



## Evaluation of the effectiveness of transvaginal ovarian drilling under ultrasound guide in patients with resistant polycystic ovary syndrome to clomiphene citrate

Asma Z Fadhil<sup>\*1</sup>, Thuraya Husamuldeen Abdullah<sup>2</sup>, Hayder Ali Lafta Mossa<sup>1</sup>

<sup>1</sup>High Institute for Infertility Diagnosis and Assisted Reproductive technologies, AL- Nahrain University, Baghdad, Iraq

<sup>2</sup>AL-Imamain Teaching Hospital, Baghdad, Iraq



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### ABSTRACT

Polycystic ovary syndrome (PCOS), is a heterogeneous disorder found in 3% - 10% of women worldwide, and it constitutes about 80 % of anovulation infertility. In cases of resistance to CC surgical option in form of ovarian drilling, for using maneuver with less invasive than laparoscopy we study the effect of transvaginal ovarian drilling under ultrasound guide in patients with resistant polycystic ovary syndrome to clomiphene citrate This study was conducted o evaluate the effectiveness of transvaginal ovarian drilling under ultrasound guide in patients with resistant polycystic ovary syndrome to CC. In this, A prospective, clinical trial study 42 infertile women with PCOS resistant to 3 months course of treatment with CC enrolled in this study. The pre-operative assessment includes history, physical examination, the serum levels of FSH, LH, AMH, testosterone, and TVS was done for ovarian morphology. Transvaginal ovarian drilling under ultrasound guide using a needle connected to manual vacuum pressure that punctured each ovary between 3 – 6 punctures. Postoperatively Signs of spontaneous ovulation, levels of FSH, LH, AMH, testosterone, and pregnancy rate were recorded. The results revealed that There is a significant reduction in the level of LH, FSH, Testosterone, and Anti-Mullerian hormones. Signs of spontaneous ovulation was developed, and the pregnancy rate after the operation was recorded. This low cost, no recorded adverse effects, and quickly done manoeuvre has an excellent result in improving fertility rate in resistant PCOS women to CC.

### \*Corresponding Author

Name: Asma Z Fadhil

Phone: +9647831156866

Email: [asmafadhil@yahoo.com](mailto:asmafadhil@yahoo.com)

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### INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex disorder characterized by psychological, reproductive and metabolic features which first described by 1935 by Stein and Leventhal in which their names were given to name this syndrome ([Azziz and Adashi, 2016](#)). The syndrome is a collection of symptoms that lead to complications and diseases affected many organs such as diabetes mellitus type 2, metabolic syndrome and infertility. However, the presentation of symptoms varies from mild to severe psychological and metabolic disturbances ([Franks and Berga, 2012](#)). In 2012 the NIH recommended that the using Eshre/ Asrm 2003

criteria, but with the description of PCOS phenotype (Mohammad and Seghinsara, 2017). The prevalence of the syndrome depending on the diagnostic criteria and the ethnic origin, its prevalence among the women within reproductive ages about 6 – 10 % by the using of NIH criteria while by the using of Rotterdam criteria it is about 14 – 20 % (Azziz et al., 2009). Ovulatory dysfunction is one of the criteria of PCOS with irregularity in menstruation that indicated ovulatory dysfunction. Regular cycles do not exclude ovulatory dysfunction. Hormonal assessment to confirm the anovulation if PCOS is clinically suspected in women with a regular cycle. Furthermore, normally irregularity in the cycles and ovulatory dysfunction are component of the transition to pubertal and menopause. Indeed, this diagnostic criterion is controversy during the pubertal transition (Bozdog et al., 2016). The abnormality in hormonal levels in women with PCOS are increasing in the serum levels of androgens and luteinizing hormone (LH), with slightly suppressed or normal level serum FSH levels lead to disturbing in the ovarian function, the WHO showed that 91% of women categorized as having WHO group 2 of ovulatory infertility met the broader diagnostic criteria for PCOS (Dhaded and Dabshetty, 2018) It is difficult to describe the exact aetiology of anovulation, therefore many explanations introduced to understand the mechanism of anovulation. High level of LH cause recruitment of more antral follicles, on another hand the androgen make follicles sensitized to the FSH. because this sensitization the follicles cannot grow more than 6 mm in the absence of FSH. Furthermore, the multiple follicular recruitments lead to an increase in serum level of estrogen and the androgen excess converted to estrogen, so the FSH rising arrested. This stimulates LH and not allow the growth of the follicles and causing an increase in the number of theca cells and stroma (Filippou and Homburg, 2017). Follicular excess may have enhanced by obesity and IR by disturb of AMH through excess of androgen. AFC and volume of the ovary correlated with AMH, androgen, and testosterone (Filippou and Homburg, 2017). Hyperinsulinemia had an increasing expression of vascular endothelial growth factor which leads to an increase in insulin-like growth factor 1 will stimulate granulosa cells, and theca cell to produce gonadotrophin stimulated steroid to lead to increasing AMH (Solorzano et al., 2012). The first-line treatment of anovulatory PCOS, A nonsteroidal that inhibits estrogen receptors in the hypothalamus, inhibiting the effect of estrogen on the release of gonadotropin (Pielecka et al., 2006). Normally at 7 days after ovulation, estrogen and progesterone

at high level inhibit GnRH, FSH, and LH, if no fertilization occurs after the ovulation period, the lack of beta-hCG lead to the corpus luteum disintegrates (Brebrowicz et al., 2012). CC prescribed on day 3 and continue for 5 days of cycles. On another hand, the level of FSH is rising, enhancing the development of follicles, which responsible for the production of the estrogen (Pielecka et al., 2006). The resistance to CC is well documented (failure of ovulation after receiving CC for five days per cycle in a dose of 150 mg for at least three cycles), and due to CC effect on the endometrium and mucosa of the cervix there is a difference between the high ovulation rates and a decrease in pregnancy rates (Pielecka et al., 2006). Because the ovaries had prominent thecal and stromal hyperplasia different surgical manoeuvres had been used such as ovarian wedge resection. Wedge resection becomes gradually less option is used in the 1970s with the appearance of CC as medical management to avoid the adverse effects of surgery postoperatively (Rosenfield and Ehrmann, 2016). Laparoscopic ovarian drilling first reported in 1984 performed by laparotomy with multiple punctures of ovarian capsule either using of laser or Electrocautery, furthermore another way introduced instead of laparotomy including transvaginal hydro laparoscopy and fertiloscopy (Tekin et al., 2008). The adverse effect of LOD related to the complication of general anaesthesia, bleeding from the drilling sites, ovarian failure, and mechanical infertility (adhesion) more common with using of laser (Solorzano et al., 2012). For a safe, less invasive, less costly and the same effect of surgical intervention an approach for drilling via the vagina using ultrasound guiding needle (TVOD) was introduced and shows there was no difference between the groups undergo LOD and groups with TVOD in miscarriage rates or spontaneous pregnancy.

## PATIENTS AND METHODS

A prospective, clinical study was carried out in High Institute for Infertility Diagnosis and assisted Reproductive technologies- AL- Nahrain University, the study was performed between November 2018 and April 2019. The study protocol was approved by the Arab Board of Health Specializations for Obstetrics and Gynecology in Iraq and High Institute for Infertility Diagnosis and assisted Reproductive technologies, AL- Nahrain University. According to the Rotterdam Consensus the diagnostic criteria for PCOS are: oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries (by gynecologic ultrasound); two of these three criteria are required with the

exclusion of other endocrine disorders (such as congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome). All participants fulfilled the diagnosis for PCOS, having polycystic ovaries on transvaginal ultrasound scan (TVS), biochemical evidence including elevated luteinizing hormone (LH) and serum testosterone levels secondary amenorrhea (<2 cycles per year), anovulation, and all with average serum level of prolactin, thyroid function test, and 17-OH-P. Forty-two women with PCOS enrolled, they met the criteria for CC resistance (on the maximum dose of CC 150 mg for 5 days at least for 3 cycles with no response) (Bremer, 2010). All patients counselled about the ovarian drilling via the vagina and discuss the benefit and the risk of the manoeuvre to both patients and their partners, also their opinion about using gonadotrophin, and we informed the couple about its cost, benefit effect, possibility of side effects and all patients chose TVOD, and verbal agreement was gained. The preoperative assessment includes the baseline serum levels of FSH, LH, AMH, and testosterone was measured using 10 ml of the patient's blood plasma and the baseline TVs for ovarian morphology, including AFC. All patients had patent fallopian tubes proved by hysterosalpingography, and normal SFA according to the modified WHO criteria. A complete blood count, serum glucose level, and serum urea level along with checking by an anaesthetic doctor for fitness of general anaesthesia.

### Surgical procedure

Patient positioned in the dorsal lithotomy position cleaning and sensitization of vagina and perineum, draping of the patient after anaesthetizing the patients with Propofol. Then transvaginal ultrasound to see the ovaries clearly and then directed the view of ultrasound to one ovary, passing of sixteen gauges, 35 cm needle connected to a continuous manual vacuum pressure that punctured each ovary between 3- 6 punctures with the aspiration of small-sized follicles. After checking by TVS, both sides of the ovary and pouch of Douglas then observed postoperatively for 2-3 hours for any complications which included: Complication of anaesthesia, intra-abdominal haemorrhage, and injuries of internal organs. The patient only had mild pain and given analgesia with antibiotics and appointment for a regular visit starting at the next cycle after operation for four weeks' intervals. At follow up visits looking for the number and size of dominant follicles at 11-12 days of the period, in addition, to the hormonal level of AMH, LH, FSH, and testosterone were checked. When dominant follicles reached 17-22 mm 5000 IU of HCG given intramuscularly and advised the couple for intercourse. Ovulation also

confirmed by the measuring of the mid-luteal serum level of progesterone (ovulation was recorded when serum progesterone was >5 ng/mL). If miss period occurs, pregnancy confirmed by biochemical plus the ultrasound on 6 weeks and the pregnancy rate was calculated.

### Statistical analysis

Data analysis were performed using of SPSS version 24, paired sample T-test and data expressed as means  $\pm$  SD, hormonal assay before and after the operation with  $P < 0.05$  considered statistically significant.

## RESULTS AND DISCUSSION

**Table 1: Demographic data of patients**

variable	Mean
Age (years)	25.4 $\pm$ 5.1
Body mass index (kg/m <sup>2</sup> )	28.8 $\pm$ 5.4
Duration of infertility (years)	4.7 $\pm$ 2.2

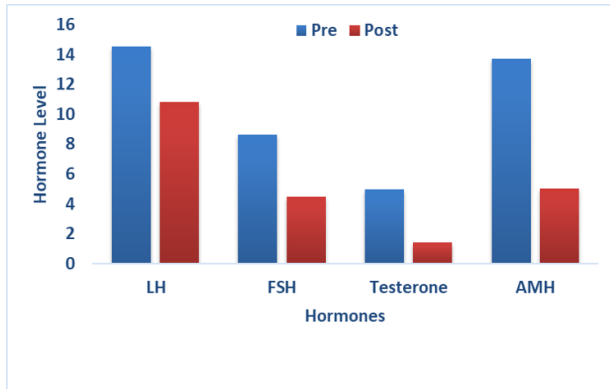
The total patients involved in the study were 42 patient with a mean age (years) 25.4  $\pm$  5.1, the mean body mass index (BMI) 28.8  $\pm$  5.4, the mean duration of infertility was 4.7  $\pm$  2.2. As shown in Table 1.

**Table 2: Serum Hormonal as say pre and post ovarian drilling**

Hormones	pre	post	P value
Luteinizing hormone (IU/L)	14.54 $\pm$ 0.72	10.8 $\pm$ 0.76	<0.05
Follicular stimulating hormone (IU/l)	8.65 $\pm$ 0.7	4.48 $\pm$ 1.16	<0.05
Testosterone (nmol/l)	4.94 $\pm$ 0.7	1.4 $\pm$ 0.5	<0.05
Anti-Mullerian Hormone (ng/ml)	13.6 $\pm$ 2.0	5.0 $\pm$ 1.1	<0.05

The hormonal assay of LH, FSH, testosterone, and Anti-Mullerian Hormones in which there is a significant reduction in the levels of these hormones with  $P$  value <0.05.

There is increasing in numbers of patients had dominant follicles with a time of follow up, as shown in

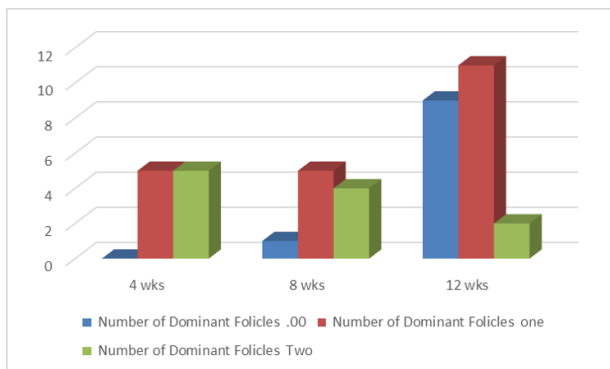


**Figure 1: Show the hormonal level before and after the operation.**

**Table 3: The numbers of patients had dominant follicles every four weeks interval for 3 months' duration.**

No. of patients	4 weeks	8 weeks	12 weeks
0	0	1	9
One	5	5	11
Two	5	4	2
Total	10	10	22

Table 3.



**Figure 2: Show distribution of numbers of follicles during 12 weeks.**

**Table 4: Clinical outcome of 42 patients undergoing transvaginal ovarian drilling**

Variable	No.
Ovulation rate	13/42
Pregnancy rate	5/42

After TVOD and ovulation induction, (5/42) of patients became pregnant. The cumulative ovulation rate after TVOD was (13/42).Table 4

**Table 5: The diagnosis of the ovulation rate.**

Diagnosis of dominant follicles	No. (%)
ultrasound	13 (100)
progesterone	8 (61.54)
Progesterone plus ultrasound	7 (53.85)

LOD is a second option for treatment of CC resistance or could be the first line when there is another reason for infertility in PCOS patients, with a good result on the ovulation and pregnancy rates. A recent study by [Haturnaz et al. \(2019\)](#) showed that transvaginal ovarian drilling was superior to LOD in which it is safer, fewer costs and with the same effect without an invasive procedure. Table 1 shows the demographic distribution of all patients in whom average age  $25.4 \pm 5.1$  which the generation of women who are suffering from infertility and they desire to become pregnant in which they on CC treatment for 3 months with no response. Most of the patients obese and overweight because of the high prevalence of PCOS in the obese patient, and they are commonly suffering from CC resistance ([Gibson-Helm et al., 2017](#); [Bremer, 2010](#)). The current study involved 42 patients who met the criteria of Rotterdam Consensus in the diagnosis of PCOS, pre-operative their hormonal assay of LH, FSH, Testosterone, and AMH were  $14.54 \pm 0.72$ ,  $8.65 \pm 0.7$ ,  $4.94 \pm 0.7$ , and  $13.6 \pm 2.0$  respectively, after operation there is a dramatic response with a decreasing in the levels of these hormones reaching the statistically significant (P value <0.05). Table 2 The numbers of patients had dominant follicles about follow up interval as in Table 3 shows there is a good outcome of ovulation rate within three months after transvaginal ovarian drilling every 4 weeks of checking to look for if there is ovulation occur during this period. [Amer \(2004\)](#) showed that the recurrence rate of ovulation after few months of laparoscopic ovarian drilling. Greenblatt ([Greenblatt and Casper, 1987](#)) concluded that the trauma to the ovary is breaking the synthesis of androgen this leads to a decrease in androgen concentration inside the ovary and this lead to the negative effects of androgen on the maturation of the follicles. Subsequently, this leads to a reduction of the conversion of androgen to estrogen that causes positive feedback on the secretion of luteinizing hormone ([Filippou and Homburg, 2017](#)). [Weerakiet et al. \(2007\)](#) assessed the effect of LOD on ovarian reserve. Anti-mullerian hormone, FSH, antral follicle coun, and ovarian volume were measured, and they compare patients underwent

LOD, and patients who did not undergo LOD.

In their study found that AMH level was lower in LOD group ( $4.6 \pm 3.16$  ng/mL) in comparison to the patient not underwent LOD ( $5.99 \pm 3.36$  ng/mL), but the difference was not recorded as statistically significant. The level of FSH was significantly higher in the LOD group (Chen *et al.*, 2008). Breborowicz *et al.* (2012) they conclude that before doing IVF, an increase in estradiol level after TVOD in women with PCOS on metformin treatment leads to an increment in the number of mature oocytes (Aal *et al.*, 2005). Mural has been showed that LOD is an excellent way to improve the endocrine properties, morphology, and function of the ovary. (Gomel and Yarali, 2004) showed that the transvaginal ovarian drilling represents a new approach for the treatment for patients with ovulation problem in PCOS. In our study, transvaginal ovarian drilling leading to ovulation. (Al-Took, 1999) concluded that the ovary volume decrease after three weeks after ovarian drilling; therefore, the ovary response will increase to induction of ovulation. This result of the study is in agreement with our study in which there is growing in follicles numbers. showed that a decrease Inhibition following the ovarian drilling, lead to increasing of the secretion of follicular stimulating hormones. So the volume of follicles and rising in the number of dominant follicles. Fernandez *et al.* (2001) in their study showed that the pregnancy rate was 33% at three months in women after doing transvaginal ovarian drilling and 71% after six months in women did transvaginal ovarian drilling; these results showed that TVOD might be a minimally invasive method in women resistant to clomiphene with PCOS. Ramzy *et al.* (2001) worked on hydro coagulation ovarian stroma under transvaginal ultrasound guide in 52 patients diagnosed as PCOS. in 73.1% ovulation occur in the group of clomiphene citrate-resistant and the pregnancy happen in 26.9% of these women. Casa *et al.* (2003) concluded that the transvaginal ovarian drilling is a useful option in treating PCOS with no abortion or ovarian hyperstimulation, wherein 66.7% of women ovulation spontaneously happened, and the pregnancy rate was 38% and 76% at three and six months respectively. Fernandez *et al.* (2004) showed that during a mean follow-up of 18.1 months, 91% of women achieved regular and ovulatory cycles. The pregnancy rate was 60% for both spontaneous and stimulated cycles, with 39.7% underwent drilling alone. They concluded again that TVOD appears to be an effective minimally invasive procedure in patients with PCOS resistant to clomiphene citrate.

## CONCLUSION

From the results of this study, they concluded that the TVOD could cause changes in the ovary with a decreasing in the hormonal levels of patients with PCOS that may be responsible for menstrual disturbance and infertility. There is improving in ovulation rate after the procedure, and there is no complication recorded.

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## Authors contribution:

Dr Asma Z. Fadhil writes the article and Dr Habib Najem participate in article preparation.

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