Efficacy of combined metformin- letrozole in comparison with metformin-laparoscopic ovarian diathermy in ovulation induction and reproductive outcome for women with clomiphene citrate resistant polycystic ovary syndrome

Yasamin Hamza Sharif AL-Shibany
Dept. of Obstetrics and Gynecology Medical College, Al-Qadisia University ,Iraq .
e-mail : yhsaso@yahoo.com
(Received 7/9/2014, Accepted 11/11/2014)

الخلاصة

اجريت الدراسة على مجموعه من النساء المصابات بمتلازمة تكيس المبيض و عددها 60 مريضة مع عدم استجابة لعقار الكلومفين في مستشفى الولادة و الاطفال التعليمي في الديوانية في شعبة العقم للفترة من حزيران 2012 و لغاية حزيران 2014 .اظهرت النتائج ان المجموعة الاولى و عددها 30 مريضة والتي اعطية عقار اللتروزول مع المتفورمين اعلى نسبة في التبويض63,33% مقارنة مع المجموعة الثانية و عددها 30 مريضة و التي اعطيت عقار المتفورمين واجريت لهن عملية تثقيب المبيض بالناظور الجراحي تحت التخدير العام 30,00% . وكانت اعلى نسبة للحمل في المجموعة الاولى 40,00% بالمقارنة مع المجموعة الثانية 16,67%.لا يوجد اختلاف في نسبة الاسقاطات ولا توجد حالات تشوهات خلقية لدى المواليد في المجموعتين.
نستنتج :ان عقار اللتروزول مع المتفورمين يعتبر بديل فعال و سليم عن التداخل الجراحي وتثقيب المبيض بالناظور في حالات تكيس المبايض المقاوم لعقار الكلومفين.

Abstract

Background and objective: polycystic ovary syndrome(PCOS) is a common cause of infertility and is associated with chronic anovulation and hyperandrogenism.The aim of current study is to compare the effect of combined letrozole-metformine to that of metformin-laparoscopic ovarian drilling (LOD) for ovulation induction in patients with PCOS.Materials and Methods: on the whole 138 ovarian cycles were studied in 60 patients with clomiphene citrate resistant PCOS in AL-Diwaniyah Maternity and Pediatrics Teaching Hospital during the period of June 2112-June 2114.
All patients (n=60) received metformin 500mg /3times per day ,group A(n=30)received letrozole 5mg daily for 5 days repeated for 6 cycles, group B(n=30) underwent LOD and followed for six cycles. Outcome measures were ovulation rates, endometrialthickness, pregnancyrates, live birth rates and miscarriage rate.
Results: ovulation rate was higher in group A than group B(63.33% versus 30.0%),a significant increase in endometrial thickness in group A than group B(9.9mm versus 9.03 mm).Live birth rate was higher in group A 83.33% compared to 33.33% in group B. There were no significant differences regarding miscarriage rates between both groups. No multiple pregnancy or ovarian hyper stimulation syndrome or congenital abnormality among live births were reported.Conclusions: Combinedletrozole-metformin seems to be a suitable second line ovulation inducing alternative to LOD in women with PCOS who do not respondwith clomiphene citrate.
Key words: PCOS ,clomiphene citrate resistant , metformin ,letrozole ,LOD ,pregnancy rate ,live birth rate ,safety.

Introduction

Anovulatory dysfunction is a common problem and is responsible for about 40% of female infertility (1) . polycystic ovarian syndrome (PCOS) remains one of its major causes and accounts for more than 75% of anovulatory infertility cases (1).The mechanism of anovulation is uncertain but there is evidence that arrested antral follicular development is associated with abnormal endocrine profile in particular , hypersecretion of luteinizing hormone (LH),hyperandrogenism, yperinsulinemia with suppression of follicular stimulating hormone level (FSH)(2) . As a result treatment methods must be balanced for optimal result and induction of ovulation that result in increased FSH release is associated with ovulatory responses in many individuals(1).

Induction of ovulation can be achieved in most cases by the use of antiestrogens such as clomiphene citrate which is considered as the drug of choice for first line treatment of anovulatory dysfunction. It is orally administered with few side effects, easily available and is inexpensive (3).Although ovulation rates are about 70-80% ,the actual pregnancy rates are significantly lower at around 30-40% (1,3) . Clomiphene blocks estrogenic hypothalamic receptors resulting in blinding of the hypothalamus –pituitary axis toendogenous circulating estrogen, and this will trigger release of FSH from the anterior pituitary ,and it also has peripheral antiestrogenic action at the level of the endometrium and cervical mucus which is partly explaining the discrepancy in ovulation rate and pregnancy rate(1).

Satisfactoryovulation is seen if clomiphene is given in a dose of 50-100 mg /day for 5 days. If the patients fail to ovulate at a dose of 150mg/day given for 5days they considered as clomiphene resistant and it occurs in 15-40% of cases(1,4).Clomiphene resistant together with side effects as cyst formation and multifollicular development with antiestrogenic side effects persist the desire for an effective alternatives (1).Although treatment with gonadotropin is often successful in those patients , yet they are expensive and have the risk of ovarian hyper stimulation syndrome (OHSS) and multiple pregnancy(5).

Letrozole is a selective aromatase inhibitor ,prevents the conversion of androgen to estrogen , this reduced estrogencauses enhanced GnRHpulsitility from the negative feedback of estrogen resulting in an increase of FSH secretion and folliculgenesis (6). Importantly, unlike clomiphene citrate ,letrozole is devoid of any antiestrogenic peripheral action and elicit a monofollicular response and dose not adversely affect the endometrium or the cervical mucus (6).It also cleared from the circulation more rapidly due to a short half-life (48 hours) as compared to clomiphene citrate which may take up to two months due to its prolonged half-life (2weeks)(6,7).

Hyperinsulinemia and decreased insulin sensitivity commonly accompanied PCOS and this directly stimulate both ovarian and adrenal androgen secretion and suppresses liver sex hormone – binding globulin synthesis resulting in an increase in free biologically active androgens and causes premature follicular atresia and anovulation . In addition it can have long term health impacts on the patient through the development of cardiovascular disease and type 2 diabetes mellitus (8).Insulin-sensitizing agent as metformin (Glucophage)is well established in the treatment of PCOS, and the mechanism of action is complex and include reduction of insulin resistant in both lean and obese women with PCOS(8). In addition studies has shown the beneficial effects of combined metformin-clomiphene therapy in clomiphene resistant PCOS patients(9).

A further treatment option for women with anovulatory infertility associated

with PCOS is by laparoscopic ovarian drilling (LOD)by diathermy or laser creating multiple perforations (no less than four and no more than ten) to a depth of 2-4mm on each ovarian surface and stroma (10).The mechanism of action of LOD is that it may destroy ovarian androgen producing tissue and reduce the peripheral conversion of androgen to estrogen with a fall in serum levels of androgen and LH ,and an increase in FSH levels have been demonstrated after ovarian drilling and this allows the development of functional follicles(10,11).If less than four punctures on each ovary results in poorer pregnancy rates but more than ten may cause ovarian damage and premature ovarian failure (12).

The aim of this study is to compare and determine the efficacy and safety of combined metformin-letrozole administration to that of metformin and LOD in ovulation induction and reproductive outcome in clomiphene – resistant infertile women with PCOS.

Materials and methods

A total of 60 patients who were clomiphene – resistant with PCOS were chosen among patients attending infertility clinic in The Maternity Hospital and the private clinic in AL-Diwaniyah city –Iraq during the period of June 2112-June 2114. All participants patients gave informed consent before inclusion in the trial and the inclusion criteria were 20-35years old patient with PCOS who were clomiphene resistant and the diagnosis of PCOS based on the revised 2003 Rotterdam criteria of PCOS(13). They had patent fallopian tubes proved by hysterosalpingo- graph and normal semen analysis for their partners according to the Modified Criteria of World Health Organization(14).

At the study entry ,all patients had basal hormonal assays at day 2or3 of progesterone induced menstruation consisting of FSH,LH,TSH, serum prolactin ,total testosterone level and blood sugar.

Exclusion criteria : were other causes of infertility ,age over 35year , BMI more than 35 , contraindications to general anesthesia , previous history of LOD , women who had received gonadotropin or oral contraception for the preceding 6 months ,congenital adrenal hyperplasia ,Cushing's syndrome ,diabetes mellitus , androgen producing tumors and history of drug hypersensitivity to metformin or letrozole.

The sonographers who performed transvaginal ultrasound follow up assessment were blinded to the treatment groups. .All participant patients (n=60) received 1500mg of metformin(Glucophage,MerckSerono)(500mg three times per day) for 6-8weeks,if pregnancy accused the patient was excluded from the study and no patient in our study got pregnant during the time of metformin treatment ,then the patients were divided into two groups: group A(n=30)the patients received 5mg letrozole (Femara ,Novartis) from day 3 of the cycle for 5 days plus metformin tablet 1500mg per day, this treatment regime continue for 6 cycles. The dominant follicular diameter and the endometrial thickness were determined bytransvaginal ultrasound at day 13 or 14 of the menstrual cycle .A total of 10,000IU of HCG was given intramuscularly(IM) to the patient when at least one ovarian follicular diameter was >18mm and the patient advised to have intercourse 24-36hours after HCG injection , serum progesterone (ng/ml) was tested at day 21-23 of the cycle (serum progesterone $\geq$ 5ng/dl indicates ovulation) .In group B(n=30) the patients received metformin tablet 1500mg per day and underwent bilateral ovarian LOD using three - puncture technique

,each ovary was cauterized at four points ,each for 4seconds at 40W for a depth of 2-4mm with a mixed current using a monopolar electrosurgical needle, then the pelvis was irrigated using ringer's lactated solution .The total procedure time was recorded and any intraoperative or postoperative complications were reported ,and there was no intraoperative or postoperative complications after LOD in our study. Follow up continue for 6months after the procedure and subsequent cycles were monitored for ovulation by transvaginal ultrasound for the dominant follicular diameter and endometrial thickness at day 13 or 14 of the menstrual cycle .All patients who showed ovulation were advised for natural intercourse 24-36hours after 10,000IU HCG injection IM ,then serum progesterone was tested at day 21-23 of the cycle.

In either group, in case of delayed menstruation in patient who had ovulation serum B-HCG level was measured and pregnancy was observed by transvaginalsonography.In cases of pregnancy ,metformin treatment was discontinued .

Results

On the whole 138 ovarian cycle were studied in 60 patients ,group A (72 cycle in 30 patients) ,group B(66 cycle in 30 patients) .No significant statistical differences wereobserved between group A and B with respect to mean demographical variables including age ,BMI ,and duration of infertility (table 1).

The mean endometrial thickness on the day of HCG administration was significantly higher in group A than group B(9.9mm versus 9.03 mm)($p<0.05$) (table 2).

The mean serum progesterone was significantly higher in group A than group B(8.30 ng/dl versus 6.05 ng/dl)($p<0.05$)(table 2).

The ovulation rate was significantly higher in group A (63.33%) while in group B was (30%)($p<0.05$).The pregnancy rate was significantly higher in group A (12 patients ,40%) while in group B(5 patients ,16.67%)($p=0.045$).

Live birth rate was higher in group A(10 patients ,83.33%) versus (4 patients ,33.33%)in group B ,but there was no significant difference regarding miscarriage rate between both groups($p>0.05$). No multiple pregnancy or ovarian hyper stimulation syndrome occur in either group. Pregnancy rate per cycle in group A was (17.04%),and in group B was(6.67%) which is not statically significant ($p=0.059$).

Table 1: Comparison of (mean ±SD) age, BMI and infertility duration between group A and group B

Characteristic	Group A			Group B			P	Significance
Age	28.00	±	4.22	28.97	±	3.98	0.365	Not significant
BMI	26.37	±	3.21	25.30	±	3.35	0.213	Not significant
Infertility Duration	3.80	±	1.30	3.93	±	1.68	0.732	Not Significant

Table 2: Comparison of (mean ±SD) endometrial thickness(mm), Ovum diameter (mm) and serum progesterone(ng/dl) between group A and group B

Characteristic	Group A			Group B			P	Significance
Endometrial Thickness	9.90	±	1.67	9.03	±	1.43	0.035	Significant
Ovum Diameter	15.70	±	3.20	12.50	±	4.16	0.002	Significant
Serum Progesterone	8.30	±	3.77	6.05	±	3.26	0.016	Significant

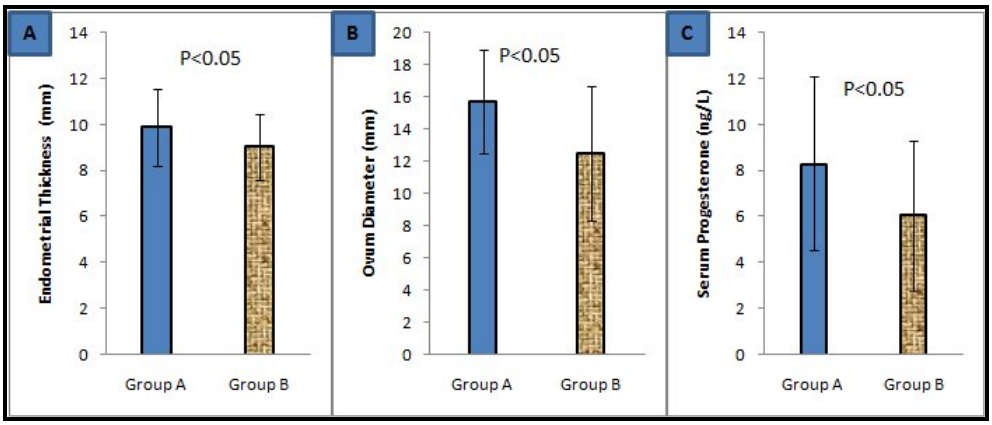

Figure 1: Comparison of mean endometrial thickness (A), Ovum diameter (B) and serum progesterone (C) between group A and group B

Table 3: Comparison of ovulation rate between group A and group B.

	Group A		Group B	
Ovulation	No.	%	No.	%
Yes	19	63.33	9	30.00
No	11	36.67	21	70.00
Total	30	100.00	30	100.00
P =	0.010	Significant		

Table 4:Comparision of pregnancy rate between group A and group B.

	Group A		**Group B**	
Pregnancy	**No.**	**%**	**No.**	**%**
No	**18**	**60**	**25**	**83.33**
Yes	**12**	**40**	**5**	**16.67**
Total	**30**	**100**	**30**	**100**
P=0.045	**Significant**			

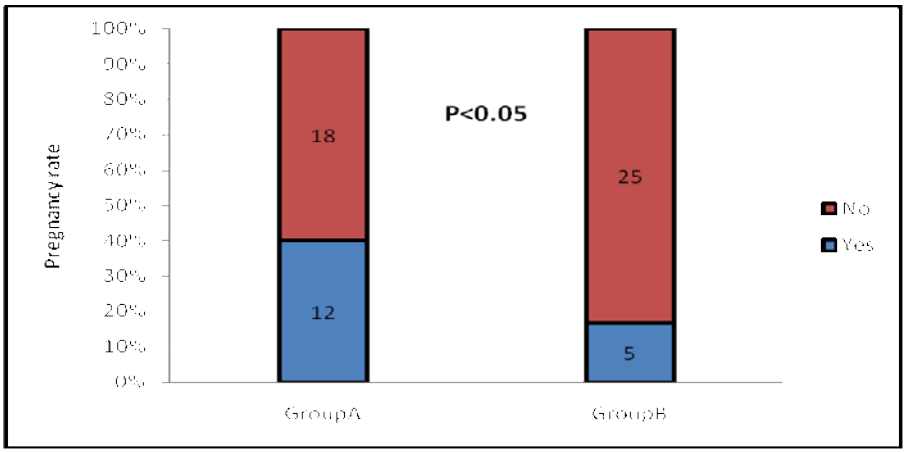

Figure 2: Comparison of pregnancy rate between group A and B.

Table 5: Comparison of live birth rate between group A and group B.

	Group A		Group B	
Live Birth	No.	%	No.	%
No	2	16.67	1	8.33
Yes	10	83.33	4	33.33
Total	12	100.00	5	41.67
P= 0.010	significant			

Table 6:Comparision of abortion rate between group A and group B.

	Group A		Group B	
Abortion	No.	%	No.	%
No	10	83.33	4	80
Yes	2	16.67	1	20
Total	12	100.00	5	100
P=1.000	Not significant			

Table 7:Comparison of pregnancy rate per cycle between group A and group B

GroupA			GroupB			P	Significance
17.04	±	4.56	6.67	±	2.84	0.059	Not Significant

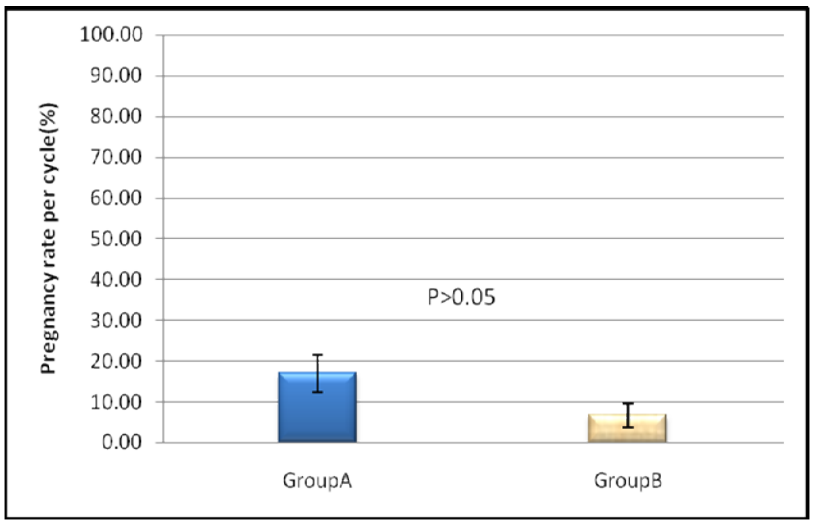

Figure 3:Comparison of pregnancy rate per cycle between group A and group B

Statistical analysis

Two software programs were used to describe ,summarized and analyze data . These were the Microsoft Office Excel 2010 and SPSS version 20.Numeric variables were expressed as mean ±SD ,while nominal variables were expressed as number (frequency) and percent. Student t-test was used to compare mean value between two groups. Chi-Square test and Fisher Exact test were used to compare frequency distribution between two groups .P-value less than or equal to 0.05 was considered significant.

Discussion

It is important to understand that couples seeking medical help for infertility would be going through serious emotional trauma and hence a sympathetic and considerable attitude should be adopted while approaching them .The primary responsibility of the clinician is to alter anxiety and to put in a sincere effort to find out the root cause of infertility .

Polycystic ovary syndrome is a common cause of counseling in infertility clinics and women with PCOS suffer infertility primarily because of chronic anovulation, however occasional ovulation may occur in women with less oligomenorrhea with unpredictable timing.Up till now patients with clomiphene resistant have been treated with expensive gonadotropins with or without GnRH analogue therapy or interventional LOD with their subsequent disadvantages .

The result of our study indicate that women with clomiphene citrate resistant PCOS experience higher ovulation rate

and pregnancy rate when they receive combined metformin-letrozole in comparison with women receiving metformin and underwent LOD.

In our study no significant relationship was observed regarding age ,BMI ,and duration of infertility between the two groups. But the mean endometrial thickness and the diameter of the dominant follicle on the day of HCG administration was significantly higher in group A than group B Which is similar to the result achieved by(Hatem A. et al ,2010)(15).In addition the study of(Abdellah M.S,2011) ,show significant increase in endometrial thickness on the day of HCG administration in women receiving letrozole than those with LOD(16). This was shown also by(Fisher S.A et al ,2002) as there is increase endometrial vascularization in patients using letrozole drugs (17).

In our study ovulation rate was significantly higher in group A than group B (63.33% versus 36.67%) which was similar to the result achieved by(Abdellah M.S ,2011) who study 140 women with clomiphene resistant which showed higher ovulation rate in the letrozole group than LOD group (59.0% versus 47.5%) ,while(Hatem A. et al 2010) study 260 women with clomiphene resistant showed that no significant difference in ovulation rate between letrazole group and LOD group (65.4% versus 69.3%)(15).First time the use of aromatase inhibitor (letrozole) for ovulation induction has been mentioned by Mitwally and colleagues (2001) who study 22anovulatory women resistant to ovulation by clomiphene ,as ovulation occurred in 75% of women and pregnancy was achieved in 25% of patients(19).

The difference in the result between our study and the result of others' study probably may be due to the more favorable effect of combined letrozole-metformin on the ovary, as many study showed that women with PCOS and anovulatory infertility are insulin resistant and there is elevated insulin secretion and this may directly stimulate ovarian androgen secretion and result in anovulation especially in overweight women who had more intenseanovulatory state,metformin used alone or in combination with clomiphene improves ovulatory function in women with PCOS which is shown by the study of(Neven et al , 2007) (20) .Also the study of(Seibert et al ,2006) showed improved ovulatory function in women who are clomiphene resistant if use metformin in the treatment courses (21).

A study of(Myers et al ,2005) showed improved live birth rates with combination therapy (22) ,and(Sinawat S. et al ,2008) study showed that metformin use has a benefit during pregnancy by decreasing the risk of miscarriage in PCOS patients(23).

In our study and according to these findings there was improved ovulation rates in both groups but more in the combined letrozole – metformin group.

Our study showed a significant increase in pregnancy rate (40% versus 16.67%),and live birth rate (83.33% versus 33.33%) in group A than group B. No significant statistical difference regarding miscarriage rate .In(Hatem A. et al study 2010) showed the pregnancy rate was similar in both groups (15.6% versus 17.5%) ,with no significant statistical differences regarding live birth rates or miscarriage rates between letrozole group and LOD group .while the study of (Abdellah M.S. ,2011) showed higher pregnancy rate in women receiving letrozole drug than LOD group (35.7% versus 28.6%) with a lower rate of miscarriage (8.0% versus 20.0%) .

In addition in our study per cycle pregnancy rate in group A was (17.04% versus 6.67%) in group B which was not statically significant and this could be more significant if larger group of patients were included in the study. All live births in both groups were healthy with no congenital abnormalities .

Although LOD is efficacious and carries with it the benefit of multiple ovulatory cycles, one shoot procedure ,relatively short operative time a decrease in spontaneous abortions and a lower risk of multiple gestations , but there may be disadvantages as well, as there are ongoing concerns about the long term effect of LOD on ovarian functions .The study of(Felemban A. et al ,2000) and (Naether O.G. ,1993) showed that bilateral ovarian drilling may result in diminished ovarian reserve and premature ovarian failure and peritubal and periovarianadhesions as well(12,18).Thus compromised fertility may result and with these potential effects on the patient , selection for this technique should be carefully assessed before proceeding .

Although some patients in group A experience some simple side effects such as hot flushes breast tenderness and headache but no risk of multiple pregnancy or ovarian cyst or ovarian hyper stimulation syndrome ,and no risk of ovarian failure or risk of general anesthesia exposure.

Conclusion

Letrozole appears to be a safe ,effective and inexpensive drug for induction of ovulation especially in clomiphene citrate resistant women with higher live birth rate than laparoscopic ovarian diathermy and the therapy does not require an elaborated monitoring .

References

1-Homburg R. Clomiphene citrate –end of an era ? A mini review. Hum Reprod.2005 ;20:2043-2051.

2-Franks Polycystic ovary syndrome : a changing perspective .Clin Endocrinal 1989 ;31:87-120.

3-Gysler M. ,March C.M ,MishellD.R.Jr ,Bailey E.J .A decades experience with an individualized clomiphene treatment regimen including its effect on the postcoital test .FertilSteril .1982 ;37:161.

4-Brown J. ,Farquhar C. ,Beck J. ,Boothroyd C. ,Hughes E. Clomiphene and anti-estrogens for ovulation induction in PCOS .Cochrane Data base System Rev.2009 ;4 .

5-Farquhar C.M ,Williamson K. , Gudex G. , Johnson N.P , Sadler L . A randomized controlled trial of Laparoscopic ovarian diathermy versus gonadotropin therapy for women with Clomiphene citrate resistant polycystic ovary syndrome .FertileSteril .2002;78 :404-411.

6-Holzer H. ,Casper R. ,TulandiT. A new era in ovulation induction .FertilSteril2006 ;85 :277-284.

7-Young S.L , Fritz M.A . Serum concentration of euclomiphene and zuclomiphene across consecutive cycles of clomiphene citrate therapy in anovulatory infertile women . FertilSteril .1999;71:639-644.

8-Tuomilehto J.,Lindstrom J.,Erilesson J.G, et al.Finnish Diabetes Prevention Study Group Prevention type 2D.M by changes in life style among subjects with impaired glucose toleranceEngl J Med.2001 ;344:1343-1350.

9-Flemina R.,HonkinsonZ.F,WallaceA.M. Ovarian function and metabolic factors in women with oligomenorreha treated with metformin in a randomized double blind placebo-controlled trial ClinEndocinolmetab. 2002;87:569-574.

10-Amer S.A,Gopalan V .Long term follow –up of patients with polycystic ovarian syndrome after laparoscopic ovarian drilling .Clinical outcome.HumReprod.2002;17:2035-2042.

11-Amer S.A ,Li TC ,Cooke I,D .Repeated laparoscopic ovarian diathermy is effective in women with an ovulatory infertility due to polycystic ovary syndrome.FertilSteril.2003;79:1211-1215.

12-FelembanA.,Lin Tan S.,TulandiLaparoscopic treatment of polycystic ovaries with insulated needle cautery .FertilSteril .2000;73:266-269.

13-Rotterdom ESHRE/ASRM –Sponsored PCOS Consensus Work Shop Group Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome .FertilSteril .2004;81:19-25.

14-Organization World Health 1990 WHO Laboratory manual for the examination of human semen and sperm-cervical mucus interactions,4th edition, Cambridge University Press, Cambridge.

15-Hatem Abu Hashim ,Abdel MagedMashaly ,Ahmed Badawy . Letrozole versus Laparoscopic ovarian diathermy for ovulation induction in clomiphene resistant women with polycystic ovary syndrome .Gynecol Obstet. 2010;282:567-571.

16-Abdellah M.S .Reproductive outcome after letrozole versus laparoscopic ovarian drilling for clomiphene resistant polycystic ovary

syndrome.Int J Gynecol Obstet. 2011;113(3):218-221.
17-Fisher S.A,Reid R.I .A randomized double blind comparison of the effects of clomiphene citrate and aromatase inhibitor letrozole on ovulatory function in normal women .FertilSteril .2002;78(2):280-285.
18-Naether O.G,Fischer R. Adhesion formation after laparoscopic electrocoagulation of the ovarian surface in polycystic ovary patients .Fertil Steril.1993;60:95-98.
19-Mitwally M.F.M , Casper R.F .Use of aromatase inhibitor for ovulation induction in patients with inadequate response to clomiphene citrate .Fertility and Sterility ,2001;75(2-8):305-309.
20-Neveu N.,Granger L. Comparison of clomiphene citrate ,metformin or the combination of both for first line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome.FertilSteril.2007;87(1):113-120.
21-Siebert T.L ,Kruger T.F ,Steyn D.W. ,etal .Is the addition of metformin efficacious in the treatment of clomiphene citrate resistant patients with polycystic ovary syndrome ?.FertilSteril.2006;86(5):1432-1437.
22-Myers E.R,Silva S.G. ,etal .National institute of child health and human development reproductive medicine network .Estimation of live birth rates after ovulation induction in polycystic ovary syndrome.ContempClin Trials.2005;26(3):271-280.
23-Sinawat S.,Buppasiri .Long versus short course treatment with metformin and clomiphene citrate for ovulation induction in women with PCOS.Cochrance Data base Syst Rev.2008;1.