Middle East Fertility Society Journal (2013) xxx, xxx–xxx

Middle East Fertility Society

Middle East Fertility Society Journal

www.mefsjournal.org
www.sciencedirect.com

ORIGINAL ARTICLE

Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome

Yasser Ibrahim Orief [a,c,*], Emad Abd Elmoneem Darwish [a,b], Mohamed Abdelmoaty Elsamra [a], Dina Hassan Aly Ragab [a]

[a] *Department of Obstetrics and Gynecology, Faculty of Medicine, Alexandria University, Egypt*
[b] *Integrated Fertility Center, Alexandria University, Egypt*
[c] *Agial Fertility Center, Alexandria University, Egypt*

Received 17 May 2013; accepted 3 June 2013

KEYWORDS

Gestagen;
Oral contraceptive pills;
PCO;
Clomiphene citrate

Abstract *Objective:* To compare between gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome.

Design: Randomized controlled trial.

Setting: Integrated Fertility Center and Agial Fertility Center.

Sample: Fifty PCO female patients.

Methods: The patients were subdivided in 2 groups according to computer generated randomized program:

Group I: Twenty five PCO female patients treated by cidolut nor 5 mg tablets (two tablets every day for 5 days).

Group II: Twenty five PCO female patients treated by cilest tablets (one tablet every day for 21 days).

All patients were observed until withdrawal bleeding followed by ovulation induction by clomiphene citrate from the second day of menses (100 mg per day for 5 days). The patients were then followed up by:

* Corresponding author at: Department of Obstetrics and Gynecology, Faculty of Medicine, Alexandria University, Egypt. Tel./fax: +20 3 544 22 64x102, mobile: +20 100 8233 121.
E-mail address: yaserorief@yahoo.com (Y.I. Orief).
URL: http://www.yaserorief.com (Y.I. Orief).

Peer review under responsibility of Middle East Fertility Society.

Production and hosting by Elsevier

1110-5690 © 2013 Production and hosting by Elsevier B.V. on behalf of Middle East Fertility Society.
http://dx.doi.org/10.1016/j.mefs.2013.06.003

- transvaginal ultrasound follicular scanning in days 10, 12, and 14 of withdrawal bleeding until ovulation was detected with additional evaluation of the endometrial thickness and pattern
- serum progesterone was measured 7 days after the expected day of ovulation
- pregnancy test 15 days after ovulation to detect pregnancy and 2 weeks later by U/S to detect fetal pulsation.

Main outcome measures: Endometrial thickness, number of mature follicles and serum progesterone level on day o f ovulation, and clinical pregnancy rate.

Results: There was no significant difference between the two groups regarding pregnancy rate.

Conclusions: A few studies show an apparent use of oral contraceptive pills in the improvement of ovulation induction by clomiphene citrate. Despite this, from the available data a causal relationship is not confirmed, so large prospective studies using larger sample size, and longer duration of treatment are needed. Meanwhile, close clinical surveillance of patients being treated with oral contraceptive pills is required.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age and is the most frequent cause of hyperandrogenism and oligoanovulation, both of which have substantial psychological, social, and economic consequences. An increased awareness of this disorder in the general population and medical communities has taken place in recent years with the knowledge that women with polycystic ovary syndrome are susceptible to metabolic syndrome and its associated co morbidities. Therefore, polycystic ovary syndrome is a persisting challenge for clinical and basic research scientists (1–5).

Three key diagnostic features of polycystic ovary syndrome are hyperandrogenism, chronic anovulation, and polycystic ovaries on ultrasonography. Importantly, other conditions like congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors which are known to cause or to mimic the features of polycystic ovary syndrome must be excluded prior to diagnosis. Although obesity, insulin resistance, and metabolic syndrome are frequently present in women with polycystic ovary syndrome, they are not regarded as intrinsic disturbances of the disorder. The prevalence of polycystic ovary syndrome, as defined by the 1990 National Institutes of Health (NIH) criteria, in unselected populations of women of reproductive age is between 6.5% and 8%. Adoption of the 2003 Rotterdam criteria for the diagnosis of this disorder will presumably increase the prevalence of polycystic ovary syndrome because the scope for inclusion is broader than it is with the 1990 NIH criteria (6–10).

Women with polycystic ovary syndrome form the largest group of women with ovulatory dysfunction, which is characterized by chronic anovulation in the presence of normal follicular stimulating hormone (FSH) and estradiol concentrations. Induction of ovulation is the first-line treatment for this class of anovulation and is aimed at introducing an endocrine milieu that promotes growth and ovulation of a single dominant follicle with consequent singleton pregnancy. According to the National Institute of Clinical Excellence (NICE) guidelines, the recommendations for ovulation induction are as follows (11):

- Anti-estrogens: women with World Health Organization Group II ovulation disorders (hypothalamic pituitary dysfunction) such as polycystic ovary syndrome should be offered treatment with clomifene citrate (or tamoxifen) as the first line of treatment for up to 12 months because it is likely to induce ovulation. Women should be informed of the risk of multiple pregnancies associated with both clomifene citrate and tamoxifen.
- Metformin: anovulatory women with polycystic ovary syndrome who have not responded to clomifene citrate and who have a body mass index of more than 25 should be offered metformin combined with clomifene citrate because this increases ovulation and pregnancy rates. Women prescribed metformin should be informed of the side effects associated with its use (such as nausea, vomiting, and other gastrointestinal disturbances).
- Ovarian drilling: women with polycystic ovary syndrome who have not responded to clomifene citrate should be offered laparoscopic ovarian drilling because it is as effective as gonadotropin treatment and is not associated with an increased risk of multiple pregnancies.
- Gonadotropin: women with World Health Organization Group II ovulation disorders such as polycystic ovary syndrome who do not ovulate with clomifene citrate (or tamoxifen) can be offered treatment with gonadotropins. Human menopausal gonadotropin, urinary follicle-stimulating hormone, and recombinant follicle-stimulating hormone are equally effective in achieving pregnancy, and consideration should be given to minimizing cost when prescribing.
- Gonadotropin-releasing hormone analogs: women with polycystic ovary syndrome who are being treated with gonadotropins should not be offered treatment with gonadotropin-releasing hormone agonist concomitantly because it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation.

Like NICE guidelines, the Society of Obstetricians and Gynecologists of Canada (SOGC) also provides guidelines for ovulation induction. The recommendations are as follows (12):

- Weight loss, exercise, and lifestyle modifications have been proven effective in restoring ovulatory cycles and achieving pregnancy in overweight women with PCOS and should be the first-line option for these women. Morbidly obese women should seek expert advice about pregnancy risk.

Please cite this article in press as: Orief YI et al. Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome, Middle East Fertil Soc J (2013), http://dx.doi.org/10.1016/j.mefs.2013.06.003

- Clomiphene citrate has been proven effective in ovulation induction for women with PCOS and should be considered the first-line therapy. Patients should be informed that there is an increased risk of multiple pregnancies with ovulation induction using CC.
- Metformin combined with CC may increase ovulation rates and pregnancy rates but does not significantly improve the live birth rate over that of CC alone. Metformin may be added to CC in women with clomiphene resistance who are older and who have visceral obesity.
- Gonadotropin should be considered second-line therapy for fertility in anovulatory women with PCOS. The treatment requires ultrasound and laboratory monitoring. High costs and the risk of multiple pregnancy and ovarian hyperstimulation syndrome are drawbacks of the treatment.
- Laparoscopic ovarian drilling may be considered in women with clomiphene-resistant PCOS, particularly when there are other indications for laparoscopy. Surgical risks need to be considered in these patients.
- In vitro fertilization should be reserved for women with PCOS who fail gonadotropin therapy or who have other indications for IVF treatment.

2. Pretreatment with oral contraceptives

Combined oral contraceptive pills (OCPs) have been a key component of the chronic treatment of polycystic ovary syndrome (PCOS) by improving androgen excess and regulating menstrual cycles. Polycystic ovary syndrome (PCOS) is a common and complex disorder characterized by androgen excess, ovulatory dysfunction, and polycystic ovaries. Women with PCOS typically present with clinical evidence of hyperandrogenism (e.g., hirsutism), menstrual irregularity, and infertility. Accordingly, current treatment regimens are directed at reduction of hirsutism and/or acne, menstrual cycle regulation, and achieving pregnancy. Combined oral contraceptive pills (OCPs) have traditionally been the mainstay of treatment for the amelioration of hyperandrogenism and regulation of menstrual cycles in PCOS patients not seeking pregnancy (13–15).

2.1. OCPs

The OCPs are oral contraceptives containing low doses of synthetic estrogens and progestins. These hormones have a direct inhibitory effect on hypothalamic release of gonadotropin releasing hormone (GnRh). Estrogens inhibit the selection and development of a dominant follicle by suppression of follicle stimulating hormone (FSH). Progestins inhibit ovulation via suppression of luteinizing hormone (LH) surge. The effects of progestins also include making the cervix hostile to sperm penetration by thickening the cervical mucus and preventing implantation through an alteration of endometrial lining (16).

Virtually all currently available OCPs contain ethinyl estradiol as the synthetic estrogenic compound. Norgestrel, levonorgestrel, norgestimate, and norethindrone are used as synthetic progestins in second generation pills, and the progestin component in third-generation pills is either desogestrel or gestodene Starting from the late 1960s, the amount of ethinyl estradiol in OCPs was significantly reduced from the initial dose of 150 mg to the current doses of 20–35 mg to increase efficacy, safety, and tolerability. Pills containing less than 50 mg of ethinyl estradiol are called "low-dose" OCPs. Most of the low-dose OCPs contain 35 mg ethinyl estradiol, and the dose of synthetic progestin ranges between 0.1 and 3 mg (17).

Most synthetic progestins used in OCPs are derived from an altered testosterone molecule, 19-nortestosterone. These progestins vary in their chemical structures, potency, and pharmacokinetics. They bind the androgen receptor with different affinities and show different degrees of androgenicity. In this group, desogestrel, norgestimate, and gestodene are less androgenic compared with levonorgestrel (18).

Three synthetic progestins with antiandrogenic effects cyproterone acetate, dienogest, and drospirenone are used in OCPs. Cyproterone acetate is derived from 17-hydroxyprogesterone, whereas dienogest and drospirenone are derivatives of 19-nortestosterone and 17-a-spirolactone, respectively. Cyproterone acetate is the most potent antiandrogenic progestin. Antiandrogenic potencies of dienogest and drospirenone measured by Hershberger test are 40% and 30% of that of cyproterone acetate, respectively (19).

The OCPs have the ability to address many of the goals of reproductive-aged women with PCOS not seeking pregnancy. They ameliorate hyperandrogenic skin manifestations, regulate menstrual cycles thereby protect from the risk of endometrial carcinoma, and provide effective and safe contraception.

In PCOS, the OCPs remain the mainstay of treatment for clinical hyperandrogenism. They suppress the secretion of LH and lead to a decrease in ovarian androgen production. The estrogenic fraction increases the levels of sex hormone binding globulin (SHBG), which, in turn, results in a decrease in free testosterone levels. The progestin in the pill can compete for 5 α reductase and the androgen receptor. The OCPs have also been shown to decrease adrenal androgen production by a mechanism yet unclear, possibly due to decrease in adrenocorticotropic hormone (ACTH) levels.

Whereas almost all of the OCPs contain ethinyl estradiol as the estrogenic fraction, progestins in the pills vary in their androgenic potential and may decrease SHBG levels as previously discussed. Norethindrone, norgestrel, and levonorgestrel are known to have androgenic activity. Alternatively, desogestrel, norgestimate, and gestodene are less androgenic and have the advantage of less metabolic side effects including the minimal impact on glucose, insulin, and lipids. Nevertheless, because PCOS is essentially an androgen excess disorder, use of OCPs containing progestins with antiandrogenic activity rather than second- and third-generation OCPs containing progestins with varying androgenic activity appears to be more appropriate. Among OCPs containing antiandrogenic progestins, ethinyl estradiol and cyproterone acetate combination has been used in many studies of PCOS, whereas only a few studies of ethinyl estradiol and drospirenone are available, and ethinyl estradiol and dienogest have not yet been studied in PCOS (20).

Ethinyl estradiol and cyproterone acetate combination has been widely used in PCOS. Cyproterone acetate is effective in the treatment of both hirsutism and acne. It acts mainly by competitively binding the androgen receptor. In mild to moderate cases, cyproterone acetate in a dose of 2 mg/day combined with 35 mg of ethinyl estradiol generally improves the symptoms (21–25). The recently approved ethinyl estradiol and drospirenone combination has also been used for the

Please cite this article in press as: Orief YI et al. Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome, Middle East Fertil Soc J (2013), http://dx.doi.org/10.1016/j.mefs.2013.06.003

treatment of PCOS. In addition to antiandrogenic activity, drospirenone has antimineralocorticoid properties, which might provide better tolerability compared with other low-dose OCPs. A recent uncontrolled pilot study on 15 PCOS patients reported that treatment with ethinyl estradiol (30 mg) and drospirenone (3 mg) combination resulted in decrease in androgen levels after 3 months and improvement in hirsutism after 6 months. Similarly, an observational study of ethinyl estradiol and drospirenone combination on 17 patients over 6 months found a decrease in androgen levels and improvement in acne without a significant change in hirsutism (26–28).

The OCPs are the treatment of choice for irregular menstrual bleeding in PCOS. Menstrual dysfunction in PCOS is clinically observed as oligomenorrhea/ amenorrhea, although 15–30% of patients might have regular uterine bleeding in the face of documentable oligo-ovulation (29). PCOS patients often contact a health care provider during their teenage years for unpredictable uterine bleeding. Use of OCPs in these patients results in regular withdrawal bleeding in addition to improvement in hyperandrogenism.

Additional noncontraceptive benefits of the long term use of OCPs in PCOS, similar to those in healthy OCP users, include a decrease in dysmenorrhea and heavy menses, a decrease in iron-deficiency anemia, and a reduction in the risk of endometrial hyperplasia or carcinoma. The potential link between PCOS and endometrial carcinoma has been reviewed in detail elsewhere Briefly, risk factors for endometrial carcinoma such as chronic anovulation, obesity, insulin resistance, and diabetes cluster in women with PCOS. However, there are no prospective studies suggesting that the incidence of or mortality from endometrial cancer is increased in PCOS. Nevertheless, it is reasonable to assume that OCP-associated benefits of the prevention of endometrial carcinoma in the general population might also be applied to women with PCOS (30–32).

3. Pretreatment with progesterone

Progesterone plays an important role in ovulation, in embryo implantation and in luteal phase support. Increasing evidence also indicates that human parturition is initiated by decreased myometrial responsiveness to progesterone, i.e., functional progesterone withdrawal. Moreover, we know that the incidence of anovulation and miscarriage in PCOS patients is high. Low levels of progesterone have been found in the early luteal phase in PCOS patients. Granulosa cells from polycystic ovaries demonstrate an altered ability to synthesize progesterone both in vivo and in vitro (33–44).

The lack of cyclical exposure to progesterone has been suggested to have a role in the development of the gonadotropin/ androgen synthesis alterations found in PCOS patients. Ovulation failure and progesterone deficiency may facilitate the development of the hypothalamic–pituitary abnormalities that determine the altered luteinizing hormone (LH) secretion which is characteristic of PCOS (44). Moreover, adults with PCOS require higher progesterone concentrations to inhibit the gonadotropinreleasing hormone (GnRh) (LH) pulse frequency compared with normal women. This contributes to establishment of the persistently rapid GnRH pulses and elevated LH levels found in PCOS (45).

All these findings may explain the presence of anovulation, the delay in conception and the high prevalence of miscarriage that occur in PCOS patients. Moreover, they also reveal the reason why PCOS patients undergoing assisted reproductive techniques represent a great challenge for the fertility specialist. Considering everything mentioned above, in these patients progesterone supplementation in in vitro fertilization (IVF) cycles is highly recommended for achieving a successful pregnancy (46,47).

An impaired adrenal function is a common characteristic of patients with PCOS. Consequently, basal androgen and 17a-hydroxy-progesterone (17-OHP) levels are routinely measured for the hormonal evaluation of suspected PCOS women. Androgen levels are generally determined to establish the presence of hyperandrogenemia whereas basal 17-OHP levels are determined to screen for 21-hydroxylase-deficient non-classic adrenal hyperplasia. Generally, to maintain sampling uniformity and avoid increases in 17-OHP levels due to corpus luteum function, these levels are obtained during the follicular phase (48–51).

However, since most hyperandrogenic patients are oligomenorrheic, it is frequently necessary to administer progestogen to induce the withdrawal bleeding and properly time the blood sampling. Progestogens such as medroxyprogesterone acetate (MPA) are commonly used to induce withdrawal bleeding in PCOS patients. Recent studies have shown that the administration of progesterone to women with PCOS results in a temporary, although clinically relevant, suppression of circulating androgen levels, which is significantly higher than the one achieved by MPA. These observations may favor the use of progesterone to induce withdrawal bleeding in these patients (52).

Undoubtedly, the treatment of anovulatory PCOS patients who are resistant to clomiphene citrate (CC) is challenging for the fertility specialist. The administration of progesterone before CC therapy has been effective in inducing the responsiveness to CC, due to the progesterone-related suppression of follicle-stimulating hormone (FSH) and LH secretion (53,54).

In summary, in clinical practice we may administer progesterone to PCOS patients in the following cases:

(1) To induce withdrawal bleeding;
(2) To suppress LH secretion in the normalization of the menstrual cycle;
(3) In ovulation induction in CC-resistant patients;
(4) To support the luteal phase after assisted reproductive techniques.

4. Objectives

The aim of this study was to compare between gestagen versus oral contraceptive pills to induce withdrawal bleeding before the induction of ovulation by clomiphene citrate in polycystic ovary syndrome and its relation to the outcome:

1. Primary outcome measures:
   – pregnancy rate.

2. Secondary outcome measures:
   – ovulation rate,
   – endometrial thickness and pattern.

Please cite this article in press as: Orief YI et al. Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome, Middle East Fertil Soc J (2013), http://dx.doi.org/10.1016/j.mefs.2013.06.003

5. Materials and methods

5.1. Design

Randomized controlled trial.

5.2. Setting

Integrated Fertility Center and Agial Fertility Center, Alexandria, Egypt.

5.3. Sample

50 PCO female patients between 20 and 35 years of age. Patients with other causes of infertility were excluded from the study.

5.4. Methods

After approval of the medical ethics committee, the patients were subdivided in 2 groups according to computer generated randomized program:

Group I: 25 PCO female patients treated by cidolut nor 5 mg tablet (two tablets every day for 5 days).

Group II: 25 PCO female patients treated by cilest tablet (Janssen-Cilag®) (one tablet every day for 21 days)

All patients were observed until withdrawal bleeding followed by ovulation induction by clomiphene citrate from the second day of menses (100 mg per day for 5 days). The patients were then followed up by:

- transvaginal ultrasound follicular scanning in days 10, 12, and 14 of withdrawal bleeding until ovulation was detected with additional evaluation of the endometrial thickness and pattern,
- serum progesterone was measured 7 days after the expected day of ovulation,
- pregnancy test 15 days after ovulation to detect pregnancy and 2 weeks later by U/S to detect fetal pulsation.

6. Results

The demographic data as well as the basal hormonal profile of both groups were demonstrated in Table 1 and showed no significant statistical differences between both groups. There was also no difference between both groups regarding the type of infertility. (Table 2)

In the Gestagen group the endometrial thickness when the mature graffian follicle reaches 18 mm in size and ranged from 5 to 9 mm with a mean of 7.44 ± 1.35 mm, while in the OCP group it ranged from 6 to 9 mm with a mean of 8.08 ± 0.996 mm. Using Student's *t* test, there was no significant difference as regards endometrial thickness between the two groups ($t = 1.901$, $p = 0.063$) (Table 3, Fig. 1).

The progesterone level 7 days after the expected day of ovulation in the Gestagen group ranged from 0.70 to 40.0 (ng/dl) with a mean of 18.30 ± 14.582 (ng/dl), while in the OCP group it ranged from 10.00 to 40.00 (ng/dl) with a mean of 28.04 ± 10.17 (ng/dl). Using Student's *t* test, the level of progesterone in OCP group was significantly higher when compared to the Gestagen group ($t = 2.620$, $p = 0.012$) (Table 4, Fig. 2).

In the Gestagen group the number of patients with mature follicle production on day 12 of the cycle was 16 (64%), while in the OCP group, 22 (88%). Using Pearson Chi-Square test there was significant difference between the two groups regarding mature follicles production in favor of the OCP group ($X^2 = 3.947$, $p = 0.047$) (Table 5, Fig. 3).

Regarding the pregnancy outcome, in the Gestagen group there were 11 (44%) pregnant patients and 14 (56%) not pregnant, while in the OCP group, there were 16 (64%) pregnant and 9 (36%) not pregnant. Using Pearson Chi-Square test there was no significant difference between the two groups regarding the pregnancy rate. ($X^2 = 2.01$, $p = 0.156$) (Table 6, Fig. 4).

Table 1 Age, duration of infertility, FSH level and LH level in the two studied groups.

	Gestagen group I	OCP group II
Age (years)		
Min	20	20
Max	34	35
Mean	26.52	27.2
S.D.	3.85	4.17
t test	0.599	
P	0.552 NS	
Duration of infertility (years)		
Min	1	1
Max	5	5
Mean	3,20	3.24
S.D.	1.19	1.09
t test	0.124	
P	0.902 NS	
FSH level (mIU/ml) on day 3		
Max	8.00	8.00
Mean	4.92	4.64
S.D.	2.177	2.099
t test	0.463	
P	0.646 NS	
LH level (mIU/ml) on day 3		
Min	8.0	8.00
Max	16.00	17.00
Mean	12.08	11.72
S.D.	2.596	2.638
t test	0.486	
P	0.629 NS	

Table 2 Distribution of patients of the two studied groups in relation to type of infertility.

			Group		Total
			Gestagen	OCP	
Infertility	Primary	Count	14	13	27
		%Within group	56.0	52.0	54.0
	Secondary	Count	11	12	23
		%Within group	44.0	48.0	46.0
Total		Count	25	25	50
		%Within group	100.0	100.0	100.0

$X^2 = 0.081$, $p = 0.777$ NS.

Please cite this article in press as: Orief YI et al. Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome, Middle East Fertil Soc J (2013), http://dx.doi.org/10.1016/j.mefs.2013.06.003

Table 3 Endometrial thickness in the two studied groups.

	Gestagen group I	OCP group II
Endometrial thickness		
Min	5	6
Max	9	9
Mean	7.44	8.08
S.D.	1.356	0.996
t test	1.901	
P	0.063 NS	

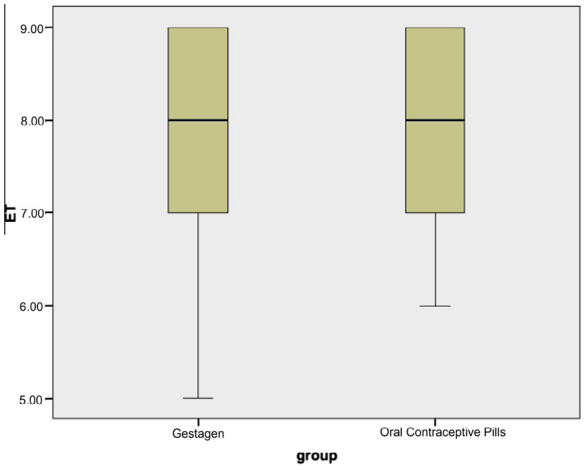

Figure 1 Box and whiskers graph of the endometrial thickness in the studied patients showing the median, inter-quartile range as well as the minimum and the maximum values.

Table 4 Progesterone level (ng/dl) in the two studied groups.

	Gestagen group I	OCP group II
Progesterone level (ng/dl)		
Min	0.70	10.00
Max	40.00	40.00
Mean	18.30	28.04
S.D.	14.582	10.17
t test	2.620	
P	0.012	

7. Discussion

Women with polycystic ovary syndrome form the largest group of women with ovulatory dysfunction, which is characterized by chronic anovulation in the presence of normal follicular stimulating hormone (FSH) and estradiol concentrations. Induction of ovulation is the first-line treatment for this class of anovulation and is aimed at introducing an endocrine milieu that promotes growth and ovulation of a single dominant follicle with consequent singleton pregnancy.

Clomiphene citrate is a selective estrogen-receptor modulator that antagonizes the negative feedback of endogenous estrogen on the hypothalamic–pituitary axis. Treatment with CC should return the luteinizing hormone (LH) to normal

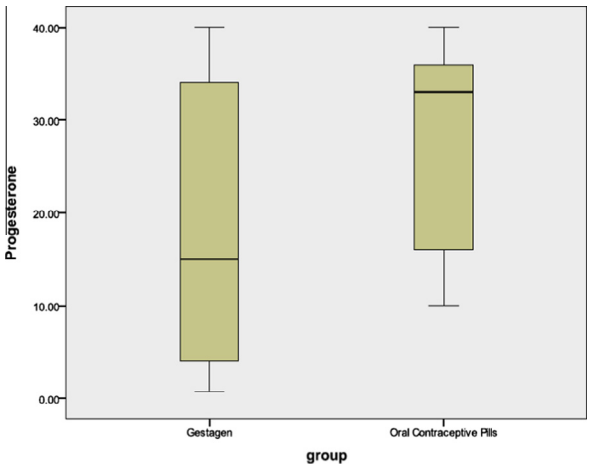

Figure 2 Box and whiskers graph of the progesterone level in the studied patients showing the median, inter-quartile range as well as the minimum and the maximum values.

and increase FSH secretion, thereby stimulating follicle growth and ovulation in PCOs patients.

The OCPs have the ability to address many of the goals of reproductive-aged women with PCOS not seeking pregnancy. They ameliorate hyperandrogenic skin manifestations, regulate menstrual cycles thereby protecting them from the risk of endometrial carcinoma, and provide effective and safe contraception.

Administration of progesterone to PCOS patients is helpful in many situations as induction of withdrawal bleeding suppresses LH secretion, in ovulation induction in CC-resistant patients and support the luteal phase after assisted reproductive techniques.

In the present study transvaginal ultrasound was done on days 10, 12, 14 of withdrawal bleeding to evaluate the endometrial thickness of each case, we found that in the Gestagen group the endometrial thickness ranged from 5 to 9 mm with a mean of 7.44 ± 1.35 mm, while in the OCP group it ranged from 6 to 9 mm with a mean of 8.08 ± 0.996 mm. Using Student's *t* test, there was no significant difference as regards endometrial thickness level between the two groups ($t = 1.901$, $p = 0.063$). Our results are in agreement to those of Branigan et al. who reported that the OCP pretreatment had developed adequate endometrial thickness but did not reach statistical significant value (55). On the contrary to our results, Homburg et al. mentioned that the progesterone pretreatment showed a better development of the endometrium that reached a statistical significance, this study used progesterone 50 mg /day IM for 5 days to induce withdrawal bleeding (56). Stefano et al. reported that the OCP pretreatment had better endometrial development that reached statistical significance, in that study the authors suppressed the hypothalamic–pituitary–ovarian axis for 2 months with OCP followed by CC at a dosage of 100 mg/day on days 5–9 of the cycle (57).

Regarding the production of mature follicles on day 12 of withdrawal bleeding, we found that in the Gestagen group, the number of patients with mature follicles was 16 (64%), while in OCP group there were 22 patients (88%), by using Pearson Chi-Square test there was a significant difference between the two groups regarding mature follicle production

Please cite this article in press as: Orief YI et al. Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome, Middle East Fertil Soc J (2013), http://dx.doi.org/10.1016/j.mefs.2013.06.003

Table 5 Distribution of patients of the two studied groups in relation to mature follicle production.

		Group		Total
		Gestagen	OCP	
No of patients showing no mature follicles on day 12	Count	9	3	12
	%Within group	36.0	12.0	24.0
No of patients showing mature follicles on day 12	Count	16	22	38
	%Within group	64.0	88.0	76.0
Total	Count	25	25	50
	%Within group	100.0	100.0	100.0

$X^2 = 3.1947$, $p = 0.047$.

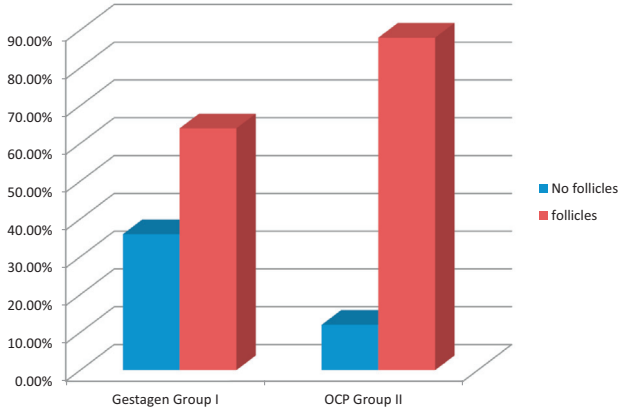

Figure 3 Mature follicle production in day 12 in the two studied groups.

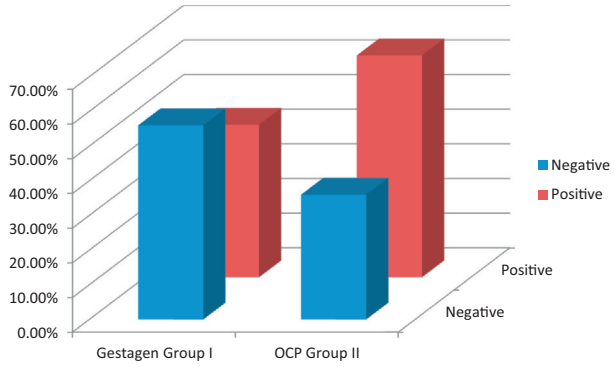

Figure 4 Pregnancy in the two studied groups.

($X^2 = 3.1947$, $p = 0.047$) in favor of the OCP group. In agreement to our study, Branigan et al. reported that the suppression of the hypothalamic–pituitary–ovarian axis with OCP followed by CC treatment results in an excellent rate of ovulation (55) that also agreed with the results reported by Stefano et al. who speculated that the OCP pretreatment for 2 months followed by CC, at dosage of 100 mg/day on days 5–9 of the cycle was related to excellent ovulation rates (57). On the other hand Homburg et al. reported that excellent rate of ovulation is achieved after progesterone pretreatment followed by CC treatment (56).

Measuring of serum progesterone 7 days after the expected date of ovulation, our results stated that in the Gestagen group the progesterone level ranged from 0.70 to 40.0 (ng/dl) with a mean of 18.30 ± 14.582 (ng/dl), while in the OCP group it ranged from 10.00 to 40.00 (ng/dl) with a mean of 28.04 ± 10.17 (ng/dl). Using Student's t test, the level of progesterone in the OCP group was significantly higher when compared to the Gestagen group ($t = 2.620$, $p = 0.012$). That was in agreement with the study of Branigan et al. who stated that the OCP pretreatment followed by CC treatment results in higher levels of progesterone when measured in the mid-luteal phase to confirm ovulation, which showed statistical significance (55). That was also the case with Stefano et al. who mentioned that OCP pretreatment followed by CC treatment results in higher levels of progesterone (57). On the contrary to our study, Homburg et al. reported that the progesterone pretreatment followed by CC treatment results in satisfactory luteal phase plasma concentration of progesterone achieved when giving progesterone 50 mg/day IM for 5 days (56).

In the present study, pregnancy test was done 14 days after ovulation to detect the occurence of pregnancy, in the Gestagen group there were 11 (44%) pregnant patients and 14

Table 6 Distribution of patients of the two studied groups in relation to pregnancy outcome.

			Group		Total
			Gestagen	OCP	
Pregnancy	Negative	Count	14	9	23
		%Within group	56.0	36.0	46.0
	Positive	Count	11	16	27
		%Within group	44.0	64.0	54.0
Total		Count	25	25	50
		%Within group	100.0	100.0	100.0

$X^2 = 2.013$, $p = 0.156$ NS.

Please cite this article in press as: Orief YI et al. Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome, Middle East Fertil Soc J (2013), http://dx.doi.org/10.1016/j.mefs.2013.06.003

(56%) were not pregnant, while in the OCP group, there were 16 (64%) pregnant cases and 9 (36%) were not pregnant. Using Pearson Chi-Square test there was no significant difference between the two groups regarding pregnancy ($X^2 = 2.013$, $p = 0.156$). Branigan et al. showed that the suppression of the hypothalamic–pituitary–ovarian axis with OCP for longer duration (between 42 and 50 days) followed by CC treatment results in an excellent pregnancy rate (55). However, Homburg et al. showed that progesterone pretreatment made more physiological hormonal environment at the time of clomiphene administration that may explain the greatly improved pregnancy rate in response to clomiphene citrate (56).

8. Conclusion

A few studies show an apparent improvement in the pregnancy rate after using of oral contraceptive pills prior to ovulation induction by clomiphene citrates. Despite this, from the available data a causal relationship is not confirmed, so large prospective studies using larger sample size, and longer duration of treatment are needed. Meanwhile, close clinical surveillance of patients being treated with oral contraceptive pills is required.

9. Disclosure of interests

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

10. Details of ethics approval and funding

Approval of the medical ethics committee of the Faculty of Medicine, Alexandria University was obtained before committing the research and the supporting documents are available on request. The current manuscript was personally funded from the researchers.

References

(1) Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab 2006;91:2–6.
(2) Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223–36.
(3) Azziz R, Marin C, Hoq L, Badamgarav E, Song P. Health care related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrinol Metab 2005;90:4650–8.
(4) Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:48–53.
(5) Essah PA, Nestler JE. The metabolic syndrome in polycystic ovary syndrome. J Endocrinol Invest 2006;29:270–80.
(6) Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.
(7) Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
(8) Goodarzi MO, Quinones MJ, Azziz R, Rotter JI, Hsueh WA, Yang H. Polycystic ovary syndrome in Mexican-Americans: prevalence and association with the severity of insulin resistance. Fertil Steril 2005;84:766–9.
(9) Davis SR, Knight S, White V, Claridge C, Davis BJ, Bell R. Preliminary indication of a high prevalence of polycystic ovary syndrome in indigenous Australian women. Gynecol Endocrinol 2002;16:443–6.
(10) Azziz R. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. J Clin Endocrinol Metab 2006;91:781–5.
(11) NICE guidelines published in February, 2004. <http://www.google.com>.
(12) Tannys DR, Vause MD, Ottawa ON, Anthony P, Cheung MD, Vancouver BC. Ovulation Induction in Polycystic Ovary Syndrome. J Obstet Gynaecol Can 2010;32:495–502.
(13) Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223–36.
(14) Yildiz BO. Recent advances in the treatment of polycystic ovary syndrome. Expert Opin Investig Drugs 2004;13:1295–305.
(15) Vrbikova J, Cibula D. Combined oral contraceptives in the treatment of polycystic ovary syndrome. Hum Reprod Update 2005;11:277–91.
(16) Petitti DB. Clinical practice. Combination estrogen-progestin oral contraceptives. N Engl J Med 2003;349:1443–50.
(17) Sitruk-Ware R. New progestagens for contraceptive use. Hum Reprod Update 2006;12:169–78.
(18) Stanczyk FZ. All progestins are not created equal. Steroids 2003;68:879–90.
(19) Elger W, Beier S, Pollow K, Garfield R, Shi SQ, Hillisch A. Conception and pharmacodynamic profile of drospirenone. Steroids 2003;68:891–905.
(20) Cerel-Suhl SL, Yeager BF. Update on oral contraceptive pills. Am Fam Physician 1999;60:2073–84.
(21) Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. Fertil Steril 2002;77:919–27.
(22) Falsetti L, Gambera A, Tisi G. Efficacy of the combination ethinyl oestradiol and cyproterone acetate on endocrine, clinical and ultrasonographic profile in polycystic ovarian syndrome. Hum Reprod 2001;16:36–42.
(23) Belisle S, Love EJ. Clinical efficacy and safety of cyproterone acetate in severe hirsutism: results of a multicentered Canadian study. Fertil Steril 1986;46:1015–20.
(24) Miller JA, Wojnarowska FT, Dowd PM, et al. Antiandrogen treatment in women with acne: a controlled trial. Br J Dermatol 1986;114:705–16.
(25) Mowszowicz I, Wright F, Vincens M, et al. Androgen metabolism in hirsute patients treated with cyproterone acetate. J Steroid Biochem 1984;20:757–61.
(26) Oelkers W. Drospirenone, a progestogen with antimineralocorticoid properties: a short review. Mol Cell Endocrinol 2004;217:255–61.
(27) Guido M, Romualdi D, Giuliani M, et al. Drospirenone for the treatment of hirsute women with polycystic ovary syndrome: a clinical, endocrinological, metabolic pilot study. J Clin Endocrinol Metab 2004;89:2817–23.
(28) Palep-Singh M, Mook K, Barth J, Balen A. An observational study of Yasmin in the management of women with polycystic ovary syndrome. J Fam Plann Reprod Health Care 2004;30:163–5.
(29) Azziz R, Waggoner WT, Ochoa T, Knochenhauer ES, Boots LR. Idiopathic hirsutism: an uncommon cause of hirsutism in Alabama. Fertil Steril 1998;70:274–8.

(30) The ESHRE Capri Workshop Group. Noncontraceptive health benefits of combined oral contraception. Hum Reprod Update 2005;11:513–25.
(31) Hardiman P, Pillay OC, Atiomo W. Polycystic ovary syndrome and endometrial carcinoma. Lancet 2003;361:1810–2.
(32) Grimes DA, Economy KE. Primary prevention of gynecologic cancers. Am J Obstet Gynecol 1995;172:227–35.
(33) Fiad TM, Cunningham SK, McKenna TJ. Role of P deficiency in the development of luteinizing hormone and androgen abnormalities in polycystic ovary syndrome. Eur J Endocrinol 1996;135:335–9.
(34) Doldi N, Gessi A, Destefani A, Calzi F, Ferrari A. Polycystic ovary syndrome: anomalies in progesterone production. Hum Reprod 1998;13:290–3.
(35) Ludwig M, Diedrich K. Evaluation of an optimal luteal phase support protocol in IVF. Acta Obstet Gynecol Scand 2001;80:452–66.
(36) Bagchi IC, Li Q, Cheon YP. Role of steroid hormoneregulated genes in implantation. Ann N Y Acad Sci 2001;943:68–76.
(37) Cavagna M, Mantese JC. Biomarkers of endometrial receptivity – a review. Placenta 2003;24(B Suppl):S39–47.
(38) Posaci C, Smitz J, Camus M, Osmanagaoglu K, Devroey P. Progesterone for the luteal support of assisted reproductive technologies: clinical options. Hum Reprod 2000;15(Suppl):129–48.
(39) Mesiano S. Myometrial progesterone responsiveness and the control of human parturition. J Soc Gynecol Investig 2004;11:193–202.
(40) Madsen G, Zakar T, Ku CY, Sanborn BM, Smith R, Mesiano S. Prostaglandins differentially modulate progesterone receptor-A and -B expression in human myometrial cells: evidence for prostaglandin-induced functional progesterone withdrawal. J Clin Endocrinol Metab 2004;89:1010–3.
(41) Neulen J, Breckwoldt M. Placental progesterone, prostaglandins and mechanisms leading to initiation of parturition in the human. Exp Clin Endocrinol 1994;102:195–202.
(42) Franks S, Roberts R, Hardy K. Gonadotrophin regimens and oocyte quality in women with polycystic ovaries. Reprod Biomed Online 2003;6:181–4.
(43) Joseph-Horne R, Mason H, Batty S, White D, Hillier S, Urquhart M, Franks S. Luteal phase progesterone excretion in ovulatory women with polycystic ovaries. Hum Reprod 2002;17:1459–63.
(44) Fleming R, McQueen D, Yates RW, Coutts JR. Spontaneous follicular and luteal function in infertile women with oligomenorrhoea: role of luteinizing hormone. Clin Endocrinol (Oxf) 1995;43:735–9.
(45) Chhabra S, McCartney CR, Yoo RY, Eagleson CA, Chang RJ, Marshall JC. Progesterone inhibition of the hypothalamic gonadotropin-releasing hormone pulse generator: evidence for varied effects in hyperandrogenemic adolescent girls. J Clin Endocrinol Metab 2005;90:2810–5.
(46) Doldi N, Marsiglio E, Destefani A, Gessi A, Merati G, Ferrari A. Elevated serum progesterone on the day of HCG administration in IVF is associated with a higher pregnancy rate in polycystic ovary syndrome. Hum Reprod 1999;14:601–5.
(47) Dale PO, Tanbo T, Abyholm T. In-vitro fertilization in infertile women with the polycystic ovarian syndrome. Hum Reprod 1991;6:238–41.
(48) Luboshitzky R, Ishai A, Shen-Or Z, Herer P. Evaluation of the pituitary–adrenal axis in hyperandrogenic women with polycystic ovary syndrome. Neuroendocrinol Lett 2003;24:249–54.
(49) Chang RJ. Polycystic ovaries in 2001: physiology and treatment. J Gynecol Obstet Biol Reprod (Paris) 2002;31:115–9.
(50) Woods KS, Reyna R, Azziz R. Effect of oral micronized progesterone on androgen levels in women with polycystic ovary syndrome. Fertil Steril 2002;77:1125–7.
(51) Azziz R. The time has come to simplify the evaluation of the hirsute patient. Fertil Steril 2000;74:870–2.
(52) Anttila L, Koskinen P, Erkkola R, Irjala K, Ruutiainen K. Serum testosterone, androstenedione and luteinizing hormone levels after short-term medroxyprogesterone acetate treatment in women with polycystic ovarian disease. Acta Obstet Gynecol Scand 1994;73:634–6.
(53) Homburg R, Weissglas L, Goldman J. Improved treatment for anovulation in polycystic ovarian disease utilizing the effect of progesterone on the inappropriate gonadotrophin release and clomiphene response. Hum Reprod 1988;3:285–8.
(54) Dale PO, Tanbo T, Kjekshus E, Abyholm T. Pregnancy after transfer of cryopreserved embryos in clomiphene citrate resistant polycystic ovarian syndrome. Fertil Steril 1990;53:362–4.
(55) Emmett F, Branigan MD, Antoinette Estes M. BS A randomized clinical trial of treatment of clomiphene citrate–resistant anovulation with the use of oral contraceptive pill suppression and repeat clomiphene citrate treatment. Am J Obstet Gynecol 2003;188:6–11.
(56) Homburg R, Weissglas L, Goldman J. Improved treatment for anovulation in polycystic ovarian disease utilizing the effect of progesterone on the inappropriate gonadotrophin release and clomiphene response Aviv University Medical School. Hum Reprod 1988;3:285–8 [Updated 2004].
(57) Stefano P, Angela F, Sterena D. Use of oral contraceptives in infertile patients: a descriptive review. Gynecol Endocrinol 2006;22(10):537–54.

Please cite this article in press as: Orief YI et al. Gestagen versus oral contraceptive pills to induce withdrawal bleeding before induction of ovulation by clomiphene citrate in polycystic ovary syndrome, Middle East Fertil Soc J (2013), http://dx.doi.org/10.1016/j.mefs.2013.06.003