

# Modern use of clomiphene citrate in induction of ovulation

E.Kousta<sup>1</sup>, D.M.White and S.Franks

Department of Obstetrics and Gynaecology, Imperial College School of Medicine at St. Mary's, London W2 1PG, UK

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**Clomiphene citrate is the treatment of first choice in the management of infertility in normally oestrogenized, anovulatory women (WHO group II). The majority of women with 'pure' anovulatory infertility respond to treatment with clomiphene citrate. The rates of pregnancy and miscarriage are close to those expected in a normal fertile population. Basal hormone concentrations do not predict outcome. An increased body mass index is the only factor which is consistently associated with a decreased response to clomiphene citrate; it follows therefore, that weight reduction should be an important part of therapy in anovulatory women. According to our data, only an increased luteinizing hormone value immediately post clomiphene citrate predicted an adverse pregnancy outcome in women who conceived. Clomiphene citrate, along with other ovulation induction therapies, can cause multiple follicular development, with a risk of ovarian hyperstimulation and multiple pregnancy. Ultrasound monitoring of treatment is important in order to choose the appropriate dose of clomiphene citrate in subsequent cycles and to minimize the risks of hyperstimulation and multiple pregnancy. When couples with other factors contributing to subfertility are excluded, the cumulative conception rate continues**

**to rise after 6 months of treatment with clomiphene citrate, reaches a plateau by treatment cycle 12 and approaches that of the normal population. It has been reported that prolonged use of clomiphene citrate may be associated with an increased risk of a borderline or invasive ovarian tumour. Taking into consideration these observations, we recommend that anovulatory women responsive to clomiphene citrate should be treated for at least 6 cycles before considering more complex or invasive methods of ovulation induction, and that treatment should probably be limited to a maximum of 12 cycles.**

*Key words:* clomiphene/induction of ovulation/LH/outcome

## Introduction

Clomiphene citrate has been used for induction of ovulation since 1962. It is the treatment of first choice in women with ovulatory disorders who are normally oestrogenized, i.e. predominantly those with polycystic ovaries (PCO). Clomiphene citrate has both oestrogenic and anti-oestrogenic properties (Adashi *et al.*, 1984). Acting as an anti-oestrogen, clomiphene citrate is thought to displace endogenous oestrogen from hypothalamic and pituitary oestrogen receptor sites. In functional terms, this has been interpreted to result in the alleviation of negative feedback exerted by endogenous oestrogens, resulting in a favourable alteration in the characteristics of pulsatile gonadotrophin-releasing hormone (GnRH) secretion. Most of the data suggest that clomiphene citrate has an oestrogenic, rather than anti-oestrogenic, effect at the pituitary and ovarian level. Whatever the primary mechanism of action, clomiphene citrate causes a >50% increase in endogenous follicle stimulating hormone (FSH) which stimulates follicular growth (Adashi *et al.*, 1984). The rise in FSH is accompanied by an equally large increase in the serum luteinizing hormone (LH) concentration. The elevated concentrations may persist during

<sup>1</sup>To whom correspondence should be addressed. Tel: +44 (0)171 724 2306; Fax: +44 (0)171 886 6037

the mid and late follicular phases of the cycle (Polson *et al.*, 1989). It is unclear whether the increase in LH influences outcome in patients being treated with clomiphene citrate and whether basal endogenous LH secretion affects outcome.

Hull *et al.* (1985), in a large population study, reported that among 708 couples who needed specialist help for infertility, failure of ovulation occurred in 21% of cases. Over 30% of patients presenting to our infertility clinic have a disorder of ovulation as the major cause of infertility. The majority of these patients have polycystic ovary syndrome (PCOS). The characteristic biochemical abnormalities associated with PCOS are hyperandrogenaemia and hypersecretion of LH.

Studies with clomiphene citrate have shown an ovulation rate of 60–85% and a pregnancy rate of 30–40% (MacGregor *et al.*, 1968; Garcia *et al.*, 1977; Gorlitsky *et al.*, 1978; Gysler *et al.*, 1982; Hammond *et al.*, 1984; Dickey *et al.*, 1996). Miscarriage rates in the same studies have been reported to be between 13 and 25%. The factors influencing response to clomiphene citrate and treatment outcome are unclear, although non-responders to clomiphene citrate tend to be overweight (Lobo *et al.*, 1982; Polson *et al.*, 1989). Hypersecretion of LH has shown to be associated with poor reproductive outcome in women who conceive spontaneously (Regan *et al.*, 1990). Hypersecretion of LH is frequently seen in women with recurrent miscarriage (Sagle *et al.*, 1988; Watson *et al.*, 1993) and persistently elevated LH concentrations predict a poor outcome in anovulatory PCOS women given human menopausal gonadotrophin (HMG) to induce ovulation (Hamilton-Fairley *et al.*, 1991). However, the mechanism whereby increased LH exerts a deleterious effect is unknown.

Induction of ovulation with clomiphene citrate is, in principle, very simple, but in practice requires careful (but not necessarily frequent) monitoring to achieve optimal results. In this article, the overall experience of induction of ovulation with clomiphene citrate, as well as possible factors affecting treatment outcome, are reviewed. In addition, the effect of LH and androgen concentrations prior to and immediately after administration of clomiphene citrate and in the luteal phase of treatment, as well as the influence of other major factors contributing to subfertility, i.e. sperm function and tubal disease, on the outcome of treatment with clomiphene citrate of 128 patients treated in our own centre are summarized.

### The use of clomiphene citrate

In anovulatory women, the aim of ovulation induction therapy is to produce a single dominant follicle. The

effectiveness of clomiphene citrate for induction of ovulation in normally oestrogenized women is well established. As previously mentioned, studies have shown an ovulation rate of 60–85% and a pregnancy rate of 30–40% (MacGregor *et al.*, 1968; Garcia *et al.*, 1977; Gorlitsky *et al.*, 1978; Gysler *et al.*, 1982; Hammond *et al.*, 1984; Dickey *et al.*, 1996). Aside from pregnancy, the criteria for ovulation included temperature charts, serum progesterone measurements, endometrial biopsies and urinary pregnanediol determinations. Temperature charts are a crude method of assessing ovulation that has been used extensively in the past. Endometrial biopsy shows whether endometrial development is synchronous with endocrine parameters. The technique is, however, painful and expensive and Jacobson and Marshall (1980) noted significantly reduced conception rates in cycles of HMG/HCG (human chorionic gonadotrophin)-treated patients who underwent biopsy, suggesting that biopsy may interfere with early nidations.

It is accepted that a single mid-luteal progesterone measurement is adequate to assess ovulation (Hull *et al.*, 1982; Talbert, 1983). In addition, serial pelvic ultrasonography provides accurate monitoring of follicular development (Polson *et al.*, 1989). The size and number of follicles within each ovary can be recorded, as well as the uterine cross-sectional area and endometrial thickness. The time of ovulation can be identified accurately, ensuring correct timing of intercourse, which is particularly helpful in women with a variable cycle length. The adequacy of the luteal phase can be assessed by the measurement of the endometrium and correct timing of serum progesterone measurement. It is also possible to identify those patients who either do not develop a dominant follicle in response to clomiphene or those with multiple follicles, and to adjust the dose up or down, accordingly, in the subsequent cycle.

The reason for the failure to ovulate in 15–40% of anovulatory women who do not respond to clomiphene citrate, remains unclear. Lobo *et al.* (1982), in a prospective study of 158 anovulatory women, pointed out that body weight was positively correlated with the dose required to achieve ovulation. Polson *et al.* (1989) studied 40 cycles of 27 anovulatory women, treated with 100 mg clomiphene citrate/day for 5 days, and confirmed that overweight women respond less well to clomiphene citrate than women of normal weight. They showed that, in most cases, absence of folliculogenesis, despite an appropriate rise in serum FSH concentrations, was the reason for anovulation. They concluded that, as most anovulatory cycles after administration of clomiphene citrate are characterized by lack of development of a dominant follicle, there is no rationale for the routine administration of a mid-cycle dose of HCG in clomiphene non-responders, apart from those

few cases who have been detected to have an absence of an LH surge (Polson *et al.*, 1989). In their experience, patients who fail to respond to 100 mg of clomiphene citrate will not ovulate when given higher doses (Polson *et al.*, 1989). Possible explanations for the failure of women to ovulate despite a significant rise in serum FSH concentrations between days 5 and 7 may be due to diminished biological activity (Reichert, 1986) or altered requirements of the follicle for FSH at the ovarian level by paracrine factors, such as the action of locally produced polypeptide growth factors (Franks *et al.*, 1988).

Clomiphene citrate, along with other ovulation induction therapies, can cause multiple follicular development, with the risk of ovarian hyperstimulation and multiple pregnancy. Reports of multiple gestation vary from 8 to 13% for patients receiving clomiphene citrate treatment (Scialli *et al.*, 1986). More recent data on triplets or higher order births from the series reported by Levene *et al.* (1992) indicated that there were more triplet pregnancies following ovulation induction therapy than in-vitro fertilization (IVF). Of the patients with a triplet pregnancy following ovulation induction, 58% had conceived after receiving clomiphene citrate compared with 42% after HMG. The risk of multiple pregnancy and the variable response of patients to different doses of clomiphene citrate emphasize the necessity to monitor at least the first clomiphene citrate cycle to ensure each patient has the appropriate dose.

Previous studies of ovulation induction with clomiphene citrate have reported a variable miscarriage rate from 13 to 25%. This is similar to the sporadic miscarriage rate, which is estimated to be up to 15%. Some of the variation between series may be explained by differing definitions of pregnancy, in particular whether biochemical pregnancies were included. In addition, women undergoing infertility treatment are more likely to have earlier detection of pregnancy and more complete ascertainment of early abortion than in the general population. In the large series reported by Dickey *et al.* (1996), the biochemical and clinical abortion rates were compared for clomiphene citrate-induced cycles in a series of subgroups that included anovulatory women and those with luteal phase deficiency. These data were compared to those for patients seen in the clinic who conceived spontaneously. In the subgroup of anovulatory women there were no differences in the total and biochemical abortion rates between the two groups, and the clinical abortion rate was lower in the clomiphene citrate-treated group (21.8 versus 17.7%,  $P < 0.05$ ). This suggests that the miscarriage rate is not significantly increased in anovulatory women given clomiphene citrate.

It has also been suggested that use of clomiphene citrate is associated with an increased risk of ectopic pregnancy, congenital malformations and adverse perinatal outcome. The majority of this information is from clomiphene citrate-induced pregnancies in the context of assisted reproductive techniques. The extensive review by Venn and Lumley (1994) assessing the available data on pregnancy outcome after administration of clomiphene citrate was careful to separate the available information for clomiphene citrate used for ovulation induction from the available data for when clomiphene citrate was used for superovulation. They concluded that there were insufficient data to indicate that clomiphene citrate was associated with an increased risk of ectopic pregnancy. Descriptive studies suggest an incidence of ectopic pregnancy after administration of clomiphene citrate of 0.5–4.4%. This compares with the estimated incidence in the general population of 0.7–0.8%. The possible increase in preterm birth or adverse perinatal outcome after clomiphene citrate may reflect the increased incidence of multiple pregnancy. With the absence of data on appropriate comparison groups, the role of clomiphene citrate has not been defined. This also applies to the possible association of clomiphene citrate and congenital malformations, particularly neural tube defects. Although concerns have been raised, there is inadequate prospective data to answer these questions and surveillance at a larger population level is required.

### LH hypersecretion, ovarian steroids and pregnancy outcome

Hypersecretion of LH, which is typically seen in women with PCOS, has been shown to be associated with poor reproductive performance. It has been suggested that a high LH concentration in the mid-follicular phase directly and adversely affects the timing of maturation of the oocyte, resulting in release of an 'aged' oocyte (Homburg *et al.*, 1988). An alternative theory is that LH has a deleterious effect on the preparation of the endometrium for implantation. HCG/LH binding sites are present in the endometrium, with the highest concentrations in the luteal phase of the cycle (Reshef *et al.*, 1989). High LH concentrations therefore have the potential to alter the local metabolism of steroids or prostaglandins and disrupt implantation. The data that have clearly shown the association between LH hypersecretion and poor pregnancy outcome are in spontaneously ovulating women in whom, despite the presence of ovulatory progesterone concentrations, mid-follicular LH measurements in the

subsequent cycle were higher than expected (Regan *et al.*, 1990). Persistently elevated LH concentrations predict a poor outcome in anovulatory PCOS women given HMG to induce ovulation (Hamilton-Fairley *et al.*, 1991). However, the serum LH concentration in anovulatory women treated with clomiphene citrate prior to induction of an ovulatory cycle predicts neither the ovulatory response to clomiphene citrate nor treatment outcome (Lobo *et al.*, 1982). These findings are similar to those in anovulatory PCOS women treated with HMG (White *et al.*, 1996). Although it has been shown that pituitary suppression of high LH concentrations by exogenous luteinizing hormone-releasing hormone (LHRH) analogue therapy does not improve the outcome of pregnancy in women with a history of recurrent miscarriage (Clifford *et al.*, 1996), this does not exclude a role for elevated LH in the mechanism of early miscarriage during induced cycles.

The association of raised LH with ovarian steroid concentrations and pregnancy outcome has also been investigated. Serum testosterone concentrations have been shown to be raised in the follicular phase and urinary oestrone-3-glucuronide excretion was found to be raised in the early luteal phase of the cycle in women with a history of pregnancy loss who ovulate spontaneously (Watson *et al.*, 1993). Altered steroid values during the early luteal phase may, therefore, be a possible cause of asynchronous endometrial development, increasing the likelihood of disordered implantation.

### Endocrine and non-endocrine factors affecting the outcome of induction of ovulation with clomiphene citrate: St. Mary's Hospital series

Over the course of 2.5 years, 167 patients presenting to the infertility clinic at St. Mary's Hospital, London were diagnosed to be anovulatory and were treated with clomiphene citrate. Of these, 39 patients were excluded from further analysis because either ovarian morphology was not documented or was uncertain ( $n = 15$ ), or the patients were perimenopausal ( $n = 3$ ), or had not responded to clomiphene citrate in the past and proceeded to ovarian diathermy as an alternative treatment for ovulation induction and subsequently restarted clomiphene citrate ( $n = 11$ ), or initially presented with recurrent miscarriage but then had a conception delay due to the development of anovulation ( $n = 10$ ). Data from the remaining 128 patients are presented here. Of these patients, 14 (11%) had normal ovarian morphology on ultrasound scan and the remaining 114 (89%) had PCO. The diagnosis of PCO was based on ultrasound criteria, although 55% of women with PCO on ultrasound also had either a raised LH and/or an elevated testosterone

measurement. Serum LH and FSH were measured using the Abbott Laboratories IMX Method, which is a microparticle enzyme immunoassay commercial kit supplied by Abbott Laboratories (Maidenhead, UK). The coefficients of intra-assay variation (%) were 4.5–6.7 for FSH and 4.4–4.7 for LH over the working range of the assay. The coefficients of inter-assay variation were 4.7 for FSH and 5.6 for LH. Testosterone was measured by radioimmunoassay as previously described (Adams *et al.*, 1986).

Fifteen (11.7%) women did not ovulate on clomiphene citrate. Only one non-responder had normal ovaries on ultrasound; the rest had PCO. Of the 113 (88.3%) patients who responded to clomiphene citrate and completed treatment, 100 had PCO. Table I compares the age, body mass index (BMI) and basal and post clomiphene citrate hormone data in responders and non-responders. Statistical comparison between groups was performed by analysis of variance following log transformation of data where appropriate. There were no significant differences in age, baseline LH, FSH and testosterone and post clomiphene citrate (day 10) LH, FSH and testosterone measurements between responders and non-responders. However, BMI was significantly elevated in the non-responders group ( $P < 0.05$ ).

**Table I.** Mean (SD) clinical and endocrine data in women given clomiphene citrate who ovulated (responders) and those who did not (non-responders). Statistical comparison between groups was by analysis of variance following log transformation of data where appropriate

	Responders ( $n = 113$ )	Non-responders ( $n = 15$ )
Age (years)	30.5 (5.3)	31.8 (5.7)
Body mass index (kg/m <sup>2</sup> )	24.9 (4.4)	27.2 (3.1) <sup>a</sup>
Basal LH (IU/l)	9.5 (7.2)	9.8 (4.6)
Basal FSH (IU/l)	5.8 (1.6)	5.9 (2.9)
Basal testosterone (nmol/l)	2.8 (1.2)	3.0 (1.2)
Post clomiphene LH (IU/l)	11.5 (7.2)	13.7 (7.5)
Post clomiphene FSH (IU/l)	6.3 (4.3)	7.4 (3.5)
Post clomiphene testosterone (nmol/l)	3.3 (1.3)	4.2 (1.8)

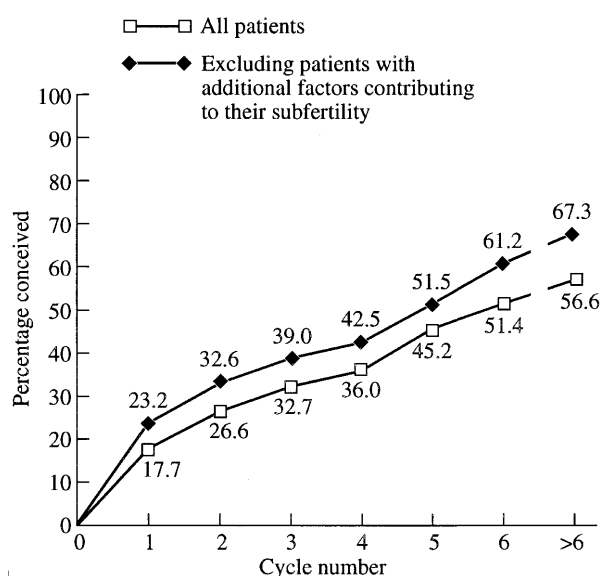
LH = luteinizing hormone; FSH = follicle stimulating hormone.  
<sup>a</sup> $P < 0.05$ .

Of the 113 patients who responded to clomiphene citrate, 55 (49%) conceived. Thirty four (29%) women completed more than six cycles of treatment but did not conceive. The remaining 24 (22%) women dropped out before completing six cycles of treatment, usually because of difficulties in the couple's relationship; only one patient stopped because of side effects of clomiphene citrate.

There were no significant differences between those who conceived on clomiphene citrate ( $n = 55$ ) and those who did not ( $n = 58$ ) in age, BMI, baseline FSH and testosterone and post clomiphene citrate (day 9–11 and mid-luteal phase) FSH and testosterone measurements. Basal LH was significantly higher in patients who conceived [mean (SD) 11.2 (8.3)] compared to women who did not conceive [7.8 (5.6);  $P = 0.03$ ]. However, there was no significant difference between the two groups when LH concentrations immediately post clomiphene citrate or in the mid-luteal phase were compared.

Thirteen (23.6%) of the 55 pregnancies ended in miscarriage. All were early pregnancy losses occurring before the 9th week of gestation. There was one ectopic pregnancy (2%) and the remaining 42 pregnancies ended in live births or are ongoing. In Table II the hormonal data in women who miscarried ( $n = 13$ ) are compared with those for patients who had a successful outcome of pregnancy ( $n = 42$ ). There was no significant difference in age, BMI, baseline LH, FSH and testosterone and post clomiphene citrate (day 10) FSH and testosterone and mid-luteal LH, FSH and testosterone between the two groups. The only difference in hormonal data between the groups was that, in the group that miscarried, the LH concentration post clomiphene citrate was significantly higher than in the patients who had a successful pregnancy [15.5 (4.4) versus 12.0 (7.9);  $P = 0.04$ ]. Despite significant overlap in LH values between the two groups, 37% of the ongoing pregnancy group had a day 10 LH  $>10$  IU/l compared with 75% in the miscarriage group.

The multiple pregnancy rate was 11%, with six twin pregnancies but no higher order pregnancies. The overall pregnancy rate per cycle was 11%; however, 71% of pregnancies occurred within the first three cycles of treatment. The cumulative conception rate calculated for the 113 patients who responded to clomiphene citrate is shown in Figure 1. The cumulative conception rate was calculated by life table analysis. For each cycle of treatment, the calculation takes into account the drop-out rate as well as the pregnancy rate (Doody *et al.*, 1993). The cumulative conception rate at six cycles was 51.4%, rising to 56.6% in the patients who continued beyond six cycles of treatment. Of the 113 patients treated with clomiphene citrate, 44 (38.9%) had other factors contributing to their subfertility. In 25 of the couples, the male partner had a suboptimal sperm count ( $<3.5 \times 10^6$ /ml) as defined by a sperm separation test. Another eight women had evidence of tubal damage upon laparoscopy or HSG, but patency of at least one tube was confirmed and the partner's sperm count was normal. Four couples had both tubal and sperm



**Figure 1.** Cumulative conception following clomiphene citrate for up to 12 cycles.

dysfunction, and an additional seven couples had other identified factors, including uterine abnormalities. After recalculating the cumulative conception rate for the remaining 69 patients who had no known additional factors contributing to their subfertility, the cumulative conception rate rose to 61.2% at six cycles and to 67.2% at the completion of clomiphene citrate treatment (Figure 1).

From these data, ovarian morphology did not predict the response rate to clomiphene citrate nor outcome of treatment. As previously reported, there was a high response rate (88% of patients ovulating) to clomiphene citrate. The only factor identified which predicted non-responders was an increased BMI.

The LH concentrations during the late follicular phase of a clomiphene citrate-induced ovulatory cycle were higher in the group who miscarried. This observation supports the association between a raised serum LH in the follicular phase and pregnancy loss and is consistent with the theory of an adverse effect on oocyte maturation. Serum testosterone concentrations were not significantly altered by clomiphene citrate treatment and did not predict either the response to treatment or pregnancy outcome. The miscarriage rate of 23.6% reported in this study is similar to those of previous reports with clomiphene citrate treatment, which range from 13 to 25%. Although high LH concentrations immediately post clomiphene citrate were associated with a higher miscarriage rate, there was wide overlap with women who had ongoing pregnancies, so the mid-follicular LH value did not predict outcome in an individual patient.

**Table II.** Mean (SD) clinical and endocrine data on the patients who conceived, comparing patients who had a successful pregnancy with those who miscarried

	Patients with ongoing pregnancies/live births (n = 42)	Patients who miscarried (n = 13)
Age (years)	26.7 (4.6)	30.0 (5.2)
Body mass index (kg/m <sup>2</sup> )	24.8 (5.3)	25.0 (4.6)
Basal LH (IU/l)	11.2 (8.7)	11.5 (4.6)
Basal FSH (IU/l)	5.8 (1.7)	5.5 (1.4)
Basal testosterone (nmol/l)	3.0 (1.3)	3.1 (1.2)
Post clomiphene LH (IU/l)	12.0 (7.9)	15.5 (4.4) <sup>a</sup>
Post clomiphene FSH (IU/l)	5.7 (2.0)	6.2 (1.8)
Post clomiphene testosterone (nmol/l)	3.2 (1.2)	3.6 (1.5)
Luteal LH (IU/l)	6.9 (5.2)	5.9 (2.5)
Luteal FSH (IU/l)	2.8 (1.1)	2.8 (1.1)
Luteal testosterone (nmol/l)	3.3 (1.2)	3.5 (1.5)

<sup>a</sup> $P < 0.05$ .

The cumulative conception rate with clomiphene citrate continues to rise after completing six cycles of treatment but reaches a plateau by treatment cycle 12. When couples with other factors contributing to subfertility are excluded, the cumulative conception rate approaches that of the normal population (61 versus 75% at 6 months; Hull *et al.*, 1985). Although Gysler *et al.* (1982) reported that 87.5% of those who conceived did so during the first three ovulatory cycles, in the St. Mary's Hospital series the conception rate continued to rise beyond six cycles. Our data support earlier recommendations that anovulatory women responsive to clomiphene citrate should be treated for 6–12 cycles (Hammond, 1984) before considering more complex or invasive methods of ovulation induction. However, following the recent retrospective report (Rossing *et al.*, 1994) that >12 cycles of clomiphene citrate might be associated with an increased risk of a borderline or invasive ovarian tumour, it would seem appropriate to limit exposure to clomiphene citrate to 12 cycles, at least until further data are available.

## Conclusions

The majority of women with oestrogen replete anovulatory infertility, most of whom have PCO, will ovulate in response to clomiphene citrate. Basal hormone concentrations do not predict outcome. An increased BMI is the only factor which is consistently associated with a decreased response to clomiphene citrate; it follows therefore, that weight reduction should be an important part of therapy in anovulatory women. Ultrasound monitoring of treatment is important in order to choose the

appropriate dose of clomiphene citrate in subsequent cycles and to minimize the risks of hyperstimulation and multiple pregnancy. The miscarriage rate in our series was 23.6% and is similar to that of previous reports. Although high LH concentrations immediately post clomiphene citrate were associated in our study with a higher miscarriage rate, supporting the theory that high LH in the mid-follicular phase adversely affects oocyte maturation; however, there was wide overlap with women who had ongoing pregnancies, so the mid-follicular LH concentration did not predict outcome in an individual patient.

The cumulative conception rate continues to rise after 6 months of treatment, reaching a plateau by treatment cycle 12 and approaches that of the normal population, when couples with other factors contributing to subfertility are excluded. There has been one retrospective report that prolonged use of clomiphene citrate is associated with an increased risk of a borderline or invasive ovarian tumour (Rossing *et al.*, 1994).

Taking into consideration these observations, we recommend that anovulatory women responsive to clomiphene citrate should be treated for at least six cycles before considering more complex or invasive methods of ovulation induction; treatment should probably be limited to a maximum of 12 cycles.

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