A comparative study of Depo-Provera® versus Norethisterone acetate in management of endometrial hyperplasia without atypia

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Abstract

Background: The objective of this study was to assess effectiveness and safety of Depo-Provera® (Medroxyprogesterone acetate - MPA) in treatment of endometrial hyperplasia (EH), and to compare it with Norethisterone acetate (NETA) as an oral progestogen treatment.

Methods: This was a prospective randomized trial where 146 women aged 35-50 years with abnormal uterine bleeding who were diagnosed as having EH were randomized to receive either Depo-Provera; one injection every 3 months (2 doses), or oral cyclic NETA; 15 mg daily for 14 days per cycle for 6 months. Primary outcome measure was regression of EH which was analyzed by intention to treat. Secondary outcome variables were side effects of treatment, persistence/progression of EH during follow-up period.

Results: After 6 months treatment, Depo-Provera was more successful in achieving regression of non-atypical EH than NETA [67 out of 73 women (91.8%) vs. 49 out of 73 (67.1%), respectively], and the difference between the two groups was statistically significant (RR: 1.37; 95% CI: 1.15-1.63, p = 0.048*). Adverse effects were relatively common with moderate differences between the two groups.

Conclusions: This study showed that Depo-Provera is an effective and safe treatment for EH without atypia. Given its availability, apparent safety, and relatively reduced cost, Depo-Provera® deserves to be considered in further larger-sized, multi-centre, double blind, randomized, placebo-controlled trials prior to recommending it for routine use in women with EH.

Keywords: Depo-Provera; Medroxyprogesterone acetate; Norethisterone acetate; endometrial hyperplasia.

Synopsis: Depo-Provera was compared with an oral progestogen (Norethisterone acetate) as a treatment for endometrial hyperplasia where it proved to be an effective and safe treatment for endometrial hyperplasia without atypia.

Introduction

Endometrial hyperplasia (EH) is defined as abnormal, non-invasive proliferation of the endometrial glands. Similar to endometrial carcinoma, EH is estrogen-dependent (1). Based on architectural complexity and nuclear cytology, EH is classified into simple or complex, without or with cytological atypia (2). Endometrial hyperplasia presents commonly with abnormal uterine bleeding (AUB) (3, 4). However, its clinical importance largely relates to the risk of progression to endometrial carcinoma (5).

Management of EH is a subject of considerable debate (3, 6). Hysterectomy has been preferred as treatment for EH with atypia, because of fear of progression to endometrial carcinoma and/or concern that un-sampled carcinoma may have been co-existing (3, 6-8). The risk of co-existing carcinoma has been reported in 17- 43% of women diagnosed as having EH

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with atypia (9-11). However, there is still argument regarding the merits of hysterectomy against progestogen treatment for women with complex and atypical EH (1, 12).

Nevertheless, treatment with oral progestogens (Norethisterone acetate - NETA, Medroxyprogesterone acetate – MPA, Megestrol – MGA …etc.) has been established as an alternative for patients where surgery is not possible or not desired (2, 3, 7, 8, 12). Regression of EH following use of progestogens has been described several decades ago and, since then, further studies indicated that even endometrial carcinoma may respond to progestogen treatment (2). However, there are limited data regarding long-term outcomes for women with EH treated with progestogens, with claims that efficacy of progestogen therapy is often limited (3, 6, 8). Several studies report a wide range of risks for recurrence, after initial regression, persistence or progression of EH in women treated with progestogens following cessation of therapy. These risks varied between 0% and 60% for complex EH, and between 10% and 100% for EH with atypia (1, 2, 13, 14).

As no universally-agreed guidelines exist, wide variations in type of progestogen, dose and length of treatment course have been noted, with lack of reference to women's characteristics that predict successful progestogen treatment (15). This makes it difficult to compare results of different studies, and to provide a basis for agreement (2, 10, 14, 16). Marsden, Hacker, in a review of the management of EH, concluded that the optimal dosage of progestogens has not been investigated and the regimens advocated are essentially arbitrary (6).

Injectable Depo-Provera® (MPA), has been proved as an effective and safe long-acting reversible contraceptive for decades. Its greater effectiveness, reduced adverse effects, and relatively reduced cost when compared with other hormonal, and non-hormonal, contraceptives, have been established (17). It is therefore reasonable to postulate that Depo-Provera®, as a long-acting progestogen, would be similarly useful as a treatment for EH, and perhaps more acceptable to some women given its relatively reduced adverse effects. Despite that the commonest reason for people not choosing this method of contraception is needle phobia; being given by injection may be an advantage as it takes compliance off women who fear forgetting taking their tablets. Also, this route of administration suits women with impaired mental capacity, and patients with other forms of special needs and disabilities (18).

Depo-Provera® up regulates progesterone receptors in the endometrium causing decidualization of the hyperplastic endometrium which promotes shedding and loss of thickness. The drug is, therefore, effective in reversing EH (18, 19).

The number of studies which have been conducted assessing efficacy and safety of Depo-Provera® in treatment of EH is not accurately known, but is believed to be very little (Luesley G, Razvi K and Ethirington I, personal communications). Data on use of Depo-Provera® in treatment of EH are, therefore, insufficient to provide go od evidence, and do not meet the necessary requirements to suggest innovative recommendations for treatment. Knowledge of these variables is of paramount importance for the objective of guiding gynecologists and other healthcare givers in management of women with EH, and also for patient education purposes. The scope for further research is, therefore, obvious.

The objective of this study was to assess effectiveness and safety of Depo-Provera® in treatment of EH, and to compare it with NETA as an oral progestogen treatment.

Subjects and methods

Study design

This prospective randomized trial was carried out at Zagazig University Hospital (ZUH), Zagazig, Egypt over the period from February 2013 to January 2015. Potential candidates for the study have been attending the gynecological out-patient clinic in view of AUB. They were investigated and treated as per the hospital protocol. Women with histologically-confirmed non-atypical EH (simple or complex), were approached for recruitment. The study protocol was approved by the local research and ethics committee of ZUH. Eligible women were counseled and a clear explanation of the interventions was given. A written informed consent was then obtained prior to start of trial from those who agreed to participate.

Sample size

On the assumption that, in women with simple EH without atypia, the rate of regression after 6 months treatment with oral progestogens was 50-80% (13, 20, 21), the authors of this study considered that an improvement of 20% in the rate of regression after treatment with Depo-Provera® would be justifiable. Accordingly, a power analysis indicated that a total of 144 participants (72 in each group) would have to be recruited to achieve a study power of 80% with 5% error and 95% confidence interval (95% CI) in order to prove the hypothesis is correct: the injectable

Depo-Provera® is more successful in achieving regression of non-atypical EH (simple and complex) than the oral cyclic progestogen. However, allowing for potential exclusions for various reasons, the aim was to recruit a total of 158 women.

Inclusion criteria

Pre-menopausal and peri-menopausal women aged 35 - 50 years with an ongoing menstrual cycle for at least 6 months before the onset of AUB, with histologically-confirmed non-atypical EH (simple or complex) according to the WHO-94 classification (14, 22), who have a negative cervical (Papanicolaou's) smear within 3 years, non-pregnant, and would like to preserve the uterus (avoid hysterectomy), were eligible.

Exclusion Criteria

Women who were pregnant, < 35 or > 50 years of age, postmenopausal (amenorrhea for at least 12 months after the last menstrual period), with histologically-confirmed EH (simple or complex) with atypia, distorted and/or enlarged (>12 cm) uterine cavity, other uterine pathology e.g., sub-mucosal fibroids, adnexal mass, previous endometrial ablation, hypersensitivity to progestogens, active genital tract infection, history of breast or genital tract cancer, liver disease, thromboembolic disease, epilepsy, migraine, asthma, cardiac or renal dysfunction, diabetes, hypertension, those declining hormonal treatment, women on any medi cation which might affect the menstrual blood loss within the previous 6 months e.g., steroid hormones or anticoagulants, and women at risk of osteoporosis, were ineligible.

Interventions

Women were subjected to thorough history taking and clinical examination. A blood sample was taken to check for hemoglobin concentration. Uterine anatomy and endometrial thickness (ET) were checked by a trans-vaginal ultrasonography (TVS).

Histopathology

A biopsy (endometrial Pipelle sample) was then taken and immediately soaked in a separate 10-ml glass with 10% formaldehyde. Biopsies were sent to the Histo-pathological Unit at the Department of Pathology, Zagazig University Faculty of Medicine (ZUFM), where they were processed and hematoxylin-eosin-stained sections were examined under a light-microscope. They were, then, interpreted according to the WHO-94 classification (14, 22). The histo-pathologist was blinded to the clinical findings and to which treatment group the woman belonged.

Management allocation (randomization)

This was carried out by an independent biostatistician not involved in the study who created a computer-generated randomization sequence using serially numbered, opaque, sealed envelopes. After recruitment, the randomization envelope was opened, by a member of the nursing staff not involved in the study. Neither researchers nor participants knew, prior to start of trial, to which group a particular woman was allocated.

Participants were divided into 2 groups according to the treatment intervention. They were randomized in a proportion of 1:1 as follows:-

- Depo-Provera group (73 participants): MPA (Depo-Provera® 150 mg/1 ml vial, Pfizer Manufacturing Belgium NV/SA, Puurs, Belgium), was administered as deep intra-muscular injection in the gluteal or deltoid muscle. For the purpose of this study, only 2 doses were given: 1st injection at start of trial, and 2nd injection after 3 months. Vials had to be shaken vigorously just before use to ensure that the dose being administered represents a uniform suspension, and

- Cyclic oral progestogen group (73 participants): cyclic oral NETA (Steronate 5 mg tablet, Hi Pharma for Manufacturing Pharmaceuticals and Chemicals, 1st Industrial Zone, El-Obour City, Cairo, Egypt), was administered as one tablet 3 times daily for 14 days per cycle starting from day 12 up to day 25 (inclusive). Treatment course lasted for 6 months.

No changes to study design took place after trial has started. Participants were reviewed 3 and 6 months after start of treatment. At each visit, a TVS was carried out to assess ET, and women were interviewed with emphasis on the menstrual history (disappearance, persistence, or worsening of AUB), compliance to scheduled treatment, and also about side effects of treatment – if any. A repeat Pipelle endometrial sample/biopsy was taken only at the 6th month visit. At the end of trial, women were asked to report whether they were satisfied with their scheduled treatment.

Histologically-confirmed EH (simple and complex) with atypia were treated and followed up as per hospital protocol. However, this part of management was beyond the scope of this study.

Outcome measures

The primary outcome measure was regression of EH. Regular proliferative endometrium or exaggerated progestogen effect with atrophic glands and pseudo-decidualized stroma was considered as a treatment effect. Secondary outcome variables included persisting or worsening AUB and reported side effects of treatment (nausea, weight gain …etc.).

Statistical methods

Statistical Package for Social Sciences version 20.0 (SPSS, Statistics for Windows, IBM Corp, Armonk, NY, USA), was used for all statistical analyses. For assessment of the primary outcome, the histological findings of the endometrial specimens were analyzed according the principle of intention to treat (excluding participants withdrawn or lost to follow-up). Main hypotheses were answered by comparing the number of women with regressed hyperplasia in each of the two treatment groups at the end of treatment using simple univariate statistics. Quantitative variables were compared between the two groups using the Student's (t) test and are presented as means and standard deviations [+ SD]. Qualitative variables were compared between the two groups using the Chi-squared (X^2) test or Fisher's exact test. Proportion, Relative Risk (RR) and 95% CI were used when appropriate. $P \leq 0.05$ was considered statistically significant.

Results

A total of 146 women with EH without atypia completed the 6 months treatment and were included in final analysis. Figure I. represents the flow chart of recruitment. Demographic and baseline characteristics of all participants are shown on Table I. The two study groups were similar in all characteristics that were recorded.

Responses after 6 months treatment are shown on Table II, while Table III shows side effects of treatment in all participants. The majority of women suffered some adverse effects during treatment, with only 18 participants reporting no adverse effects at all; 8 in the Depo-Provera group, and 10 in the cyclic oral group. However, the overall satisfaction with treatment was high with no statistically significant difference between the two groups ($p > 0.05$).

Discussion

Endometrial carcinoma (ECa) is the most common gynecological malignancy in many parts of the world, especially industrialized countries, and the incidence is on the rise (14). Because EH represents precursor lesions of endometrial cancer, it seems likely that adequate treatment of its early stages would contribute to reducing the rapid increase in ECa (15). Very little is known about the incidence of EH. However, an incidence ranging between 56/100,000 woman-years for EH with atypia and 213/100,000 woman-years for complex EH, with an intermediate incidence of 142/100,000 woman-years for simple EH, has been reported with peak incidence in the early 50's and 60s (2, 8).

In this study, efficacy of Depo-Provera® in treatment of simple and complex EH without atypia in pre-menopausal and peri-menopausal women was evaluated by comparing it with oral NETA. This group of women was chosen as they represent the greatest number of AUB-sufferers who require further investigation and management.

Norethisterone acetate was the chosen oral progestogen in this study because the most commonly used progestogens (MPA and MGA) are not available in Egypt (13). Bese et al., showed that 3 months of cyclic NETA (15 mg/day for 10 days each cycle) treatment reduced both proliferative and apoptotic activities in endometrial tissue with simple non-atypical EH (16). Similarly, Horn et al., treated pre-menopausal and peri-menopausal women with complex and atypical EH with NETA (5 mg/ day) or MPA (10 mg/day) for 3-5 months, with an overall remission rate of 61.5% (14).

After 6 months treatment in this study, the injectable Depo-Provera® was more successful in achieving regression of non-atypical EH (simple and complex) than the oral cyclic NETA [67 out of 73 women (91.8%) vs. 49 out of 73 women (67.1%), respectively], and the difference between the two groups was statistically significant (RR: 1.37; 95% CI: 1.15-1.63, $p = 0.048$*).

As shown, treatment for 6 months with NETA used in this study reduced the treatment failure to 32.9%, while Vereide et al., showed that nearly 50% of their participants had persisting EH after 3 months treatment with MPA 10 mg daily for 10 days per cycle (21). Treatment time of not less than 6 months to achieve an adequate response was also recommended by Gunderson et al., in a recent review of women receiving progestogen treatment for atypical EH (7). However, when meta-analyses of studies were evaluated, the results were less comparable because of variation in type, dose, regimen and duration of oral treatment (2, 10, 14, 16, 21, 23).

In this study, number of women who showed regression of their EH but requested a hysterectomy due to persistent AUB was less in the Depo-Provera® group than in the NETA group [3 out of 67 participants (4.5%) vs. 9 out of 49 (18.4%), respectively], and the difference between the two groups showed a high statistical significance (RR: 0.24; 95% CI: 0.07 – 0.85*; $p = 0.003$*).

Most women using Depo-Provera® experience disruption of menstrual bleeding patterns (e.g., irregular or unpredictable bleeding/spotting, rarely, heavy or continuous bleeding), following the administration of either a single or multiple doses of the drug. As women continue using Depo-Provera®, fewer experience

irregular bleeding and more experience amenorrhea (24). Persistent AUB makes it difficult to rely on patient symptoms to assess response to treatment of EH (13).

In this study, the statistically significant reduced hysterectomy rate noted with the use of Depo-Provera® is comparable to that achieved with the use of Levonorgestrel-intrauterine system (LNG-IUS) and supports the view that future use of long-acting progestogen to treat non-atypical EH can reduce the number of potentially unnecessary hysterectomies (25, 26).

No atypia or frank carcinoma were noted in the hysterectomy specimens in this study. This may be attributed to the accuracy of both the initial diagnosis of EH and the further follow-up assessments which were carried out using Pipelle endometrial sampling. The accuracy of Pipelle endometrial sampling as compared to endometrial biopsies obtained by cervical dilatation and curettage (D&C) in diagnosing EH has been proved. Demirkiran et al., in a recent trial which investigated 673 patients noted that the outcomes of Pipelle and D&C were concordant with each other (27). However, Pipelle biopsy is a cheaper and easier technique compared with D&C. Nevertheless, the same researchers recommended that ultrasonographic findings of endometrium should be considered prior to using whichever modality of endometrial biopsy.

A great challenge in endometrial tissue studies is diagnostic reproducibility (11, 28). The lack of standardized pathology review by research pathologists in most studies may contribute to the observed variability in outcomes (2).

It has been argued that conservative management of EH should be limited to young women who want to preserve their fertility or patients with medical co morbidities for whom surgery is hazardous or not feasible (10). Nevertheless, a recent UK survey pointed out that 52.6% of the UK gynecologists would prefer two conservative choices (oral progestogen or LNG-IUS) before embarking on hysterectomy for non-atypical EH. On the other hand, for atypical EH, the majority of them (83.2%) would perform a hysterectomy and would only consider LNG-IUS or oral progestogens as a second or third option in women who wish to retain fertility (29).

In view of the low (< 5%) progression rate of EH without atypia into endometrial cancer, it may be debated that, in this study, hysterectomy was not necessary for those women who have not responded to progestogen treatment in 6 months and consideration should have been given to continued treatment for a longer period of time (5). However, these patients opted for hysterectomy rather than continued progestogen therapy.

A few limitations of this study need to be addressed. With the exception of the histo-pathologist who was blinded to the clinical findings of participants and also to which treatment group women belonged, the study was neither blinded nor placebo-controlled. Participating women in the two treatment groups, and their treating healthcare givers might have been biased. Although designing an injectable placebo was a possible alternative, on dealing with premalignant disorders, treatment with placebo is unethical. Compliance to scheduled treatment was not verified. Finally, follow-up for more than 6 months was not possible due to limited resources.

Conclusions

This study compared injectable Depo-Provera® with an oral progestogen as a treatment for EH. It proved that Depo-Provera® is an effective and safe treatment for EH without atypia. Given its availability, apparent safety, and relatively reduced cost, Depo-Provera® deserves to be considered in further larger-sized, multi-centre, double blind, randomized, placebo-controlled trials prior to recommending it for routine use in women with EH.

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Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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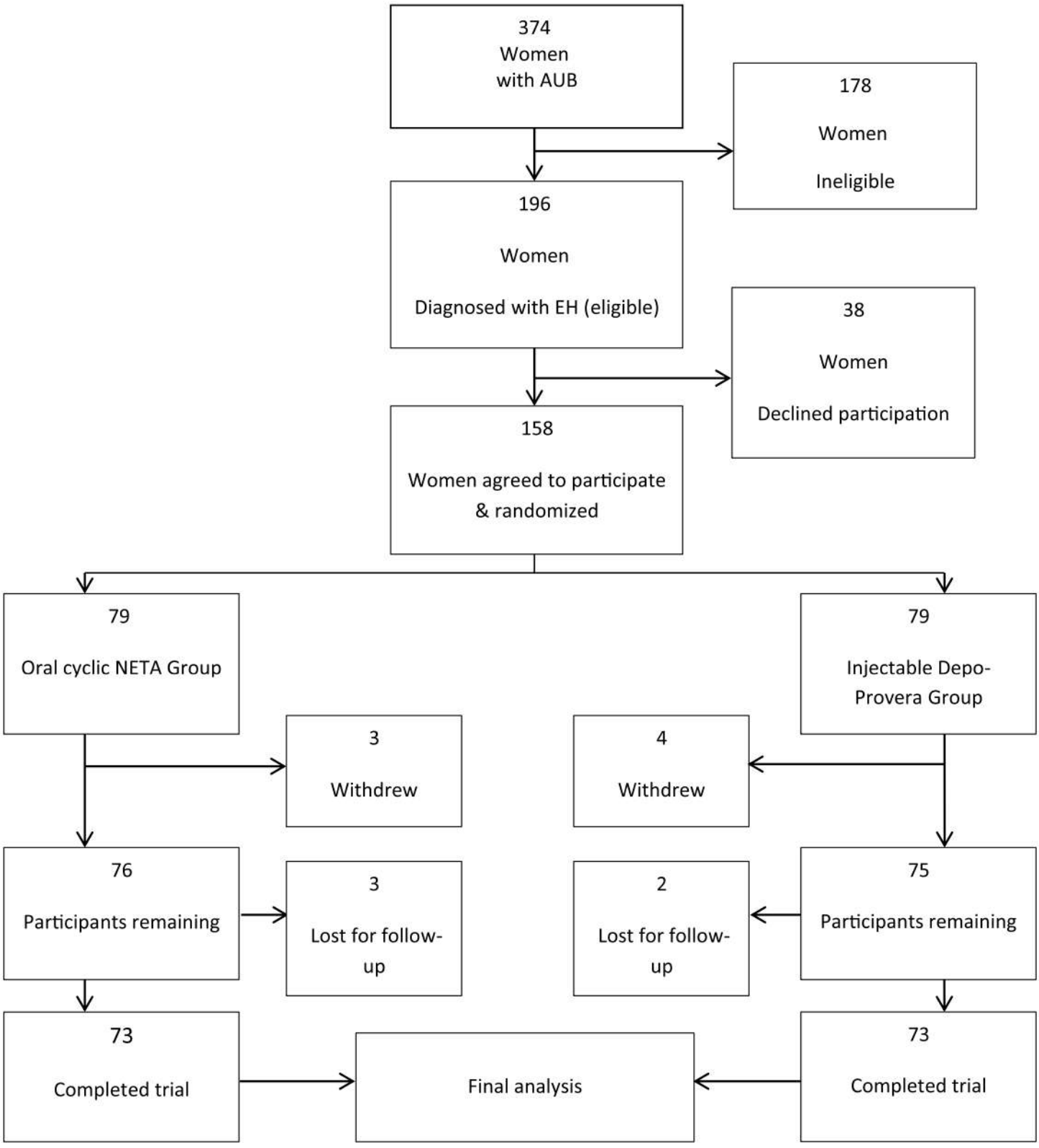

Figure I: Flow chart of recruitment

AUB: Abnormal uterine bleeding
EH: Endometrial hyperplasia
NETA: Norethisterone acetate

Table I: Demographic data of all participants

Variable		Depo-Provera (*n*=73)	Oral Cyclic (*n*=73)	*P*
Age (years)		38 ± [3.9] (35 – 49)	39 ± [5.3] (35 – 48)	0.19
BMI (kg/m^2)		28.5 [± 4.1]	29 [± 4.1]	0.45
Parity	**0**	11 (15.1%)	12 (16.4%)	0.81
	≥ 1	62 (84.9%)	61 (83.6%)	
Hypertension		13 (17.8%)	12 (16.4%)	0.82
Diabetes		8 (11%)	9 (13.3%)	0.64
Non-Atypical EH	**Simple**	27 (37%)	26 (35.6%)	0.86
	Complex	46 (63%)	47 (64.4%)	
Hb (gm%)	**≥ 11.5**	36 (49.3%)	35 (47.9%)	0.87
	< 11.5	37 (50.7%)	38 (52.1%)	

[Data are presented as mean ± [SD], (range), or number (%)]
BMI: Body mass index
EH: Endometrial hyperplasia
Hb: Hemoglobin

Table II: Treatment responses after 6 months in all participants

Variable		Depo-Provera (*n*=73)	Oral Cyclic (*n*=73)	RR (95% CI)	*P*
Regressing non-atypical hyperplasia	**Simple**	25/27 (92.6%)	17/26 (65.4%)	1.4 (1.1-1.92)*	0.031*
	Complex	42/46 (91.3%)	31/47 (65.9%)	1.38 (1.11-1.73)*	0.04*
	Total	67/73 (91.8%)	49/73 (67.1%)	1.37 (1.15-1.63)*	0.048*
Hysterectomy/regression		3/67 (4.5%)	9/49 (18.4%)	0.24 (0.07-0.85)*	0.003*
Hysterectomy/all cases		9/73 (12.3%)	17/73 (23.3%)	0.53 (0.25-1.11)	0.06

[Data are presented as number (%)]
RR: Relative risk
95% CI: 95% Confidence interval

Table III: Side effects in all participants

Side effects	Depo-Provera (*n*=73)	Oral Cyclic (*n*=73)	RR (95% CI)	*p*
Irregular bleeding	12 (16.4%)	15 (20.5%)	0.8 (0.4-1.5)	0.49
Nausea	9 (12.3%)	27 (37.0%)	0.33 (0.17-0.66)*	0.0003**
Weight gain	18 (24.7%)	9 (12.3%)	2.0 (0.96-4.16)	0.045*
Amenorrhea	42 (57.5%)	0 (0%)	NA	0.00**
Headache	7 (9.6%)	8 (11.0%)	0.88 (0.33-2.29)	0.75
Mood swings	10 (13.7%)	16 (21.9%)	0.6 (0.3-1.28)	0.17
Breast discomfort	8 (11.0%)	18 (24.7%)	0.44 (0.21-0.96)*	0.026*

[Data are presented as number (%)]
RR: Relative risk
95% CI: 95% Confidence interval