N-Acetyl cysteine and clomiphene citrate for induction of ovulation in polycystic ovary syndrome: a cross-over trial

Objective. To compare clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for inducing ovulation in patients with polycystic ovary syndrome. Design. Prospective cross-over trial. Setting. University teaching hospital and a private practice setting. Patients. Five hundred and seventy-three patients were treated with clomiphene citrate for one menstrual cycle among which 470 patients were treated with clomiphene citrate plus N-acetyl cysteine for another cycle. All women suffered from polycystic ovary syndrome. Interventions. Patients had clomiphene citrate 50-mg tablets twice daily alone or with N-acetyl cysteine 1,200 mg/day orally for 5 days starting on day 3 of the menstrual cycle. Outcome measures. Primary outcomes were number of mature follicles, serum E2, serum progesterone, and endometrial thickness. Secondary outcome was the occurrence of pregnancy. Results. Ovulation rate improved significantly after the addition of N-acetyl cysteine (17.9% versus 52.1%). Although the number of mature follicles was more in the N-acetyl cysteine group (2.19/0.88 versus 3.29/0.93), the difference was not statistically significant. The mean E2 levels (pg/ml) at the time of human chorionic gonadotropine injection, serum progesterone levels (ng/ml) on days 21-23 of the cycle, and the endometrial thickness were significantly improved in the N-acetyl cysteine group. The overall pregnancy rate was 11.5% in the N-acetyl cysteine group. Insulin resistance occurred in 260 patients (55.4%). There was no significant difference between the insulin resistance group (n=260) and non-insulin resistance group (n=210) as regards ovulation rate, number of follicles, serum E2 (pg/ml), serum progesterone (ng/ml), endometrial thickness (mm), or pregnancy rate. Conclusion. N-Acetyl cysteine is proved effective in inducing or augmenting ovulation in polycystic ovary patients.

Extending clomiphene treatment in clomiphene-resistant women with PCOS: a randomized controlled trial

The purpose of this study was to test the effect of extended clomiphene citrate treatment compared with gonadotrophin therapy for the management of clomiphene-resistant women with polycystic ovary syndrome (PCOS). The study comprised 318 women (802 cycles) with clomiphene-resistant PCOS randomized to two treatment groups. Patients in the clomiphene citrate group were given 100 mg of clomiphene citrate daily starting on day 2 of menses for 9 days (160 patients, 405 cycles) while patients in the gonadotrophin group were given human menopausal gonadotrophin 75 IU intramuscularly daily for 5 days starting on day 3 of menses (158 patients, 397 cycles). The number of ovulating
patients was significantly higher (P = 0.001) in the gonadotrophin group (57.6 versus 28.1%). The total number of follicles during stimulation was significantly greater (P = 0.01) in the gonadotrophin group (6.7 0.3 ± 1 versus 4.1 0.4 ± 1). Pregnancy occurred in 46/405 cycles in the clomiphene citrate group (11.4%) and in 80/397 cycles (20.2%) in the gonadotrophin group; the difference was statistically significant (P = 0.03). The extended clomiphene citrate regimen resulted in modest ovulation and pregnancy rates with no side effects. This therapy seems to offer economic, efficacy and safety advantages and it is worth undergoing before starting more expensive or sophisticated alternatives.

3-

**Low-molecular weight heparin in patients with recurrent early miscarriages of unknown aetiology**

The aim of this randomised prospective study was to assess the efficacy of early thromboprophylaxis with low-molecular weight heparin (LMWH) in women with a history of recurrent first trimester spontaneous abortion or miscarriages without identifiable causes vs no treatment. The study comprised of 340 women with unexplained spontaneous recurrent miscarriages. Patients in group A were prescribed LMWH (Enoxaparin sodium 0.2 ml, 20 mg, once daily subcutaneously) from the time of confirmation of fetal viability by ultrasonography until 34 weeks' gestation, and folic acid tablets 0.5 mg daily until 13 weeks' gestation. Patients in group B were given folic acid tablets 0.5 mg daily until 13 weeks' gestation. Termination of pregnancy was the primary outcome. There was a significant difference in the incidence of both early (4.1% vs 8.8%) and late miscarriages (1.1% vs 2.3%) in group A than in group B, respectively. There were no differences between both groups as regards the occurrence of pre-eclampsia, placental abruption, caesarean delivery, intra-partum bleeding or ecchymosis at operative wounds. There were no differences in most of the neonatal values between both groups. However, the mean birth weight was significantly higher in group A. LMWH seems to be a safe drug and effective in significantly reducing the incidence of recurrent miscarriages of unknown aetiology when given in the first trimester and continued throughout pregnancy.

4-

**Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial**

Objective: To compare the effects of letrozole (5 mg) and clomiphene citrate (100 mg) for ovulation induction in women with polycystic ovary syndrome (PCOS).

Design: Prospective randomized trial.
Setting: University teaching hospital and private practice setting.
Patient(s): The study comprised a total of 438 infertile women (1063 cycles) with PCOS.
Intervention(s): Patients were randomized to treatment with 5 mg of letrozole daily (218 patients, 545 cycles) or
100 mg of clomiphene citrate daily (220 patients, 518 cycles) for 5 days starting on day 3 of menses. Timed
intercourse was advised 24 to 36 hours after hCG injection.
Main Outcome Measure(s): Number of follicles, serum estradiol, serum progesterone, endometrial thickness, and
pregnancy and miscarriage rates.
Result(s): The mean age, parity, and duration of infertility in both groups were similar. The total number of
follicles was statistically significantly greater in the clomiphene citrate group (6.8 ± 0.3 versus 4.4 ± 0.4). Endometrial
thickness at the time of hCG administration was statistically significantly greater in the CC group (9.2 ± 0.7 mm versus 8.1 ± 0.2 mm). The duration to reach a dominant follicle was statistically significantly longer in the
letrozole group (12.1 ± 1.3 versus 8.8 ± 2.9 days). Ovulation occurred in 365 out of 540 cycles (67.5%) in letrozole
group and 371 out of 523 cycles (70.9%) without a statistically significant difference. Levels of serum estradiol and
progesterone were statistically significantly higher in the clomiphene citrate group. The pregnancy rate per cycle
was 15.1% in the letrozole group and 17.9% in the clomiphene citrate group without statistically difference
between the groups.
Conclusion(s): The results of this study did not show any advantage to the use of
letrozole over clomiphene citrate
as a first-line treatment for induction of ovulation in women with PCOS. (Fertil Steril 2007;87:2290. 2007 by
American Society for Reproductive Medicine.)

5-

**Anastrozole or letrozole for ovulation induction in clomiphene-resistant women with polycystic ovarian syndrome: a prospective randomized trial**

Objective: To compare the effects of letrozole (2.5 mg) and anastrozole (1 mg) meant for
ovulation induction in clomiphene (CC)-resistant women with PCOS.
Design: Prospective randomized trial.
Setting: University teaching hospital and private practice setting.
Patient(s): The study comprised a total of 220 infertile women (574 cycles) with CC-resistant PCOS.
Intervention(s): Patients were randomized to treatment with 2.5 mg of letrozole daily
(111 patients, 295 cycles) or
1 mg of anastrozole daily (109 patients, 279 cycles) for 5 days from day 3 of menses.
Main Outcome Measure(s): Number of follicles, serum E2, serum P, endometrial
thickness, pregnancy rate (PR), and miscarriage rate.

Result(s): The total number of follicles was significantly more in the anastrozole group (5.4 ± 0.4 vs. 5.8 ± 0.4). The number of follicles R14 mm (3.1 ± 0.3 vs. 2.7 ± 0.2) and R18 mm (2.3 ± 0.1 vs. 3.1 ± 0.2) were significantly higher in the anastrozole group. The endometrial thickness at the time of hCG administration was significantly more in the anastrozole group (9.1 ± 0.2 vs. 10.2 ± 0.7 mm). The duration to reach a dominant follicle was longer in the letrozole group (12.1 ± 1.3 days vs. 8.8 ± 1.9 days) but without statistical significant difference. Ovulation occurred in 183/295 cycles (62%) in the letrozole group and 177/279 cycles (63.4%) in the anastrozole group, whereas pregnancy occurred in 36/295 cycles (12.2%) in the letrozole group and 42/279 cycles (15.1%) in the anastrozole group and the differences were not statistically significant.

Conclusion(s): The results of this study did not show a significant difference in PR or miscarriage rate between anastrozole and letrozole when used for ovulation induction in women with CC-resistant PCOS. (Fertil Steril 2007;--:--. 2007 by American Society for Reproductive Medicine.)

6-

**Luteal phase clomiphene citrate for ovulation induction in women with polycystic ovary syndrome: a novel protocol**

Objective: To test a novel protocol of luteal phase administration of clomiphene citrate (CC) for ovulation induction in women with polycystic ovary syndrome (PCOS).

Design: Prospective, randomized, controlled trial.

Setting: University teaching hospital and private practice settings.

Patient(s): The study comprised a total of 212 women (438 cycles) with PCOS.

Intervention(s): Patients in the early CC group received 100 mg of CC daily starting the next day after finishing medroxyprogesterone acetate (MPA) for 5 days (110 patients, 227 cycles), whereas the patients in the late CC group received 100 mg of CC daily for 5 days starting on day 3 of the menses (102 patients, 211 cycles).

Main Outcome Measure(s): Number of growing and mature follicles, serum E2 (in picograms per milliliter), serum P (in nanograms per milliliter), endometrial thickness (in millimeters), occurrence of pregnancy and miscarriage.

Result(s): There were more ovulating patients in the early CC group (59.1% vs. 51.9%), without significant differences. The total number of follicles and the number of follicles R14 mm and R18
were significantly greater in the early CC group. The endometrial thickness at the time of hCG administration was significantly greater in the early CC group (9.1 ± 0.23 vs. 8.2 ± 0.60 mm). Serum E2 and P were not significantly different between the two groups. Pregnancy occurred in 23/110 cycles in the early CC group (20.9%) and 16/102 cycles (15.7%) in the late CC group; the difference was not statistically significant. The miscarriage rate was similar in the two groups.

Conclusion(s): Early administration of CC in patients with PCOS will lead to more follicular growth and endometrial thickness, which might result in a higher pregnancy rate (PR). (Fertil Steril 2008;–:–:–).

Key Words: Ovulation induction, polycystic ovary syndrome, clomiphene citrate

Effect of sperm morphology and number on success of intrauterine insemination

Objective: To assess the effects of the number of motile spermatozoa inseminated and percentage of morphologically normal spermatozoa on the success of IUI.

Design: A prospective observational study.

Setting: University teaching hospital and private practice setting.

Patient(s): The study comprised 393 couples who underwent 714 IUI cycles.

Intervention(s): All IUI cycles were preceded by ovarian superovulation with clomiphene citrate 50 mg tablets orally twice daily for 5 days starting on the second day of menses and one hMG ampule 75 IU IM daily for 5 days starting day 5 of the cycle. Cycles were monitored by transvaginal ultrasound. The IUI was performed with a catheter 36 ± 4 hours after hCG injection.

Main Outcome Measure(s): Clinical pregnancy.

Result(s): A total of 79 clinical pregnancies were obtained, for a pregnancy rate per cycle of 11.06%. The pregnancy rate per cycle was 5.55% when the number of motile spermatozoa was <5 ± 10^6 and 24.28% with normal motile sperm >5 ± 10^6. For patients <25 years old, with number of motile spermatozoa >5 ± 10^6, the pregnancy rate per cycle was 28.2%, which is significantly higher than that of other age groups. Above the age of 35 years, no pregnancies were reported with number of motile spermatozoa <5 ± 10^6, and the pregnancy rate was very low (0.84%) with number of motile spermatozoa >5 ± 10^6. When the normal sperm morphology was >30% and number of motile spermatozoa inseminated >5 ± 10^6, the pregnancy rate was 20.77%.
Conclusion(s): Intrauterine insemination used for treating male factor infertility has little chance of success when the woman is older than 35 years, the number of motile spermatozoa inseminated is $<$5 $\times$ 106, or normal sperm morphology is $<$30%. (Fertil Steril 2008;--:--–-. 2008 by American Society for Reproductive Medicine.)

8-

Ultrasound-guided transvaginal ovarian needle drilling (UTND) for treatment of polycystic ovary syndrome: A randomized controlled trial

Objective: To evaluate the outcome of ovarian needle drilling using transvaginal ultrasound guidance as an alternative to the traditional laparoscopic electrosurgical drilling for patients with polycystic ovary syndrome (PCOS).

Design: A randomized controlled study.

Setting: University teaching hospital and private practice setting.

Patient(s): The study comprised 163 patients with clomiphene-resistant PCOS.

Intervention(s): Patients were randomly allocated to either treatment with ultrasound-guided transvaginal needle ovarian drilling (UTND; n = 82) or laparoscopic electrosurgery ovarian drilling (n = 81).

Main Outcome Measure(s): Hormonal changes (FSH, LH, T), ovulation and pregnancy.

Result(s): There were no significant differences between the two groups with regard to body mass index, hormonal profiles, clinical manifestations, and ultrasound findings of PCOS. The duration of UTND was 15.3 $\pm$ 5.61 minutes (10.5–22.3 minutes), while it was 25.6 $\pm$ 8.2 minutes (20.3–38.1 minutes) in laparoscopic drilling, with a statistically significant difference between the two groups. There were no significant differences between the two groups with regard to resumption of normal menstruation, hirsutism, acne, ovulation, and pregnancy. UTND resulted in significant improvement in the ovulation, pregnancy, hirsutism, and acne. There were significant decreases in the serum LH and T levels but not in the FSH or LH/FSH levels after UTND as well.

Conclusion(s): UTND can be adopted as an outpatient office procedure. The ease of scheduling, reduced costs, and rapid recovery suggest it as a first-line treatment for PCOS cases resistant to clomiphene citrate. (Fertil Steril 2008;--:--–-. 2008 by American Society for Reproductive Medicine.)

9-

Clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for augmenting ovulation in the management of unexplained infertility: a randomized double-blind controlled trial
Objective: To compare clomiphene citrate with N-acetyl cysteine vs. clomiphene citrate alone for augmenting ovulation in management of unexplained infertility.

Design: Prospective randomized double-blind controlled trial.

Setting: Department of obstetrics and gynecology in a university medical faculty in Egypt.

Patient(s): Four hundred four patients as a study group (clomiphene citrate plus N-acetyl cysteine group) and 400 patients as a control group (clomiphene citrate alone group). All women had unexplained infertility.

Intervention(s): Patients in the study group were treated with clomiphene citrate (50-mg tablets) twice per day and with N-acetyl cysteine (1,200 mg/d orally) for 5 days starting on day 2 of the cycle. Patients in the control group were treated with clomiphene citrate with sugar powder.

Main Outcome Measure(s): The primary outcomes were number and size of growing follicles, serum E2, serum P, and endometrial thickness. The secondary outcome was the occurrence of pregnancy.

Result(s): There were no statistically significant differences between the two groups in the number of follicles sized ≥18 mm, mean E2 levels, serum P, or endometrial thickness. Pregnancy rate was comparable in both groups (22.2% vs. 27%). Miscarriage rate was comparable in both groups (6.7% in the study group vs. 7.4% in the control group).

Conclusion(s): N-Acetyl cysteine is ineffective in inducing or augmenting ovulation in patients with unexplained infertility and cannot be recommended as an adjuvant to clomiphene citrate in such patients. (Fertil Steril 2006; 86:647–50. ©2006 by American Society for Reproductive Medicine.)

Key Words: N-Acetyl cysteine, clomiphene citrate, unexplained infertility

Genital tract tuberculosis among infertile women: an old problem revisited

Abstract

Objective To estimate the prevalence of genital tract tuberculosis (TB) among infertile women during laparoscopic evaluation for infertility in a prospective observational study.

Methods A total of 420 infertile women were included. All patients had laparoscopy and all suspicious lesions were biopsied and peritoneal fluids aspirated. Full endometrial curettage followed by histopathological examination was done for specimens. Polymerase chain reaction test (PCR) was performed for all peritoneal fluid samples and tissue biopsy.
Results Genital tract tuberculosis was diagnosed with laparoscopy and confirmed by tissue biopsy in 24 patients (5.7%). Visual laparoscopic findings and direct tissue biopsy had the highest sensitivity and specificity (92%–94%, respectively) followed by PCR (83%–85%) and lastly endometrial biopsy (75%–80%) for diagnosis of genital tuberculosis. The incidence of genital tuberculosis was higher among rural patients with low socioeconomic and educational levels.

Conclusion Genital tuberculosis has a role in the etiopathogenesis of infertility. Laparoscopy and direct tissue biopsy are the gold standards for its diagnosis.

Keywords Genital tuberculosis · Infertility · Laparoscopy

Can flowcytometric DNA studies forecast the prognosis of endometrial hyperplasia?

Objectives: The study is investigating the relation of the ploidy pattern and cell cycle kinetics to different types of endometrial hyperplasia to select the high-risk women who will need strict follow up surveillance.

Study design: An observational study of 152 patients with endometrial hyperplasia. Endometrial samples were subjected to flowcytometric study of the nuclear DNA content to determine the ploidy pattern and cell cycle kinetics.

Results: The mean age of women was 46.3 ± 3.6 years. 15.8% of women were nulliparae, 36.8% were diabetic and 43.6% were hypertensive. 48.7% of women were obese (BMI > 30). Most of endometrial samples (88.2%) were simple endometrial hyperplasia without atypia. The cell cycle kinetics in different types of endometrial hyperplasia shows that there were significant statistical differences as regards the S-phase fraction and proliferative index (PI) between typical and atypical hyperplasia.

Conclusion: The study of cell cycle kinetics by flowcytometry might help in picking up, among all women with endometrial hyperplasia, the group of patients who need further close and strict follow up by endometrial pathologic study. This is going to minimize the cost and invasiveness of surveillance of patients with various grades of endometrial hyperplasia.

# 2005 Published by Elsevier Ireland Ltd.

Keywords: Endometrial hyperplasia; Flowcytometry

Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial

Objective: To compare clomiphene citrate (CC) and letrozole used for superovulation before intrauterine insemination (IUI) in unexplained infertility.

Design: Prospective randomized trial.
Setting: A university teaching hospital and a private practice setting.
Patient(s): Four hundred and twelve infertile women with unexplained infertility.
Intervention(s): Patients were randomized to treatment with 100 mg of CC daily (207 patients, 404 cycles) or 5mg of letrozole daily (205 patients, 400 cycles) for 5 days starting on day 3 of menses. The IUI was done 36-4 hours after human chorionic gonadotropin (hCG) injection.
Main Outcome Measure(s): Number of follicles, serum estradiol level, serum progesterone level, endometrial thickness, and pregnancy and miscarriage rates.
Result(s): The total number of follicles during stimulation was statistically significantly greater in the CC group (3.1 ± 0.36 vs. 1.6 ± 0.41). There was no statistically significant difference in pretreatment endometrial thickness between the two groups or endometrial thickness at the time of hCG administration. Serum E2 and progesterone concentrations were statistically significantly higher in the CC group. The days to hCG injection were similar in both groups. Pregnancy occurred in 73 out of 205 patients (400 cycles) in the letrozole group (35.6% and 18.2%, respectively) and 78 out of 207 patients (404 cycles) (37.6% and 19.3%, respectively) in the CC group; the differences were not statistically significant. Two twin pregnancies occurred in the CC group.
Conclusion(s): This study found no superiority between letrozole and CC for inducing ovulation in women with unexplained infertility before IUI. (Fertil Steril 2008;89:1381–1385. 2008 by American Society for Reproductive Medicine.)

Key Words: Clomiphene citrate, letrozole, intrauterine insemination

Clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for augmenting ovulation in the management of unexplained infertility: a randomized double-blind controlled trial

Objective: To compare clomiphene citrate with N-acetyl cysteine vs. clomiphene citrate alone for augmenting ovulation in management of unexplained infertility.
Design: Prospective randomized double-blind controlled trial.
Setting: Department of obstetrics and gynecology in a university medical faculty in Egypt.
Patient(s): Four hundred four patients as a study group (clomiphene citrate plus N-acetyl cysteine group) and 400 patients as a control group (clomiphene citrate alone group). All women had unexplained infertility.
Intervention(s): Patients in the study group were treated with clomiphene citrate (50-mg tablets) twice per day and
with N-acetyl cysteine (1,200 mg/d orally) for 5 days starting on day 2 of the cycle. Patients in the control group were treated with clomiphene citrate with sugar powder.

Main Outcome Measure(s): The primary outcomes were number and size of growing follicles, serum E2, serum P, and endometrial thickness. The secondary outcome was the occurrence of pregnancy.

Result(s): There were no statistically significant differences between the two groups in the number of follicles sized >18 mm, mean E2 levels, serum P, or endometrial thickness. Pregnancy rate was comparable in both groups (22.2% vs. 27%). Miscarriage rate was comparable in both groups (6.7% in the study group vs. 7.4% in the control group).

Conclusion(s): N-Acetyl cysteine is ineffective in inducing or augmenting ovulation in patients with unexplained infertility and cannot be recommended as an adjuvant to clomiphene citrate in such patients. (Fertil Steril 2006; 86:647â€“50. 2006© by American Society for Reproductive Medicine.)

Key Words: N-Acetyl cysteine, clomiphene citrate, unexplained infertility.

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Effect of sperm morphology and number on success of intrauterine insemination

Objective: To assess the effects of the number of motile spermatozoa inseminated and percentage of morphologically normal spermatozoa on the success of IUI.

Design: A prospective observational study.

Setting: University teaching hospital and private practice setting.

Patient(s): The study comprised 393 couples who underwent 714 IUI cycles.

Intervention(s): All IUI cycles were preceded by ovarian superovulation with clomiphene citrate 50 mg tablets orally twice daily for 5 days starting on the second day of menses and one hMG ampule 75 IU IM daily for 5 days starting day 5 of the cycle. Cycles were monitored by transvaginal ultrasound. The IUI was performed with a catheter 36 ± 4 hours after hCG injection.

Main Outcome Measure(s): Clinical pregnancy.

Result(s): A total of 79 clinical pregnancies were obtained, for a pregnancy rate per cycle of 11.06%. The pregnancy rate per cycle was 5.55% when the number of motile spermatozoa was <5 10^6 and 24.28% with normal motile sperm >5 10^6. For patients <25 years old, with number of motile spermatozoa >5 10^6, the pregnancy rate per cycle was 28.2%, which is significantly higher than that of other age groups. Above the age of 35 years, no pregnancies were reported with number of motile spermatozoa <5 10^6, and the pregnancy rate was very low.
(0.84%) with number of motile spermatozoa >5 $10^6$. When the normal sperm morphology was >30% and number of motile spermatozoa inseminated >5 $10^6$, the pregnancy rate was 20.77%.

Conclusion(s): Intrauterine insemination used for treating male factor infertility has little chance of success when the woman is older than 35 years, the number of motile spermatozoa inseminated is <5 $10^6$, or normal sperm morphology is <30%. (Fertil Steril 2009;91:777-81. ©2009 by American Society for Reproductive Medicine.)

Key Words: Intrauterine insemination, sperm parameters