Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density

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Context: Women with premature ovarian failure (POF) face many years of estrogen deficiency. One of the major consequences is bone loss. The optimal form of estrogen replacement is unknown and management is not evidence based. The 2 broad options are combined hormone replacement therapy (HRT) or the combined oral contraceptive pill (COCP).

Objectives: To compare the effects of HRT and COCP on bone density and turnover in women with spontaneous POF and to observe the effects of no treatment.

Design: Two-year open randomized trial comparing HRT and COCP and nonrandomized observation of women declining treatment using the same protocol.

Setting: London teaching hospital.

Participants: A total of 59 women with spontaneous POF aged 18–44, 30 women elected to take treatment and were randomized, and 29 declined treatment.

Intervention: Randomization was to HRT (Nuvelle) or COCP (Microgynon 30).

Main Outcome Measures: The primary outcome was change in lumbar spine bone mineral density. Changes in total hip and femoral neck bone density and bone turnover markers were also assessed.

Results: A total of 36 women (61%) completed the trial (no treatment 52%; HRT 60%; COCP 80%). In comparison with COCP, treatment with HRT increased bone density at the lumbar spine at 2 years (+0.050 g/cm^2; 95% confidence interval 0.007–0.092; $P = .025$). Bone turnover markers showed similar reductions in the 2 treatment groups. In the no treatment group, bone density dropped at all sites and bone turnover markers remained relatively unchanged.

Conclusions: The results suggest that HRT is superior to COCP in increasing bone density at the lumbar spine in women with spontaneous POF. The limitations of a small sample size and high drop-out rate mean that further research is required to confirm the findings. However, either treatment is clearly superior to no treatment. **(*J Clin Endocrinol Metab* 101: 3497–3505, 2016)**

Premature ovarian failure (POF) is a loss of ovarian function under the age of 45 (1). Spontaneous POF affects around 1% of women under the age of 40 and 5% under 45 (2). Estrogen is produced by the ovaries and women with POF have very low estrogen levels. Arguably the most important effect of this is bone loss, which can

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Abbreviations: ANCOVA, analysis of covariance; BMD, bone mineral density; COCP, combined oral contraceptive pill; CTX, C-terminal cross-linked telopeptide; HRT, hormone replacement therapy; P1NP, procollagen type I N-terminal propeptide; POF, premature ovarian failure.

ultimately lead to osteoporosis and fractures. Several cross-sectional studies have shown that women with POF have lower bone density than controls (3–5) and another found that early menopause is associated with increased fracture risk in later life (6). A recent prospective observational study demonstrated that women with a menopause before 47 have an increased risk of osteoporosis and fractures in later life compared with controls (7). A service evaluation at Guy's and St Thomas' National Health Service Foundation Trust POF clinic showed that bone health was a major concern for 70% of women. This has been illustrated in another recent London Hospital questionnaire study, which found that bone loss was a concern for 92% (8). Estrogen replacement is advised in POF to treat menopausal symptoms, prevent bone loss, and promote cardiovascular health, but there is very little research on the optimal form of estrogen replacement and so management is not evidence based. This is acknowledged in most reviews on the subject (1, 9, 10). In 2004, the Royal College of Obstetricians and Gynaecologists Menopause and Hormone Replacement study group advised that research is recommended "to develop and assess treatment strategies in women with premature menopause."

Currently, combined hormone replacement therapy (HRT) or the combined oral contraceptive pill (COCP), both of which contain estrogen and progestin, are commonly prescribed. HRT is often considered more "physiological," because most preparations contain estradiol, which is found naturally, whereas COCPs contain the synthetic ethinyloestradiol and also higher doses of progestin. COCPs are recognized to increase the risk of venous thrombo-embolism (it is doubled with levonorgestrel-containing COCPs) and are also considered a risk factor for cardiovascular and cerebrovascular disease (11). Oral HRT also increases venous thromboembolism (12). Estradiol has less thrombotic effect than ethinyloestradiol (13) but its clinical effect in younger women has not been evaluated. In women under 60 HRT does not increase cardiovascular disease (12). However, many young women dislike the idea of taking a medication designed for older women and find the COCP more "peer friendly." To date, only one small crossover trial has compared the effects of HRT vs COCP in POF (14). Most of the women included in this trial had Turner's syndrome or iatrogenic POF. No difference in bone density between the regimens was found, but only 18/34 completed follow-up, and each treatment was taken for just one year. No studies have compared HRT and the COCP in purely spontaneous POF. It is also recognized that there are a significant number of women who decline estrogen treatment in spite of the recommendation to take it (3, 15, 16), and we have no specific information on which to advise these women on the likely effects of this choice.

The aim of this study was to assess the effects of HRT, the COCP, and no treatment on bone density and turnover over 2 years in women with spontaneous POF. The no treatment group was not randomized, because estrogen treatment is advised in POF, and it would not be ethical to randomize to no treatment. In addition, women tend to have strong views on whether they wish to take estrogen or not and recruitment to a trial including a placebo group would not be acceptable. Despite this limitation, data obtained from the no treatment group in this study will be valuable in enabling this significant minority to make truly informed choices. We chose an oral HRT preparation, because we find that this is the route that most young women prefer, and also skin irritation can be problematic with the transdermal route, as illustrated in the only similar study in POF in which 12% of participants withdrew because of a patch reaction (14). The HRT chosen also had the same progestagen as the COCP used. Unfortunately this HRT preparation is no longer available but there are several other oral sequential combined HRTs containing the same dose of estradiol.

Materials and Methods

The protocol for this trial has previously been described (17). This was an open-label randomized trial for women choosing estrogen treatment, with observation of women who chose not to take treatment using the same protocol.

Participants

Women aged 18–44 diagnosed with spontaneous POF within the last 3 years were eligible to participate. The diagnosis of POF was confirmed by 2 FSH levels of over 30 IU/L taken over 4 weeks apart. Desire for pregnancy and any absolute contraindications to hormone therapy were exclusion criteria from the treatment group. Women taking hormone therapy had a 2-month "washout" period. Participants were asked not to take herbal medications or calcium supplements. Women taking any medication known to affect bone density or with a condition which could affect bone density were excluded.

Women were recruited from the POF and reproductive medicine clinics, referrals from colleagues, and advertisement through the Daisy Network (www.daisynetwork.org.uk; a patient-run charity for women with POF), the British Menopause Society, and a press release that resulted in coverage on the hospital intranet, BBC online, and several newspapers and magazines.

Randomization

After confirmation of eligibility and written informed consent, participants chose to be in either the no treatment group or to take treatment. Those who opted for treatment were

randomized using the secure internet randomization website www.sealedenvelope.com to receive either HRT or the COCP.

Intervention

The HRT used was Nuvelle; estradiol 2 mg daily, with the addition of levonorgestrel 75 mcg for 12 days a month. The COCP was Microgynon 30; ethinyloestradiol 30 mcg and levonorgestrel 150 mcg taken daily for 21 days followed by a 7-day break.

Trial procedures

Women were seen in the Menopause Research Unit at Guy's Hospital at baseline then at 3, 6, 12, 18, and 24 months. Medication for the treatment groups (HRT or COCP) was provided at 6 monthly intervals. Compliance was monitored by requesting participants to return medication packets with any unused or forgotten pills. Baseline measures were taken after randomization. A dual energy x-ray absorptiometry scan of the hip and lumbar spine (L1–L4) was performed at baseline, 6, 12, and 24 months. Fasting morning blood samples were taken for procollagen type I N-terminal propeptide (P1NP) and C-terminal cross-linked telopeptide (CTX) at baseline, 6, 12, and 24 months.

Dual energy x-ray absorptiometry scans (Hologic Discovery model) were performed in the Osteoporosis Research Unit at Guy's Hospital by a small number of radiographers. The machines were calibrated each morning using phantom models, with a coefficient of variation over the course of the study of 0.4%. In vivo reproducibility is good, with a coefficient of variation for lumbar spine and total hip bone mineral density (BMD) of 1%–1.5% (18).

Serum was spun immediately in a chilled centrifuge at 3000 revolutions/min for 10 minutes. The samples were frozen in aliquots of 1 mL for storage at −20°C for up to 3 months, then transferred to −80°C and analyzed in batches at the end of the trial. P1NP and CTX were analyzed by GSTS Pathology at St Thomas' Hospital. P1NP was measured by the automated Roche Elecsys total P1NP test. CTX was measured using the automated Roche Elecsys β-CrossLaps/serum assay.

Outcomes

We prespecified the primary outcome as change in lumbar spine bone density at 2 years. Changes in total hip and femoral neck bone density, P1NP, and CTX were also assessed.

Statistical analysis

Our initial target for recruitment was 90 women (30 in each group). Assuming that the BMD in each group varies with a SD of 4%, 22 in each group would be enough to detect a difference of 4% between groups at 2 years, assuming a 5% significance level and power of 90%. A total of 30 in each group was aimed for to allow for withdrawals.

Statistical Package for the Social Sciences (SPSS) version 19 was used for statistical analysis. Independent sample *t* tests were used to compare baseline characteristics between the treatment and no treatment groups when the variables were normally distributed, and the Mann-Whitney *U* test was used in cases of nonparametric distribution (demographics).

Comparison of changes in BMD and bone markers between the groups were performed using multiple linear regression with adjustment for baseline values and potential confounding factors (analysis of covariance [ANCOVA]), as described by Vickers and Altman (19). To test the possibility of undetectable bias due to missing data, a series of analyses under different missing not at random assumptions was undertaken for the primary endpoint (20). All variables were tested for normality using histograms and found to be normally distributed. For bone density, comparisons with baseline values were made using paired *t* tests, because it is useful clinically to be able to advise a woman how much she can expect her bone density to go up (or down). The Consolidated Standards of Reporting Trials guidelines were followed in reporting the trial results (21).

This study was approved by Guy's Research Ethics Committee on December 18, 2008 (reference 08/H0804/140) and the Medicines and Healthcare Products Regulatory Agency (EudraCT number 2008–002599–86). Participants gave informed consent before participation in the study. Trial registration number: ISRCTN87011615.

Results

A total of 64 women were screened. Five were not eligible due to a first or second FSH level of under 30 IU/L. A total of 59 women were recruited between May 2009 and March 2011, when recruitment was stopped due to time constraints, at which time there were 15 women in each treatment group and 29 in the no treatment group. Demographic characteristics of the participants are shown in Supplemental Table 1. The trial was completed in April 2013. Overall, 36 out of 59 women completed the study (61%). The percentage completing follow-up in each group was 52% in the no treatment group, 80% in the HRT group, and 60% in the COCP group. The flow of participants with timing of drop-outs and reasons is shown in Figure 1. Numbers included in each analysis are shown in Supplemental Table 2.

There was a slightly higher drop-out rate in the COCP group compared with the HRT group, due to loss of follow-up. One participant in each of these groups withdrew because she felt that the medication was contributing to symptoms of depression and wished to change medication. One participant in each treatment group withdrew due to side effects. There was one serious adverse event, which was a pregnancy in the no treatment group resulting in a live birth. Participants were reminded of visits by their preferred choice of letter or e-mail and a phone call. Every attempt was made to contact women who did not attend and reasons for withdrawal sought. Compliance from counting remaining pills was 98% in the HRT group and 95% in the COCP group. Another indirect measure of compliance was unscheduled bleeding which was considered an adverse event and was not reported in the trial, supporting high compliance rates.

Baseline comparisons between the treatment and no treatment groups did not reveal any differences in baseline bone density, age, or time since diagnosis (Supplemental

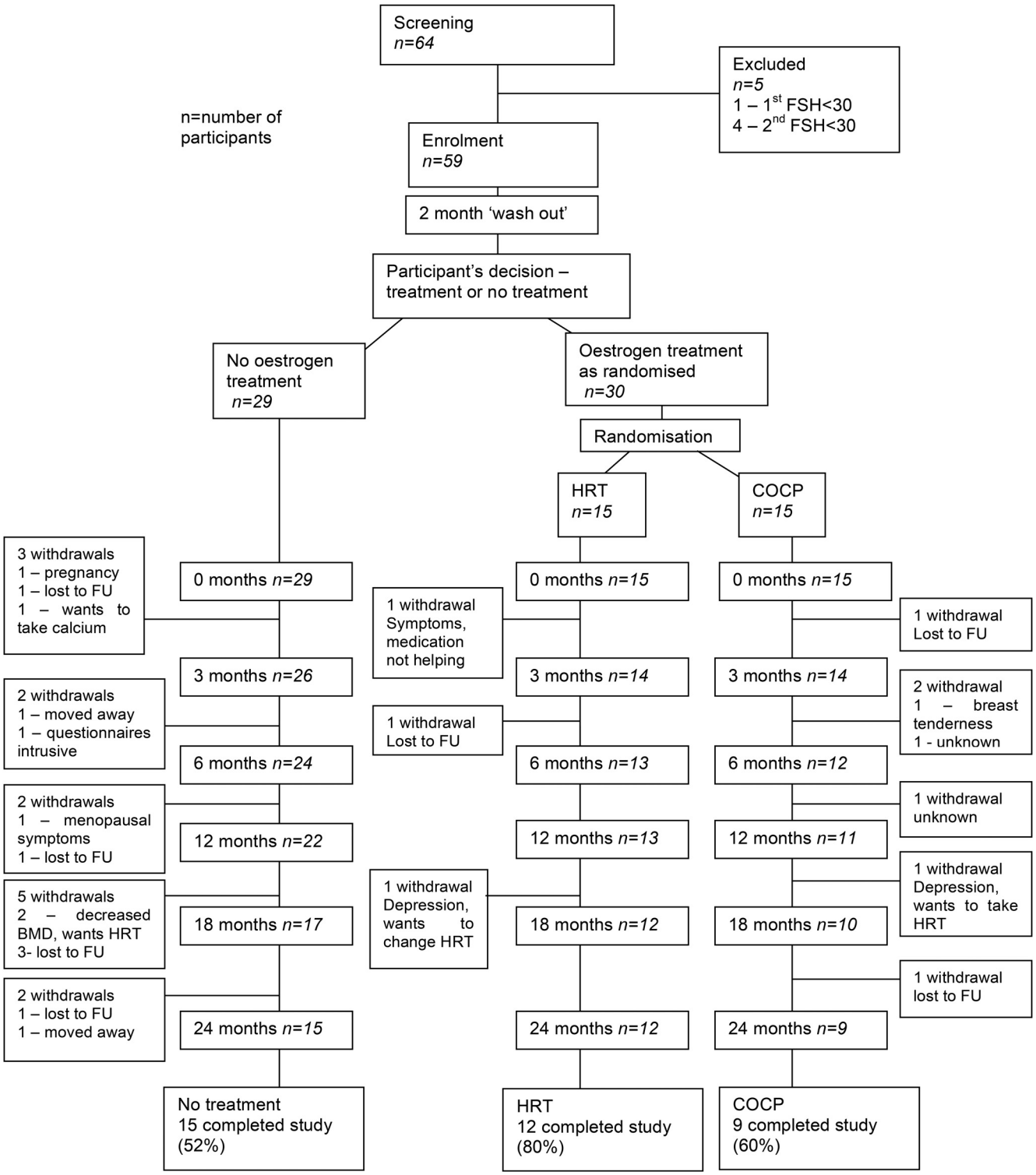

Figure 1. Flow of trial participants.

Table 3). Baseline characteristics of the HRT and COCP groups were not compared as these groups were randomized. However, we noted that there were some baseline discrepancies between the 2 groups, for example, in alcohol, smoking, and parity. We therefore included these potential confounding factors in the analysis. Supplemental Table 4 illustrates the lack of effect of these factors on the results. The HRT group had a shorter time since diagnosis than the COCP group. However, the time since the last period was similar, suggesting that there were more delays in diagnosis in the COCP group but the stage of ovarian failure was comparable. Among women with complete data collection, baseline hip BMD was lower in the COCP group than the HRT group (see figure 3 below). However,

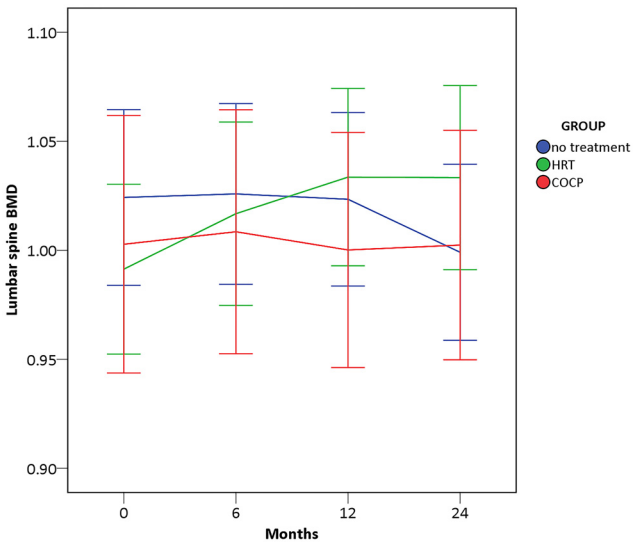

Figure 2. Lumbar spine BMD (g/m^2) in participants with complete data collection. Data shown as mean ± 1 SD.

the baseline differences in hip BMD are within the range of chance variation: less than 1 SD; and much less than a SD. None of them approach significance.

Primary outcome

At the lumbar spine, there was a significant gain in BMD with HRT at all time points, a drop in BMD in the no treatment group at 12 and 24 months and no significant change in BMD in the COCP group (see Figure 2 and Supplemental Table 5). Comparison between the groups (Table 1) revealed a significant difference between the COCP and HRT groups in lumbar spine BMD at 12 and 24 months, in favor of HRT.

Comparisons between the HRT and no treatment groups at the lumbar spine were highly significant at all time points in favor of HRT. Comparison of the COCP and no treatment groups revealed significant differences in favor of COCP at 6 and 12 months and a trend towards this at 24 months.

A sensitivity analysis allowing for possible selective bias in missing data (missing not at random) showed that the results did not change significantly provided that the missing values were on average the same as the corresponding values observed in women with similar baseline levels, or no more than 0.015/cm^2 higher.

Secondary outcomes

At the total hip, bone density was maintained in the HRT and COCP groups over 24 months, whereas in the no treatment group, there was a significant drop at all time points (Figure 3 and Supplemental Table 5). At the femoral neck, there was a smaller reduction in bone density in the no treatment group over the course of the trial and no significant changes in the HRT or COCP groups (Supplemental Table 4 and Supplemental Figure 4).

Comparison between the groups did not reveal any differences between the COCP and HRT groups in change in total hip BMD at 24 months (Table 1). At the femoral neck, there was a trend at 12 months in favor of HRT, but no significant differences. Comparison between the HRT

Table 1. BMD (g/m^2) Comparisons Between the Groups at the Lumbar Spine (Primary Endpoint), Total Hip, and Femoral Neck

	6 Months	12 Months	24 Months
Lumbar spine			
HRT minus COCP lumbar spine BMD	0.014 (−0.014–0.042) $P = 0298$	0.040 (0.072–0.007) $P = .019$	0.050 (0.092–0.007) $P = .025$
HRT minus no treatment lumbar spine BMD	0.028 (0.010–0.045) $P = .003$	0.052 (0.033–0.068) $P < .001$	0.062 (0.032–0.093) $P < .001$
COCP minus no treatment lumbar spine BMD	0.012 (0.003–0.021) $P = .011$	0.013 (0.002–0.024) $P = .018$	0.009 (−0.003–0.036) $P = .088$
Total hip			
HRT minus COCP total hip BMD	−0.013 (−0.031–0.006) $P = .162$	−0.001 (−0.020–0.017) $P = .895$	0.008 (−0.016–0.032) $P = .497$
HRT minus no treatment total hip BMD	0.014 (0.000–0.028) $P = .044$	0.021 (0.009–0.033) $P = .001$	0.028 (0.012–0.044) $P = .002$
COCP minus no treatment total hip BMD	0.012 (0.005–0.019) $P = .002$	0.012 (0.004–0.020) $P = .004$	0.014 (0.004–0.024) $P = .010$
Femoral neck			
HRT minus COCP femoral neck BMD	0.004 (−0.036–0.044) $P = .829$	0.027 (−0.004–0.057) $P = .083$	0.010 (−0.014–0.035) $P = 0.386$
HRT minus no treatment femoral neck BMD	−0.004 (−0.093–0.085) $P = .934$	0.013 (−0.076–0.103) $P = .761$	−0.007 (−0.110–0.096) $P = .890$
COCP minus no treatment femoral neck BMD	−0.014 (−0.058–0.030) $P = .030$	−0.016 (−0.069–0.036) $P = .523$	−0.004 (−0.070–0.063) $P = .911$

Data shown as mean (95% confidence interval). Analysis was performed using multiple linear regression (ANCOVA) with adjustment for baseline BMD, smoking, alcohol, and parity.

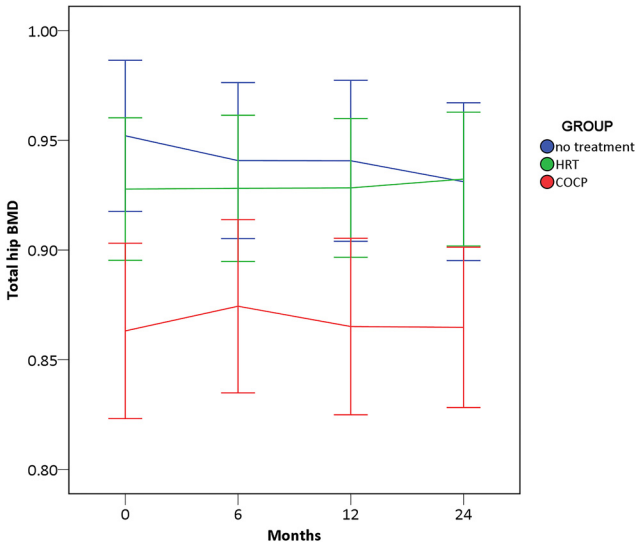

Figure 3. Total hip BMD (g/m^2) in participants with complete data collection. Data shown as mean ± 1 SD.

and no treatment groups at the total hip were significant at all time points in favor of HRT, whereas at the femoral neck, there were no significant differences. Comparison between the COCP and no treatment groups at the total hip showed results similar to the HRT/no treatment comparison, with significant differences between the COCP and no treatment groups at all time points in favor of COCP. Except at 6 months, there were no significant differences between the COCP and no treatment groups at the femoral neck.

Both P1NP and CTX were reduced from baseline at all time points in the HRT and COCP groups (Supplemental Figures 1 and 2). There was a trend towards a greater reduction in P1NP in the HRT group, but on statistical comparison there were no significant differences between the HRT and COCP groups on the extent of reduction of either CTX or P1NP (see Table 2). In the no treatment group, there was a slight increase in P1NP and CTX over the course of the trial. When each treatment group was compared with the no treatment group, the differences were significant at every time point for both CTX and P1NP, with the exception of COCP/no treatment at 24 months ($P = .082$). Baseline values for women with complete data collection were very similar between the groups for both P1NP and CTX (Supplemental Figures 1 and 2).

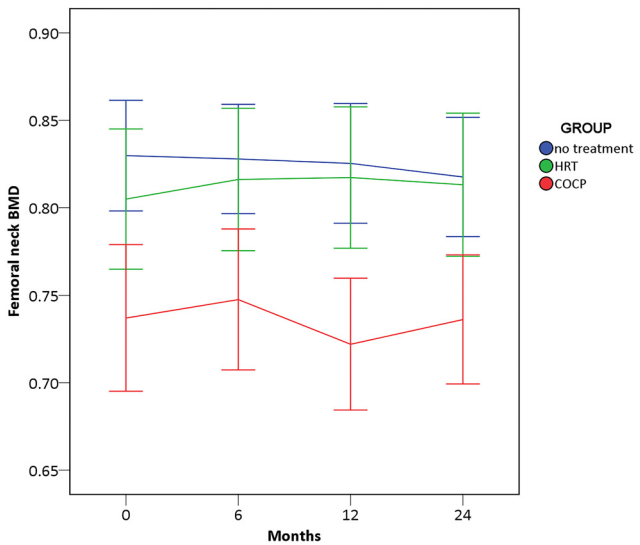

Figure 4. Femoral neck BMD (g/m^2) in participants with complete data collection. Data shown as mean ± 1 SD.

Discussion

Main findings

This open-label randomized trial comparing HRT and the COCP on bone density in spontaneous POF demonstrated that after 12 and 24 months of treatment the HRT group had a significantly increased bone density at the lumbar spine compared with the COCP group. As expected in such a small trial the confidence intervals of the differences were large. In the HRT group, bone density increased significantly at the lumbar spine and remained stable at the total hip and femoral neck over the course of the trial. In the COCP group bone density remained stable at all sites. In the no treatment group, there was a decrease in bone density at all sites and this became more pronounced as the trial progressed. There were no significant differences in bone markers between the HRT and COCP groups, but there was a trend towards a greater reduction with HRT. In the no treatment group, there were significant differences in bone markers compared with each treatment group at every time point.

Strengths

A major strength of this study is that it only includes women with spontaneous POF, which represent a distinct population. There is also a high proportion of ethnic minorities represented. There are very few other trials in this area and as such this trial adds significantly to the body of evidence on treatment of spontaneous POF and paves the way for future research.

Limitations

The main limitations of this trial were the small sample size and relatively high drop-out rate. In the treatment groups 80% completion in the HRT arm and 60% in the COCP arm was achieved. The excess drop-out rate in the COCP group was due to loss to follow-up. Although every effort was made to remind women of appointments and contact those who did not attend, there were many who avoided contact. This may in part be because of the difficult psychological aspects of the condition. Another lim-

Table 2. CTX (mcg/L) and P1NP (mcg/L) Comparisons Between the Groups

	6 Months	12 Months	24 Months
CTX			
HRT minus COCP CTX	−0.03 (−0.10–0.03) $P = .304$	−0.04 (−0.13–0.04) $P = .316$	−0.07 (−0.22–0.08) $P = .318$
HRT minus no treatment CTX	−0.16 (−0.28–−0.05) $P = .009$	−0.21 (−0.10–−0.31) $P < .001$	−0.17 (−0.27–−0.08) $P = .001$
COCP minus no treatment CTX	−0.07 (−0.12–−0.01) $P = .023$	−0.11 (−0.17–−0.04) $P = .002$	−0.07 (−0.14–0.01) $P = .082$
P1NP			
HRT minus COCP P1NP	−2.5 (−19.9–14.8) $P = .760$	−12.4 (−26.8–2.0) $P = .086$	−10.5 (−29.2–8.1) 0.247
HRT minus no treatment P1NP	−26.1 (−39.0–−13.2) $P < .001$	−29.6 (−47.1–−12.0) $P = .002$	−29.8 (−43.5–−16.0) $P < .001$
COCP minus no treatment P1NP	−13.7 (−20.7–−6.7) $P < .001$	−13.2 (−24.5–−1.8) $P = .025$	−16.4 (−27.4–−5.5) $P = .006$

Data shown as mean (95% confidence interval). Analysis was performed using multiple linear regression (ANCOVA) with adjustment for baseline CTX or P1NP, BMD, smoking, alcohol, and parity.

itation is that the no treatment group was not randomized. The main comparisons of value are those between the HRT and COCP groups. However, the no treatment group illustrates the natural course of bone density in women who choose (and continue to choose at each time point, with knowledge of bone density results) to not take treatment. Recruitment to the treatment arm of the study was slow. This was partly due to women who were hoping for a pregnancy not being suitable to participate (due to the chance of being randomized to COCP) and partly due to women who were settled on treatment either not wanting to consider a different regimen or not wanting to complete a 2-month no treatment washout before participating. The trial was open label due to a lack of funding for blinding. It is worth noting that some countries use the cut-off of 40 rather than 45 to define POF. However, a woman who experiences POF at the age of 44 has 8 extra years of estrogen deficiency compared with a woman who has her menopause at 52. She is exposed to all the risks of early estrogen deficiency, including bone loss. We therefore use the British Menopause Society's definition (1) both in clinical practice and for this research project.

Interpretation

It is clear from our study that choosing to take no treatment in POF causes a loss of bone density and that either HRT or the COCP is preferable to no treatment. This confirms current opinion and recommendation for estrogen treatment in POF (1, 22). Our finding of a possible superiority of HRT compared with COCP at the lumbar spine may be surprising given the relatively higher biological potency of ethinyloestradiol compared with estradiol (23). There are some plausible reasons for our findings. With the COCP taken in the conventional manner, as it was in this trial, there is a 7 day break from estrogen every 28 days, whereas with HRT, the estrogen is continuous. The estrogens are different and although both act via estrogen receptors may have different tissue effects, although there is little published data on this. Ethinyloestradiol has a longer half-life than estradiol. We did not measure estradiol, oestrone or ethinyloestradiol levels and this should be considered in future trials to aid evaluation of whether the different effects are dose related or due to the inherent effects of the different estrogens. The COCP also contains double the dose of levonorgestrel taken for 21/28 days vs 12/28 days with sequential HRT. It has been suggested that at higher doses as well as having a direct stimulatory effect on osteoblasts (the cells which make bone) through both the progesterone and androgen receptors, levonorgestrel may bind to glucocorticoid receptors and inhibit osteoblasts (24). A study on ovariectomized rats investigating the effect of continuous vs cyclical progesterone with estrogen replacement on bone density showed that continuous progesterone was less beneficial than cyclical, with down-regulation of bone estrogen and progesterone receptors cited as a possible mechanism (25). However, this effect is not seen in older women taking continuous combined HRT.

The other explanation is that this is a chance finding and it certainly needs to be confirmed with a larger study, but we did see a significant difference at the lumbar spine from 12 months, when there was minimal drop-out. Trials in older recently postmenopausal women have also found an increase in bone density after estrogen treatment (26) and it is recognized that the first 3–4 years after menopause give the highest response to treatment due to a reversal of bone resorption and rapid regain of bone density (27). The lack of a difference between COCP and HRT groups at the hip and in the bone markers is not surprising given the small numbers in the trial. The spine is more sensitive to estrogen, and also changes more quickly in

response to treatment than the hip (28). The lack of a significant difference between the treatment groups in the bone markers is likely to be due to the high variability of these markers, meaning that a larger sample size is required to find a significant difference.

There are few other trials in this area, but those which have been completed include mainly women with iatrogenic POF and Turner syndrome (14, 29). These conditions may have inherent effects on bone density which are separate to ovarian function and it is important to consider women with spontaneous POF as a separate population. Previous studies have also been much shorter. The only other prospective trial comparing HRT and COCP on bone density in POF included mainly women with Turner's syndrome or iatrogenic POF (14). Markers of bone formation were in favor of HRT, but there were no differences in bone breakdown markers or bone density. This trial was shorter than ours and had a higher drop-out rate of almost 50%.

Currently, either HRT or the COCP are offered as estrogen treatment options to women with POF. Our small study suggests that HRT has a more favorable effect on lumbar spine bone density than COCP. It is recommended that women with POF take estrogen treatment until at least the average age of menopause (51–52) to prevent bone loss, reduce cardiovascular risk and alleviate symptoms (1, 22). The clinical importance of loss of bone density is that it is related to fracture risk (30). An increased fracture risk has been demonstrated in women with early menopause (6, 7) and therefore the question of the optimal regime to prevent bone loss in these young women who will be taking estrogen replacement for many years is an important one. However, due to the limitations of the trial as described above, the findings need to be confirmed with a larger study. There are also a significant proportion of women who will not accept hormonal treatment, especially when first seen in clinic. It is clear from this trial that choosing to take no treatment has a poor effect on bone health and that it is preferable to take either form of estrogen treatment than nothing at all. This confirms current opinion and recommendations. We do not feel that this part of the study needs to be repeated in future trials. However, regarding the question of taking HRT or the COCP in POF, it is not possible to base treatment decisions or guidelines on a single small trial with the limitations outlined above. A larger, longer multicenter trial needs to be undertaken to confirm or refute our findings of a superiority of HRT compared with COCP on lumbar spine bone density in spontaneous POF. Our study could be used to guide future research, in particular taking into consideration the difficulties of recruitment and retention in this population.

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