administration, no pregnancies occurred during clomiphene cycles, HMG cycles, or spontaneous cycles, irrespective of the endometrial pattern (Dickey *et al.*, 1993a, 1993b; Table II). Before this was discovered, 9% of all clomiphene-IUI patients had received HCG when endometrium thickness was <6 mm. In the same study, maximum pregnancy rates occurred when the endometrium was ≥9 mm on the day of HCG administration. Furthermore, all bioclinical abortions occurred in clomiphene-IUI patients whose endometrial thickness was 6–8 mm on the day of HCG administration (Table III). Although numerous ultrasound studies have shown that clomiphene may reduce endometrial thickness (Fleischer *et al.*, 1984, Imoedemhe *et al.*, 1987; Eden *et al.*, 1989; Randall and Templeton, 1991; Rogers *et al.*, 1991), we believe this to be the first study to show the relationship between endometrial thickness on the day of HCG administration and conception for clomiphene cycles.

Table XI. Relationship of initial semen quality to pregnancy clomiphene citrate–intrauterine insemination (wash preparation)[a]

Parameter[b]	No. of cycles	No. pregnant	% Pregnant
Sperm concentration ($\times 10^6$/ml)			
<5	61	1	1.6
5–20	249	17	6.8
20–90	710	50	7.0
≥90	408	40	9.8
Total sperm count ($\times 10^6$)			
<10	64	1	2.4
10–40	237	10	4.2
40–90	540	44	7.5
≥90	1340	119	8.9
% Normal morphology[c]			
<30	38	0	0.0
30–50	218	9	4.1
>50	1507	154	8.9
% Progressive motile spermatozoa			
<20	59	0	0.0
20–35	297	12	4.0
35–50	388	32	8.3
≥50	1507	131	8.7
Total motile spermatozoa ($\times 10^6$)			
<5	131	2	1.5
5–10	377	21	5.6
20–55	584	48	7.9
≥55	1154	108	9.1

[a]Adapted and revised from Dickey *et al.* (1993b): data for endometriosis and tubal disease were excluded and additional cycles added from 1993–1995 (unpublished data). Reproduced with permission of the publisher, American Society of Reproductive Medicine (The American Fertility Society).
[b]Lowest value of sperm parameter for which pregnancy was recorded: sperm concentration, 3×10^6/ml; total sperm count, 5.5×10^6; normal morphology, 30%; progressive motility, 20%; total motile spermatozoa, 1.7×10^6.
[c]Abnormal forms included tapered heads, micro and macro heads, amorphic forms, different acrosomes, and any neck abnormality, including bent necks and collars.

Methods of increasing endometrial thickness on the day of HCG administration include starting clomiphene earlier in the cycle, on day 2 or 3 instead of day 5 or later (R.P.Dickey, unpublished data), adding oestradiol (Yagel *et al.*, 1992; Figure 9), and administering low doses of HMG or FSH for 3 days following clomiphene (R.P.Dickey, unpublished data). Addition of oestrogen following clomiphene to improve cervical mucus has been done empirically, despite a lack of evidence that any improvement seen in mucus was greater than would normally occur in the days preceding ovulation. Endometrial thickness spontaneously increases in clomiphene cycles in the days before ovulation (Randall and Templeton, 1991; Figure 8). Beneficial effects of oestrogen on conception rates, believed to be due to improved mucus, thus may have been due to an increase in endometrial thickness. We have previously suggested that endometrial thickness and conception rates in clomiphene-HCG cycles may be improved simply by delaying the administration of HCG by 1 or 2 days (Dickey *et al.*, 1993b).

An antagonistic effect of clomiphene on the endometrium based on histological studies has long been known (Van Hall and Mastboom, 1969; Garcia *et al.*, 1977; Sterzik *et al.*, 1988) and has been shown to relate to ultrasound findings (Rogers *et al.*, 1991). Lamb *et al.* (1972) found mid-luteal endometrial biopsies to be normal in 13 of 14 clomiphene cycles. Guzich and Zeleznik (1990) reported that luteal defects observed at endometrial biopsy in spontaneous cycles were corrected by clomiphene in eight of 10 patients if more than one follicle developed after clomiphene administration, but were corrected in only two of eight patients if only one follicle developed after clomiphene. Endometrial changes associated with clomiphene use are most probably related to oestrogen and progesterone concentrations during the luteal phase of the cycle.

Lack of oocyte release following LH surge, commonly called luteinized unruptured follicle syndrome (LUF), is a well recognized reason for failure of conception. This can be diagnosed by pre- and post-ovulatory ultrasound and by diagnostic laparoscopy performed during the mid-luteal phase of the cycle, when an operculum of ovulation should be seen. Reasons for spontaneous LUF have never been identified. Treatment with HCG when lead follicles are ≥18 mm is frequently successful. Administration of oestrogen to improve mucus or endometrium does not interfere with ovulation in clomiphene cycles, according to Taubert and Dericks-Tan (1976).

Other reasons proposed for failure of conception are a poor hormonal milieu for oocyte maturation before ovulation (i.e. raised LH and androgen concentrations or low FSH and oestradiol concentrations) and poor endometrial development post-ovulation causing failure of implantation. Oestrogen concentrations before ovulation are related to the number of pre-ovulatory follicles (Guzick and Zeleznik, 1990; Dickey *et al.*, 1991). Oestrogen levels may be increased in clomiphene cycles by increasing the dose of clomiphene (Fukuma *et al.*, 1983). It is unknown,

however, whether androgen concentrations are also increased when clomiphene is increased. Another method of increasing oestrogen concentrations and pregnancy rates is to administer HMG or FSH for 3 days following or concurrently with clomiphene (Table XV; Dickey *et al.*, 1993c). It has been found that the addition of HMG following clomiphene (clomiphene + HMG) resulted in doubling of the number of implantations per follicle to 0.10 and doubling of the oestradiol concentration per follicle ≥12 mm diameter to 456 pg/ml, while the number of follicles ≥12 mm increased by only 33% and total oestradiol increased by only 50% compared to clomiphene alone (Dickey *et al.*, 1993c). These findings suggest that the increased implantation rate in response to the administration of HMG following clomiphene was related to the higher oestradiol concentration per follicle. However, the possibility that the increased implantation rates were due to improved endometrial environment cannot be excluded, since endometrial thickness was not measured.

Effect of clomiphene on the luteal phase

Fukuma *et al.* (1983) reported that mid-luteal phase endometrial glycogen content as well as serum oestradiol and progesterone were increased in clomiphene cycles in proportion to the clomiphene dose. Dickey (1984) showed that serum progesterone concentrations during the mid-luteal phase averaged 2700 ng/dl in spontaneous cycles and 3200 ng/dl in clomiphene cycles of pregnancies which went to term, and that progesterone concentrations rose to much higher levels in clomiphene-induced pregnancy than in spontaneous pregnancy during gestational weeks 5–8, before becoming equal again at week 10. Subsequently, Dickey and Hower (1995) reported that serum oestradiol is increased through the first 16 gestational weeks and progesterone concentrations are increased through the first 7 weeks in clomiphene cycles compared to spontaneous cycles which continued to term (Figure 5). Maclin *et al.* (1990) found that, in addition to absolute amounts of progesterone and oestradiol alone, the progesterone/oestradiol ratio was important to conception and the continuation of pregnancies. These authors observed that high oestradiol doses could be used to prevent conception (Yanagimachi and Sato, 1968) and suggested that low conception rates (Berguist *et al.*, 1983) and increased rates of spontaneous abortion associated with ovulatory induction agents (Jansen, 1982) and IVF (Gidley-Baird *et al.*, 1986; Howles *et al.*, 1987) might be related to excessive endogenous oestradiol secretion. Goldstein *et al.* (1982) found that oestradiol concentrations that were either too low or too high, associated with normal progesterone concentrations, caused desynchronized endometrial development, and that the highest pregnancy rates occurred when progesterone and oestradiol concentrations were both high.

Does clomiphene adversely affect pregnancy outcome?

One of the most perplexing questions about clomiphene is whether it causes an increased incidence of miscarriage. In initial clinical trials, Macgregor *et al.* (1968) reported the outcome of 2196 pregnancies, of which 452 were undelivered or outcomes were unavailable. Known pregnancy losses were 379 spontaneous abortions (17.2%), four therapeutic or iatrogenic abortions and 24 ectopic pregnancies. Included in spontaneous abortions were four hydatidiform moles and one fetus papyraceous. Initial clinical trials eventually included 2635 pregnancies, of which 455 (17.3%) ended in spontaneous abortion (Merrill Dow Pharmaceutical Company, Clomid® Package Insert, 1988). The ages of patients who had been given clomiphene were not reported.

The impression that clomiphene causes an increase in spontaneous abortion is due to the fact that there has been no comparable group of infertile women not using clomiphene for whom spontaneous abortion rates were known, and that studies reporting high rates were small or inadequately controlled (Goldfarb *et al.*, 1968; Roland, 1970; Garcia *et al.*, 1977), and in one case fraudulent (Johnson and Pearce, 1990). For example, Toshinobu *et al.* (1979) reported a 23.6% abortion rate in the clomiphene group and an inexplicably low 8.9% rate in the control group of infertility patients receiving other unspecified treatment. In another report, 25.3% of pregnancies conceived in clomiphene cycles ended in abortion, compared to 11% after clomiphene had been discontinued (Garcia *et al.*, 1977).

Two important studies suggest that abortion rates may not be increased in clomiphene cycles. Adashi *et al.* (1979) found an abortion rate of 26% in 86 PCO patients treated with clomiphene and 22% in patients treated by bilateral ovarian wedge resection. A prospective 5-year multi-hospital study in Japan compared outcomes in 1034 pregnancies conceived following clomiphene, 186 pregnancies conceived following HMG and 29 900 spontaneous conceptions. Abortion rates were not significantly different for clomiphene (14.8%) than for spontaneous ovulation (13.9%), but were higher following HMG (19.4%; Kurachi *et al.*, 1983).

Table XII. Pregnancy, birth and multiple birth rates per cycle following intrauterine insemination in clomiphene citrate (CC) and human menopausal gonadotrophin (HMG)-treated patients without pelvic disease when semen quality is normal[a]

Regimen	No. of cycles	No. (%) pregnancies	No. (%) births	No. of multiple births	
				Twin	Triplet
CC + HMG[b]	119	26 (22)	21 (18)[c]	5	2[d]
CC	524	59 (11)	44 (8)	2	0
HMG	57	10 (18)	8 (14)	3	0
HMG and CC[e]	79	15 (19)	12 (15)	3	0

[a]Adapted from Dickey *et al.* (1993c). Reproduced with permission of the publisher, American Society for Reproductive Medicine (The American Fertility Society).
[b]Sequential CC followed by HMG.
[c]Pregnancies and births per cycle, compared to CC; $P < 0.005$.
[d]Multiple births, compared to those for patients receiving CC only; $P < 0.002$.
[e]Concurrent HMG and CC.

Table XIII. Relationship of follicle size and number to pregnancy, birth, numbers of implantations and multiple births in clomiphene citrate–intrauterine insemination cycles[a,b]

Follicle diameter (mm)	No. of follicles[c]	No. of cycles	No. (%) pregnancies	Gestational sacs		No. (%) births	No. of multiple births		No. of implantations/ follicle	No of babies/ follicle
				Two	Three		Twin	Triplet		
≥12	0	9	0 (0)	0	0	0 (0)	0	0	0	0
	1	305	24 (7.9)	3	0	21 (6.9)	1	0	0.088	0.072
	2	452	46 (10.2)	3	1	36 (7.9)	2	1	0.056	0.044
	3	305	34 (11.1)	4	0	24 (7.9)	2	0	0.042	0.028
	4	189	23 (12.2)	2	2	17 (9.0)	2	1	0.038	0.028
	≥5	139	19 (13.7)	1	2	16 (11.5)	1	0	0.029	0.021
All ≥12		1390	146 (10.4)	13	5	114 (8.4)	8	2	0.046	0.034
≥15	0	61	4 (6.6)	1	0	3 (4.9)	1	0	0	0
	1	568	47 (8.3)	4	2	37 (6.5)	1	1	0.097	0.070
	2	452	51 (11.3)	3	1	42 (9.3)	2	0	0.062	0.049
	3	205	24 (11.3)	3	1	16 (7.8)	2	1	0.047	0.032
	≥4	113	20 (17.7)	2	1	16 (14.2)	2	0	0.038	0.027
All ≥15		1338	142 (10.6)	12	3	111 (8.3)	7	2	0.063	0.047
>18	0	281	24 (8.5)	2	1	19 (6.8)	2	0	0	0
	1	653	59 (9.0)	4	1	47 (7.2)	1	1	0.100	0.076
	2	317	41 (12.9)	3	2	31 (9.8)	1	1	0.076	0.054
	≥3	148	22 (14.9)	4	1	17 (11.5)	4	0	0.055	0.044
All ≥18		1118	122 (10.9)	11	4	95 (8.5)	6	2	0.093	0.070
≥21	0	691	67 (9.7)	4	4	50 (7.2)	3	2	0	0
	1	488	49 (10.0)	5	0	40 (8.2)	3	0	0.111	0.088
	≥2	220	30 (13.6)	4	1	24 (10.9)	2	0	0.071	0.052
All ≥21		708	79 (11.2)	9	1	64 (9.0)	5	0	0.091	0.070
≥24	0	1063	112 (10.5)	11	5	86 (8.1)	7	2	0	0
	1	277	26 (9.4)	2	0	22 (7.9)	1	0	0.101	0.083
	2	59	8 (13.6)	0	0	6 (9.4)	0	0	0.064	0.048
All ≥24		336	34 (10.1)	2	0	28 (8.3)	1	0	0.090	0.072

[a]Adapted from Dickey *et al.* (1992a). Reproduced with permission of the publisher, American Society for Reproductive Medicine (The American Fertility Society).
[b]There were no pregnancies, births, twins, and triplets for follicles <12 mm diameter. The percentages of pregnancies, births, twins, and triplets for follicles <15 mm diameter = 2.7,2.6, 12.5 and 0.0 respectively; for follicles <18 mm = 16.4, 16.7, 25.0, 0.0 respectively; for follicles <21 mm = 45.9, 43.8, 37.5, 100.0 respectively; for follicles <24 mm = 76.7, 75.4, 87.5, 100.0 respectively.
[c]Pearsons correlation coefficients for (i) relationship of follicle number to pregnancies: Foll 12, $r = 0.078$, $P = 0.001$; Foll 15, $r = 0.106$, $P = 0.001$; Foll 18, $r = 0.089$, $P = 0.001$; Foll 21, $r = 0.038$, P = NS; Foll 24, $r = 0.012$, P = NS; (ii) relationship of follicle number to births: Foll 12, $r = 0.068$, $P = 0.005$; Foll 15, $r = 0.099$, $P = 0.001$; Foll 18, $r = 0.089$, $P = 0.001$; Foll 21, $r = 0.057$, P = NS; Foll 24, $r = 0.021$, P = NS; (iii) relationship of follicle number to implantations: Foll 12, $r = 0.094$, $P = 0.001$; Foll 15, $r = 0.108$, $P < 0.001$; Foll 18, $r = 0.089$, $P = 0.001$; Foll 21, $r = 0.057$, P = NS; Foll 24, $r = 0.021$, P = NS. NS = not significant.

Table XIV. Effect of age on the number of pre-ovulatory follicles ≥12 mm and on the number of implantations per follicle in clomiphene citrate–intrauterine insemination cycles[a]

Age (years)	No. of cycles	Average no. follicles ≥12	No. (%[b]) pregnancies	No. (%[b]) implantations	Average no. implantations per follicle	Average no. follicles per implantation
<30	311	2.25	42 (13.5)	48 (15.4)	0.069	14.5
30–34	382	2.35	38 (10.0)	47 (12.3)	0.052	19.1
35–39	134	2.34	16 (11.9)	17 (12.7)	0.054	18.5
≥40	33	2.42	3 (9.1)	4 (12.1)	0.050	20.2
Total	860	2.32	99 (11.5)	116 (13.5)	0.058	17.2

[a]From unpublished data of the Fertility Institute of New Orleans, 1983–1995.
[b]Percentage per cycle.

Table XV. Comparison of follicle number, oestradiol concentrations, oestradiol per follicle, and implantations per follicle for clomiphene citrate (CC) and human menopausal gonadotrophin (HMG) ovulation induction regimens[a]

Ovulation induction regimen	No. of cycles	No. of follicles per cycle ≥12 mm	No. of patients	Mean oestradiol per cycle on day of HCG (pg/ml)	Mean oestradiol per follicle ≥12 mm (pg/ml)	Implantations per follicle
CC + HMG[b]	119	3.2 ± 0.2[c]	106	962 ± 80	456 ± 76[d]	0.100
CC	524	2.4 ± 0.1	62	613 ± 48	254 ± 18	0.047
HMG	57	4.6 ± 0.6	75	1194 ± 161	278 ± 37	0.054
HMG and CC[e]	79	5.9 ± 0.5	56	1674 ± 739	329 ± 21	0.040

[a]From Dickey *et al.* (1993c). Reproduced with permission of the publisher, American Society for Reproductive Medicine (The American Fertility Society).
[b]CC + HMG = sequential clomiphene citrate and human menopausal gonadotrophin.
[c]Significantly different number of follicles per cycle compared to: CC regimen, $P < 0.001$; to HMG, $P < 0.001$; to HMG and CC, $P < 0.001$.
[d]Significantly different amount of oestradiol, compared to CC regimen, $P = 0.011$; to HMG, $P = 0.038$.
[e]HMG and CC = concurrent HMG and CC.

A scarcity of information about the incidence of early spontaneous abortion in the general population is partially responsible for the perception that abortion rates are increased in clomiphene patients. The latter are customarily followed more closely and are more apt to have a quantitative HCG performed as soon as their menstrual cycle is late. Zinaman *et al.* (1996) reported that preclinical abortions occurred in 13% and clinical abortions in 18% of 200 couples with medium to upper incomes (wife's average age 30.6 years, nulliparous 52%), who were followed with daily urine HCG analysis during the luteal phase of their cycle and in whom serum quantitative HCG was measured if menses were 1 day later than expected.

In our own 20-year prospective study, the incidence of spontaneous abortion was 23.7% for all 1738 pregnancies with known outcome up to 14 weeks that were initiated with clomiphene, compared to 20.4% for 3471 spontaneous pregnancies, 28.8% for 292 clomiphene + HMG pregnancies and 36.4% for 107 HMG + FSH pregnancies (Table XVI). When stratified by age, the incidence of preclinical abortion (serum HCG ≥25 mIU, no gestational sac) in clomiphene compared to spontaneous pregnancies was higher only for patients ≥30 years of age (8.0 compared to 4.9%; $P < 0.01$), whereas the incidence of clinical abortion (after a gestational sac was seen on ultrasound) was higher for patients aged <30 years (15.9 versus 11.2%; $P < 0.01$; Table XVII). The increase in incidence of preclinical abortions was small, 5.8% in clomiphene versus 3.9% in spontaneous pregnancies (Table XVI), and might be the result of closer monitoring of clomiphene patients. The percentage of total abortions which were preclinical for both clomiphene and spontaneous cycles was less than observed by Zinaman *et al.* (1996) in closely monitored spontaneous cycles. We have shown, however, that a more likely cause is deficient endometrial development, due to the anti-oestrogenic effect of clomiphene (Table III; Dickey *et al.*, 1993b).

The finding of a much greater incidence of total abortion and preclinical abortion in HMG/FSH pregnancies (36.4%/11.3%; Table XVI) is inconsistent with either clomiphene being uniquely a cause of abortion or a deficiency of endometrial thickness being the primary factor in preclinical abortion, because thickness is greater in HMG/FSH than in clomiphene cycles (Dickey *et al.*, 1993a,b). However, it does not preclude the supposition

that most preclinical abortions are due to poor endometrial environment, since other endometrial factors may be responsible.

Some investigators have suggested that clomiphene adversely affects the quality of the oocyte or conceptus, based on in-vitro studies in mice (Laufer *et al.*, 1982) and observations that chromosomal abnormalities are more common in abortions of clomiphene cycles (Boué and Boué, 1973). However, use of clomiphene for IVF does not appear to impair oocyte quality or reduce the implantation rate (Dlugi *et al.*, 1985). Moreover, we found no relationship between clomiphene dose and abortion rates (Table XVIII) in IUI cycles, as would be expected if there were a direct effect of clomiphene on oocytes or embryos.

Regan *et al.* (1990) and Clifford *et al.* (1994) have postulated that increased spontaneous abortions in clomiphene patients may be related to raised pre-ovulatory LH or androgen concentrations. More recently, Clifford *et al.* (1996) have shown in a double-blind, controlled study of patients with raised LH suppressed by GnRH or left unsuppressed, that LH is not responsible for increased abortions. Others (Garcia *et al.*, 1977; Hammond and Taubert, 1982; Rodin *et al.*, 1994) have speculated that clomiphene might prevent abortions due to luteal insufficiency by increasing the concentration of progesterone. We found no evidence that total abortions were higher in clomiphene-IUI cycles in patients with PCO or ovulation disorders in general than in patients with ovulatory cycles (Table XIX). When the outcome of all pregnancies in patients with PCO was investigated, clomiphene use was associated with a decreased incidence of clinical abortion in patients diagnosed with PCO (15.3 compared with 20.7%) and luteal insufficiency (17.5 compared with 24.4%). The incidence of preclinical abortion was not affected by the use of clomiphene in patients with PCO or luteal insufficiency (Dickey *et al.*, 1996).

Effect of clomiphene dose

Information about the relationship of drug dose to pregnancy or multiple births is limited to four studies (Corson *et al.*, 1983; Hammond *et al.*, 1983; Groll, 1984; Dickey *et al.*, 1992a). Such information is important because, in many clinics, no more than 100 mg/day of clomiphene is used, in the hope of preventing multiple pregnancy and hyperstimulation. There is, however, no documentation that this is effective in preventing either of these events, and such a restriction may, in fact, markedly reduce the possibility of pregnancy (Dickey *et al.*, 1992). The effect of clomiphene dose, from 25 to 250 mg, in clomiphene-IUI cycles is shown in Table XVIII. The dose of clomiphene was positively related to pregnancy rates and birth rates, but not to multiple birth rates, abortion or ectopic pregnancies. Doses >100 mg/day were responsible for 16% of births and 11% of multiple births. Doses >100 mg were required for pregnancy in 27% of women who weighed >90 kg (198 lb), compared to 11% who weighed 45–59 kg (100–131 lb) (Table I). Doses of 25 mg were enough for pregnancy in 3% of women.

Table XVI. Pregnancy outcome according to ovulation induction regimen. Values in parentheses are percentages[a]

Pregnancy outcome	None	CC	CC + HMG/FSH	HMG/FSH
Total[b]	3484	1744	292	107
Outcome unknown				
Before 14 weeks	13 (0.4)	6 (0.3)	0 (0.0)	0 (0.0)
After 14 weeks	317 (9.1)	40 (2.3)	0 (0.0)	0 (0.0)
Delivered[c]	2446 (100.0)	1286 (100.0)	208 (100.0)	68 (100.0)
Single	2404 (98.3)	1166 (90.7)	174 (83.6)	48 (70.6)
Multiple	42 (1.6)	120 (9.3)[g]	34 (16.3)[g,j]	20 (29.4)[g,j]
Twins	42 (1.6)	116 (9.0)[g]	28 (13.4)[g,h]	18 (26.5)[g,j]
Triplets	0 (0.0)	4 (0.3)[g]	6 (2.9)[g,j]	2 (2.9)[g]
Spontaneous abortions[d]	708 (20.4)	412 (23.7)[f]	87 (28.8)[e]	39 (36.4)[f,i]
Preclinical	137 (3.9)	100 (5.8)[f]	28 (9.6)[g]	12 (11.3)[e,h]
Clinical	571 (16.4)	312 (18.0)	56 (19.2)	27 (25.2)

[a]Adapted from Dickey (1996). Reproduced with permission of the publisher.
[b]Exclusive of ectopic pregnancy ($n = 255$) and in-vitro fertilization or gamete intra-Fallopian transfer ($n = 654$).
[c]Percentage of delivered pregnancies.
[d]Percentage of total pregnancies with known outcome at 14 weeks exclusive of ectopic pregnancies.
[e–j]Results of χ^2 analysis: compared to no ovulation induction regimen (none), [e]$P < 0.05$, [f]$P < 0.01$, [g]$P < 0.001$; compared to clomiphene, [h]$P < 0.05$, [i]$P < 0.01$, [j]$P < 0.001$.
CC = clomiphene citrate; HMG = human menopausal gonadotrophin; FSH = follicle stimulating hormone.

Table XVII. Relationship of age to abortion in spontaneous and clomiphene-induced pregnancies[a]

Age (years)	Spontaneous pregnancies				Clomiphene pregnancies			
	No. of pregnancies[b]	No. (%) preclinical abortions	No. (%) clinical abortions	Total no. (%) abortions	No. of pregnancies[b]	No. (%) preclinical abortions	No. (%) clinical abortions	Total no. (%) abortions
<30	1617	49 (3.0)	182 (11.2)	231 (14.3)	895	33 (3.7)	142 (15.9[e])	175 (19.6[e])
>30	1803	88 (4.9)	388 (21.5)	476 (26.4)	841	67 (8.0[d])	170 (20.2)	237 (28.2)

[a]Adapted from Dickey *et al.* (1996). Reproduced with permission of the publisher.
[b]Exclusive of ectopic and in-vitro fertilization or gamete intra-Fallopian transfer; outcome unknown before 14 weeks (spontaneous, $n = 13$; clomiphene, $n = 6$) and missing maternal age (spontaneous, $n = 51$; clinical abortion, $n = 1$; clomiphene, $n = 2$; abortion, $n = 0$)
[c]Percentage of total pregnancies.
[d,e]Results of χ^2 analysis for clomiphene versus spontaneous pregnancy: [d]$P < 0.01$; [e]$P < 0.001$.

Table XVIII. Relationship of clomiphene citrate (CC) dose to pregnancy in intrauterine insemination cycles[a].

Dose of CC[d] (mg)	Cycle no.	No. (%) pregnancies	% Preclinical abortions[b]	% Clinical abortions[b]	% Ectopic pregnancies[b]	No. (%) births	No. (%[c]) multiple births	
							Twins	Triplets
25	145	10 (6.9)	0.0	20.0	10.0	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)

[a]Adapted from Dickey *et al.* (1997). Reproduced with permission of the publisher.
[b]Percentage of pregnancies.
[c]Percentage of births.
[d]Relationship of CC dose to pregnancy rate : $r = 0.05$, $P = 0.004$, and to birth rate : $r = 0.04$, $P = 0.011$.

Effect of clomiphene on outcome of multiple pregnancy

Twin births occur in ~10–12.3% of clomiphene pregnancies, according to information from series comprising ≥1000 births. In the original study conducted during the 1960s (Macgregor *et al.*, 1968), 123 of the 1201 live births (10.2%) were twins and 13 (1.1%) were triplets or higher order, including quadruplets and quintuplets. In our experience, the incidence of twin births was 9.0% and triplets was 0.3% (Table XVI). The slightly higher incidence of multiple births observed by Macgregor *et al.* (1968), in a study performed at least a decade earlier, may have been due to younger age of his patients, although the age was not stated, or to the higher percentage of his patients with WHO type II anovulation (86%). In our series, the average age of patients who became pregnant after treatment with clomiphene was 29.4 years, and 50% had WHO type II anovulation, including luteal insufficiency. Multiple pregnancies were unrelated to clomiphene dose in our series and also in that of Groll (1984), who analysed the outcome of 700 clomiphene pregnancies from his practice.

Schneider *et al.* (1979) reported resorption of one sac in 63% of spontaneous pregnancies and in 64% of clomiphene pregnancies in a study of 78 twin pregnancies diagnosed by ultrasound during the first trimester. In our larger study of 292 similarly diagnosed twin pregnancies, we found that two babies survived to term in 65% of clomiphene pregnancies, compared to 40% of spontaneous pregnancies, and that reabsorption of one or both sacs occurred in 35% of clomiphene pregnancies, compared to 60% of spontaneous ovulation pregnancies (Table XX; Dickey *et al.*, 1990). The percentage of twin sacs ending in twin births was also increased in HMG cycles, compared to unstimulated cycles, but the difference was not significant. The higher survival rate of twins in clomiphene pregnancies may have been due to higher oestrogen and progesterone concentrations during the first trimester (Dickey and Hower, 1995). Higher survival rates may also have been the result of greater uniformity of follicular and oocyte development at the time of ovulation. Twin pregnancies are more likely to progress to term if the difference in diameter of gestational sacs when first visualized by ultrasound during the fifth to sixth week of gestation is <3 mm (Dickey *et al.*, 1992b).

Table XIX. Effect of diagnosis on abortion in clomiphene and spontaneous pregnancies. For each patient, more than one diagnosis was possible[a]

Diagnosis	Spontaneous pregnancies				Clomiphene pregnancies			
	No. of pregnancies	No. (%[b]) preclinical abortions	No. (%[b]) clinical abortions	Total no. (%[b]) abortions	No. of pregnancies	No. (%[b]) preclinical abortions	No. (%[b]) clinical abortions	Total no. (%[b]) abortions
Ovulation	2481	91 (3.7)	357 (14.8)	448 (18.0)	408	24 (5.9[c])	70 (17.2)	94 (23.2[c])
Anovulation	990	46 (4.6)	214 (21.6)	260 (26.3)	1330	72 (5.4)	225 (16.9[d])	297 (22.3[c])
Polycystic ovaries	403	19 (4.7)	83 (20.7)	102 (25.4)	476	19 (4.0)	73 (15.3[c])	92 (19.4[c])
Luteal insufficiency	430	23 (5.3)	105 (24.4)	128 (29.8)	804	49 (6.1)	141 (17.5[d])	190 (23.6[c])
Other	167	4 (2.4)	28 (16.6)	32 (18.9)	45	5 (7.4[d])	14 (20.6[c])	19 (27.9[c])

[a]Adapted from Dickey *et al.* (1996). Reproduced with permission from publisher.
[b]Percentage of total pregnancies.
[c,d]Results of χ^2 analysis for comparisons to spontaneous pregnancy: [c]$P < 0.05$, d$P < 0.01$.

Table XX. Effect of ovulation induction on number of babies born when twin gestational sacs are present[a]

Treatment	No. of patients	No. (%) of babies born			No. of babies per sac
		0	1	2	
None	37	7 (18.9)	15 (40.5)	15 (40.5)	0.608
CC	113	7 (6.2)	33 (29.2)	73 (64.6)[b]	0.792
HMG	71	8 (11.3)	25 (35.2)	38 (53.5)	0.711
IVF/GIFT	43	6 (13.9)	15 (34.9)	22 (51.2)	0.686
Other	28	2 (7.1)	10 (35.7)	17 (57.1)	0.750

[a]From Dickey *et al.* (1990). Reproduced with permission from publisher.
[b]Different from 'none', $P = 0.012$.
CC = clomiphene citrate; HMG = human menopausal gonadotrophin; IVF = in-vitro fertilization; GIFT = gamete intra-Fallopian transfer.

Table XXI. Occurrence of ectopic pregnancy in clomiphene-treated and untreated infertility patients[a]

Diagnosis	No clomiphene		With clomiphene	
technique	No. of pregnancies	No. (%) ectopic pregnancies	No. of pregnancies	No. (%) ectopic pregnancies
No pelvic disease				
None[b]	1151	16 (1.4)	765	6 (0.8)
IVF	4	0 (0.0)	17	0 (0.0)
GIFT	2	0 (0.0)	38	1 (2.6)
Tubal disease				
None[b]	336	38 (11.3)	134	24 (17.9)
IVF	10	1 (10.0)	35	1 (2.8)
GIFT	0	0 (0.0)	10	1 (10.0)
Endometriosis				
None[b]	599	18 (3.0)	492	17 (3.4)
IVF	9	1 (11.1)	24	1 (4.2)
GIFT	8	1 (12.5)	68	3 (4.4)
Total				
None[b]	2086	72 (3.4)	1391	47 (3.4)
IVF	23	2 (8.7)	76	2 (2.6)
GIFT	10	1 (10.0)	116	5 (4.3)

[a]From Dickey *et al.* (1989). Reproduced with permission of the authors and the publisher.
[b]The category 'none' includes intrauterine insemination.
IVF = in-vitro fertilization; GIFT = gamete intra-Fallopian transfer.

Table XXII. Percentage of male births by drug and technique in singleton pregnancies and the effect of clomiphene on birth and sex ratio[a]

Source[b]	Category	Total births	Known outcome	Total births	No. (%) female births	No. (%) male births	Sex ratio male/female
A	No drug, no insemination	2715	2346	1885	963 (51.1)	922 (48.9)	0.957
A	Clomiphene, no insemination	1186	1133	904	453 (50.1)	451 (49.9)	0.996
B	Clomiphene, no insemination	2155	2026	1568	777 (49.5)	791 (50.5)	1.018
A	No drug, husband or donor insemination	76	75	59	26 (44.1)	33 (55.9)	1.269
C	No drug, donor insemination	195	187	162	64 (39.5)	98 (60.5)	1.531
A	Clomiphene, husband or donor insemination	191	187	149	80 (53.7)	69 (46.3)	0.862
C	Clomiphene, donor insemination	123	119	89	48 (53.9)	41 (46.1)	0.854

[a]Adapted and revised from Dickey *et al.* (1995a). Reproduced with permission from publisher.
[b]A = Fertility Institute of New Orleans, unpublished data; B = Holtkamp (1984) cited in Corson *et al.* (1984); C = Sampson *et al.* (1983).

Does clomiphene increase the rate of ectopic pregnancy?

Although several reports have suggested that the rate of ectopic pregnancies is increased following use of clomiphene in cycles of coitus (Powell-Phillips, 1979; Chaukin, 1982; Marchbanks *et al.*, 1985) or when clomiphene was used in combination with HMG for IVF (Cohen *et al.*, 1986; Snyder and del Castillo, 1988), these studies were not controlled for endometriosis and tubal disease. In a previous study, we found no difference in the incidence of ectopic pregnancy between 2086 spontaneous and 1391 clomiphene pregnancies following coitus or IUI in patients who did not have pelvic disease or endometriosis (Table XXI; Dickey *et al.*, 1989). All evidence points to underlying endometrial or tubal disease as the cause of ectopic pregnancy when ovulation induction drugs are used.

Does clomiphene affect sex ratio?

The impression that clomiphene results in an increased proportion of female births is based on mainly small studies, or meta-analysis with all the bias and errors that are inherent in such analyses. The papers most often cited as evidence of decreased male births are James (1980) and James (1985). These papers include many cases in which HMG, not clomiphene, was used. The majority of patients in James' 1980 report had received HMG and 43% of those births were male, which negates James' argument for a clomiphene-specific effect. His 1985 meta-analysis included 496 singleton births of which 48.4% were male (95% confidence interval is 44–52.8%). James' (1985) findings are contravened by other much larger studies from single sources (Holtcamp cited in Corson *et al.*, 1984; Corson *et al.*, 1983; Dickey *et al.*, 1995a,b; Table XXII).

In the largest series of clomiphene births to date (Holtkamp, 1984; cited in Corson *et al.*, 1984), 50.5% of 1568 singleton births were male. In our own series of 904 consecutive singleton births following clomiphene without IUI, we found 49.9% males compared to 48.9% males in 1885 births following spontaneous ovulation (Table XXII; Dickey, 1995a). The male birth rate dropped to 46.3% when IUI was performed after clomiphene. Sampson *et al.* (1983) noted 60.5% male births in a total of 162 births following spontaneous ovulation and donor insemination, which fell to 46.1% male births when clomiphene was used before donor insemination. Similarly, but in a smaller group of patients, we noted 46.3% male births when clomiphene was used before IUI. Therefore, the most that it is possible to conclude is that the male birth rate following coitus is not affected by clomiphene. It is possible, but remains to be proven in sufficiently large and properly designed studies, that male births may be increased by IUI and that clomiphene may negate that effect when used in cycles of IUI.

Conclusions

Clomiphene remains the drug of first choice both for women suffering from anovulation and ovulating women with inadequate follicular or luteal development. Conception in clomiphene cycles of women who have adequate cervical mucus and whose husbands have normal semen is related to four factors: the number and size of pre-ovulatory follicles, the state of the endometrial lining, presence or absence of pelvic disease, and inherent oocyte quality, which in turn is in part age-related. The largest series of clomiphene patients, analysed by life-table or per-cycle methods, show that clomiphene is effective through at least six cycles of treatment, and that there is no

evidence that clomiphene significantly increases spontaneous abortion and ectopic pregnancy rates, or decreases the number of male births.

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