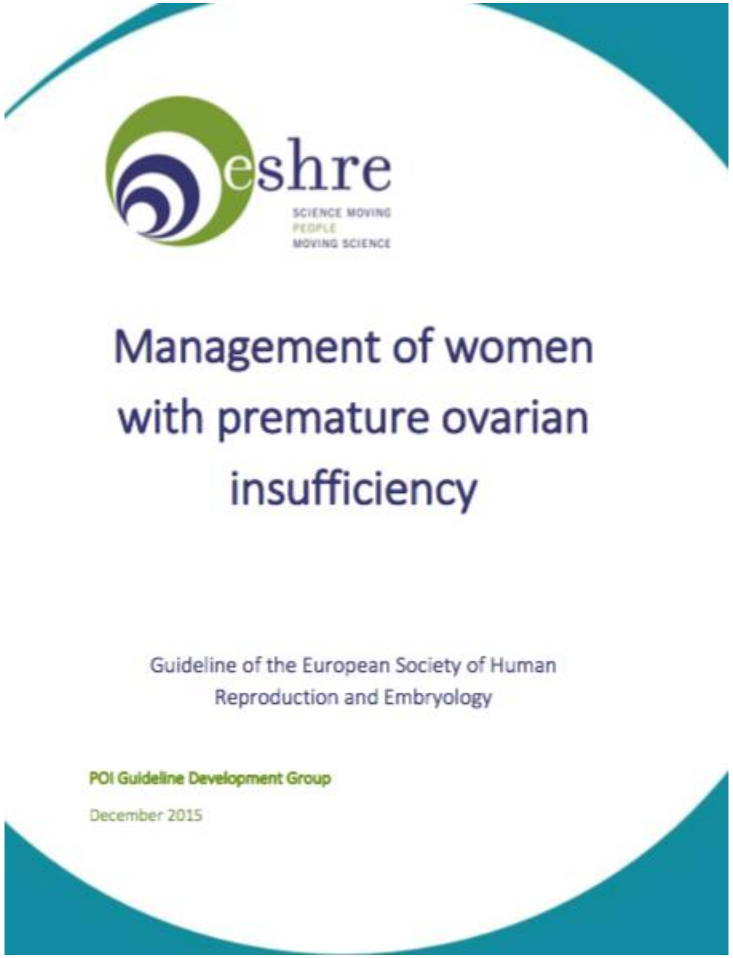
(Premature ovarian failure)
Premature ovarian insufficiency

Aila Tiitinen

Disclosures

- Professor, reproductive medicine, Helsinki University
- Chief physician, Head of IVF unit, Helsinki University Hospital
- Nothing to disclose concerning this topic or presentation

The outline of the lecture


eshre

SCIENCE MOVING PEOPLE MOVING SCIENCE

Management of women with premature ovarian insufficiency

Guideline of the European Society of Human Reproduction and Embryology

POI Guideline Development Group

December 2015

- diagnosis and assessement
- impact of POI on woman’s health
- monitoring
- hormone replacement therapy

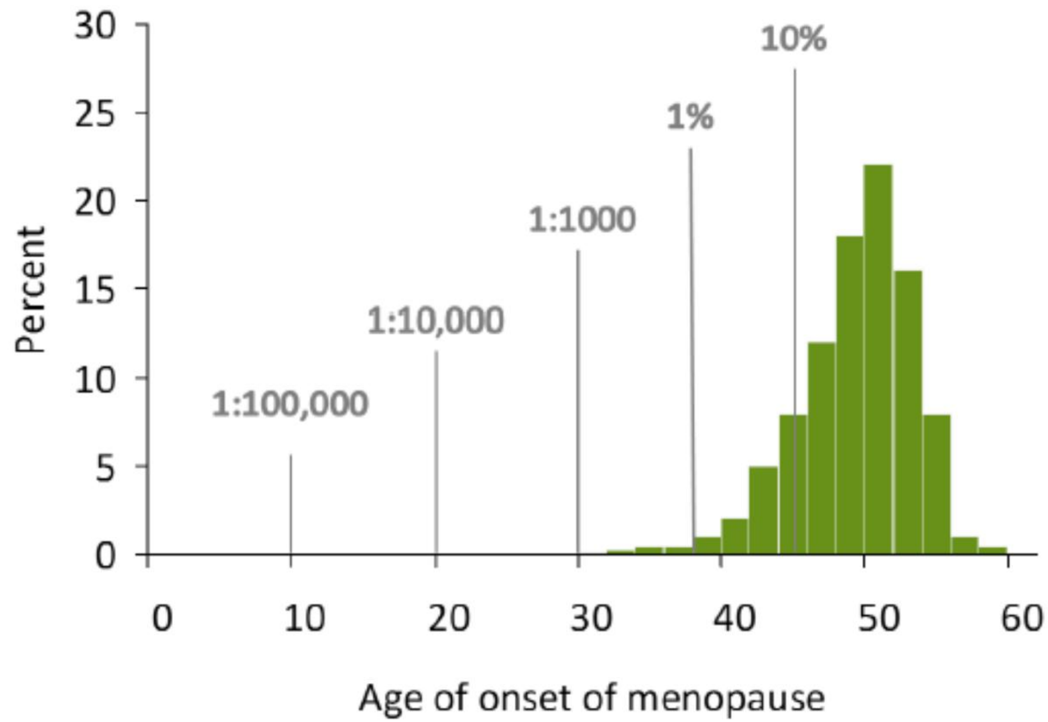
Different terms and definitions

Table 1.1 Number of papers retrieved in PUBMED in total and in the last 5 years, for the different terms used for POI.

	Number of papers retrieved in PUBMED	Number of papers retrieved in PUBMED, published in the last 5 years
Primary Ovarian Insufficiency	1581	663
Premature Ovarian Failure	1601	573
Gonadal dysgenesis	3057	408
Premature menopause	1011	228
Early menopause	620	170
Hypergonadotropic hypogonadism	346	86
Premature Ovarian Insufficiency	79	70
Ovarian dysgenesis	204	26
Primary ovarian failure	145	20
Hypergonadotropic amenorrhea	52	9
Climacterium praecox	5	0
Menopause praecox	1	0

The age of natural menopause

Figure 1.2. Distribution of age at menopause.



ESHRE recommendations

Premature Ovarian Insufficiency (POI)

What should this condition be called?

The term "premature ovarian insufficiency" should be used to describe this condition in research and clinical practice.	GPP

GPP = expert opinion
ESHRE Guideline group

How should POI be defined?

Premature ovarian insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40. POI is characterised by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins and low estradiol.

Prevalence of POI in general population

- <u>The prevalence of POI is approximately 1%</u>
- The prevalence of early menopause (in the 40 to 44 age group) is 10x higher
- Ethnicity may affect the prevalence
- Lifestyle: smoking is a risk factor for earlier onset of menopause
- Of current concern is the rising incidence of iatrogenic POI in cancer survivors
- Surgery, including surgery for endometriosis

Diagnosis of POI, symptoms

- POI needs to be excluded in women with oligo/amenorrea >4 months or estrogen-deficiency symptoms below the age of 40 years
- Symptoms may be transient or intermittent, and may be variable in severity, reflecting the fluctuations in ovarian activity that occur during spontaneous onset of POI
- Young women with primary amenorrhea rarely experience symptoms at presentation, implying that these symptoms are due to estrogen withdrawal rather than estrogen deficiency

Diagnosis of POI, ESHRE criteria

- elevated <u>FSH level >25 IU/l</u> on two occasions >4 weeks apart
  - Since patients with autoimmune POI should be included, the GDG decided to use a cut off level of FSH > 25 IU/l.
- The AMH assay used by most to date is insufficiently sensitive in this context, as AMH levels become undetectable approximately 5 years before the menopause.
- There is no evidence to include ultrasound

ESHRE recommendation

Recommendations

The diagnosis Premature Ovarian Insufficiency is based on the presence of menstrual disturbance and biochemical confirmation.

Although proper diagnostic accuracy in POI is lacking, the GDG recommends the following diagnostic criteria: • oligo/amenorrhea for at least 4 months, and • an elevated FSH level > 25 IU/l on two occasions > 4 weeks apart.	GPP

Assessment of causation of POI

- chromosomal analysis should be performed
- fragile-X premutation testing is indicated (but the implications should be discussed before)
- autosomal genetic testing only if specifically indicated
- screening for 21OH-Ab (or adrenocortical antibodies) should be considered
- screening for thyroid antibodies (TPO-Ab) should be performed

Implications

Test	Implications	
	Positive test	Negative test
Genetic/Chromosomal		
Karyotyping (for diagnosis of Turner syndrome)	Refer to endocrinologist, cardiologist and geneticist	a second analysis of the karyotype in epithelial cells (in case of high clinical suspicion)
Test for Y-chromosomal material	Discuss gonadectomy with the patient	
Fra-X	Refer to geneticist	
Autosomal genetic testing[a]		
Antibodies[b]		
ACA/21OH antibodies	Refer to endocrinologist	Re-test in case of clinical signs or symptoms
TPO-Ab	Test TSH every year	

[a] *not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).*

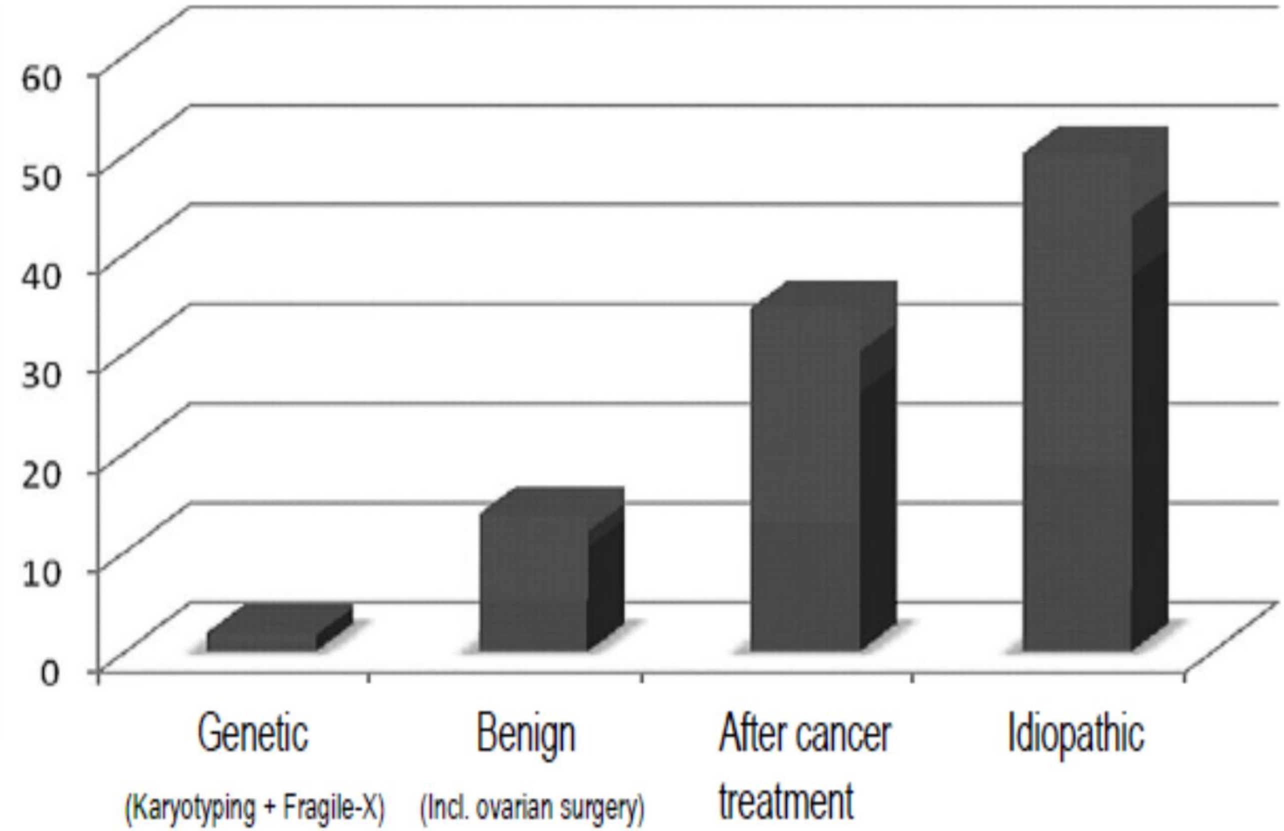
[b]. *POI of unknown cause or if an immune disorder is suspected.*

Genetics of primary ovarian insufficiency
Rossetti et al; Clin Genet 2017; 91:183-198

Table 2. List of genetic defects associated with POI and their estimated frequencies

	Estimated frequency in POI	References
X chromosome defects		
Turner's syndrome and related defects	4–5%	(9, 55, 59, 60)
Triple X syndrome	1–4%	(62)
Fragile X syndrome (*FMR1* premutation)	3–15%	(119, 120, 122, 132)
DIAPH2 disruption (translocation)	Unknown	(18, 19)
BMP15 variants	1.5–12%	(143–149)
PGRMC1 variants	1.5%	(155)
Autosomal defects		
Complex diseases	Rare	
Galactosemia (*GALT*)		(94, 95, 98)
BPES (*FOXL2*)		(79, 88)
APECED (*AIRE*)		(65, 70, 71)
Mitochondrial diseases (*POLG*)		(102, 103)
Demirhan syndrome (*BMPR1B*)		(109)
PHP1a (*GNAS*)		(101)
Ovarioleucodystrophy (*EIF2B*)		(106)
Ataxia telangiectasia (*ATM*)		(108)
Perrault syndrome (*HSD17B4, HARS2, CLPP, LARS2, C10ORF2*)		[a]
Premature aging syndromes:		
Bloom syndrome (*BLM*)		(113, 114)
Werner syndrome (*WRN*)		(117)
GAPO disease (*ANTXR1*)		(118)
Isolated disease		
FSH/LH resistance (*FSHR* and *LHCGR*)	0–1%	(42, 47, 134, 135)
INHA variants	0–11%	(138, 139)
GDF9 variants	1.4%	(32, 146, 150)
FOXL2 variants	Rare	(50, 92, 93)
FOXO3 variants	2.2%	(168, 169)
NOBOX variants	0–6%	(50, 175, 177–179, 182)
FIGLA variants	1–2%[b]	(183, 184)
NR5A1 variants	1.6%	(164, 165)
LHX8 variants	Rare	(50, 185, 186)
DNA replication/meiosis and DNA repair genes variants (*DMC1, MSH4, MSH5, SPO11, STAG3, SMC1β, REC8, POF1B, HFM1, MCM8, MCM9, SYCE1, PSMC3IP, NUP107, FANCA, FANCC,FANCG*)	Unknown	(35, 38–41, 45, 156–162)

Figure 3.1: Aetiology of premature ovarian failure cases managed at the West London Menopause and PMS Centre, London, UK (Maclaran and Panay, 2011).



Consequences for life expentancy

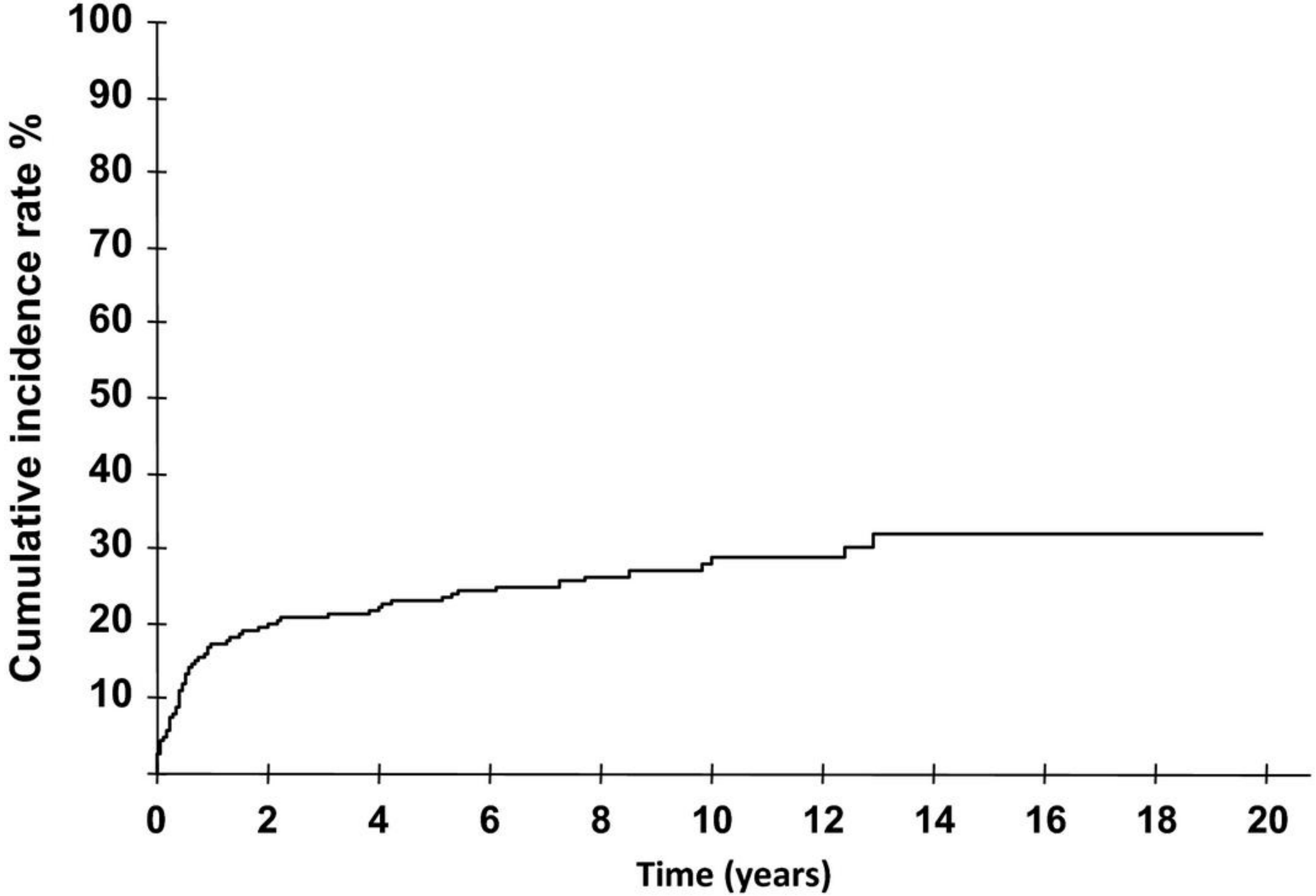
- POI is associated with increased risk of premature death from cardiovascular disease
- Both iatrogenic and natural menopause are implicated

Fertility and pregnancy

- Loss of fertility is one of the key accompanying features of the diagnosis
- 358 consecutive women with idiopathic POI:
  - 25% showed evidence of ovarian function (at least 2 consecutive menstrual cycles), the great majority within 1 year of diagnosis.
  - pregnancy occurred in 4.8%
  - predictive factors included markers of ovarian activity at diagnosis and the detection of ovarian follicles by ultrasound

(Bidet, *et al.*, 2011).

Long-term outcome of ovarian function in women with intermittent premature ovarian insufficiency



Clinical Endocrinology
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http://onlinelibrary.wiley.com/doi/10.1111/cen.13105/full#cen13105-fig-0002

Recommendations

- Ovarian activity may occur in women with POI, especially early in the natural history of the condition
- The possibility for spontaneous conception is up to 5%
- Women with POI should be advised to use contraception if they wish to avoid pregnancy
- There are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.

Bone health in women with POI

- The effect of POI-associated estrogen deficiency on bone is among the most clearly established adverse consequences of the condition
- Women with POI have been shown to have reduced BMD and possibly an increased risk of fracture later in life

Councelling

- Balanced diet, adequate calcium and vitamin D intake, weight-bearing exercise, maintaining a healthy body weight and cessation of smoking and moderation of alcohol intake are primary goals in reducing fracture risk

How should bone health be monitored?

- Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially if there are additional risk factors
- If BMD is normal and adequate systemic estrogen replacement is commenced, no need for repeated DEXA scan
- If diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years

Cardiovascular health

- Many cohort studies have shown that women with natural POI before the age of 40 years have earlier onset of coronary heart disease and increased CVD mortality
- A meta-analysis involving 10 observational studies comprising 190,588 women followed for 4-37 years found POI an independent though modest risk factor of ischemic heart disease and overall CVD, but not of stroke (Roeters van Lennep, *et al.*, 2014)

Remember: Turner syndrome

- higher prevalence of aortic coarctation and bicuspid aortic valve
- more than doubled chance of developing coronary heart and cerebrovascular disease, and an increased risk of aortic dilatation and rupture
- all patients with newly diagnosed Turner sdr should be evaluated by a cardiologist (ECG and/or CT or MRI) and periodically monitored

Wellbeing and quality of life

- A diagnosis of POI has a significant negative impact on psychological wellbeing and quality of life
- Psychological and lifestyle interventions should be accessible to women with POI
- Routinely inquire about sexual wellbeing and sexual function in women with POI

Hormone replacement therapy (HRT)

- Hormone replacement therapy is indicated for the treatment of symptoms of low estrogen in women with POI
- Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection
- Women with POI should be informed that HRT has not been found to increase the risk of breast cancer before the age of natural menopause

Is estrogen treatment cardioprotective?

- Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in women with POI to control future risk of cardiovascular disease; it should be continued at least until the average age of natural menopause

Hormone therapy, recommendations

What are the options for hormone replacement therapy?

17β-estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement.[87; 66]	C
Women should be informed that whilst there may be advantages to micronized natural progesterone, the strongest evidence of endometrial protection is for oral cyclical combined treatment.	GPP
Patient preference for route and method of administration of each component of HRT must be considered when prescribing, as should contraceptive needs.	GPP

Monitoring

Once established on therapy, women with POI using HRT should have a clinical review annually, paying particular attention to compliance.	GPP
No routine monitoring tests are required but may be prompted by specific symptoms or concerns.	GPP

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

J Clin Endocrinol Metab. 2016;101(9):3497-3505. doi:10.1210/jc.2015-4063

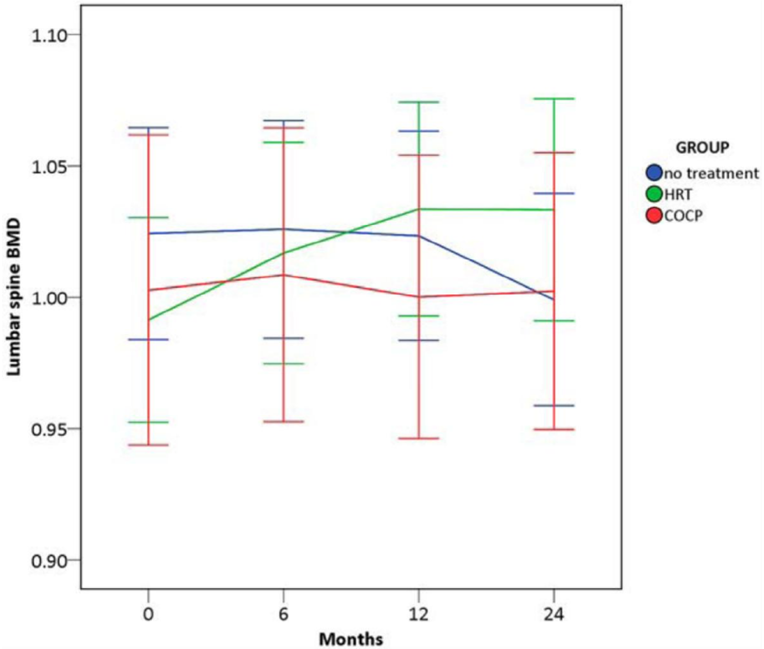
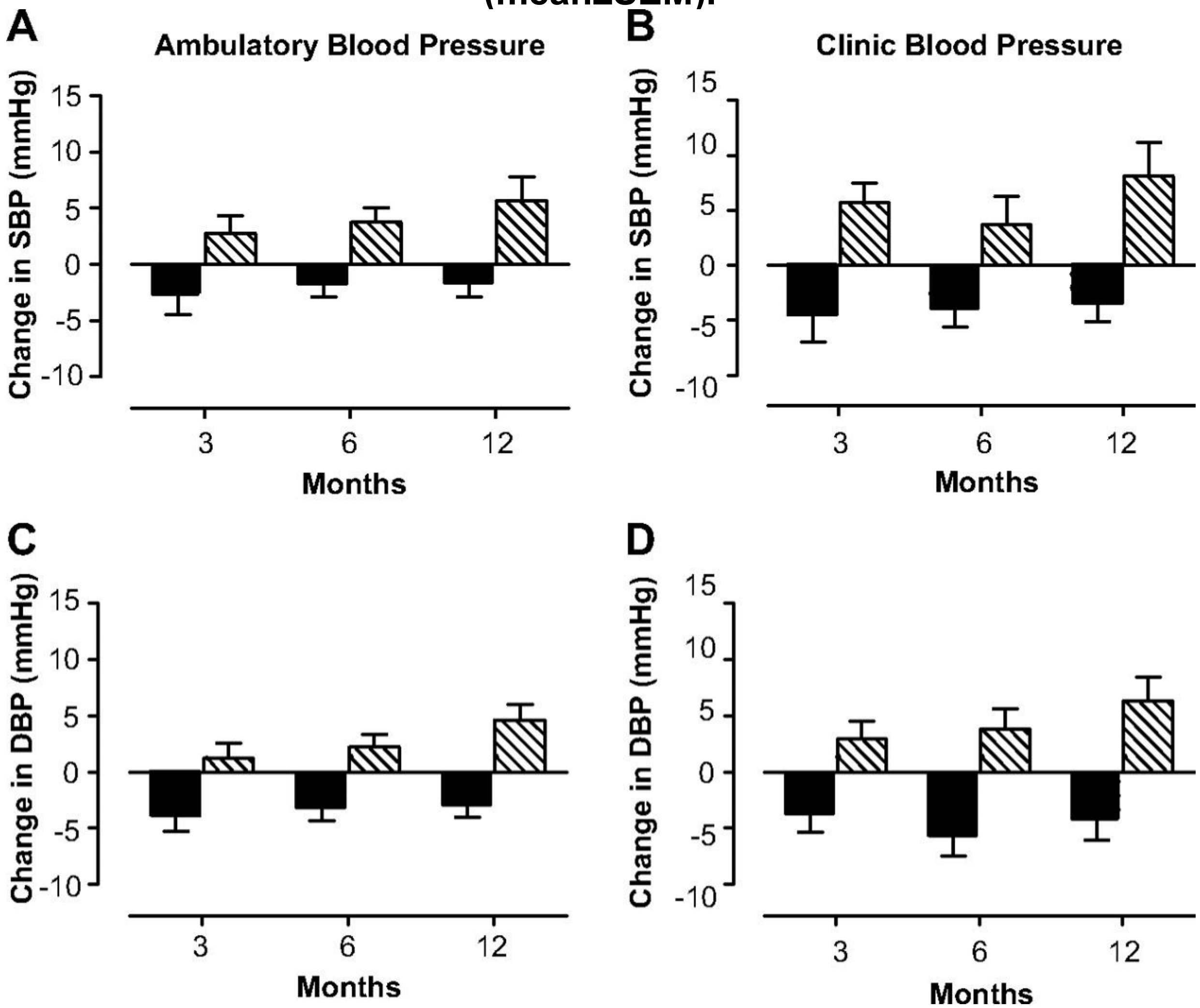


Figure Legend:

Lumbar spine BMD (g/m^2) in participants with complete data collection.

Data shown as mean ± 1 SD.

Figure 2. Changes in mean 24-hour ambulatory systolic (A) and diastolic (C) and clinic systolic (B) and diastolic (D) blood pressures with physiological sex steroid (▪) and standard () regimens (mean±SEM).



Jeremy P. Langrish et al. Hypertension. 2009;53:805-811

Patient information – important!

https://daisynetwork.org.uk/