

Physiological versus synthetic oestrogen therapy and bone mineral density in premature ovarian insufficiency

Aim:

To compare the effects of the physiological versus synthetic oestrogen therapy on bone mineral density in 46XX women with primary or secondary POI.

Introduction

Premature ovarian insufficiency (POI) affects approximately 1% of females [1]. POI is a loss of ovarian function before the age of 40, resulting in raised LH and FSH, low oestradiol levels and amenorrhea. Women with POI suffer symptoms including hot flushes, night sweats and sleep disturbances. In addition, long term consequences of POI include a reduction in bone mineral density, leading to an increased risk of osteoporosis.

In POI, hormone replacement manages symptoms and reduces the risk of bone mineral density (BMD) loss. Oestrogen acts to enhance bone deposition in bone remodelling [2]. Oestrogen may be given either as synthetic oestrogen (ethinylestradiol) as in most combined oral contraceptives (COCP), or as physiological oestrogen (oestradiol) as in hormone replacement therapy (HRT preparations) and a select few COCPs. In clinical practice patients are prescribed either the COCP or HRT; it is still unclear which of these provides optimal treatment.

There is limited evidence comparing physiological vs synthetic oestrogen use in patients with POI. We investigated the BMD in females with primary and secondary POI who were taking either physiological (HRT & COCPs containing physiological oestrogen) or synthetic oestrogen therapy (COCP).

Methods

Participants

66 patients with a diagnosis of POI established under the age of 40 and a 46XX karyotype were identified under the gynaecological services at Addenbrooke's hospital. POI was diagnosed based on clinical amenorrhoea, raised LH and FSH levels and low oestradiol. 28 women were excluded due to lack of BMD data. 8 women received alternating treatment with COCP and HRT prior to BMD measurements, hence were excluded. The 30 remaining women were included in the study.

Data extraction

30 females (46XX karyotype) received oestradiol ($n=15$) or ethinylestradiol ($n=15$). Patient data, evidence of POI diagnosis and hormone replacement therapy were obtained from clinic letters, patient correspondence and patient notes. Spine and hip BMD Z scores were obtained from DEXA scans. Z scores were chosen instead of T scores to control for age differences between groups. Mean duration of therapy was 4.7 years for ethinylestradiol and 4.0 years for oestradiol.

Statistical analysis

Two – tailed student t - tests assuming equal variances were used to establish whether differences in Z scores between women treated with oestradiol versus ethinylestradiol were statistically significant.

Results

Mean BMD at the lumbar spine was significantly greater with oestradiol (Z score -0.5 ± 0.7) than with ethinylestradiol therapy (Z score -1.5 ± 0.5 , $p < 0.05$, $p = 0.03$). No significant difference was found in the BMD at the hip ($p > 0.05$).

Discussion

Analysis

The findings of this study suggest that physiological oestrogens may be better for lumbar spine density in primary or secondary POI when compared to synthetic oestrogens. This may help to guide the joint decision-making process between patients and clinicians when opting for physiological or synthetic oestrogen replacement. Interestingly, the spine density at the hip does not seem to be affected. This has been postulated by previous authors to be due to differences in bone content and turnover [3].

Limitations of the study

Limitations of this study include a small patient cohort, in addition to differences in the aetiology of POI in women between groups. Patient compliance and other confounding factors, including the use of calcium and vitamin D supplements, were difficult to assess from patient records and may have influenced results.

Areas for further research

There is a need for research regarding the optimal dose of oestrogen and progesterone replacement; route of administration; type of regime (intermittent, continuous or cyclical) and type of progesterone replacement for bone mineral density outcomes in patients with POI.

Our study did not include patients with Turner's syndrome (45X0). This patient group requires separate consideration due to differences in disease course and outcomes.

Conclusion

These findings suggest that physiological oestrogen may have additional beneficial effects for lumbar spine density when compared to synthetic oestrogen replacement. This may have implications when advising patients with POI on their hormone replacement.

Further research, involving larger patient cohorts and randomised control trials, is required to provide a better understanding of the implications of different hormone replacement therapies in the management of POI.

References

- [1] L. Webber et al. Hum. Reprod. Adv. Access Publ. March. 31 (2016) 928.
- [2] G.E. Krassas, P. Papadopoulou. J Musculoskel Neuron Interact. 2 (2001) 143–151.
- [3] B. Cartwright et al. J. Clin. Endocrinol. Metab. 101 (2016) 3497–3505.

BOX PLOT DEMONSTRATING LUMBAR SPINE Z SCORES OF WOMEN WITH POI: OESTRADIOL VS ETHINYLESTRADIOL

