Review of Literature
For the successful conception and ovulation whole of the genital tract must be anatomically normal and physiologically healthy. Before proceeding toward treatment of any female for infertility, cause of infertility must be detected, whether it is failure of ovulation or hostile mucus or any other defect in genital tract related to tubes or uterine cavity. Ovulation failure is most common type of treatable cause of infertility. There are various methods to determine the ovulation and response of ovulation induction.

In 1987 Michael Vermish, Ascad A. Itzby, Val Davajan and Robert Israel presented monitoring techniques to predict and detect ovulation. Various methods were: Daily transvaginal ultrasonography, rapid measurement of S.leutinizing hormone, S. estradiol hormone levels, determination of urinary LH Kit with and recording of basal body temperature. The result demonstrated that 'Transvaginal Ultrasound' detected ovulation in all cycles.

Various methods, drugs, regimens are described by different authors to treat the ovulation defects. Most commonly used drug for ovulation induction is clomiphene citrate.

It was first synthesized in 1959 and was known as compound MRL/41. Unexpected and interesting biological activity in the field of reproduction

MRL/41 - Proprietary name of clomiphene citrate. physiology was encountered while evaluating an experimental compound MRL/41 as an infertility agent. In the rat, this compound has been known to have
pituitary gonadotrophic inhibiting and antifertility properties. Instead MRL/41 was found to possess a surprising potential for the induction of ovulating type cycle in amenorrhic female.

Robert B. Greenblatt, William E. Barfield, Edwin C. Jungech and Albert W. Ray in 1961 first employed this compound for ovulation induction in doses of 25-50 mg 2 or 3 times per day for period ranging from 8 days to 8 months.

They concluded their results as:

1. MRL/41, an analogue of non steroidal estrogenic, substance chlorotriansene (TGGE) appear to have a wide spectrum of biological activity. No toxic reaction of haemopoietic, renal, hepatic function have therefore been detected.

2. MRL/41 is not a progesterone like substance. This may be deduced from the fact that the thermogenic response was noticed only in the luteal phase of cycle in spite of continuous administration of the compound.

3. An anti estrogenic effect has been suggested by the occurrence of hot flushes in quite a few patients and by the fact that regressive changes took place in vaginal mucosa.

4. A salient feature of this drug is its apparent ability to modify pituitary ovarian imbalance in the human with resultant induction of ovulatory type menses. Such an action was evidenced by the secretory changes in the endometrium. The inhibition of ferning of cervical mucus and sustained corpus luteal effect as noted by prolonged thermogenic effect before the onset of menstruation.
In 1964, Mathew and Seller, C.W. used MER 29, another nonsteroidal estrogen antagonist for the ovulation induction. But this drug proved to be too toxic for use and was withdrawn from clinical trial.

In 1966, Fluker, Wang, Rowe carried out a study on 30 cases. They prescribed clomiphene citrate for 10 days and ovulation was observed in 47% of cases.

In 1974, Rust, Israel, Daniel and Mishell described individualized graduated therapeutic regime of clomiphene citrate starting from 50 mg x 5 day/cycle and increased upto 250 mg/day x 5 day. Ovulation rate was 91.4% and conception rate was 38.1%. Most of those who failed to conceive had additional infertility factors. When these multiple infertility factors are eliminated, pregnancy rate in clomiphene treated patients was 85.7%.

In 1976, James Evan & Laule Townsend described the different methods of induction of ovulation. Treatment plan utilized placebo, cyclical steroid therapy, clomiphene citrate and human pituitary gonadotropin for the induction of ovulation in carefully selected potentially fertile females. Successful ovulation was induced in 99.5% and pregnancy rate was 61.9%. The success rates for ovulation with placebo therapy was 35%, with cyclical steroid therapy was 18.4%, with clomiphene citrate was 80.7% and with gonadotropin it was 100%. Pregnancy rate was recorded 56% with clomiphene citrate and 92% with gonadotropins.

Herlihy et al in 1981 presented their experienced with 30 cases, out of which 21 ovulated after receiving 50-250 mg clomiphene citrate upto 25th day of the cycle. In the same year Lobo et al. tried clomiphene
Garcia-Florus and Vazquez Mendez studied in 1984 the effect of progressive increasing doses and duration of clomiphene citrate in anovulatory cases. Majority of patients (85.7%) ovulated within the first 3 cycles after receiving 100 mg of clomiphene citrate from day 5th of menstrual cycle. Remaining cases except one ovulated after receiving 150 mg clomiphene citrate/day from day 5th to increasing duration up to 25th day.

In the same year (1984) Douglas C. Daly Walter Salo Albors concluded their randomized study on use of clomiphene citrate with dexamethasone in induction of ovulation when only clomiphene was used as standard regime, out of 22 only 14 cases ovulated but when used with dexamethasone all cases had evidence of ovulation.

In Jan. 1988, Davis and Ravnikar used high doses of clomiphene citrate in combination with prednisone and oral micronized-estradiol for premature ovarian failure.

In March 1988 Ronen, Bauchiecter, Wiswedel and Hendrinhs used clomiphene citrate in combination with low dose human menopausal gonadotropin for ovulation induction for in vitro fertilization. Results concluded in successful ovulation with 27.80/0 pregnancy rate.

In Jan 1988 Kaloszar and Bartfal used human menopausal gonadotropins in pulsatile manner for ovulation induction. In Aug. 1988, Flemming Haxton & Hamilton used combined gonadotropins releasing hormone analogue and exogenous gonadotropin for ovulation induction in infertile females. In the same year Bacchi Modena, Vadlana Fiaschetti
analogue both, in pulsatile manner for induction in chronic anovulatory patients.

In Jan 1989 Bonmaventuera described the practical aspect of ovulation induction. He used pergonal at the fixed doses. The overall pregnancy rate was 59%. He also described that use of this regime in private practice appears to be safe and effective.

In April 1989 Quartero Dixon Westwood, Licks and Chapman used pure FSH in chronic low dose pulsatile through subcutaneous route and through intramuscular route in polycystic ovarian disease for ovulation induction. They concluded that chronic low dose pulsatile administration of pure FSH has no advantage over chronic low dose intramuscular administration.

Stilnovic, Jurekovik, Grljusic and Ivanovic in April 1989 used combination of clomiphene and human gonadotropins for ovulation induction.

Authors stimulated 21 cycles in 14 females. Ovulation was proved in 20 cycles of the combined stimulation. Altogether 11 pregnancies of all induced cycle were obtained.

Schivardi, Falsathi, Omodei and Jumla in September, 1989 used pulsatile intravenous gonadotropin releasing hormone for ovulation induction. Ovulation occurred in 93.7% of treatment cycles. No over stimulation or any other serious complication was noted. In conclusion, therapy with GnRH provides an elevated probability of therapeutic success.
Letierre & Miyazawa in 1989 used combination of gonadotropin-releasing hormone agonist and human menopausal gonadotropins for ovulation induction in a patient with premature ovarian failure. A paradoxical suppression of ovarian response was noted despite increasing, doses of human menopausal gonadotropins.


Michioka, Kobayashi, Narimatsu, Yamashita & Yakabe in 1990 described the ovulation induction in polycystic ovarian syndrome. Successful induction of ovulation in patients with PCOS was observed in treatment cycles with daily subcutaneous injections or pulsatile subcutaneous administration of human menopausal gonadotropin (hmG) and bromocriptine, or the combination of clomiphene citrate and hmG.

In May 1990, Check Nowroozi, Chase, Hazari, Shapse & Vaze used human menopausal gonadotropins to induce ovulation in women with hypergonadotropic amenorrhoea. Ovulation was achieved in 19% of cycle. The pregnancy rate was 5.2% of ovulatory cycles. Coney, Gibbons, Christiansen & Sjulin in 1990 reviewed the results of ovulation induction in patients with ovulatory dysfunction and luteal phase defect/short luteal phase. 86 patients received clomiphene citrate for minimum of 4 cycles,
human menopausal gonadotropins. Seventeen completed a minimum of four cycles and 13 conceived. The number of clomiphene citrate treated patients with poor mucus quality in the face of adequate follicular development was 48%. In summary close monitoring during ovulation induction to confirm ovulation and assess mucus quality and luteal function allow detection and correction of inadequate response. Induction of ovulation can be highly successful if patients can follow thorough and complete protocols of therapy.


Homburg, West, Torresani & Jacobs (1990) had a comparative study of single-dose growth hormone therapy as an adjuvant to gonadotropin treatment for ovulation induction. Protocol is one intramuscular injection of biosynthetic human growth hormone (24 IU) administered on the first day of gonadotropin treatment for ovulation induction. It significantly augmented the ovarian response to gonadotrophic stimulations in 7 patients. Compared with a protocol involving six smaller dose had an immediate but highly significant effect in reducing the amount, duration of treatment and daily effective dose of HMG needed to induce ovulation. The difference between the effect of the one dose and six dose protocols was small. The action of growth hormone on the human ovary, probably mediated by insulin like growth factor appears effective in enhancing the response to gonadotropin therapy even when given in a single dose.
Holmberg West Obsergaard & Jacobs in 1991 had studied successful uses of growth hormone and gonadotropin for ovulation induction.

Bringer, Lmoret, Hedon and Lefebvre in 1994 explained the use of growth hormone in ovulation induction. There are increasing evidence for local ovarian action of growth hormone due to presence of receptors for GH in human granulosa cells. The ability of GH to enhance estradiol (E2) production by human granulosa cells withdrawn in late follicular phase. In the same year Katz E. emphasized the use of growth hormone in enhancing the ovarian response to gonadotropins. It reduces the effective gonadotropin dosage.

Porcile, Gallardo & Venegas in 1990 presented the role of bromocriptine in normoprolactinemic anovulation nonresponsive to clomiphene citrate. With bromocriptine alone, ovulation occurred in 28.6%. In same subjects when bromocriptine was subsequently added with clomiphene citrate - 50% ovulated.

In year 1991 various methods of ovulation induction in polycystic ovarian syndrome were described. Neyro Barrenetxea, Montoya & Rodriguez in 1991, used pure FSH for ovulation induction in PCOD patient. Ovulation rate was 83% and pregnancy rate was 36%.

Mizunuma, Takagi, Yamada, Andoh, Ibuki & Igarashi studied the effect of step down administration of purified urinary follicle stimulating hormone in PCOD patient. Kupferming, Lessing and Peyser induced the ovulation with hMG and HCG.

Krause, Moller and Goretzlehner in 1991 described the possibility of ovulation induction using Naltrexone in women with hypothalamic
amenorrhoea. In 1992, Sir Alba Riveral Devoto described the use of chronic administration of naltroxone in patient with secondary hypothalamic amenorrhoea.

Lydic & Jacobs in May, 1992 studied the comparative effect of Nafarelin versus Leuprolide in ovulation induction for in vitro fertilization. Nafarelin acetate administered by intranasal route and Leuprolide acetate as subcutaneous route. The use of Nafarelin acetate may decrease a patient's hMG requirement and increase the number of frozen embryos available for later transfer as compared with Leuprolide acetate.

'0' Amato, Vizziello and Faniza in 1992 observed the effect of pulsatile administration of GnRH, in patients with polycystic ovaries. The paper reports the result of 12 ovulation induction cycles using GnRH micropump without and after GnRH analogues.

In 1992, Meldrum highlighted the ovulation induction protocols for in vitro fertilization. Ovulation induction protocols for oocyte retrieval have evolved from clomiphene citrate/human menopausal gonadotropins alone and finally, a combination of human menopausal gonadotropins and an agonist of gonadotropin releasing hormone, the almost abandonment of clomiphene use is due to findings from studies that showed reduced implantation due to the anti estrogenic effect of clomiphene. The use of GnRH-a was introduced to maintain low levels of leutinizing hormone late in follicular development to prevent premature ovulation or premature senescence of the oocyte. The long GnRH-a/hMG protocol is currently used for most patients to prepare for oocyte retrieval.

Suginami, Kitagawa, Nakahashi, Yano and Matsubara in 1993 gave a novel therapy for ovulation induction i.e. clomiphene citrate and
Tamoxifen citrate combination. Rate of ovulation was 75% and pregnancy rate per ovulatory cycle was 8.6. All the pregnancies were normal and single. None of the treatments was combined by any remarkable side effects.

In 1993, Homburg described the ovulation induction in gonadotropin resistant women. The treatment strategies offer only partial solution to specific subgroups of poor respondent. It include protocols of clomiphene/HMG, mini-dose-GnRH agonist regime and co-treatment with GH, each of which may be found to be effective in individual cases.

Polycystic ovarian syndrome is a challenge for physician. Various methods of ovulation induction are described from time to time for PCOD patients. In year 1993, Dale, Tanbo, Lunde and Abyholm described the use of low dose follicular stimulating hormone with ovulation rate of 35% and pregnancy rate of 22%. Bregieiro, Moura, Ferriani and Bailao in 1993 described the low dose of pure follicular stimulating hormone using a fixed protocol of 75 IU/day for 8-10 days from 2nd or 3rd day of cycle. HCG was given when follicular diameter reached more or equal to 18 mm, resulted in 100% ovulation.

It was concluded that fixed protocol of low dose pure FSH produces good results, especially combined with hCG, which is effective upto 48 hr after last injection of FSH. Buckler, Critchley, Cantrill, Shalet, Anderson and Robertson in 1993 evaluated the efficacy of low dose purified FSH in ovulation induction following pituitary desensitization in polycystic ovarian syndrome. They concluded that regardless of the starting dose the use of pure FSH in patients with polycystic ovarian syndrome, where LH has been completely down regulated may be associated with multiple follicular development and poor outcome. Their
results strongly suggest that a basic minimum amount of LH is necessary for normal ovulatory development.

In the same year Turhan, Artini, Ambrogio, Droghini, Battaglia and Genazzani had a comparative study of three ovulation induction protocols in polycystic ovarian disease patients.

**Patients were treated with:**

1. Clomiphene citrate plus gonadotropin (hMG).
2. Pure follicular stimulating hormone plus human menopausal gonadotropin
3. Pure FSH/HMG plus gonadotropin releasing hormone analogue (GnRH-a).

Conclusion of the study show although the suppression of the hypothalamic-pituitary ovarian axis with gonadotropin releasing hormone-a in PCOD patients improved follicular synchrony and oocyte maturity. None of the ovulating induction protocols was superior to the others with respect to pregnancy rates and pregnancy outcome.

Greenblatt in 1993 described the surgical options in polycystic ovary syndrome patients who do not respond to medical ovulation induction. For women who fail to respond to clomiphene citrate therapy, and for whom gonadotropin therapy is unsuccessful or unavailable, surgical therapy should be considered. There is a very limited role, if any, for ovarian wedge resection (OWR) in the treatmnt of anovulation due to PCOS. Although effective in inducing ovulation in approximately 80% of women, with pregnancy rates approximately 60%, OWR requires major surgery and is associated with significant adhesion formation. Newer less invasive techniques are emerging for the anovulatory women those who fail to respond medical management. These include
laparoscopic ovarian cautery and laparoscopic ovarian Laser vaporization. These surgical techniques can be combined with diagnostic laparoscopy. Knowledge of the long term effects of these techniques is still limited but results appear promising, with spontaneous ovulation being initiated in 70 to 90% of women. The patients those remain anovulatory or oligoovulatory after these procedures, must would have been rendered sensitive to clomiphene citrate. Conception rates approximate 60%. The mechanism of action remains uncertain but is likely to involve alteration of the intraovarian steroid environment and in turn, the feedback to the hypothalamic-pituitary axis. The overall result is normalization of gonadotrophine and follicular microenvironment, allowing follicular recruitment and development to proceed to ovulation. The risk of post operative adhesion formation and the role of second look laparoscopy in the prevention of this undesirable complication remains uncertain.

In 1994, Smitz, Devroey, Mannaerts, Coeling, Bennink and Vansteir Tlegnem tested recombinant FSH for ovulation induction. They concluded supraovulation for IVF was successful and safe by using recombinant FSH alone or in combination with various GnRHa dosage and protocols.

Franks and Hamilton Fairley in 1994 described the role of body weight and metabolic anomalies in ovulation induction. Obese women with polycystic ovary syndrome require higher doses of gonadotropins for induction of ovulation than their lean counterparts. They also have lower rate of ovulation and higher prevalence of miscarriage.

Dickey and Holtkamp in 1996 reviewed the development, pharmacology and clinical experience with clomiphene citrate. The study
describes 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 because of poor sperm quality or an unsatisfactory post coital test. The result shows that (i) conception in clomiphene citrate cycle is related to the number and size of pre-ovulatory follicles, endometrial thickness, patient age, pelvic adhesion type of anovulatory disorder and semen quality. (ii) Pregnancy rates per clomiphene IUI cycle are constant throughout last six cycles (iii) multiple births cannot be prevented by with holding 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. They also reviewed pregnancy outcome (number of gestational sacs, preclinical and clinical abortion, ectopic pregnancy and birth sex) in 1744 clomiphene pregnancies. They 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 abortion 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 showed that clinical outcome may be improved by preovulatory ultrasound monitoring of ovarian and endometrial response.

In 1996, Hugues, Cedrin, Avril, Bulwa, Herve and Uzam gave the sequential step up and step down dose regime, an alternative method for
ovulation, induction with follicular-stimulating hormone in polycystic ovarian syndrome. In this study, infertile, clomiphene citrate resistant polycystic ovarian syndromes patients were treated with FSH in usual manner. The dose was reduced by half when the leading follicle reached 14 mm in diameter.

Decreasing the FSH dose following step up follicular selection may be an alternative method to avoid multifollicular development.

Silverberg in 1996 suggested ovulation induction in ovulatory women as a controlled ovarian hyperstimulation as emperic therapy for the treatment of unexplained infertility. Treatment prescribed in the form of either clomiphene citrate or gonadotropins. It is often combined with intrauterine insemination and offered to patients as a less expensive and less invasive alternative to the assisted reproductive technologies. Published data suggest an improvement in pregnancy rates when compared to expected management.

Kettle and Hummel in 1996 presented their experience on ovulation induction in the estrogenized anovulatory patients. In estrogenized women there are many different techniques to reverse the condition of chronic anovulation. With clomiphene citrate, upto 80% of patients will ovulate and approximately half will conceive. In women those who do not respond to clomiphene therapy, injectable gonadotropins are usually successful in inducing ovulation. New protocols for administrating these powerful agents have minimized the risk of ovarian hyperstimulation and multiple pregnancy when medical therapy fails to result in successful ovulatory cycles. Surgical treatments can be considered. Laparoscopic ovarian ablation or conventional ovarian wedge resection are the method of choice.
Fluker, Wang and Rowe in 1996 gave an extended 10 days course of clomiphene citrate in women with clomiphene citrate resistant ovulatory disorders. They offered 100 mg of clomiphene citrate from 3rd day to 12th day. Ovulation occurs in 65% of cycles and conception in 17% of females. Conclusion is that it is a simple, non-invasive and inexpensive alternative for a subset of women with ovulatory disorders that are refractory to standard CC treatment.

In the same year Gol, Gurso Y, Karabacak and Yiildirim used clomiphene citrate for 3 days with 50 mg/day to decrease the peripheral antiestrogenic effects of clomiphene citrate. Result in study and control group (50 mg/day cc for 5 days) showed that ovulation in study group was 82.53% while in control group ovulation rate was 95%. But pregnancy rate in study group was 17.3% while in control group was 10.5%.

Peled, Rabinerson, Kaplan, Harel and HOD in 1996 July gave a interesting word - A "sweet" indication for ovulation induction. In diabetic patient, euglycemia at the time of conception is crucial for the success of the pregnancy. In consideration of the difficulty in achieving and maintaining tight glycemic control for long period. They administered clomiphene citrate, which is usually indicated in cases of absent or infrequent ovulation, to enhance the fecundibility. All conceived within one to three cycles of the drug. No effect of the drug on the diabetes was noted as based on measurements of glycosylated haemoglobin and fructosamine concentrations and the absence of changes in the patients' insulin requirements. In the light of these beginning of diabetic pregnancies a new "sweet" indication for the use of clomiphene citrate is added.
Trott, Plouffe, Hansen, Hines, Brann and Mahesh in Sept. 1996 evaluated the effect on ovulation of a 1st day course of dexamethasone initiated concurrently with a 5-day course of clomiphene citrate in CC-resistant patients with normal dehydroepiandrosterone sulfate levels. The study results in ovulation in 11 women out of 13 and five clinical pregnancies were achieved.

Laonprasitipom, Barbieri and Yeh in 1996 suggested the sole use of clomiphene citrate in late-onset 21-hydroxylase deficiency for ovulation induction. Late onset 21-hydroxylase deficiency (21-0HD) is a congenital enzymatic defect in the glucocorticoid and mineralocorticoid steroidogenic pathways. The manifestations including, hirsutism and infertility, usually occur with 21-0HD. The usual therapy is glucocorticoids for ovulation induction. In this study patient was treated with clomiphene citrate alone for ovulation induction and she was conceived in her 4th cycle.

Roozenburg, Vandessel, Evers and Bots in Aug. 1997 had successful induction of ovulation in normogonadotrophic clomiphene resistant anovulatory women by combined naltrexane and clomiphene citrate treatment. 19 patients out of 22 patients ovulated and resumption of a regular menstrual cycle was achieved and in 12 out of 19 a singleton pregnancy was observed. In conclusion, ovulation can be induced successfully using naltroxane alone or naltroxane in combination with an antiestrogen in clomiphene citrate resistant anovulatory patient. Compared to goandotropin induction of ovulation. This method is safe, simple and inexpensive.

Orvieto, Homburg, Farhi, Bar-Hava and Ben-Rafael in 1997 gave a new concept of co-treatment with human growth hormone and
menotropins in ovulation induction protocols. Follicular development in the primordial and preantral stages is almost completely independent of gonadotropins or steroids and is mainly dependent on growth factors and local regulators. Since human growth hormone was found to facilitate ovarian response to gonadotropin stimulation. So treatment with human GH prior to menotropin administration may be useful to improve results for poor responders to gonaaotropins.

Messinis, Milingos in 1997 discussed the current and future status of ovulation induction in polycystic ovary syndrome. Clomiphene citrate remains the first line of treatment for all anovulatory women with PCOD, since in properly selected cases, the cumulative pregnancy rate approaches that of normal women. Human urinary gonadotropins have been used extensively for ovulation induction, but the development of low dose regimes has opened a new era in the management of anovulation related to PCOS. Other method including pulsatile gonadotropin releasing hormone and GnRH agonist, Recombination gonadotropins, GnRH antagonist, controlled leutinizing hormone secretion. Disorders of ovulation resulting in impaired fertility constitute one of the most common cause of involuntarily childlessness. Medication facilitate ovulation, have been in clinical use for last two decades. An increasing number of patients are being conceived during or shortly after therapy with these agents. It is relevant, then, to determine whether the use of ovulation induction places a pregnant women at greater risk of an abnormal outcome, such as spontaneous abortion, fetal malfonnation or intrauterine growth retardation.

The reproduction toxicity of ovulation inducing drugs are analysed from time-to-time by different authors. Before going in details of toxicity of clomiphene citrate or other ovulation inducing drug, first come to know the mechanism of action of Clomiphene citrate.
Clomiphene citrate is a non-steroidal compound, weak synthetic estrogen but it acts clinically as an estrogen antagonist for ovulation action at typical pharmacological doses. It binds to the cytoplasmic estrogen receptors and thus acts as antiestrogenic in humans. It induces gonadotropin (Gn) secretion by blocking feedback inhibition of the pituitary and also antagonizes some of the peripheral actions of estrogen. The ovaries respond to Gn stimulation by producing ovulation. Conception occurs in women suffering from anovulation infertility.

In 1986, Anthony R. Scialli, discussed the toxicity of clomiphene citrate, human menopausal gonadotropins and bromocriptine.

He described ovulation induction with clomiphene citrate may cause luteal phase defect with consequent failure of implantation or early pregnancy loss this may be due to the anti estrogenic action of this medication within the preovulatory follicle or on the endometrium. There are few adequately controlled studies on the possible adverse pregnancy effects of clomiphene citrate. It appears, however, that once pregnancy is established, the only complication reproducibly related to clomiphene citrate therapy is an increase in twinning and miscarriage. Fetal growth and development appears to be normal in these pregnancies.

Bromocriptine therapy may successfully induce ovulation in hyperprolactinemic women. Published experience does not identify a risk of adverse pregnancy outcome attributable to the medication. Although it has been said that bromocriptine should be stopped as soon as possible after a diagnosis of pregnancy is made, a number of cases in which high dose bromocriptine is continued through much of pregnancy have not identified a hazard of this medication for the fetus.
The primary indication for clomiphene citrate administration is to include ovulation in the infertile anovulatory patients with normal estrogen.

Production often clomiphene citrate administration is the first approach used either without a complete workup or even after a work up without a demonstration of anovulation. Even when the diagnosis of anovulation is made and clomiphene citrate prescribed, a number of abuses are common. The proper approach to therapy of clomiphene citrate requires starting at a relatively low dose, continuing the same dose as long as ovulation occurs, and increasing the dose only if there is no ovulatory response.

Other abuses stem from a failure to seek and then correct the possible cause of conception failure in the face of ovulation. One should repeat an endometrial biopsy after 3 month of clomiphene citrate therapy to be sure that a luteal phase defect has not been created by clomiphene citrate. This can be corrected by the addition of progesterone vaginal suppositories. A post coital test should be repeated during therapy to be sure than an anticervical mucus effect has not taken place. Levels of dehydroepiandrosterone sulfate and prolactin should be measured to rule out adrenal and pituitary contributions to the anovulation.

One of the other widely proclaimed abuses of CC is in treatment of luteal phase deficiency. Down & Gibson reported that if the endometrium was 5 days or more out of phase there was a significant response to
clomiphene citrate. But where endometrium was less than 5 days out of phase clomiphene citrate did not help. In cases of leuteal phase defect without a short leuteal phase progesterone vaginal suppositories rather than clomiphene citrate should be the first approach to therapy.

A final abuse of clomiphene citrate is its use in the treatment of unexplained infertility. All the evidence suggests that if a woman has a normal spontaneous ovulation one cannot make it move normal by driving the pituitary harder. All one does is sometimes create a luteal phase defect or cause an adverse effect on cervical mucus, both of which have antifertility effects.

Tucker in 1996 reviewed the reproduction toxicity of ovulation induction. No doubt that pregnancy rates have been improved with the use of agents such as: clomiphene citrate, human menopausal gonadotropins (HMG) with gonadotropic-releasing hormone (GnRH) and its analogue. These drugs stimulate the development of multiple ovarian follicles and increasing the number of fertilizable oocytes.

The negative effects from superovulation can occur during follicle development, decreasing the number of healthy oocytes and embryos capable of leading to viable pregnancy. Ovulation induction can lead not only to higher incidence of spontaneous abortion, and multiple and ectopic pregnancies, but also to poor pregnancy rates, due in part to asynchrony between embryonic development and the uterine environment. Disease such as hyperstimulation syndrome resulting in the secretion of supraphysiological levels of estradiol, can lead to severe health complication, possibly requiring hospitalization. Most drugs used for ovulation induction can lead to ovarian hyperstimulation syndrome (OHSS). Although incidence of OHSS following CC use are less
frequent, CC has been associated with hot flushes, multiple gestations, visual disturbances, cervical mucus abnormalities and luteal phase deficiency. Finally there are reports that links any or all of the ovulation inducing drugs with a higher incidence of ovarian and breast cancer, however cause effect relationship has yet to be proven.