GYNECOLOGY

Levonorgestrel-releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials

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We sought to evaluate the therapeutic efficacy of levonorgestrel-releasing intrauterine system (LNG-IUS) with oral progestins for treatment of non-atypical endometrial hyperplasia (EH). Searches were conducted on PubMed, SCOPUS, and CENTRAL databases to August 2014, and reference lists of relevant articles were screened. The search was limited to articles conducted on human beings and females. The PRISMA Statement was followed. Seven randomized controlled trials (n = 766 women) were included. Main outcome measures were the therapeutic effect rate (histological response) after 3, 6, 12, and 24 months of treatment; rate of irregular vaginal bleeding; and the hysterectomy rate per woman randomized. The Cochrane Collaboration risk of bias tool was used for quality assessment. Metaanalysis was performed with fixed effects model. LNG-IUS achieved a highly significant therapeutic response rate compared with oral progestins after 3 months of treatment (odds ratio [OR], 2.30; 95% confidence interval [CI], 1.39–3.82; $P = .001$, 5 trials, $I^2 = 0\%$, n = 376), after 6 months of treatment (OR, 3.16; 95% CI, 1.84–5.45; $P < .00001$, 4 trials, $I^2 = 0\%$, n = 397), after 12 months of treatment (OR, 5.73; 95% CI, 2.67–12.33; $P < .00001$, 2 trials, $I^2 = 0\%$, n = 224), and after 24 months of treatment (OR, 7.46; 95% CI, 2.55–21.78; $P = .0002$, 1 trial, n = 104). Subgroup analysis showed evidence of highly significant therapeutic response following LNG-IUS compared with oral progestins for non-atypical simple as well as complex EH (OR, 2.51; 95% CI, 1.14–5.53; $P = .02$, 6 trials, $I^2 = 0\%$, n = 290; and OR, 3.31; 95% CI, 1.62–6.74; $P = .001$, 4 trials, $I^2 = 0\%$, n = 216, respectively). Compared with oral progestins, LNG-IUS achieved significantly fewer hysterectomies (OR, 0.26; 95% CI, 0.15–0.45; $P < .00001$, 3 trials, n = 362, $I^2 = 42\%$). No difference was observed in the rate of irregular vaginal bleeding between both groups (OR, 1.12; 95% CI, 0.54–2.32; $P = .76$, 2 trials, n = 207, $I^2 = 77\%$). Funnel plot analysis was not performed because of the relatively small number of included studies. For treatment of non-atypical EH, LNG-IUS achieves higher therapeutic effect rates and lower hysterectomy rates than oral progestins and should be offered as an alternative to oral progestins in these cases.

Key words: endometrial hyperplasia, levonorgestrel-releasing intrauterine system, progestins, progestogens, randomized trials

Endometrial hyperplasia (EH) is a histological diagnosis characterized by proliferation of endometrial glands resulting in a greater gland-to-stroma ratio than observed in normal endometrium. It is typically classified into simple or complex hyperplasia, with or without cytological atypia.[1,2] Recently, among women aged 18-90 years, the overall incidence of EH was 133/100,000 woman-years and it peaks in the early 50s and early 60s.[3] It is worth remembering that EH is a commonly seen clinical entity, presenting mainly with abnormal uterine bleeding including heavy, prolonged, or irregular perimenopausal bleeding as well as postmenopausal bleeding.[4,5] Apart from this problematic symptomatology, the real clinical significance of EH is the potential risk of progression to endometrial carcinoma, which is low for women with non-atypical EH compared with women with cytologic atypia (<5% vs approximately 30%, respectively).[6,7]

Unfortunately, despite a long history of our knowledge about EH, no guidelines were issued for its optimal treatment.[6,8] Hysterectomy is the preferred treatment in most women with EH with atypia who are no longer interested in childbearing in view of the risk of concomitant carcinoma in up to 42.6% of cases[9] or progression to carcinoma.[6,7] Oral progestins, mainly norethisterone acetate (NET), megestrol acetate, and medroxyprogesterone acetate (MPA), are a popular therapeutic choice especially in non-atypical cases of EH.[10,11] However, the levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena; Bayer Schering Pharma Oy, Turku, Finland) represents an appealing option for treatment of EH without atypia and even selected cases with atypia, in view of achieving higher local progestin concentrations by many folds compared with oral therapy.[12,13] A recent metaanalysis of 24 observational studies including 1001 women showed that oral

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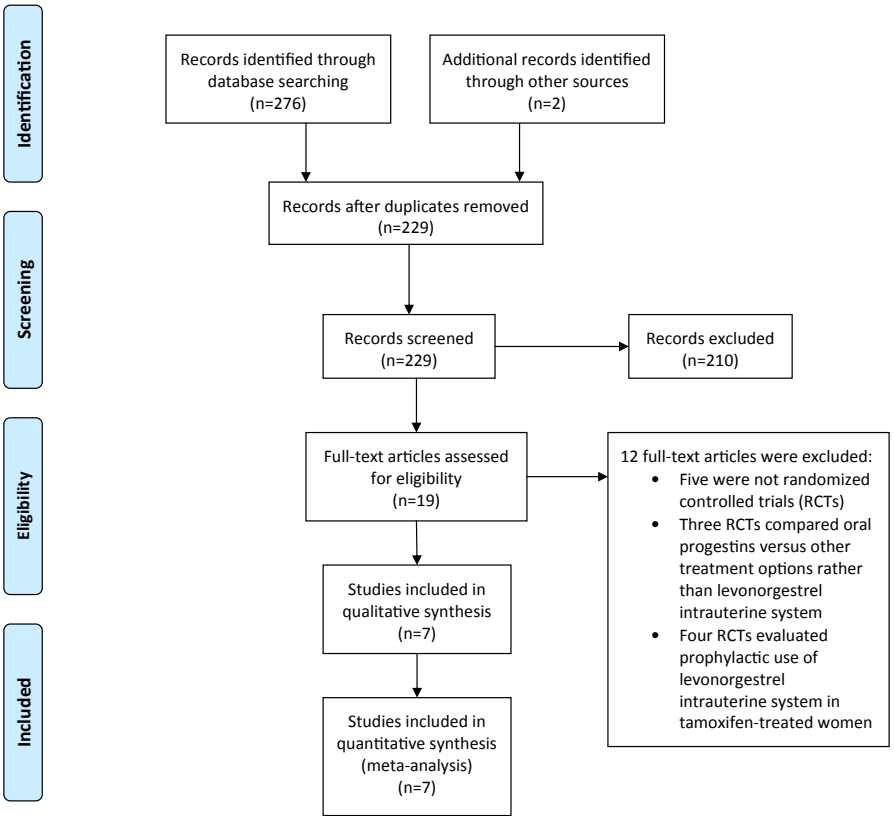
FIGURE 1
PRISMA flow diagram of study selection



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progestins achieved a significantly lower pooled regression rate compared with LNG-IUS for non-atypical complex EH (66% vs 92%), but not for non-atypical simple EH.[14] Of note, the authors admitted the poor quality of the included studies and the need for randomized controlled trials (RCTs) to generate the best evidence.[14]

More recently, the efficacy of LNG-IUS vs oral progestins for treatment of non-atypical EH has been tested in RCTs.[15-17]

In view of the aforementioned context and given that this is a clinically important area to address, this systematic review and metaanalysis was conducted to evaluate the therapeutic efficacy of LNG-IUS vs oral progestins for treatment of non-atypical EH on the basis of the available evidence so far in RCTs.

Materials and methods

The methodology of this systematic review and metaanalysis followed the PRISMA statement.[18] The clinical question posed was: in women with non-atypical EH, does LNG-IUS represent a more effective therapy compared with oral progestin treatment?

Information sources and search strategy

An electronic search was performed using the following databases: PubMed, SCOPUS (each from inception through August 2014), and CENTRAL (Cochrane Central Register of Controlled Trials, Issue 8, 2014) with the following search terms, adjusting for each database as necessary: "endometrial hyperplasia" AND "levonorgestrel-releasing intrauterine system" OR "LNG-IUS" AND "progestins" OR "progestogens" AND "randomized trials." The search was limited to articles conducted on human beings and females. Manual screening of references of the retrieved articles was also performed to identify other pertinent studies.

Study selection

The titles and abstracts of retrieved citations were subsequently screened for eligibility by 2 independent reviewers (H.A. and E.G.) using the following inclusion criteria: (1) women diagnosed histologically with non-atypical EH according to the World Health Classification (simple, complex, and atypical)[1,2]; (2) only RCTs that compared LNG-IUS with oral progestin treatment and reported therapeutic response after 3, 6, 12, or 24 months of treatment were included; (3) a study with multiple treatment groups including cases with atypical EH was considered, however, only information from cases with non-atypical EH was utilized; and (4) a study including different oral progestin arms or different dosage control groups was considered, however, information from the oral progestin arm with the highest therapeutic effect was utilized. Exclusion criteria were: quasi-RCTs, non-RCTs, concurrent endometrial cancer, or other malignancy. Full texts were obtained by contacting the author when it could not be obtained online.

Data extraction

The data from each included trial were extracted independently by 2 reviewers (H.A. and E.G.) on a data extraction form designed in accordance with the Cochrane Checklist of items.[19] Details included; source, eligibility, methods, participants, interventions, outcomes, results, as well as any other important miscellaneous data. The primary efficacy outcome was the therapeutic effect rate (histological response) after 3, 6, 12, and 24 months of treatment, diagnosed according to the last endometrial biopsy by Pipelle (Laboratoire C.C.D, Paris, France) or curettage. Proliferative, secretory, inactive, or atrophic pattern endometrium was considered a therapeutic effect.[20] Secondary clinical outcomes were rate of irregular vaginal bleeding during treatment and the hysterectomy rate. The unit of analysis was per woman randomized.

Assessment of risk of bias

The methodological quality of each included study was independently