



Continues Norethisterone Acetate versus
Cyclical Drospirenone 3 mg/ethinyl Estradiol
20 μ g for the Management of Primary
Dysmenorrhea in Young Adult Females

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calendar

The next IV ACE
will be in Jordan

19-21st

November 2015

www.ace2015jordan.com

The poster features a background image of ancient stone ruins, possibly a temple or palace, set against a reddish-brown rock face. In the top left corner, there is a circular logo with a globe and a person. The main title 'ACE 2015' is written in large, bold, yellow-orange letters. Below it, '4th Asian Conference on Endometriosis' is written in a smaller font, followed by the dates 'November 19 (Thu) ~ 21 (Sat), 2015' and the location 'Jordan-Kempinski Hotel Dead Sea'. At the bottom, there is a paragraph of text describing the conference's aims.

ACE 2015

4th Asian Conference on Endometriosis
November 19 (Thu) ~ 21 (Sat), 2015
Jordan-Kempinski Hotel Dead Sea

Aims: to bring together leading academic scientists, researchers and research scholars from Asia and leading experts from the world to exchange and share their experiences and research results about all aspects of Endometriosis.

Welcome to the lowest point on Earth and embrace the magic of Jordan's most enchanting setting where nature and history have so wonderfully conspired. Kempinski Hotel Ishtar Dead Sea is the most ideal venue from which to explore the rich culture and deep history of the area. This 5 star luxury hotel is situated on the edge of the famous salt lake, the lowest point on earth, and provides uninterrupted views across the vast sea towards the west bank and access to some of the most beautiful scenery in the world, including religious sites and majestic countryside.

4th Asian Conference on Endometriosis Organizing Committee
The Jordanian Society of Obstetricians and Gynecologists



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Primary dysmenorrhea

- It is the most common gynecologic complaint among adolescent and young adult females (Harel 2006)
- Reported prevalence between 50 and 90%
(Hillen, et al. 1999)
- Leading cause of morbidity in this population, leading to school absence and activity nonparticipation (Al-Jefout, et al. 2014)
- The concept of “Pain Normalization”
(Harel 2002, Berkley 2013)
- Despite the high prevalence of dysmenorrhea, many young women either do not seek medical advice or are under-treated
(Harel 2006)

Combined oral contraceptive pills (OCP) for PD

- OCP are a widely used treatment for PD in women, and are perhaps an ideal treatment for adolescent dysmenorrhea.
- Several non-contraceptive health benefits.
- A survey from the Netherlands revealed that almost one third of young women reported that their primary reason for using birth control pills was for relief of menstrual pain rather than contraception (Hooff, et al. 1998).
- OCP been proved to decrease dysmenorrhea pain scores (Davis and Westhoff 2001, Davis, Westhoff et al. 2005, Harel 2006, Dragoman 2014).
- A review and meta-analysis by the Cochrane Collaboration concluded that OCs may be more effective than placebo based on 5 controlled trials of OCs compared with placebo (Proctor, Roberts et al. 2000)

Possible mechanism of OCP on PD

- Chan (Chan and Hill 1978) reported that $\text{PGF2}\alpha$ levels in menstrual fluid were lower in two women with dysmenorrhea effectively treated with COC than in six women with untreated dysmenorrhea or normal controls.
- Ovulation inhibition is known to relieve dysmenorrhea, and oral contraceptives (OCs) that contain synthetic estrogen and progestin may be used for this purpose

(Wood, et al. 2001)

- OCs suppress ovulation and reduce the growth of endometrial tissue, thus reducing both menstrual flow and prostaglandin production

(Crosignani, et al. 2006)

3 mg DRSP/20 µg EE-24/4

- Drospirenone (DRSP), is a fourth-generation progestin that has potent progestogenic, antimineralocorticoid, and antiandrogenic activity.
- Has the additional medical benefit of providing a good parallel treatment for premenstrual dysphoric disorder and moderate acne.
- Has reliable contraceptive efficacy, acceptable bleeding pattern and satisfactory safety profile

(Fenton, Wellington et al. 2007; Sulak 2008; Hernádi, Marr et al. 2009, Bresciani 2010).

- Moreover, some studies have shown that COC pills with low dose estrogen are promising in the treatment of endometriosis related dysmenorrhea and dyspareunia

(Harada, et al. 2008; Mabrouk, et al. 2012).

Norethisterone acetate (NET-a)

- NET-a is a synthetic gestagen that was developed from testosterone.
- Besides its connection with progesterone receptors, NET-a has the affinity of linking to both, estrogenic and androgenic receptors.
- It has been shown to control uterine bleeding and reduce the pain and disease severity of endometriosis
(Muneyyirci-Delale and Karacan 1997, Vercellini, Fedele et al. 2003, Vercellini, Pietropaolo et al. 2005, Rodgers and Falcone 2008).
- NET-a is metabolized to an ethinyl estradiol, thus providing enough estrogenic activity to protect against side effects but not enough to stimulate endometriosis and increase pain.
- NET-a and deeply infiltrating and rectal endometriosis
(Ferrero, et al. 2010, Vercellini, et al. 2013)

Aims & Ethics approvals

- The aim of this prospective open-labeled study is to explore the efficacy and safety of NET-a and COC pill containing drospirenone 3 mg/ethinyl estradiol 20 μ g in the treatment of dysmenorrhea in young adult females.
- The Ethics Committee of Mutah University approved the study (N- 201322).

Participants

- Initially we enrolled 43 single young adult Jordanian females between 18 and 23 years of age, suffering from dysmenorrhea for at least 6 months.
- At the end of study after six months only 38 participants were included.
- The final total number of participants was 38 participants: 20 in the N group and 18 in the P group.
- Enrollment criteria included:
 - a history of severe dysmenorrhea associated with two conditions: the cyclical use of analgesics for pain control and history of negative impact of dysmenorrhea on work or school attendance or performance,
 - a recent history of regular menstrual cycles, and body mass index (BMI) in the range of 18 to 30 kg/m².
- None of participants was sexually active.
- Exclusion criteria included:
 - history of high blood pressure, clotting disorders, history irregular periods and history of fibrocystic breast disease, lumps, nodules, or an abnormal mammogram.

Assessments

- Each participant's underwent full clinical and gynecological assessment at baseline.
- Compliance with treatment and adverse events were recorded by the investigator during and at the end of the study period.
- The investigator also assessed the likelihood that adverse events were related to the treatment.
- The participants were provided with menstrual cycle diaries to record all aspects of her periods and the presence or absence and severity of dysmenorrhea from the treatment start onwards, such that each woman was her own control.

Groups: P and N

- Treatment allocation was decided on the basis of the preference of the patients.
- **Group P:**
 - Patients taking cyclic COCP were instructed to start their pills on the first day of their subsequent menstrual cycle for 28 days and then to start the new package.
 - In case of missing one active COC pill, participants were instructed to record that and to take two pills on the day that they remember. Then take one pill per day for the rest of the pack.
- **Group N:**
 - The group taking continuous NET-a, was instructed to continuously take the pill for 6 months.
- The patients were evaluated at 3 months after initiation of therapy and then at 6 months

Follow up visits

- On each visit, patients were asked to complete a detailed 25-item self-administered questionnaire in Arabic, related to the presence of pain (dysmenorrhea and non-menstrual pelvic pains), irregular bleeding episodes, and other side effects such as breast tenderness, headaches, and need of analgesics.
- Compliance with the medication was evaluated by directly asking the patients whether they had been taking both medications properly as recommended and by calculating the days between each visit and the number of pills consumed.
- Physical examinations and tranabdominal sonographic examinations were performed, and the findings were documented, those with endometrioma or any ovarian pathology were excluded.
- Only patients who completed the whole study period of 6 months of treatment were included in the study..

Efficacy of treatment

- To assess the efficacy of the treatment in alleviating dysmenorrhea, patients had been asked to grade the severity of pain by using a 10-points visual analogue scale (VAS) (Huskisson 1983)
- Furthermore, main outcome measures were: variations in VAS score between baseline and follow-up in the groups, symptoms at follow-up and percentage of adverse effects, discontinuation of the therapy.
- Difference between the two groups was analyzed for all the variables considered.

Table 1: Characteristics of participants in the two treatment allocation groups

Variable	Group N (n=20)	Group P (n=18)	p-value (t test)
Age years, (mean ± SD)	20.30 ± 1.45	20.06 ± 1.73	0.602
Age of menarche, years (mean ± SD)	13.35 ± 1.46	12.83 ± 1.15	0.154
Cycle length/days, (mean ± SD)	27.40 ± 2.70	28.00 ± 2.6	0.734
Period duration/days, (mean ± SD)	4.95 ± 0.94	5.06 ± 0.87	0.845
BMI, (mean ± SD)	21.08 ± 2.67	22.58 ± 2.46	0.949
Smoking status N (%)	4 (20.0%)	1 (5.6%)	0.188*

*Chi-square test

Table 2: VAS score at basal, 3 months and at 6 months in the two groups (N&P)

VAS score	Group	Mean Std. Deviation	p-value (t test)
VAs score basal	N	6.70± 1.17	0.618
	P	6.89± 1.13	
VAS score at 3 months	N	3.35± 0.81	0.218
	P	3.00± 0.91	
VAS score at 6 months	N	1.30± 1.22	0.949
	P	1.28± 0.83	




Table 3: Side effects frequency in both groups

Side effect	Group N (n (%))	Group P (n (%))	Statistics
Bloating or swelling, N (%)	10 (50.0)	2 (11.1%)	0.010*
Mood change, N (%)	6(30.0)	3(16.7%)	0.334*
Spotting, N (%)	2(10.0)	6(33.3%)	0.078*
Breakthrough bleeding, N (%)	5(25.0)	2(11.1%)	0.270*
Headache, N (%)	2(10.0)	4(22.2%)	0.302*
Irritability, N (%)	3(15.0)	2(11.1%)	0.723*
Breast tenderness, N (%)	2(10.0)	7(38.9%)	0.036*
Weight gain (kg)(mean ±SD)	0.350 ±1.31	0.22± 1.06	0.75

* T test

** Chi-square test

Table 4: The frequency of NSAID usage and impact of dysmenorrhea on work and school in both groups

Variable		Group N (n=20)	Group P (n=18)	P value T test
NSAIDs usage, N (%)	At first month	4(20%)	8(44%)	0.006
	At 3 months	1(5%)	3(17%)	0.019
	At 6 months	0	0	NS
Drop from work or school due to pain, N (%)		none	none	NS

Discussion

- NET-a is well-tolerated, effective option to decrease pain and bleeding in young adults with dysmenorrhea.
- Continuous NET-a and OCP with 24/4 cyclic regimens has no significant difference in pain symptoms relief.
- The importance of good counseling.
- Acceptance of the concept of amenorrhea.

Perception of amenorrhea

- Depends on cultural beliefs:
 - Amenorrhea is unhealthy and that monthly bleeding is necessary Vs monthly bleeding as, at best, an inconvenient nuisance.
- There is substantial evidence that women desire to have less periods or even no periods if they suffer from menstruation related problems

(Loudon, 1977, Andrist, 2004, Ferrero, 2006)

- A survey of over 300 adolescents in the Netherlands ages 15 to 19 years found that 71% would prefer to menstruate less frequently than monthly or never

(Den Tonkelaar and Oddens 1999)

Safety of NET-a

- We administered only 5 mg/day of NET-a, which is within the recommended add-back dose to prevent bone loss in patients with endometriosis treated with GnRH analogs
(Surrey, 2002)
- The long term safety of NET-a on mineral bone density has been proven (Riis, 2002) and in fact, a small fraction of norethisterone acetate (between 0.20 and 0.33%) is converted to ethinyl estradiol
(Chu, 2007)

Possible advantages of NET-a for PD

- Participants using continuous NET-a were less likely to use analgesics in the first and third months in comparison with the P group. However, both groups did not use any analgesics at the end of the study.
- The most common side effect in the N group was bloating and swelling (50%); while breakthrough bleeding was reported only in 25 %, this much less than breakthrough reported in another study as the most common side effect (57.6%) (Muneyyirci-Delale and Karacan 1997)
- Moreover, the total cost of the NET-a (Primolut-Nor[®]; Bayer Schering Pharma) in the Jordanian market for 6 months therapy is 14.4 JD (20.33 US\$) while the cost of YAZ[®]; Bayer Schering Pharma - is 71.4 JD (100.81 US\$).
- This clearly showed that NET-a, is a cheap option for pain control for long term use.

PD and future endometriosis

- Dysmenorrhea in young adults may be associated with future diagnosis with endometriosis.
- About two-thirds of adolescent girls with CPP or dysmenorrhea have laparoscopic evidence of endometriosis
(Janssen, 2013)
- Moreover, recent study have shown that a history of OC use for severe primary dysmenorrhea is associated with surgical diagnosis of endometriosis, especially DIE, later in life
(Chapron, 2011)
- This fact may make the use of continuous NET-a regimen more clinically based than the use of the pill.
- How many of our participants is having or will have endometriosis is a big question.
- A future study should examine the effect of use of NET-a in the future development of endometriosis.

Study limitations

- Small sample size in both groups. However, this is the first study to be conducted in our community in this young age group.
- We with great difficulty could recruit the number for the study as menstruation and its co-morbidities in this age group of single females in Arabic population is considered a social “Taboo”

(Delaney 1988; Jarrah and Kamel 2012)

- We also did not measure of all aspects of dysmenorrhea impact on quality of life.
- No randomization

Conclusions

- **Both continuous NET-a and 3 mg DRSP/20 µg EE-24/4 pills are equally good in suppressing dysmenorrhea in this age group.**
- NET-a is effective, cheap and safe.
- The equivalence between cyclic 24/4 COC pill and continuous NETA-a regimens permits a medical treatment choice for dysmenorrhea which considers patient's preference.
- Finally, we have asked the participants if they are going to continue with the treatment proposed during the study and all of them were happy to do so.
- We will follow them up during the coming years.