Management of Abnormal Uterine Bleeding Associated with Polycystic Ovary Syndrome (2009)

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Management of abnormal uterine bleeding associated with polycystic ovary syndrome*

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*An excerpt; taken from Chapter 4 (pages 30-40) of the book Consensus Statements on POLYCYSTIC OVARY SYNDROME 2009, 262 pages, by the Philippine Society of Reproductive Endocrinology and Infertility

Menstrual dysfunction

Statement 1: Menstrual dysfunction is commonly the reason for consultation of women who are eventually diagnosed with polycystic ovary syndrome. B

Overall between 60 and 85% of patients with PCOS exhibit overt menstrual dysfunction. Among 273 Chinese women diagnosed as having PCOS, some menstrual irregularity was reported by 94.1% of the women.

Even in this subset of patients, an abnormality in the expected cyclical pattern of menstruation may not be urgently interpreted as a cause for concern. In the spectrum of menstrual disorders associated with PCOS, women tend to be more tolerant of oligomenorrhea and amenorrhea than experiencing episodic heavy menstural bleeding.

Evaluation of abnormal uterine bleeding

Statement 2: PCOS is suspected to be a risk factor for endometrial cancer and endometrial surveillance is reasonable. GPP

It is widely assumed that in anovulatory states such as PCOS, the hormonal milieu of unopposed estrogen activity which favors endometrial growth and irregular endometrial shedding predisposes the woman to abnormal uterine bleeding (AUB), endometrial hyperplasia (EH) and even endometrial carcinoma (EC). Several studies have been published to support this association.

In addition to the elevated estrogen (without the opposing effects of progesterone in the absence of ovulation), hyperinsulinemia, elevated free insulin-like growth factor-I and androgens, and obesity are all proposed to contribute to endometrial dysfunction in women with PCOS, leading to endometrial hyperplasia and endometrial cancer.

However, epidemiological evidence to support the hypothesis that PCOS predisposes to endometrial cancer is limited. Still it is common practice among gynecologists and physicians to apply strategies to detect and/or prevent endometrial cancer in PCOS women.

Statement 3: Endometrial biopsy need not be done in PCOS women if the sonographic endometrial thickness is less than 7 mm or the intermenstrual interval is less than 3 months. B

In a prospective study of 56 PCOS women to determine the predictive value of sonographic endometrial thickness and the menstrual history, 36 women (64.3%) had proliferative endometrium and 20 (35.7%) had endometrial hyperplasia. Five of the latter (25%) had cytologic atypia. The endometrial thickness correlated positively with endometrial hyperplasia (P =.018) and, together with the average intermenstrual interval, were significant predictors of endometrial hyperplasia (P <.001). However, endometrial thickness less than 7 mm or intermenstrual interval less than 3 months (corresponding to more than four menstrual periods yearly) was associated with proliferative endometrium only. Thus, endometrial hyperplasia is effectively excluded when the endometrial thickness in PCOS women is less than 7 mm.

These findings point to the usefulness of obtaining a detailed menstrual history in women with PCOS by identifying those at increased risk of endometrial hyperplasia and who require an endometrial biopsy.

Statement 4: Endometrial biopsy should be done in PCOS women if the endometrial lining is more than 10 mm thick on transvaginal ultrasound done between days 6-10 and if there is hyperinsulinemia. GPP

The mean thickness of the endometrium was found to be statistically higher (P<0.001) in women with PCOS (11.1 mm) and in women with insulin resistance (9.6 mm) compared with women without PCOS and insulin resistance (6.2 mm). It was concluded that both in women with PCOS without insulin resistance and in women with insulin resistance without PCOS, the ultrasonographically estimated thickness of the endometrium is relatively high and a closer follow-up of these women is required in order to detect those in risk to develop hyperplasia and/or atypia.

A targeted endometrial biopsy can identify those patients with increased risk for endometrial hyperplasia. The risk of endometrial carcinoma may be reduced by facilitating the normalization of ovulation and insulin metabolism.

Statement 5: Any PCOS patient with prolonged oligoamenorrhea or who is older than 35 years and has irregular bleeding should have an endometrial biopsy to rule out carcinoma. GPP

An important point to remember is that advancing age per se is not a factor in deciding to obtain endometrial aspiration in patients with PCOS as it is in non-PCOS patients.

Management of abnormal uterine bleeding

Statement 6: The use of oral contraceptive pills for a 21-day period followed by a 7-day pill free interval improves menstrual regularity among women with PCOS, regardless of body mass index. B

Improved menstrual cyclicity, in both obese and non-obese patients, was reported with the use of ethinyl estradiol 35 µg combined with cyproterone acetate 2 mg over a period of 3-6 months. This benefit of OCPs was superior to the use of metformin alone. In a Cochrane review of four clinical trials, metformin was less effective than the OCP in improving menstrual pattern (Peto OR 0.08, 95% CI 0.01 to 0.45). There are no trials assessing whether this more favorable
OCP effect leads to a reduction in the long-term risk of endometrial cancer compared with metformin.\textsuperscript{12} There has been no head to head comparison done to compare the effectiveness of the continuous and cyclic OCP regimens in the treatment of PCOS women with abnormal uterine bleeding.

**Statement 7: The most important parameter in the choice of OCPs for the treatment of PCOS is the type of progestin. GPP**

The most important parameter in the selection of OCP for the treatment of women with PCOS is the type of progestin, since most progestins also possess variable androgenic effects. The androgenic property of a progestin determines the changes in sex hormone binding globulin production. SHBG production is the critical factor which determines the level of circulating free fraction of androgens.\textsuperscript{13}

With increasing androgenic activity, the stimulatory effect of combined OCP on SHBG synthesis is decreased. Differences observed in SHBG level can be attributed to the intrinsic androgenic (or anti-androgenic) properties of the progestogens.\textsuperscript{14} In healthy users after six cycles the mean changes in SHBG reached +270\% versus +80\% if combined OCP contained low or higher androgenic progestins.\textsuperscript{13}

The first choice of combined OCP for the treatment of women with PCOS should be progestins with low androgenic activity, which do not decrease estrogen-stimulated production of SHBG.\textsuperscript{13} Norgestimate and desogestrel are virtually nonandrogenic progestins.\textsuperscript{15}

Drospirenone, an analogue of spironolactone with unique antimineralocorticoid and antiandrogenic activities, has been approved for use in combination with ethinyl estradiol; thus, it is potentially ideal for the treatment of women with the polycystic ovary syndrome.\textsuperscript{17}

**Statement 8: Treatment protocols for OCP use in PCOS patients with abnormal uterine bleeding recommend a minimum duration of 3-6 months. B**

Treatment protocols for OCP use in PCOS patients recommend a minimum duration of 3-6 months wherein most studies report improved menstrual cyclicity measured in terms of days in between menses. The suppression of androgenic production by OCPs underlies the improvement of the menstrual dysfunction observed in women with PCOS.

There is no current recommendation on how long OCP can be used. It would seem that prolonged use would be influenced by considerations such as risk for diabetes mellitus, coronary artery disease, and endometrial cancer. However, there are no prospective studies confirming the effect of long-term use of OCP on the risk of these conditions. On the other hand, it is generally accepted that OCP does not modify the absolute risk of coronary heart disease in healthy users <35 years of age with no cardiovascular risk factors, who do not smoke, and who have had their blood pressure checked before starting OCP use.

In PCOS, there are only a few short-term studies with contradictory results evaluating potential adverse effects of OCPs on cardiovascular risk factors and glucose homeostasis. Nevertheless, limited available data support the benefits of long-term OCP use in PCOS.\textsuperscript{18}

Prospective data about the influence of OCPs on the risk of diabetes mellitus, coronary artery disease and endometrial cancer in PCOS women are lacking.\textsuperscript{19}

**Statement 9: Cyclic oral progestogens may be effective in regulating and reducing bleeding in anovulatory dysfunctional uterine bleeding. C**

No randomized trials of progestogens for anovulatory dysfunctional bleeding, particularly PCOS, have been identified.\textsuperscript{20} A small, non-randomized study in 6 women treated with either norethisterone (NET) 5 mg three times daily or medroxyprogesterone acetate (MPA) 10 mg three times daily for 14 days from day 12 to 25. There was a significant reduction in menstrual blood loss from a pretreatment mean of 131 ± 40 mL to 80 ± 31 mL during the first treatment cycle, and 64 ± 14 mL in the second cycle (paired t test, t = 4.638, P < 0.005 in the first cycle and t = 4.025, P = 0.01 in the second). The duration of bleeding was also reduced following treatment, from a mean of 8.5 ± 2.4 days before treatment to 6.2 ± 1.7 days in the first treatment cycle, and 5.5 ± 1.1 days in the second (t = 3.105, P = 0.027). No obvious difference was observed between the two progestogens.\textsuperscript{20}

Larger randomized studies are needed to confirm the role of progestogens in anovulatory DUB associated with PCOS and to compare its types, dosages and routes of administration.

**Statement 10: Progestogen-releasing intrauterine systems are more effective than no treatment for heavy menstrual bleeding. B**

Progestogen-releasing intrauterine systems that have been used for menorrhagia include Mirena™ (levonorgestrel- intrauterine system) and Progestasert™. Although these devices have not been compared to either placebo or no treatment control groups in randomized controlled trials, there were significant reductions in women treated with both Mirena™ and Progestasert™.\textsuperscript{21,22} Progestasert™ is not available in the Philippines.

An open randomized study compared 1821 women using the LNG-IUS to 937 women using the copper-releasing device Nova T during 5 years of use.\textsuperscript{21} The local effect of levonorgestrel in the uterine cavity caused reduction of menstrual blood loss and development of oligo-amenorrhea, and the termination rates because of heavy and/or prolonged menstrual flow were significantly (P < 0.001) lower among LNG-IUS users. Hemoglobin increased during use of the LNG-IUS and decreased during Nova T use, and the difference between the devices was statistically significant.

In 12 women with menorrhagia (greater than or equal to 80 ml per menstrual period) Progestasert, the menstrual blood loss was significantly reduced after 1 month but the duration of bleeding was somewhat prolonged. Twelve months after insertion the menstrual blood loss amounted to 35\% of the blood loss before the insertion.\textsuperscript{22}

**Statement 11: LNG-IUS was more effective than cyclical progestogens and mefenamic acid but sig-**
A randomized study compared the LNG-IUS and norethisterone in 45 women with heavy regular periods and a measured menstrual blood loss exceeding 80 ml. The LNG-IUS was inserted within the first 7 days of menses and norethisterone 5 mg was given 3 times daily from day 5 to day 26 of the cycle for 3 cycles. Compared to baseline, the LNG-IUS reduced menstrual blood loss by 94% (median reduction, 103 ml) and oral norethisterone reduced it by 87% (median reduction, 95 ml).

In 51 women with menorrhagia randomized to receive the LNG IUS or oral mefenamic acid for six cycles, LNG-IUS produced greater reduction in menstrual blood loss, total menstrual fluid loss, and pictorial blood loss assessment chart score at the third and sixth cycle of treatment.

The LNG-IUS was compared with endometrial resection in women with menorrhagia and demonstrated comparable reduction in the menstrual bleeding in two studies, and somewhat less satisfactory results in another two studies. The advantage of the LNG-IUS was that it is reversible and has no operative hazards.

Three trials compared LNG-IUS with balloon ablation. In two randomized studies with a total of 129 women with menorrhagia, respectively, the Theremochoice™ endometrial ablation and the LNG-IUS were equally effective in the management of menorrhagia. In another study of 36 women randomized to LNG-IUS or outpatient thermal balloon ablation, the LNG-IUS was not as effective as thermal balloon ablation in reducing the menstrual blood loss at one year. However, the LNG-IUS was found to be as effective as thermal balloon ablation in increasing the hemoglobin values.

Statement 12: The LNG-IUS is associated with a higher rate of progestogenic side effects such as intermenstrual bleeding and breast tenderness than endometrial ablation.

Three trials comparing LNG-IUS with ablation reported a higher rate of side effects within one year, most of which were progestogenic, in the women with LNG-IUS in situ. Higher rates of weight gain, bloating, acne or greasy skin, nausea and breast pain were likewise reported.

Statement 13: Metformin should be used as an adjunct to general lifestyle improvements but not as a replacement for weight loss, improved diet and increased exercise in treating abnormal uterine bleeding in women with PCOS.

Although metformin is an effective treatment for anovulation in PCOS, many women will still experience menstrual irregularities. Further studies are needed to elucidate the risk-benefit ratio of long term metformin use in the PCOS patient population not presenting with infertility.
did not differ significantly between groups. However, when data were analyzed by presence or absence of weight reduction in subjects, independent of treatment group, the estimated odds ratio for weight loss was 9.0 (95% CI 1.2-64.7) with respect to regular ovulation. If weight loss occurred during metformin therapy, the odds ratio for regular ovulation was 16.2 (95% CI 4.4-60.2).38

**Statement 15:** Maintenance of a hypocaloric diet (1200-1400 kcal/day) and sustained exercise regimen over a period of 6 months or more improve ovulation rates and menstrual regularity independent of metformin use. A

Studies have demonstrated that compliance with a weight loss regimen achieved by an exercise schedule combined with a hypocaloric diet over a 6 month period, improved insulin sensitivity, endocrine parameters and menstrual regularity.39 In studies involving the use of metformin, after adjusting for baseline BMI and age, only weight loss alone, but not use of metformin alone, was associated with a significant improvement in menstrual cyclicity.40

In women with BMI > 39, patients taking metformin 850 mg twice a day and adhered to a lifestyle modification regimen showed improved ovulation rates and menstrual cyclicity after 12 months.38

Maintaining a hypocaloric diet (1200-1400 kcal/day) and targeting 150 minutes of exercise per week over a 24 week period was necessary to observe improved ovulatory rates. However investigations noted increased dropout rate due to time commitment of subjects.38 Since most studies involve women who are overweight, the optimal dietary strategies and exercise regimen and efficacy of lifestyle changes in women stratified by weight need to be addressed. The role of utilizing antiobesity pharmacologic treatments and surgery are still being studied.

**Statement 16:** If hormonal treatments are not acceptable to the woman, then either tranexamic acid or nonsteroidal anti-inflammatory drugs can be used. A

A review of the treatment modalities for dysfunctional uterine bleeding showed that the antifibrinolytic tranexamic acid (TXA) is the most effective medical therapy to treat dysfunctional uterine bleeding showed that the antifibrinolytic tranexamic acid (TXA) is the most effective medical therapy to treat dysfunctional uterine bleeding.41 It causes a greater reduction in objective measurements of heavy menstrual bleeding when compared to placebo or other medical therapies (NSAIDs, oral luteal phase progestagens and ethamsylate).41 TXA in a dose of 2-4 gm/day is highly effective and a safe option for menorrhagia. The lower dose of 2 gm/day is an effective and safe option in DUB when compared to cyclical medroxyprogesterone acetate (MPA) 10 mg twice daily.42

As a group, NSAIDs were more effective than placebo at reducing heavy menstrual bleeding, of comparable efficacy with ethamsylate, but less effective than either tranexamic acid or danazol.43 In 76 women with DUB, ethamsylate 500 mg 6-hourly did not reduce mean menstrual blood loss; mefenamic acid 500 mg 8-hourly reduced MBL by 20%, and tranexamic acid 1 gm 6-hourly reduced MBL by 54%. In women with BMI > 39, patients taking metformin 850 mg twice a day and adhered to a lifestyle modification regimen showed improved ovulation rates and menstrual cyclicity after 12 months.38

Danazol appears to be an effective treatment for heavy menstrual bleeding compared to other medical treatments, though it is uncertain whether it is acceptable to women. The use of danazol may be limited by its side effect profile, its acceptability to women and the need for continuing treatment. Overall no strong recommendations can be made due to the small number of trials, and the small sample sizes of the included trials.45

**Statement 17:** Chinese herbal medicine seems to show an encouraging comparative effectiveness with conventional Western medicine. B

A meta-analysis of four RCTs or quasi-RCTs involving 525 PCOS patients with dysfunctional uterine bleeding treated with Chinese herbal medicine showed encouraging results but the methodological quality was poor in all trials except one.46 With the lack of trials comparing CHM with no treatment or placebo, it is impossible to accurately evaluate the efficacy of CHM. More RCTs with a higher quality are required.46

**References**

12. Costello M, Shrestha B, Eden J, Sjoblom P, Johnson N. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. Cochrane Database...
troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database of Systematic Reviews 2003 (2);CD003055.


### Appendix

#### Levels of evidence for intervention studies

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* Studies with a level of evidence "-" should not be used as a basis for making a recommendation  


#### Grades of recommendation**

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### Index of Drugs Mentioned in the Guideline

This index lists the products and/or their therapeutic classifications mentioned in the guideline. For the doctor’s convenience, brands available in the PPD references are listed under each of the classes. For drug information, refer to the PPD references (PPD, PPD Pocket Version, PPD Text, PPD Tabs, and www.TheFilipinoDoctor.com).

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- **Famila 28 F**
- **Levonorgestrel-Intrauterine System (LNG-IUS)**
- **Medroxyprogesterone acetate**
- **DepoTrust**
- **Lyndavel**
- **Provera**
- **Medroxyprogesterone acetate + Estrogen**
- **PremroLle**
- **Norgestimate**
- **Norgestrel + Ethinyl estradiol**
- **Femenal**
- **Norethisterone**
- **Primolut N**
- **Norethisterone + Estradiol**
- **Micropol**
- **Norfam**
- **Norethisterone + Estradiol + Ferrous fumarate**
- **Micropol Plus**
- **Progesterone-Releasing IUD**
- **Androgens**
- **Danazol**
- **Elle**
- **Ladogal**
- **Analgesics**
- **NSAIDS**
- **Mefenamic Acid**