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Hormone Therapy in women with premature ovarian insufficiency: a systematic review and meta-analysis

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Hormone Therapy in women with premature ovarian insufficiency: a systematic review and meta-analysis

Dissertação apresentada ao Programa de Pós-Graduação em Saúde da Mulher da Universidade Federal de Minas Gerais como requisito para obtenção do título de Mestre

Orientador: Prof. Dr. Fernando M. Reis

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A Comissão considerou a dissertação:

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RESUMO

Esta revisão sistemática e meta-análise buscou avaliar os efeitos de diferentes terapias hormonais (HT) sobre os resultados clínicos em mulheres com insuficiência ovariana prematura (POI). Foram incluídos 31 estudos, totalizando 4.142 participantes com POI de diversas etiologias, dos quais 2.619 receberam HT e 201 receberam suplementação de cálcio, vitamina D, placebo ou nenhum tratamento. HT foi superior ao não tratamento, placebo, calcitriol ou cálcio para preservar a densidade mineral óssea (DMO) em mulheres com POI. A TH foi associada a uma redução de até 80% na prevalência de fogachos e à estabilidade ou melhora nos escores de qualidade de vida. HT induziu aumentos significativos no volume uterino e espessura endometrial em mulheres com POI. No geral, os estudos tiveram boa qualidade, embora alguns não tivessem cegamento dos participantes e do pessoal ou tivessem dados de resultados incompletos. Encontramos evidências de qualidade moderada a alta de que a TH com estrogênio e progesterona ou progesterona é benéfica para mulheres com POI, não apenas para mitigar os sintomas da menopausa, mas também para preservar a DMO e evitar a atrofia uterina. Mais estudos são necessários para assegurar a segurança em longo prazo dessa terapia e para avaliar seu possível impacto sobre o risco de outros desfechos clínicos, como fraturas ósseas e eventos cardiovasculares.

Palavras-chave: insuficiência ovariana prematura; terapia hormonal; estrogênio; progesterona; densidade mineral óssea; meta-análise.

ABSTRACT

The aim of this systematic review and meta-analysis was to evaluate the effects of different hormone therapies (HT) on clinical outcomes in women with premature ovarian insufficiency (POI). We included 31 studies totalizing 4142 participants with POI from diverse etiologies, of whom 2619 received HT and 201 received calcium supplementation, vitamin D, placebo, or no treatment. HT was superior to non-treatment, placebo, calcitriol or calcium to preserve bone mineral density (BMD) in women with POI. HT was associated with up to 80% reduction in the prevalence of hot flushes and with stability or improvement in the quality of life scores. HT induced significant increases in uterine volume and endometrial thickness in women with POI. Overall, the studies had good quality, although some lacked blinding of participants and personnel or had incomplete outcome data. We found moderate to high quality evidence that HT with estrogen and progesterone or progestin is beneficial to women with POI, not only to mitigate menopausal symptoms but also to preserve BMD and avoid uterine atrophy. More studies are needed to reassure the long-term safety of this therapy and to assess its possible impact on the risk of hard outcomes such as bone fractures and cardiovascular events.

Keywords: premature ovarian insufficiency; hormone therapy; estrogen; progesterone; bone mineral density; meta-analysis.

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LISTA DE ABREVIATURAS E SIGLAS

AHRQ:	Agency for Health Research and Quality
BMD:	Bone Mineral Density
CI:	Confidence Interval
CNPq	National Council of Scientific and Technological Development
COC:	Combined oral contraceptives
DH-DATA:	Health Administration, Medical Toxicology & Environmental Health
ESHRE:	European Society of Human Reproduction and Embryology
FSH:	Follicle-Stimulating Hormone
GH:	Growth Hormone
GRADE:	Grading of Recommendations, Assessment, Development and Evaluation
HDL:	High Density Lipoprotein
HT:	Hormone Therapy
INCT Hormona:	National Institute of Science and Technology in Hormones and Women's Health
LDL:	Low Density Lipoprotein
MEDLINE:	Medical Literature Analysis and Retrieval System Online
NIH:	National Institutes of Health
PICOS:	Problem, Intervention, Comparison, Outcome, Study Design.
POI:	Premature ovarian insufficiency
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta Analyses
PROSPERO:	International Prospective Register of Systematic Reviews
RCTs:	Randomized Controlled Trials
RevMan:	Review Manager

SUMÁRIO

1. Introduction

Premature ovarian insufficiency (POI) is an important medical issue concerning women of reproductive age. POI is a clinical syndrome defined by loss of ovarian activity before the age of 40 years. Along the years, several terms have been used to denominate this condition, such as “primary ovarian insufficiency”, “premature menopause” and “premature ovarian failure”, but the latest guideline of the European Society of Human Reproduction and Embryology (ESHRE) adopted “premature ovarian insufficiency” as standard nomenclature (Webber et al., 2016). The diagnostic criteria are not fully standardized, but they do not differ that much. ESHRE recommends the following diagnostic criteria: oligo/amenorrhea for at least four months, and an elevated FSH level > 25 IU/l on two occasions with at least four weeks apart (Webber et al., 2016). Ovarian insufficiency is caused by several different mechanisms, but in most of spontaneous POI cases (90%) no cause can be found. There may be reduced peak follicle number, increased atresia of follicles through apoptosis, or failure of follicle maturation (Panay et al., 2020; La Marca and Mastellari, 2021).

The prevalence of POI varies among ethnic groups across the world, and studies show a prevalence that ranges from 1% (Coulam et al., 1986) up to 5.5% (Group, 2003; Luborsky et al., 2003; Jungari and Chauhan, 2017; Mishra et al., 2017). If not timely treated, women living with POI face the short and long-term consequences of prolonged hypoestrogenism. They can develop symptoms such as lack of libido, vaginal dryness, humor disorders, rise in cardiovascular risk, and cognitive impairment (Panay et al., 2020). Decreased mineral density promotes osteopenia and osteoporosis, as well as bone fractures. The health provider should be aware of POI signs and symptoms in order to promote prompt diagnosis (Lambrinoudaki et al., 2021). The time from onset of symptoms until the diagnosis has been evaluated in just a few studies, a structured interview survey conducted in the National Institutes of Health (NIH) Clinical Center between September 2000 and June 2001 found that the median time from the onset of disordered menses until the diagnosis of premature ovarian failure was established was two years. In a quarter of the women, it was more than five years after the onset of a disordered menstrual pattern before the diagnosis of premature ovarian failure was established (Alzubaidi et al., 2002). A small case

series published by Bhat in 2019 showed that the mean time to diagnose POI from the onset of symptoms was six years (Bhatt et al., 2019).

The therapeutic approach for POI patients relies mainly on hormone therapy (HT), which is largely available. The targets for HT include improving of cardiovascular, urogenital, bone and mental health as well as quality of life. However, most hormonal formulations, regimens and dosages prescribed to women with POI are based on studies with older women experiencing natural menopause, while much less is known about the effects of different types of HT in the specific population with POI, mainly when it comes to long term results.

Therefore, this systematic review aims at evaluating the available evidence about the effects of different hormone therapies on clinical outcomes in women with POI.

2. Methods

2.1 Review registration and literature search

This review followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42018115998), available in the page 38.

A systematic search in ProQuest, Allied & Complementary Medicine™, DH-DATA: Health Administration, Medical Toxicology & Environmental Health, PubMed, Embase®, MEDLINE® was performed from the earliest available date to May 31, 2021. The search terms used were: (Menopause hormone therapy) OR (hormone replacement therapy) OR (Estrogen Replacement Therapy) OR (oral contraceptive/exp) AND (ovarian insufficiency) OR (ovarian failure) OR (premature ovarian failure) OR (primary ovarian Insufficiency) OR (menopause, premature). Search results were imported and managed via EndNote X8 (Thomson Reuters, New York, USA).

2.2 Study selection and data extraction

Studies were included if they met the following PICOS criteria. Patients: women aged 13-40 years diagnosed with POI; Intervention: any kind of estrogen, progestogen or androgen therapy, or tibolone; Comparison: placebo, non-hormonal treatments, no treatment; Outcomes: bone mineral density (BMD),

incidence of bone fractures, vasomotor symptoms (hot flushes), quality of life, cardiovascular disease, cardiovascular events, lipid levels, uterine morphology/blood flow, body growth, adverse effects; Study design: randomized controlled trials (RCTs) or cohort studies.

The following exclusion criteria were used: case-control studies, cross-sectional studies, animal studies, basic experiments, literature reviews, meta-analyses, editorials, commentaries, opinion pieces, study protocols, or case reports. Duplicates were removed electronically and then manually.

Two investigators independently extracted data using a standard data collection form and any discrepancies were evaluated and discussed by a third author. The data extracted from each study included study design, year of publication, country, setting, age range of participants, criteria used to diagnose POI, etiology of POI, number of POI cases, number of non-POI controls, drug, dose and regimen used in HT, comparator, duration of intervention (months), follow-up (months), number of participants lost to follow-up, study completion rate, and main findings.

2.3 Evaluation of the methodological quality of the included studies

Two reviewers evaluated separately the quality of the included randomized clinical trials according to Cochrane Risk of Bias Tool for seven domains, as follows: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. The studies were judged as having low, unclear, or high risk of bias (Higgins and Green, 2011). Cohort studies were evaluated using the Newcastle-Ottawa scale (Wells et al., 2000) converted to Agency for Health Research and Quality (AHRQ) standards into three categories: low, medium or high quality (Modesti et al., 2016).

2.4 Grading the quality of evidence

The quality of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al., 2011). For each outcome, the quality of evidence was initially classified as high (mostly based on RCTs) or moderate (based on cohort studies). Two researchers then assessed downgrading factors such as serious study limitations, inconsistency of findings between studies, indirectness of outcome measures, imprecision of the results, and publication bias, and upgrading factors such as large effect and dose-dependent response. Finally, the quality of evidence was graded as high, moderate, low, or very low (Guyatt et al., 2011).

2.5 Meta-Analysis

The only outcome with sufficient quantitative data to be meta-analyzed was the variation in BMD of the lumbar spine. Data were extracted as g/cm^2 and the changes observed after the treatments were converted to percentage of baseline levels and adjusted for the duration of treatment (Table 1).

The meta-analysis was conducted using the free software Review Manager (RevMan) version 5.4 (Collaboration, 2020). Random effects model was used to compute the pooled group differences because we decided not to assume that all studies would share a common effect size and direction (Higgins and Green, 2011). Heterogeneity between studies was evaluated using the chi-square-based Q test and I^2 metric. The heterogeneity was considered statistically significant if $P < 0.10$ and $I^2 > 50\%$. The influence of a single study on the overall pooled estimate was evaluated by excluding one trial in each turn. Funnel plots were not used to assess the risk of publication bias because the number of included studies was not sufficient (Higgins and Green, 2011).

Table 1: Source data of bone mineral density (BMD) and calculations performed to obtain the ΔBMD (%/year) when it was not reported.

Study	Treatment	N	BMD basal (g/cm^2)	BMD final (g/cm^2)	ΔBMD (g/cm^2)	ΔBMD (% of basal)	Years of follow-up	ΔBMD (%/year)
Cartwright, 2016	Estradiol 2mg oral cont + LNG 75µg 12d/mo	12	0.990 ± 0.040	1.040 ± 0.050	0.050 ± 0.000	5.051 ± 0.204	2	2.525 ± 0.204
	COC (EE 30µg + LNG 150µg 21d/mo)	9	1.000 ± 0.060	1.000 ± 0.060	0.000 ± 0.000	0.000 ± 0.000	2	0.000 ± 0.000
	All hormone treatments (merged)	21	0.994 ± 0.048	1.023 ± 0.057	0.029 ± 0.000	2.876 ± 0.140	2	1.438 ± 0.140
	No treatment	15	1.030 ± 0.030	1.000 ± 0.030	-0.030 ± 0.000	-2.913 ± 0.085	2	-1.456 ± 0.085
Crofton, 2010	Estradiol 100-150µg cont + progesterone 200mg BID cyclic	18	0.933 ± 0.102[a]	missing	0.019 ± 0.026[b]	2.036 ± 2.786	1	2.036 ± 2.786
	COC (EE 30µg + LNG 150µg 21d/mo)	18	0.933 ± 0.102[a]	missing	0.010 ± 0.029 [b]	1.072 ± 2.037	1	1.072 ± 2.037
Gazarra, 2020	COC (EE 30µg + LNG 150µg cont)	45	0.890 ± 0.110	missing	0.018 ± 0.056	2.022 ± 6.292	2	1.011 ± 6.292
	CEE 0.625mg + MPA or estradiol 1mg cont + NET	92	0.960 ± 0.150	missing	-0.021 ± 0.093	-2.188 ± 9.688	2	-1.094 ± 9.688
	CEE 1.25mg + MPA or estradiol 2mg cont + NET	45	0.930 ± 0.110	missing	0.012 ± 0.093	1.290 ± 10.000	2	0.645 ± 10.000
	Both doses of menopausal HT (merged)	137	0.950 ± 0.138	missing	-0.010 ± 0.094	-1.053 ± 9.895	2	-0.526 ± 9.895
	All hormone treatments (merged)	182	0.935 ± 0.134	missing	-0.003 ± 0.087	-0.321 ± 9.294	2	-0.160 ± 9.294
	No treatment	20	0.950 ± 0.110	missing	-0.034 ± 0.055	-3.579 ± 5.789	2	-1.789 ± 5.789
Kung, 1999	CEE 0.625mg 21d/mo + MPA 5mg 12d/mo	13	0.910 ± 0.080	missing	missing	2.000 ± 0.100	2	1.000 ± 0.100
	Calcitriol	15	0.880 ± 0.120	missing	missing	-1.740 ± 0.400	2	-0.870 ± 0.400
Lyritis, 1995	Tibolone 2.5mg cont + elementary calcium 1g/d	15	missing	missing	missing	-0.500 ± 0.050[c]	1	-0.500 ± 0.050
	Elementary calcium 1g/d	10	missing	missing	missing	-15.200 ± 3.200[c]	1	-15.200 ± 3.200
Popat, 2014	Estradiol 100µg cont + MPA 10mg 12d/mo + T	18	0.960 ± 0.150	missing	missing	6.300 ± 5.515[d]	3	2.100 ± 5.515
	Estradiol 100µg cont + MPA 10mg 12d/mo + placebo	22	0.940 ± 0.120	1.020 ± 0.110	0.080 ± 0.027	7.700 ± 5.159[d]	3	2.567 ± 5.159
Shea, 2015	Estradiol 75µg cont	35	missing	missing	missing	-0.600 ± 0.300	0.5	-1.200 ± 0.300
	Placebo	35	missing	missing	missing	-3.000 ± 0.500	0.5	-6.000 ± 0.500
Zuckerman-Levin, 2009	COC (EE 20µg + Gestodene 75µg) + oral 1.5 mg/d methyl-T	14	1.040 ± 0.100	missing	0.024 ± 0.030	2.308 ± 2.885	1	2.308 ± 2.885
	COC (EE 20µg + Gestodene 75µg) + placebo	14	1.060 ± 0.130	missing	0.017 ± 0.070	1.604 ± 6.604	1	1.604 ± 6.604

Data are expressed as mean ± SD.

[a]Merged from subgroups of Table 2 of the original article.

[b]Calculated from the 95% confidence intervals of Table 4 of the original article.

[c]Measured in the distal radius. Lumbar spine BMD was not available.

[d]Calculated from the standard errors of Figure 3 of the original article.

Abbreviations: cont, continuous regimen; LNG, levonorgestrel; d, day; mo, month; CEE, conjugated equine estrogens; EE, ethinyl estradiol; BID, twice daily; COC, combined oral contraceptive; NET, norethisterone; MPA, medroxyprogesterone acetate; HT, hormone therapy; T, testosterone.

3. Results

3.1 Literature Search Results

We identified 1602 records through electronic database search. After removing 411 duplicates, we screened 1191 records and excluded 1069, leaving 122 reports sought for retrieval. After reading titles and abstracts, 62 reports were retrieved and assessed in full text for eligibility. In this phase we excluded 31 reports for several reasons and remained with 31 studies included in the review (Figure 1). The included studies comprised 15 RCTs (Li et al., 1992; Lyritis et al., 1995; Kung et al., 1999; Fatemi et al., 2007; Langrish et al., 2009; Zuckerman-Levin et al., 2009; Crofton et al., 2010; Ross et al., 2011b; O'Donnell et al., 2012; Guerrieri et al., 2014; Popat et al., 2014; Shah et al., 2014; Shea et al., 2015; Cartwright et al., 2016; Kraus et al., 2018a) and 16 cohort studies (Emans et al., 1990; Achiron et al., 1995; Biljan et al., 1995; Castelo-Branco et al., 1996; Hartmann et al., 1997; Gökmen and Yapar Eyi, 1999; Khastgir et al., 2003; Kalantaridou et al., 2004; Chatterjee et al., 2011; Naessén et al., 2014; Benetti-Pinto et al., 2015; Nakamura et al., 2015; Kim et al., 2016; Vermeulen et al., 2017; Yang et al., 2017; Gazarra et al., 2020).

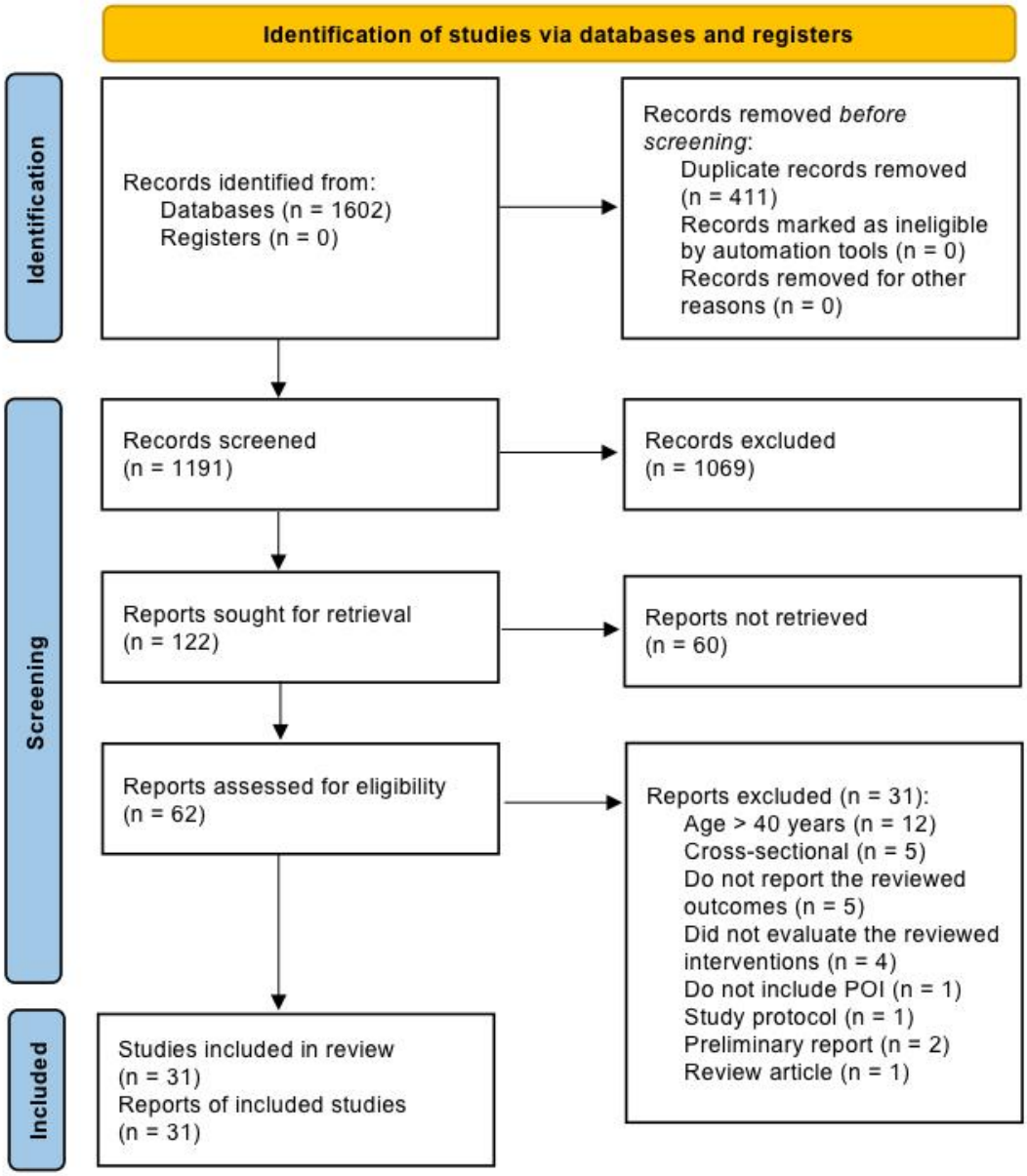


Figure 2 - Study flow chart.

3.2 Characteristics of Participants

The 31 studies included totalized 4142 participants with POI (median 34, range 6 to 2184 participants per study), of whom 2619 received HT and 201 received calcium supplementation, vitamin D, placebo, or no treatment (Table 2). The mean age of participants at the time of enrolment varied according to the predominant etiology of POI, being typically younger in studies of patients with Turner Syndrome (Khastgir et al., 2003; Zuckerman-Levin et al., 2009; Ross et

al., 2011b; Nakamura et al., 2015; Kraus et al., 2018b) than in patients with bilateral oophorectomy (Lyritis et al., 1995; Gökmen and Yapar Eyi, 1999; Vermeulen et al., 2017).

Most participants were selected and followed in hospitals, and the geographical distribution included North and South America, Europe and Asia (Table 2).

3.4 Interventions

Estrogen types included conjugated equine estrogens, estradiol valerate and ethinyl estradiol by oral route, and 17β estradiol by transdermal route, either continuous or 21 days per month. Ethinyl estradiol was used only in combined oral contraceptives (COC). Progestins were administered in cyclic regimens during 10 to 21 days per month, while tibolone was used continuously (Table 2).

3.5 Outcomes

The selected studies evaluated most of the outcomes pre-specified in the review protocol (Table 2). However, there were two exceptions, as our literature search did not return any RCT or cohort study evaluating the effects of HT on the incidence of bone fractures or cardiovascular events (myocardial infarction, thromboembolism, stroke) in women with POI (Table 3).

Table 2: Summary of the studies included in the systematic review

Study	Design	Cases	Etiology	Place	Setting	Treatment	No. Treated	Control / Comparator	No. Controls	Intervention (months)	Follow-up (months)	Lost to follow-up	Outcomes
Achiron 1995	Cohort	18	Not specified	Israel	Hospital	Oral estradiol valerate, variable doses + vaginal progesterone 100mg/d for 6 days.	18	Baseline measures	18	1	1	0	Resistance index in endometrial blood flow measured by transvaginal color doppler
Benetti-Pinto 2015	Cohort	72	Not specified	Brazil	Hospital	CEE + MPA, 17β-estradiol + norethisterone, or EE + levonorgestrel	72	Baseline measures	72	>24	24 to 96	0 (24 months); 54 (96 months)	BMD
Biljan 1995	Cohort	16	Turner syndrome, ovarian surgery, idiopathic	England, UK	Hospital	Estradiol valerate 2 mg 30d/month oral + norgesterel 500µg 10d/month oral	16	Baseline measures	16	0.5	0.5	0	Pulsatility index of the uterine arteries
Cartwright 2016	RCT	59	Spontaneous	England, UK	Hospital	Estradiol 2mg 30d/month oral + levonorgestrel 75µg 12d/month oral, or EE 30µg + levonorgestrel 150µg 21d/month oral	30	No treatment	29	24	24	23	BMD, bone turnover markers
Castelo-Branco 1996	Cohort	13	Bone marrow transplantation	Spain	Hospital	CEE 0.625mg or 17β-estradiol 50µg + MPA 5mg 12d/month	13	Baseline measures	13	12	12	0	BMD, liver enzymes
Chatterjee 2011	Cohort	375	Not specified	England, UK	Hospital	CEE 0.625mg 30d/month oral + norgestrel 0.15mg 12d/month oral (Prempack C®)	375	Baseline measures	375	>12	60	Unknown	BMD, bone turnover markers
Crofton 2010	RCT crossover	34	Turner syndrome, chemotherapy, radiation therapy, oophorectomy, idiopathic	Scotland, UK	Hospital	EE 30µg 21d/month oral + norethisterone 1.5mg/21d/month oral	34	Estradiol 100µg 7d/month transdermal + estradiol 150µg 21d/month transdermal + progesterone 400mg 14d/month vaginal	34	12	12	16	BMD, bone turnover markers

Emans 1990	Cohort	28	Turner syndrome, radiation therapy, idiopathic	USA	Hospital	CEE 0.625mg 21d/month + MPA 10mg/12d/month oral	21	No treatment	7	24	24	0	BMD
Fatemi 2007	RCT crossover	6	Not specified	Belgium	Hospital	Estradiol Valerate 4-6mg/26d/month + Dydrogesterone 20mg oral 12d/month	6	Estradiol Valerate 4-6mg/26d/month + progesterone 200mg vaginal 12d/month	6	1	1	0	Endometrial histology
Gazarra 2020	Cohort	210	Not specified	Brazil	Hospital	EE 30µg + levonorgestrel, continuously, or CEE 0.625-1.25mg + oral progestin, or tibolone 2.5mg daily	190	No treatment	20	24	24	0	BMD
Gökmen 1999	Cohort	2184	Bilateral oophorectomy	Turkey	Hospital	CEE 0.625mg/30d/month oral	1102	Transdermal estradiol	1082	12-84	84	0	Lipid–lipoprotein concentrations
Guerrieri 2014	RCT	128	Spontaneous	USA	Hospital	Estradiol 100µg /28d/month Transdermal + MPA 10mg/12d/month oral + Testosterone 150µg 28d/month transdermal	67	Estradiol 100mcg/28d/month Transdermal + MPA 10mg/12d/month oral + Placebo	61	12	12	5	Quality of life, self-esteem, mood
Hartmann 1997	Cohort	24	Idiopathic	Austria	Hospital	Estradiol Valerate 2mg + progesterone 400mg 10d/month	24	Baseline measures	24	12	12	0	Plasma GH and IGF1 levels post-GnRH injection
Kalantaridou 2004	Cohort	18	Not specified	Greece	Hospital	CEE 0.625mg/30d/month oral + MPA 5mg cyclically	18	Baseline measures	18	6	6	0	Endothelial function, lipids
Khastgir 2003	Cohort	21	Turner syndrome	England, UK	Hospital	Estradiol 50mg subcutaneous implant + MPA 5mg 10d/month oral	21	Baseline measures	21	36	36	0	BMD
Kim 2016	Cohort	25	Turner syndrome, chemotherapy	Korea	Medical Center	Estradiol valerate 0.5-2mg + MPA 10mg/12d/month oral	25	Baseline measures	25	24	24	0	Ultrasonographic uterine changes
Kraus 2018	RCT	11	Turner syndrome	Chile	Hospital	17β Estradiol 0.5mg/21d/month (titration to 1, 1.5, 2mg accordingly to serum estradiol levels) oral + MPA 10mg/7d/month oral	7	Transdermal estradiol	4	12	12	0	Ultrasonographic uterine changes

Kung 1999	RCT	28	Systemic lupus erythematosus	China	Hospital	CEE 0.625mg/21d/month oral + MPA 5mg/12d/month oral + calcium carbonate 1g/30d/month oral	13	Calcitriol + calcium	15	24	24	0	Prevention of bone loss, systemic lupus erythematosus disease activity
Langrish 2009	RCT crossover	34	Turner syndrome, chemotherapy, radiation therapy, oophorectomy, idiopathic	Scotland, UK	Hospital	EE 30µg 21d/month oral + norethisterone 1.5mg/21d/month oral	34	Estradiol 100µg 7d/month transdermal + estradiol 150µg 21d/month transdermal + progesterone 400mg 14d/month vaginal	34	12	24	12	Cardiovascular health: blood pressure, serum angiotensin levels, plasma creatinine levels
Li 1992	RCT crossover	21	Turner syndrome, chemotherapy, radiation therapy, idiopathic	England, UK	Hospital	Estradiol valerate 1, 2 or 4 mg 21d/month oral + norgestrel	21	Estradiol valerate at variable doses	21	1	2	0	Endometrial thickness, endometrial morphometry and mitoses
Lyritis 1995	RCT	25	Oophorectomy	Greece	Hospital	Tibolone 2.5mg cont	15	Calcium	10	12	12	0	Prevention of bone loss
Naessén 2014	Cohort	52	Chemotherapy	Sweden	Community	Combined oral contraceptive	51	Baseline measures	51	108-156	108-156	3	BMD, reproductive function, serum PTH and calcium levels
Nakamura 2015	Cohort	100	Turner Syndrome	Japan	Hospital	CEE 0.625mg/21d/month oral + MPA 5mg/10d/month	72	No treatment	16	60-384	60-384	0	Uterine growth, BMD
Odonnell 2012	RCT crossover	34	Turner syndrome, chemotherapy, radiation therapy, oophorectomy, idiopathic	Scotland, UK	Hospital	EE 30µg 21d/month oral + norethisterone 1.5mg/21d/month oral	34	Estradiol 100µg 7d/month transdermal + estradiol 150µg 21d/month transdermal + progesterone 200mg 2xd 14d/month vaginal	34	12	12	4	uterine volume, endometrial thickness, blood flow
Popat 2014	RCT	145	Not specified	USA	Community	Estradiol 100µg 30d/month transdermal + MPA 10mg/12d/month	73	Estradiol 100µg 30d/month transdermal +	72	36	36	10	BMD

						oral + calcium + Testosterone patch 150µg 30d/month transdermal		MPA 10mg/12d/month oral + calcium + Placebo					
Ross 2011	RCT	149	Turner Syndrome	USA	Primary care	Oral estradiol	40	Placebo	39	132	132	2	Height
Shah 2014	RCT	20	Turner Syndrome, bone marrow transplantation	USA	Hospital	CEE 0.15mg/d increasing up to 0.625mg/d 26d/month oral + Micronized progesterone 200mg/10d/month	20	Baseline measures	20	24	24	3	Feminization, puberty, biochemical markers
Shea 2015	RCT	70	Leuprolide acetate for 20 weeks	USA	Hospital	Estradiol 75µg continuous	35	Placebo	35	5	5	9	Body composition (fat-free mass), BMD
Vermeulen 2017	Cohort	57	Risk-reducing salpingo-oophorectomy	The Nether-lands	Hospital	Tibolone or estrogen and progestin (oral, transdermal or topical)	27	No treatment	30	9	9	4	Vasomotor symptoms, sexual functioning
Yang 2017	Cohort	150	Chemotherapy	China	Hospital	Estradiol valerate 2 mg/day 21d/month + dydrogesterone 10mg or cyproterone acetate 1mg 10d/month	130	Baseline measures	130	24	24	17	Kupperman Menopausal Index, vasomotor symptoms
Zuckerman-Levin 2009	RCT crossover	15	Turner Syndrome	Israel	Hospital	EE 20mcg + gestodene 75µg 21d/month oral + Methyl Testosterone 1.5mg/30d/month oral	15	EE 20mcg + gestodene 75µg 21d/month oral	15	12	24	1	Body composition, BMD, lipids, neurocognitive evaluation, QOL

Abbreviations: BMD, bone mineral density; CEE, conjugated equine estrogens; EE, ethinyl estradiol; MPA, medroxyprogesterone acetate; RCT: randomized controlled trial.

Table 3: **Supplemental Table 2**: Quality the cohort studies included in the systematic review

Reference	A	B	C	D	E	F	G	H	Quality*
Achiron, 1995	✓	✓	✓	✓	✓	✓	✓	✓	Good
Benetti-Pinto, 2015	✓	✗	✓	✓	✓	✓	✓	✓	Good
Biljan, 1995	✓	✗	✓	✓	✓	✓	✓	✓	Good
Castelo-Branco, 1996	✓	✗	✓	✓	✓	✗	✓	✓	Good
Chatterjee, 2011	✓	✗	✓	✓	✓	✓	✓	✓	Good
Emans, 1990	✓	✓	✓	✓	✓	✗	✓	✓	Good
Gazarra, 2020	✓	✓	✓	✓	✓	✓	✓	✓	Good
Gökmen, 1999	✓	✗	✓	✓	✓	✓	✓	✓	Good
Hartmann, 1997	✓	✗	✓	✓	✓	✓	✓	✓	Good
Kalantaridou, 2004	✓	✗	✓	✓	✓	✓	✓	✓	Good
Khastgir, 2003	✓	✗	✓	✓	✓	✗	✓	✓	Good
Kim, 2016	✓	✗	✓	✓	✓	✓	✓	✓	Good
Naessén, 2014	✓	✗	✓	✓	✓	✓	✓	✓	Good
Nakamura, 2015	✓	✓	✓	✓	✓	✓	✓	✓	Good
Vermeulen, 2017	✓	✓	✓	✓	✓	✗	✓	✓	Good
Yang, 2017	✓	✗	✓	✓	✓	✗	✓	✓	Good

According to the Newcastle-Ottawa scale (Wells et al., 2000), with the following criteria:

A: Representativeness of the exposed cohort

B: Selection of the non-exposed cohort

C: Ascertainment of exposure

D: Demonstration that outcome of interest was not present at start of study

E: Comparability of cohorts on the basis of the design or analysis controlled for confounders

F: Assessment of outcome

G: Duration of follow-up

H: Adequacy of follow-up of cohorts

✓ : fulfills the criterion satisfactorily

✗: does not fulfill the criterion satisfactorily

* Converted to Agency for Health Research and Quality (AHRQ) standards (Modesti et al., 2016).

_____

3.6 Excluded studies

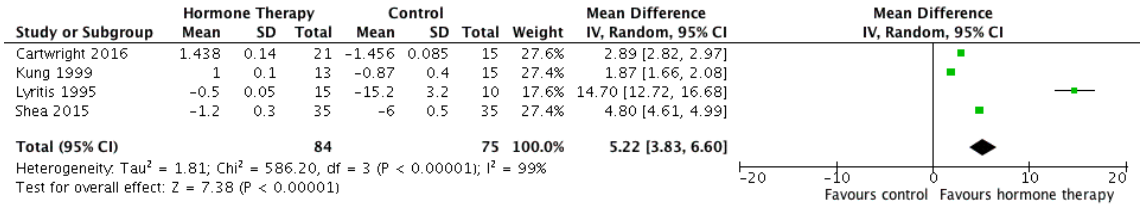
Most studies that were about normal menopause or did not evaluate the effects of HT were excluded at the screening phase. Among the articles excluded through full text reading there were 12 excluded because the study participants were older than 40 years at enrolment and 9 because the study interventions or outcomes were not compatible with the review entry criteria (Figure 1). We also excluded 5 studies that evaluated HT in women with POI but had a cross-sectional design (Kurabayashi et al., 1993; Madalinska et al., 2006; Bachelot et al., 2016; Giraldo et al., 2017; Benetti-Pinto et al., 2019).

3.7 Summary of Results

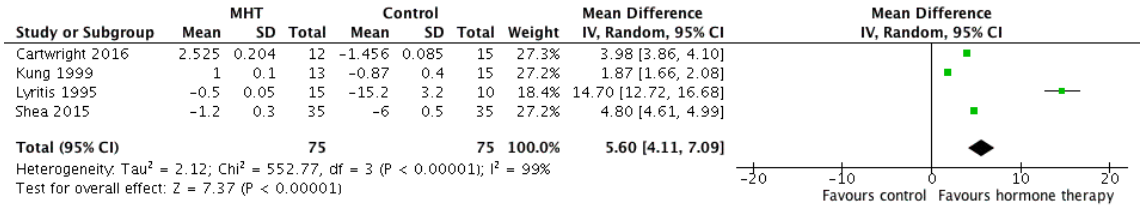
All studies have consistently shown that HT in different regimens increased or conserved BMD. Six studies (4 RCTs) showed that hormone therapies were superior to non-treatment, placebo, calcitriol or calcium to preserve BMD in women with POI. As shown in Figure 2A, meta-analysis of RCTs indicated that HT induced a greater gain in BMD compared to control (mean difference 5.22% BMD increase per year, 95% CI 3.83 – 6.60). When the analysis excluded COCs and considered only formulations labeled for menopausal HT (Figure 2B), the BMD gain remained greater in the HT group than in the control group (mean difference 5.60% BMD increase per year, 95% CI 4.11 – 7.09). The same size of HT benefit was seen adding a cohort study to the pooled data (Figure 2C). There was no significant difference between COC and menopausal HT as regards BMD gain (Figure 3A). Also, adding testosterone on the estrogen-progesterone regimen did not change BMD gain (Figure 3B). Sensitivity analysis with the exclusion of study by study showed no significant modifications in these results.

Figure 3 - Effects of hormone therapy on bone mineral density in women with POI.

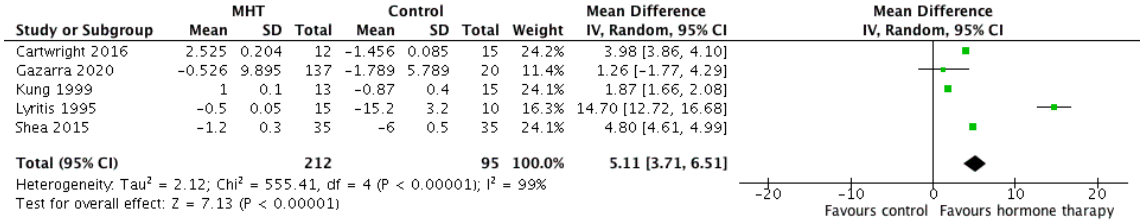
A



B



C



Data are shown as mean difference [95% confidence interval] between hormone therapy and control groups. Data were extracted as g/cm2 and the changes observed after the treatments were converted to percentage of baseline levels and adjusted for the duration of treatment.

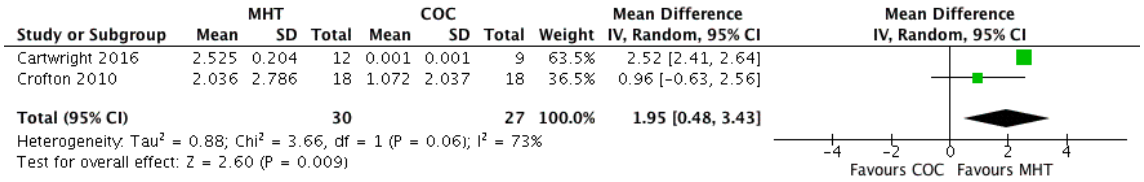
A) Only randomized controlled trials, all types of hormone therapy.

B) Only randomized controlled trials, excluding treatment with combined oral contraceptives.

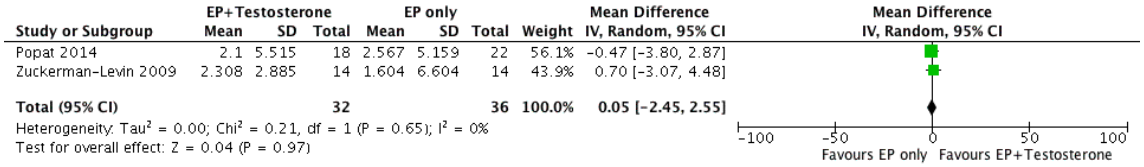
C) Including a cohort study.

Figure 4 -: Effects of different types of hormone therapy on bone mineral density in women with POI.

A



B



Data are shown as mean difference [95% confidence interval] between groups. Data were extracted as g/cm2 and the changes observed after the treatments were converted to percentage of baseline levels and adjusted for the duration of treatment.

A) Comparison between “menopausal” hormone therapies (MHT) and combined oral contraceptives (COC).

B) Comparison between estrogen and progestin (EP) plus testosterone and EP alone.

Vasomotor symptoms were measured in two cohort studies. HT was associated with up to 80% reduction in the prevalence of hot flushes (Vermeulen et al., 2017) and 50% reduction in Kupperman Menopausal Index (Yang et al., 2017). Two RCTs evaluated quality of life (Zuckerman-Levin et al., 2009; Guerrieri et al., 2014). Although designed to compare groups treated with and without testosterone, both studies showed that women treated with estrogen plus progestin had stability or improvement in the quality of life scores after 1 year.

Cardiovascular health was assessed in one small RCT whose endpoints were blood pressure, arterial stiffness, urea, creatinine, renin and angiotensin II (Langrish et al., 2009). In this study, HT with transdermal estradiol and vaginal progesterone resulted in lower blood pressure compared to ethinyl estradiol and norethisterone. Circulating lipids and lipoproteins were measured in one RCT (Zuckerman-Levin et al., 2009) and two cohort studies (Gökmen and Yapar Eyi, 1999; Kalantaridou et al., 2004). The largest cohort (Gökmen and Yapar Eyi, 1999) showed a reduction of total cholesterol and LDL and a rise in HDL levels during HT, compared to baseline. Triglycerides decreased with transdermal estradiol (with or without progesterone), whereas women using conjugated equine estrogens had a rise in plasma triglycerides.

HT induced significant increases in uterine volume and endometrial thickness in women with POI (O'Donnell et al., 2012; Kim et al., 2016; Kraus et al., 2018a). Uterine volume increased regardless of estrogen type or route. Endometrial blood flow increased during HT accompanying plasma estradiol levels (Achiron et al., 1995; Biljan et al., 1995; Fatemi et al., 2007).

In prepubertal girls with Turner’s Syndrome, the addition of estrogen to GH increased the adult height compared to GH alone (Ross et al., 2011a). In adolescent girls with hypogonadism, height increased similarly among different schemes of HT (Shah et al., 2014).

Adverse effects of HT were evaluated in three of the selected studies, totalizing only 62 participants. In these studies, HT was not associated with significant changes in liver enzymes (Castelo-Branco et al., 1996), endometrial mitoses (Li et al., 1992) or lupus erythematosus disease activity (Kung et al., 1999).

3.8 Risk of Bias

Among the included RCTs, there was no evidence of selection bias, although only half of the reports included details about the method of randomization (Figure 4). The most concerning risk was that of performance bias due to open-label rather than blind interventions. However, blinding of outcome assessment was often reported even in studies that opened the intervention to the participants (Kung et al., 1999; Fatemi et al., 2007; Langrish et al., 2009; Crofton et al., 2010), therefore the risk of detection bias was high in only two RCTs (Lyritis et al., 1995; Cartwright et al., 2016). Most included RCTs had no evidence of attrition or reporting biases (Figure 4 and Figure 5).

Figure 5 – Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

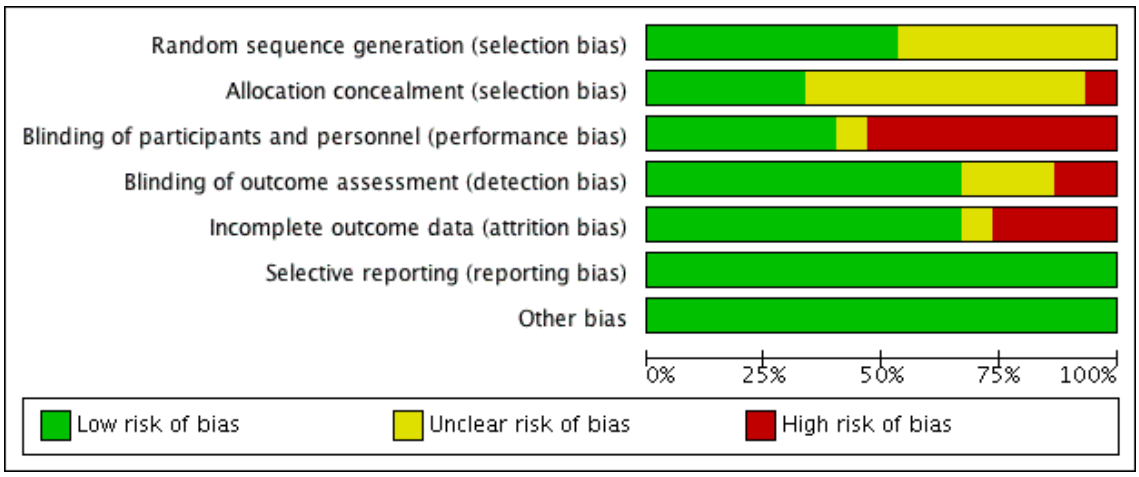
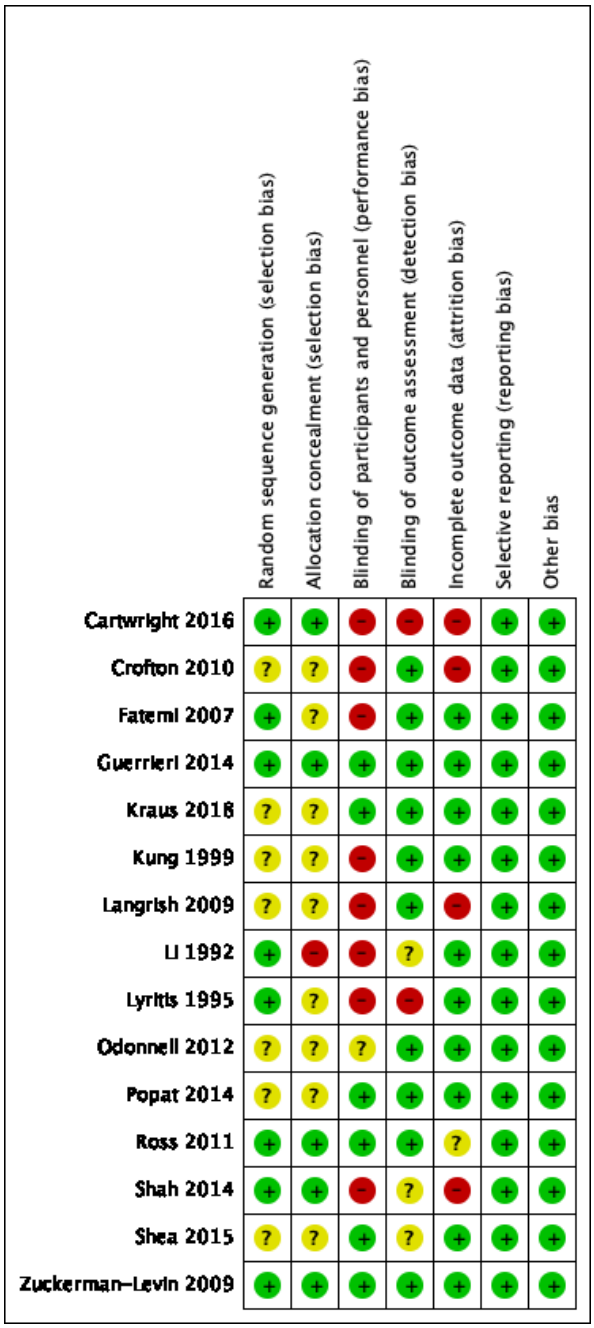


Figure 5: Risk of bias in included studies. +, low risk; ?, unclear risk; −, high risk.



The included cohort studies were all classified as having good quality after assessment of selection, comparability and outcome domains of the Newcastle-Ottawa scale (Table 3).

Table 4: GRADE synthesis of the evidence

Outcome	Studies and participants	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Findings	Quality of evidence
Bone mineral density	7 RCTs and 8 cohort studies, 1275 participants	Serious. Most RCTs had high risk of bias.	No concerns	No concerns	No concerns	No concerns	All studies have consistently shown that hormone therapy in different regimens increased or conserved BMD. Six studies (4 RCTs) showed that hormone therapies were superior to non-treatment, placebo, calcitriol or calcium to preserve BMD in women with POI. Two studies evaluated adding testosterone on the estrogen-progesterone regimen and there was no difference in BMD.	⊕⊕⊕◯ Moderate
Bone fractures	x	x	x	x	x	x	No studies have evaluated the incidence of bone fractures.	x
Vasomotor symptoms	2 cohort studies, 207 participants	No concerns	No concerns	No concerns	No concerns	No concerns	HT was associated with up to 80% reduction in the prevalence of hot flushes and 50% reduction in Kupperman Menopausal Index.	⊕⊕⊕◯ Moderate
Quality of life	2 RCTs, 143 participants	Serious. There were no studies comparing HT vs. no therapy or placebo. Both RCTs compared EP vs. EPT.	No concerns	No concerns	No concerns	No concerns	Both studies showed that women treated with EP therapy had stability or improvement in the quality of life scores after 1 year.	⊕⊕⊕◯ Moderate
Cardiovascular disease	1 RCT, 34 participants	Serious. The study was open-label and there was no control (untreated) group.	Does not apply	Serious. The outcomes were blood pressure, arterial stiffness, urea, creatinine, renin and angiotensin II.	No concerns	No concerns	HT with transdermal estradiol and vaginal progesterone resulted in lower blood pressure compared to ethinyl estradiol and norethisterone.	⊕⊕◯◯ Low
Cardiovascular events	x	x	x	x	x	x	No studies have evaluated the incidence of cardiovascular events.	x
Lipids	1 RCT and 2 cohort studies, 2217 participants	In the largest cohort study the follow-up extends beyond age 40, although the mean age at	No concerns	No concerns	No concerns	No concerns	A small RCT (n=14) compared HT regimens with and without testosterone. Total colesterol, HDL and triglycerides levels were unchanged in the EP only group and decreased in the EPT group. A cohort study (n= 2184) showed a reduction of total cholesterol and LDL and a	⊕⊕⊕⊕ High

		oophorectomy was 36 years.					rise in HDL with HT. Triglycerides decreased with transdermal estradiol (with or without progesterone). CEE groups had a rise in triglycerides.	
Uterine morphology and blood flow	3 RCTs and 3 cohort studies, 110 participants	The RCTs had no placebo or untreated groups	No concerns	No concerns	No concerns	No concerns	HT induced significant increases in uterine volume and endometrial thickness. Uterine volume increased regardless of estrogen type or route. Endometrial blood flow increased during HT accompanying plasma estradiol levels.	⊕⊕⊕◯ Moderate
Body Growth	2 RCTs, 169 participants	No concerns	No concerns	No concerns	No concerns	No concerns	In prepubertal girls with Turner's Syndrome, the addition of estrogen to GH increased the adult height compared to GH alone. In adolescent girls with hypogonadism, height increased similarly among different schemes of HT.	⊕⊕⊕⊕ High
Adverse Effects	2 RCTs and 1 cohort study, 62 participants	Serious. The studies were not powered to this outcome	No concerns	No concerns	No concerns	No concerns	After HT there was no change in liver enzymes, endometrial mitoses or lupus erythematosus disease activity	⊕⊕⊕◯ Moderate

Abbreviations: BMD, bone mineral density; CEE, conjugated equine estrogens; EP: estrogen-progestin; EPT: estrogen-progestin-testosterone; GH: growth hormone; HDL: high density lipoprotein cholesterol; HT: hormone therapy; LDL: low density lipoprotein cholesterol; POI: premature ovarian insufficiency; RCT: randomized controlled trial.

3.9 Quality of the Evidence

As shown in Table 4, we found only low-quality evidence about the effects of HT on cardiovascular disease markers in women with POI. Moderate quality evidence was found about the effects of HT on BMD, vasomotor symptoms, quality of life, uterine morphology/blood flow and adverse effects, whereas high quality evidence was available regarding lipids and body growth (Table 4).

4. Discussion

This study aimed to explore the association between the use of HT and several clinical outcomes in POI patients. Available data made possible a meta-analysis to stipulate BMD changes with and without HT. Our results confirm that HT with estrogen and progesterone or progestin either increases or stabilizes BMD. There was no improvement in BMD when testosterone was added to the scheme. HT use was associated with several benefits, such as reduction in Kupperman Menopausal Index, total cholesterol, LDL, and the prevalence of hot flushes. It has also increased or preserved quality of life scores and improved endometrial blood flow. None of the studies included in the systematic review evaluated frequency of bone fractures or cardiovascular events (stroke or myocardial infarction), whereas adverse effects were seldom evaluated.

Those findings support the indication of HT with estrogen and progestogen for POI patients, bringing to light specific benefits of ovarian steroid replacement in this group. This study helps providers to align the expectations towards the medical management of POI and supports decision-making in clinical practice.

A systematic review published in 2017 by Burgos *et al*. found that in women with POI the use of HT either maintains lipid levels or associates with a reduction in LDL and an increase in triglycerides. As for bone health, estrogen + progestogen therapy either stabilizes or increases bone mass, compared to non-POI controls. Regarding quality of life, the review included only one study that reported an important reduction in vasomotor symptoms after the therapy was established (Burgos et al., 2017).

In our systematic review, we made, for the first time in the literature, a meta-analysis evaluating changes in BMD and the use of menopausal HT or

COCs. The results showed that HT led to a greater gain in BMD compared to controls. We identified a trend to benefit regarding menopause-specific formulations versus COC in relation to bone mass gain, but this difference was not statistically significant. This can be a basis for further comprehension about which hormonal formulations are most suitable for women with POI. Essentially, the BMD data are reassuring for both types of HT and the choice may consider other aspects such the need of contraception (considering the rare but existing probability of spontaneous pregnancy in some subgroups of POI (Dragojević Dikić et al., 2020)) and patient preferences and adherence.

As for cardiovascular health, our findings indicate different outcomes in the lipid profile depending on the hormone route of administration, with a better plasma triglyceride profile with the use of transdermal estradiol. Furthermore, another benefit of transdermal and vaginal hormone administration was the lower blood pressure profile. Our findings about the benefits of HT on vasomotor symptoms in women with POI are consistent with previous reviews (Burgos et al., 2017; Webber et al., 2017). We also found relevant information about the assessment of the Kupperman Menopausal Index, quality of life scores and height in adolescents, in addition to measurements of endometrial thickness, uterine volume and endometrial blood flow. Scarce information was obtained about adverse effects, and all three studies that documented such effects were published before the year 2000.

This review has some strengths such as the comprehensive search of relevant clinical outcomes and the investigation of possible differences between HT drugs and regimens, which have practical importance for decision making. The included observational studies were of good quality and it was possible to perform a meta-analysis for BMD. There are also several limitations, some of them related to included RCTs that lacked blinding of participants and personnel or had incomplete outcome data. The number of subjects of the meta-analysis was small, although the findings were predominantly consistent between studies. The origin of the participants was from teaching hospital clinics, making it difficult to associate the findings with the general population, but this is not a problem to estimate the effect of treatments. The study could not provide a simple answer to which is the best HT regimen for women with POI, although we found evidence

that any HT is better than no HT, and that non-oral administration results in lower blood pressure and triglycerides.

In summary, this systematic review found moderate to high quality evidence that HT with estrogen and progesterone or progestin is beneficial to women with POI, not only to mitigate menopausal symptoms but also to preserve BMD, reduce plasma cholesterol levels, avoid uterine atrophy and increase adult height (in prepubertal girls with Turner's syndrome). More studies are needed to reassure the long term safety of this therapy and to assess its possible impact on the risk of hard outcomes such as bone fractures and cardiovascular events.

5. Conflict of Interest

The authors have nothing to disclose.

6. Funding

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8. Attachment - PROSPERO Registration

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Caroline Reis Goncalves, Fernando M Reis. The effectiveness and adverse effects of hormone therapies for women with primary ovarian insufficiency (POI): a systematic review and meta-analysis. PROSPERO 2018 CRD42018115998 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018115998

Review question

To assess the effectiveness and adverse effects of hormone therapy for primary ovarian insufficiency.

Searches

The following databases will be searched for relevant literature:

Published, unpublished and ongoing trials will be searched in the MEDLINE (1960 to present), EMBASE (1960 to present), Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, PubMed Clinical Queries, Scopus, LILACS and the WHO International Clinical Trials Registry Platform.

Although search syntaxes will be constructed individually for each database, all will include the words: gonadotropin-releasing hormone, chemotherapy, premature ovarian failure, primary ovarian insufficiency. In addition, we will perform hand search on conference abstracts (e.g. ESHRE, ASRM and MEFS), and we will cross-reference the cited trials in Scopus.

Terms used in PubMed include ("Primary Ovarian Insufficiency"[MeSH] OR "Menopause, Premature"[MeSH] OR "surgical menopause") AND (Therapy OR "Contraceptive Agents, Female"[MeSH] OR "Hormone Replacement Therapy"[MeSH])

We will handsearch reference lists of articles retrieved by the search and contact experts in the field to obtain additional data.

Limitations:

Humans only (women).

Search will be restricted to trials written in English, Spanish, Chinese, Portuguese and Italian language.

Types of study to be included

1) Randomized controlled trials will be included with no limits on the randomization generation or blinding methods employed.

2) Patient-preference trials

Condition or domain being studied

Women with primary ovarian insufficiency.

Participants/population

It involves women aged from 13 to 50 years with primary ovarian insufficiency, defined as menopausal levels of FSH and absent or irregular menstrual cycles before the age of 40 years, or premenopausal bilateral oophorectomy.
Inclusion criteria:
Women between 13 and 50 years with POI.

Exclusion criteria:

Children (under 13 years of age) and women over 50 years of age.

Intervention(s), exposure(s)
The interventional therapies involve hormonal therapy - defined as estrogen, progestin and/or androgen, alone or combined (including hormonal contraceptives). No limits will be imposed on the route of administration, frequency of the dosage, or on the dosage itself.

Comparator(s)/control
There can be a non-exposed control group receiving no Hormone Therapy (HT) or receiving placebo or another type of HT. No limits will be imposed on the type of medication control group will be receiving.

Context
Studies in hospital settings and outpatient clinics will be included.

Main outcome(s)
Changes in bone mineral density from lumbar spine, femur neck or total hip by dual energy X-ray absorptiometry (DEXA), frequency of fractures, Kupperman index, ICQSF, Cardiovascular morbidity (stroke or myocardial infarction) and mortality. Quality of life, adverse effects, and relief of vasomotor symptoms (hot flashes or night sweats). Growth hormone and IGF1 levels. Live births in women with idiopathic POI.

Additional outcome(s)
Changes in metabolic lipid profile [total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides (TG)]

Data extraction (selection and coding)
Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion between the two reviewers.

A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement; indicators of acceptability to users; suggested mechanisms of intervention action; information for assessment of the risk of bias. Two review authors will extract data independently, discrepancies will be identified and resolved through discussion (with a third author where necessary). Missing data will be requested from study authors.

Risk of bias (quality) assessment
Two review authors will independently assess the risk of bias in included studies by considering the seven criteria adopted by Cochrane Collaboration's tool (Randomisation sequence generation, Treatment allocation concealment, Blinding, Completeness of outcome data, Selective outcome reporting and Other sources of bias).

Strategy for data synthesis
The data will be analyzed using RevMan 5.3 software. The dichotomous variable measure will be summarized by risk ratio (RR) with a 95% confidence interval (CI). For the continuous variables (e.g. Z-score), the results will be pooled and expressed as mean differences (MD) using inverse variance methods and the random-effects model with 95% confidence intervals (CI). Heterogeneity among studies will be assessed using Cochran's Q and I^2 statistic. When $P>0.1$, $I^2<50\%$, we will use a fixed effect model; when $P<0.1$, $I^2>50\%$, we will explore the reasons for heterogeneity.

Analysis of subgroups or subsets
None planned.

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Type and method of review
Meta-analysis, Systematic review

Anticipated or actual start date
25 February 2019

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25 February 2021

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None

Conflicts of interest

Language
English, Portuguese-Brazil

Country
Brazil

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Female; Humans; Primary Ovarian Insufficiency

Date of registration in PROSPERO
26 November 2018

Date of first submission
07 November 2018

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

26 November 2018